## Detection of Candida: A marker of chronic disease?

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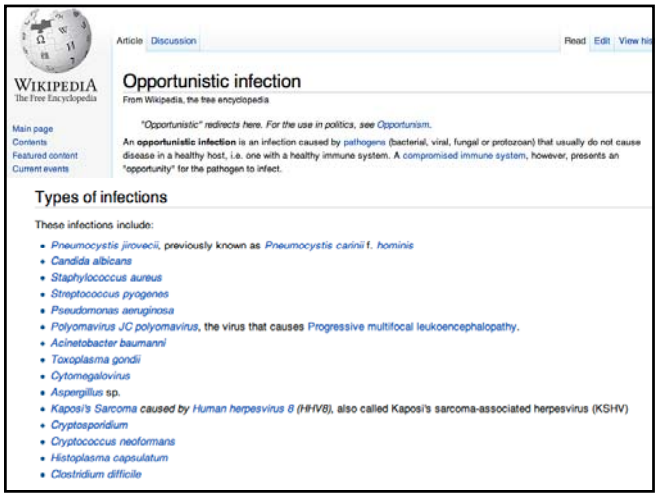

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### Opportunistic infection

From Wikipedia, the free encyclopedia

*"Opportunistic" redirects here. For the use in politics, see Opportunism.*

An **opportunistic infection** is an infection caused by pathogens (bacterial, viral, fungal or protozoan) that usually do not cause disease in a healthy host, i.e. one with a healthy immune system. A compromised immune system, however, presents an "opportunity" for the pathogen to infect.

#### Types of infections

These infections include:

- *Pneumocystis jirovecii*, previously known as *Pneumocystis carinii* f. *hominis*
- *Candida albicans*
- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Pseudomonas aeruginosa*
- *Polyomavirus JC polyomavirus*, the virus that causes Progressive multifocal leukoencephalopathy.
- *Acinetobacter baumanni*
- *Toxoplasma gondii*
- *Cytomegalovirus*
- *Aspergillus* sp.
- *Kaposi's Sarcoma caused by Human herpesvirus 8 (HHV8)*, also called Kaposi's sarcoma-associated herpesvirus (KSHV)
- *Cryptosporidium*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- *Clostridium difficile*

## Candida is part of normal flora

- oral cavity
- gut
- vagina
- moist areas of the skin

## Candida may cause

- Candida vaginitis
- Oral candidosis (thrush)
- Skin and nail infections
- Balanitis (?)
- Sepsis and disseminated disease

**Detection of Candida: A marker of chronic disease?**

## Candida does not cause

- yeast syndrome
- sinusitis
- allergies (?)
- pneumonia (?)
- diarrhoea (?)


- Up to 75% of women will have candidal vulvovaginitis, or vaginal thrush at some point in their lives
- Commonly caused by ***Candida albicans***.
- Candida is found naturally in the vagina, and is usually harmless. However, if the **conditions in the vagina change**, it can cause the symptoms of thrush: **itching, burning and discharge (fissuring, oedema)**
- Uncomplicated thrush: less than **four episodes** in a year, symptoms are mild or moderate, and caused by the *Candida* ***albicans***.
- Complicated thrush: is four or more episodes in a year or symptoms are severe or if coupled with pregnancy, poorly controlled diabetes, an immune deficiency, or if it is not caused by the *Candida albicans*
- **Riskfactors**:
  - Child-bearing age
  - Hormonal changes (pregnancy, birth control pills)
  - Antibiotics
  - Diabetics with poorly controlled diabetes.
  - Immune deficiency, immunosuppression.
  - Tight-fitting clothing

## Candidal Skin Infection

A rash caused by candida is usually not serious, and is usually easily treated with an antifungal cream.

### What is candida?

Candida is a yeast (a type of fungus). Small numbers of candida normally live on the skin and do no harm. Sometimes, under certain conditions, they can multiply and cause infection. The common sites for candida to cause infection are the vagina (vaginal thrush), the mouth (oral thrush), and the skin. This leaflet just deals with candidal skin infections. See separate leaflets called *'Vaginal Thrush'* and *'Oral Thrush'* for further details.

### Is a candidal skin infection serious?

Usually not. Most infections occur in people who are otherwise healthy (although they are more common if you are overweight). Treatment usually works well. In some people, the candidal skin infection may be the first indication of another condition such as diabetes.

### Why does candida sometimes multiply and cause infection on the skin?

The chance of a candidal skin infection developing is more likely in the following situations:

- Areas of skin that are moist or sweaty are ideal for candida to thrive. Therefore, the common sites affected are in the folds of skin in the groin, armpits, and under large breasts. (Another name for inflammation within a fold of skin or under a breast is 'intertrigo'. Candida infection is a common cause of intertrigo.) Nappy rash is sometimes due to candida. Obese people may develop candida infection between folds of skin. It can also affect skin between fingers and toes, and the corners of the mouth.
- If you have diabetes.
- If you take a long course of antibiotics or steroid medication.
- If you have a poor immune system. For example, if you have AIDS, or have chemotherapy, or have certain types of serious blood disorder.

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Article Discussion

## Oral candidiasis

From Wikipedia, the free encyclopedia

- An infection of **yeast fungi** of the genus *Candida* on the mucous membranes of the mouth frequently caused by ***Candida albicans***, or less commonly by ***Candida glabrata*** or ***Candida tropicalis***.
- Oral infections by *Candida* species usually appear as thick white or cream-colored deposits on mucosal membranes. The infected mucosa of the mouth may appear **inflamed** (red and possibly slightly raised).
- **Riskfactors**:
  - Newborn babies.
  - Diabetics with poorly controlled diabetes.
  - As a side effect of medication, most commonly having taken antibiotics.
  - Inhaled corticosteroids for treatment of lung conditions.
  - People with an immune deficiency.
  - Denture users.

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## Detection of Candida: A marker of chronic disease?

- unusually often (recurrent disease)
- unusual infections (sites and manifestations)
- systemic infections

in the absence of known predisposing factors

## Acute pseudomembranous candidosis

= thrush: white plaques that can be scraped off

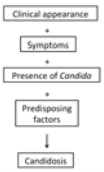
Clinical appearance
+
Symptoms
+
Presence of *Candida*
+
Predisposing factors
↓
Candidosis

## Acute atrophic candidosis

Clinical appearance
+
Symptoms
+
Presence of *Candida*
+
Predisposing factors
↓
Candidosis

- Superficial epithelium becomes eroded and underlying connective tissue is exposed.
- In patients with immunosuppression

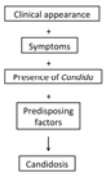
## Chronic atrophic candidosis




In medically / immunologically compromised patients

## Chronic hyperplastic candidosis

– Clinically resembles leukoplakia
– Potentially malignant




Clinical picture

Aetiology:
- immunological
- microbiological
- pathological
- anatomical
- trauma (mechanical, chemical, physical)
- drug side effect

Investigations:
- patient history
- clinical picture
- biopsy
- microbiology
- serology, immunology

Diagnosis

Treatment

## Predisposing factors

- impaired local defence mechanisms
- impaired systemic defence mechanisms
- altered oral flora
- poor oral hygiene

## Impaired local defence mechanisms

- decreased saliva production
- smoking
- atrophic oral mucosa
- mucosal diseases (Lichen)
- decreased blood supply (radiotherapy)
- topical corticoids

## Impaired systemic defence mechanisms

- Diabetes
- Primary or secondary immunodeficiency
- Malnutrition
- Immunosuppressive medication

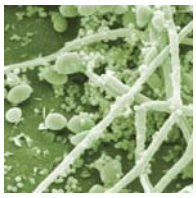
## Altered oral flora

Yeast favouring

- antibiotic treatment
- narrow spectrum mouthwashes
- high alcohol consumption
- reflux, low pH
- diet
- artificial materials (dentures)
- diabetes

## Poor oral hygiene

- mixed oral biofilms on non-renewing surfaces: teeth, dentures, intubation tube, tongue jewellery



## Where is the source of the oral candidosis?

1. Plaque (own colonisation)
2. Porous artificial materials (dentures, bite splints, orthodontic appliances)
3. Tooth brush
4. Saliva contact (?)

## Oral candidosis is a symptom!

- of imbalance of the normal flora
- of failure of the immune system
- of failure of oral hygiene

> Find the true reason and treat it when possible

## If thrush does not respond to treatment….

…. the diagnosis is probably wrong.

## Treatment of oral candidosis

1. Control of the predisposing factors
   - hydration
   - diet
   - probiotics
2. "Clearance of infection foci"
   - removal of oral biofilms = oral hygiene
   - dentures, toothbrushes etc
3. Antifungals

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Oral Diseases (2005) 11, 163–169
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ORIGINAL ARTICLE

**Improved oral hygiene and *Candida* species colonization level in geriatric patients**

AM Grimoud[1], JP Lodter[1], N Marty[2], S Andrieu[3], H Bocquet[1], MD Linas[4], M Runcan[5], JC Cazard[6]

[1]Odontology Department, Hôtel-Dieu Saint-Jacques University Hospital; [2]Laboratory for Microbiology and Hygiene, Rangueil University Hospital, avenue Jean Poulhès; [3]Department of Epidemiology and Public Health, Faculty of Medicine, allées Jules Guesde; [4]Laboratory for Mycology, Rangueil University Hospital, avenue Jean Poulhès; [5]Geriatrics Department, La Grave University Hospital, place Lange, Toulouse Cedex, France

- 110 geriatric patients in a nursing home
- 3 month intervention study
- assessment of the level of oral hygiene, yeast colonization and mucositis.
- improvement of oral hygiene (teeth and dentures)
- Results: improving oral hygiene **significantly reduced the incidence and level of yeast colonization, incidence of oral thrush and need for antifungals**

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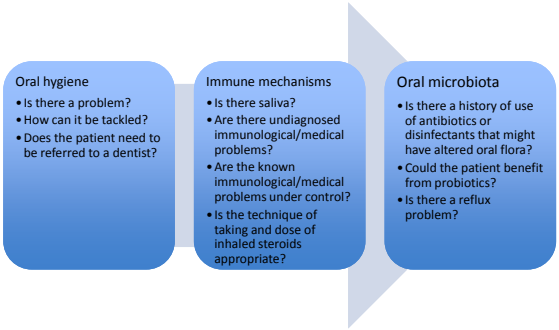
## Antifungals in the treatment of oral thrush

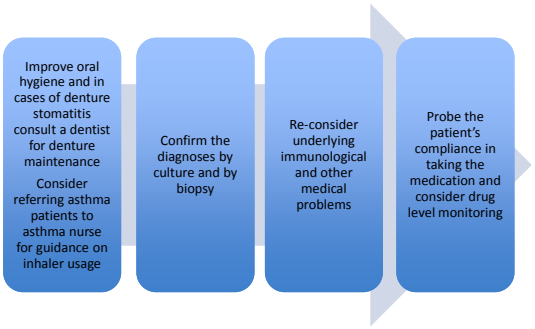
1. Primarily topicals continuing for 1 week after resolution of symptoms (4-6 wks)
   - good local concentrations
   - independent of saliva production
   - primarily polyenes
   - if the oral hygiene is poor use a topical with effect against all components of the oral biofilms (=CHX rinse)
2. If the patient is immunocompromised combine with systemic antifungal for 1 wk
   - appropriate dosage
   - efficacy poor in patients with dry mouths

## Aspects to consider when diagnosing oral candidosis




Rautemaa and Ramage, Crit Rev Microbiol 2011 in press

**Actions to consider in cases with a poor response to the given treatment**




Rautemaa and Ramage, Crit Rev Microbiol 2011 in press

## When to treat oral *Candida*?

- patient has symptoms and they are caused by *Candida*
- patient has mucositis and it is caused by *Candida*

## When not to treat oral *Candida*?

- patient has symptoms but they are not caused by *Candida*
- patient is not responding to appropriate antifungal treatment
- patient is afraid of getting candidosis but does not have it "yet".

## Why treat oral candidosis?

- systemic effects (malnutrition, dissemination of candida, portal of entry for other oral microbes)
- chronic infection is potentially carcinogenic

## Systemic effects of oral candidosis: malnutrition

*British Journal of Nutrition* (2004), **92**, 861–867
DOE: 10.1079/BJN20041264


**Oral candidiasis and nutritional deficiencies in elderly hospitalised patients**

Elena Paillaud[1], Isabelle Merlier[1], Catherine Dupeyron[2], Elisabeth Scherman[2], Joël Poupon[3] and Phuong-Nhi Bories[2,4]*

- 97 hospitalised patients
- 37% had oral candidosis
  - most suffered from vitamin C and zinc deficiency
  - daily energy intake was low
  - 30 days on fluconazole improved nutrition markedly!

Oral Oncology (2006) xxx, xxx–xxx

available at www.sciencedirect.com

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journal homepage: http://intl.elsevierhealth.com/journals/oron/

ORAL ONCOLOGY

**Oral and oesophageal squamous cell carcinoma – A complication or component of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED, APS-I)**

Riina Rautemaa [a,b,c,*], Jarkko Hietanen [d,e], Sirkku Niissalo [e,f], Sinikka Pirinen [f,g], Jaakko Perheentupa [f]

## APECED

- **A**utoimmune **p**oly**e**ndocrinopathy-**c**andidiasis-**e**ctodermal **d**ystrophy (APECED) an autosomal recessive autoimmune disease affecting various endocrine glands.
- Most patients have chronic or recurrent oral candidosis since early childhood.
- Patients receive repeated treatment and prophylactic courses of antifungals throughout life and azole resistance is common.
- The chronic candidosis presents with leukoplacic and hyperplastic lesions as well as with atrophy.
- The chronic candidosis is potentially carcinogenic; 10% of the patients above the age of 25 have developed oral cancer at the site of chronic mucositis lesions.

Oral Oncology (2007) 43, 607–613

available at www.sciencedirect.com

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journal homepage: http://intl.elsevierhealth.com/journals/oron/

**Oral and oesophageal squamous cell carcinoma – A complication or component of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED, APS-I)**

Riina Rautemaa [a,b,c,*], Jarkko Hietanen [d,e], Sirkku Niissalo [e,f], Sinikka Pirinen [f,g], Jaakko Perheentupa [f]

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[g] Department of Orthodontics, Institute of Dentistry, University of Helsinki, Helsinki, Finland

## Oral cancer

- The most important environmental risk factors for upper digestive tract cancers are tobacco **smoking, alcohol** intake and **poor oral hygiene**.
- They all result in increased acetaldehyde (ACH) levels in saliva.
- Alcohol itself is not mutagenic but the first metabolite of ethanol, ACH, is.
- Some alcoholic beverages contain high ACH concentrations as a congener.

## Acetaldehyde

WHO International Agency for the Research on Cancer (IARC) has classified ACH as a Class I carcinogen (Oct 2009).

- carcinogenic in experimental animal studies and in aldehyde dehydrogenase-2 (ALDH2) deficient Asians
- ACH can facilitate mutagenic DNA-adduct formation in clinically relevant concentrations (40-100 µM).

## ACH and poor oral hygiene

- Many oral microbes possess alcohol dehydrogenase (ADH) enzyme activity (*Neisseria*, *Streptococci*, *Candida*) and have been shown to be able to produce carcinogenic (40-100 µM) amounts of ACH from clinically relevant amounts of ethanol (11 mM) *in vitro.*
- 11 mM EtOH concentration can be found in saliva after drinking 0.5 g of alcohol per kg body weight (3 glasses of wine for an average 80 kg male).
- Microbial ACH production can explain extra-hepatic alcohol related carcinomas.

## Results

- Most *Candida* species can produce carcinogenic levels of ACH from clinically relevant concentrations of EtOH
- Many *Candida* species can produce carcinogenic levels of ACH from clinically relevant concentrations of glucose (100mM, equivalent to 18 g/L commonly found in food and drinks)

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uicc
global cancer control

IJC
International Journal of Cancer

**Xylitol inhibits carcinogenic acetaldehyde production by *Candida* species**

Johanna Uittamo[1,2], Mikko T. Nieminen[1,2,3], Pertti Kaihovaara[1], Paul Bowyer[4], Mikko Salaspuro[1] and Riina Rautemaa[2,3,4,5]

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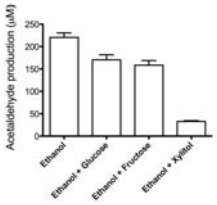
[5]The University of Manchester, Manchester Academic Health Science Centre, School of Translational Medicine and University Hospital of South Manchester, Manchester, United Kingdom




In the presence of **xylitol** ACH production from EtOH was inhibited by **84% (p<0.001) below the carcinogenic levels of 40-100µM**

**The triad of APECED, *Candida* and oral cancer**

1. Most APECED patients suffer from chronic oral candidosis. The mechanisms leading to this are not known
2. Colonising *Candida* are capable of producing of carcinogenic acetaldehyde and of DNA adduct formation
3. Chronic candidosis is carcinogenic in these patients. APECED patients deficient in *AIRE* may have a poor ability for clearance of altered autologous cells

# Allergic Bronchopulmonary Aspergillosis [ABPA]

Tobias Welte

Department of Respiratory Medicine

Medizinische Hochschule Hannover, Germany

Medizinische Hochschule Hannover

## Pulmonary Aspergillosis

- Classification of respiratory diseases caused by Aspergillus depending on the host immunity and the organism virulence
  - saprophytic
    - Aspergilloma
  - Allergic
    - allergic Aspergillus sinusitis
    - allergic bronchopulmonary aspergillosis [ABPA]
    - hypersensitivity pneumonias
  - Invasive
    - airway invasive aspergillosis
    - chronic necrotizing pulmonary aspergillosis
    - invasive aspergillosis)

Soubani AO et al. Chest 2002; 121:1988–1999



## Allergic Bronchopulmonary Aspergillosis Defintion and Manifestations

- ABPA is an allergic pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus*
  - *Allergic Bronchopulmonary Mycosis is a* rare syndrome similar to ABPA, but caused by fungi other than *A. fumigatus*
- Clinical signs and symptoms
  - chronic asthma
  - Recurrent pulmonary infiltrates,
  - bronchiectasis

Greenberger PA. J Allergy Clin Immunol 2002; 110:685– 692

## Allergic Bronchopulmonary Mycosis

| Fungi | Study/Year |
|---|---|
| *A niger* | Sharma et al[218]/1985 |
| Helminthosporium spp | Dolan et al[226]/1970 |
| Penicillium spp | Sahn and Lakshminarayan[227]/1973 |
| *Aspergillus ochraceus* | Novey and Wells[225]/1978 |
| Stemphylium spp | Benatar et al[229]/1980 |
| *Aspergillus terreus* | Laham et al[230]/1981 |
| Drechslera spp | McAleer et al[231]/1981 |
| Torulopsis spp | Patterson et al[232]/1982 |
| Mucor-like spp | Patterson et al[232]/1982 |
| Candida spp | Akiyama et al[234]/1984 |
| Pseudallescheria spp | Lake et al[235]/1990 |
| Bipolaris spp | Lake et al[236]/1991 |
| Curvularia spp | Lake et al[236]/1991 |
| Schizophyllum spp | Kamei et al[237]/1994 |
| Fusarium spp | Backman et al[238]/1995 |
| Cladosporium spp | Moreno-Ancillo et al[239]/1996 |
| Saccharomyces spp | Ogawa et al[240]/2004 |

Agarwal R. CHEST 2009; 135:805–826

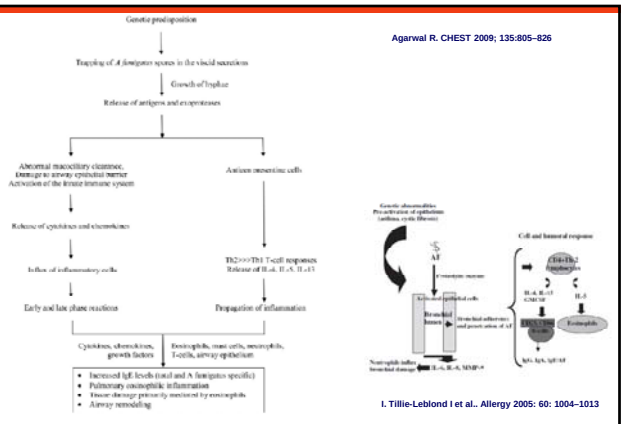


## Allergic Bronchopulmonary Aspergillosis Immunologic Classification

- **immediate hypersensitivity (type I)**
- **antigen-antibody complexes (type III)**
- **eosinophil-rich inflammatory cell responses (type IVb)**

Rajan TV. Trends Immunol 2003; 24: 376–379





Agarwal R. CHEST 2009; 135:805–826



I. Tillie-Leblond I et al.. Allergy 2005: 60: 1004–1013

## Allergic Bronchopulmonary Aspergillosis Epidemiology

- **Prevalence of ABPA**
  - **1 to 2% in patients with asthma**
  - **2 to 15% in patients with cystic fibrosis (CF)**
- **The condition remains underdiagnosed with reports of mean diagnostic latency of even 10 years between the occurrence of symptoms and the diagnosis**
- **There has been an increase in the number of cases of ABPA due to the heightened physician awareness and the widespread availability of serologic assays**

Agarwal R. CHEST 2009; 135:805–826



## Allergic Bronchopulmonary Aspergillosis Prevalence in Asthma

| Study/Year | Type of Study | Type of Skin Test | Type of Antigen | Criteria Used for Diagnosis of ABPA | Prevalence of AH in Asthma (n/N) | Prevalence of ABPA in Asthma (n/N) |
|---|---|---|---|---|---|---|
| Aitapattu[21]/1991 | Prospective | Intradermal | Commercial (Bencard Allergie; Munich, Germany) | Major (A/R/T/E/P)<br>Minor (C) | 58/134 | 8/134 |
| Eaton et al[22]/2000 | Prospective | Prick | Commercial (Hollister-Stier Laboratories) | Major (A/R/T/E/P/I/C/S) | 47/255 | 9/55 |
| Kumar and Gaur[24]/2000 | Prospective | Intradermal | Locally prepared | Major (A/R/T/E/P/I/C/S)<br>Minor (C/S/B) | 47/200 | 32/200 |
| Al-Mobeireek et al[20]/2001 | Prospective | Prick | Commercial (Soluprick; ALK Laboratories, Wallingford, CT) | | 12/53 | |
| Maurya et al[25]/2005 | Prospective | Intradermal | Locally prepared | Major (A/R/T/E/P/I/C/S)<br>Minor (C/S) | 30/105 | 8/105 |
| Agarwal et al[23]/2007 | Prospective | Intradermal | Commercial (Hollister-Stier Laboratories) | Major (A/R/T/E/P/I/C/S)<br>Minor (S/B) | 291/755 | 155/755 |
| Prasad et al[26]/2008 | Prospective | Intradermal | Not available | Major (A/R/T/E/P/I/C/S)<br>Minor (C/S/B) | 74/244 | 15/244 |

Agarwal R. CHEST 2009; 135:805–826



## Allergic Bronchopulmonary Aspergillosis Prevalence in CF

| Study | Year | Nature of Study | Patients, No. | AH in CF | ABPA* in CF | Diagnosis of AH |
|---|---|---|---|---|---|---|
| Mearns et al[164] | 1967 | Prospective | 56 | 26/56 | | Skin test |
| Allan et al[165] | 1975 | Prospective | 30 | 11/30 | | Skin test |
| Silverman et al[166] | 1978 | Prospective | 45 | 17 | | Skin test |
| Nelson et al[167] | 1979 | Prospective | 46 | 18/46 | 5/46 | Skin test |
| Laufer et al[177] | 1984 | Prospective | 100 | 53/100 | 10/100 | Skin test |
| Feanny et al[168] | 1985 | Prospective | 117 | 15/117 | 12/117 | Skin test |
| Schonheyder et al[169] | 1985 | Prospective | 200 | | 10/200 | |
| Zeuske et al[170] | 1985 | Prospective | 75 | 44/75 | 10/75 | Skin test |
| Knutsen et al[176] | 1990 | Prospective | 73 | 18/73 | 9/73 | Skin test |
| Nicolai et al[179] | 1990 | Prospective | 148 | 58/148 | | Serology |
| Simmonds et al[191] | 1990 | Prospective | 137 | | 8/137 | |
| Hutcheson et al[192] | 1991 | Prospective | 79 | 24/79 | | Skin test |
| el-Dahr et al[193] | 1994 | Prospective | 147 | 30/147 | 22/147 | Serology |
| Marchant et al[194] | 1994 | Retrospective | 160 | | 16/160 | Skin test |
| Mroueh and Spock[178] | 1994 | Retrospective | 236 | 38/87 | 15/236 | Skin test |
| Becker et al[197] | 1996 | Prospective | 53 | 15/51 | 1/53 | Skin test |
| Hutcheson et al[198] | 1996 | Prospective | 118 | 47/112 | 6/118 | Skin test |
| Geller et al[199] | 1999 | Prospective | 14,210 | | 281/14,210 | |
| Nepomuceno et al[183] | 1999 | Retrospective | 172 | | 16/172 | |
| Cimon et al[196] | 2000 | Prospective | 128 | | 5/128 | |
| Mastella et al[174] | 2000 | Prospective | 12,447 | | 967/12,447 | |
| Taccetti et al[197] | 2000 | Prospective | 3,059 | | 191/3,059 | |
| Ritz et al[200] | 2005 | Prospective | 160 | 20/160 | 11/160 | Serology |
| Skov et al[193] | 2005 | Retrospective | 277 | | 13/277 | |
| Almeida et al[196] | 2006 | Prospective | 32 | 11/32 | 2/32 | Skin test |
| Kraemer et al[173] | 2006 | Prospective | 122 | | 16/122 | |
| Chotirmall et al[199] | 2008 | Prospective | 50 | | 6/50 | |
| Bapaka and Kolls[200] | 2008 | Retrospective | 440 | | 31/440 | |

## Allergic Bronchopulmonary Aspergillosis Clinical Features

| Clinical Features | Behera et al[16]/1994 | Chakrabarti et al[21]/2002 | Agarwal et al[22]/2007 |
|---|---|---|---|
| Patients, No. | 35 | 59 | 155 |
| Male/female gender, No. | 14/21 | 53/35 | 79/76 |
| Mean age, yr | 34.3 | 36.4 | 33.4 |
| Mean duration of asthma, yr | 11.1 | 12.1 | 8.9 |
| History of asthma | 94% | 90% | 100% |
| Expectoration of sputum plugs | Not available | 69% | 46.5% |
| Mean eosinophil count, per μL | | | 1,264 |
| AEC > 500/μL, % | 12/28 (43%) | 100% | 76.1% |
| Fleeting shadows | 77% | 74% | 40% |
| History of intake of antituberculous drugs | 34% | 29% | 44.5% |
| Skin test against Aspergillus | | | |
| Type I | 51% | 85% | 100% |
| Type III | 25.7% | 16.9% | 83.2% |
| Mean IgE levels | Not done | Not done | 6,434 |
| Elevated IgE levels, % | | | 100% |
| Aspergillus-specific IgE/IgG | Not done | Not done | 100% |
| Serum precipitins against Aspergillus | 77% | 71.9% | 86.5% |
| Central bronchiectasis | 71% | 69% | 76.1% |

Behera D et al. Indian J Chest Dis Allied Sci 1994; 36:173–179
Chakrabarti A et al. Mycoses 2002; 45:295–299
Agarwal R et al. Chest 2007; 132:1183–1190



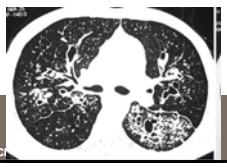
1. Chest radiographic findings
   - Transient changes
     - Common
       - Patchy areas of consolidation
       - Radiologic infiltrates: toothpaste and gloved finger shadows due to mucoid impaction in dilated bronchi
       - Collapse: lobar or segmental
     - Uncommon
       - Bronchial wall thickening: tramline shadows
       - Air-fluid levels from dilated central bronchi filled with fluid
       - Perihilar infiltrates simulating adenopathy
       - Massive consolidation: unilateral or bilateral
       - Small nodules
       - Pleural effusions
   - Permanent changes
     - Common
       - Parallel-line shadows representing bronchial widening
       - Ring-shadows 1–2 cm in diameter representing dilated bronchi en face
       - Pulmonary fibrosis: fibrotic scarred upper lobes with cavitation
     - Uncommon
       - Pleural thickening
       - Mycetoma formation
       - Linear scars

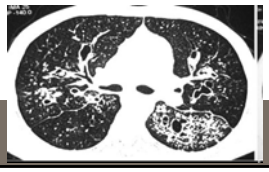
transient pulmonary opacities
in the right lower lobe
before and after treatment



## Allergic Bronchopulmonary Aspergillosis HRCT Findings

- Common
  - Central bronchiectasis
  - Mucus plugging with bronchoceles
  - Consolidation
  - Centrilobular nodules with tree-in-bud opacities
  - Bronchial wall thickening
  - Areas of atelectasis
  - Mosaic perfusion with air trapping on expiration
- Uncommon
  - High-attenuation mucus (finding most helpful in differential diagnosis)
  - Pleural involvement
  - Randomly scattered nodular opacities





## Laboratory and Pulmonary Function Tests

- *Serum Precipitins Against* A fumigatus
  - The precipitating IgG antibodies are elicited from crude extracts of *A fumigatus* and can be demonstrated using the double gel diffusion technique
  - Problem: Also be present in other pulmonary disorders and thus represent supportive not diagnostic evidence forABPA
- *Peripheral Eosinophilia*
  - A blood absolute eosinophil count > 1,000 cells/L is a major criterion for the diagnosis of ABPA.
  - Problem: Half of the patients without eosinophilia. A low eosinophil count does not exclude the diagnosis of ABPA
- *Sputum Cultures for* A fumigatus
  - Problem: A. fumigatus can also be grown in patients with other pulmonary diseases due to the ubiquitous nature of the fungi
- *Role of Specific Aspergillus Antigens*
  - Problem: Lack of reproducibility and consistency and cross-reactivity with other antigens.
  - Recombinant allergens Asp f1, Asp f2, Asp f3, Asp f4, and Asp f6 may be promising in the diagnosis of ABPA
- *Pulmonary Function Test:*
  - Help to categorize the severity of the lung disease but have no diagnostic value in ABPA
  - Usual finding is an obstructive defect of varying severity



## Allergic Bronchopulmonary Aspergillosis Rosenberg-Patterson Diagnostic Criteria

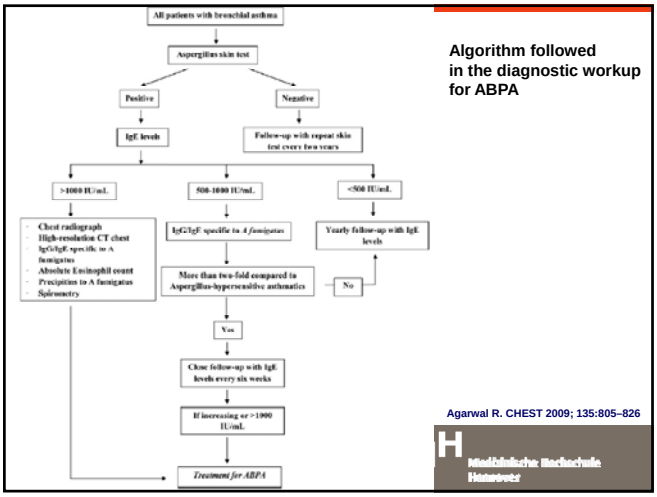
- Major criteria (ARTEPICS)
  - A Asthma
  - R Roentgenographic fleeting pulmonary opacities
  - T Skin test positive for Aspergillus (type I reaction, immediate cutaneous hyperreactivity)
  - E Eosinophilia
  - P Precipitating antibodies (IgG) in serum
  - I IgE in serum elevated ( 1,000 IU/mL)
  - C Central bronchiectasis
  - S Serums *A fumigatus*-specific IgG and IgE (more than twice the value of pooled serum samples from patients with asthma who have Aspergillus hypersensitivity)
- Minor criteria
  - Presence of Aspergillus in sputum
  - Expectoration of brownish black mucus plugs
  - Delayed skin reaction to Aspergillus antigen (type III reaction)
- Six of eight major criteria makes the diagnosis almost certain
- ABPA-S or
  - the absence of central bronchiectasis
- ABPA-CB
  - The presence of central bronchiectasis



## Allergic Bronchopulmonary Aspergillosis Minimal Diagnostic Criteria

Rosenberg M, Patterson R et al. Ann Intern Med 1977; 86:405–414

- Minimal ABPA-CB
  - Asthma
  - Immediate cutaneous hyperreactivity to Aspergillus antigens
  - Central bronchiectasis
  - Elevated IgE
  - Raised *A fumigatus*-specific IgG and IgE
- Minimal ABPA-S
  - Asthma
  - Immediate cutaneous hyperreactivity to Aspergillus antigens
  - Transient pulmonary infiltrates on chest radiograph




**Algorithm followed in the diagnostic workup for ABPA**

Agarwal R. CHEST 2009; 135:805–826



## Allergic Bronchopulmonary Aspergillosis Diagnostic Criteria in CF

- **Classic Diagnostic Criteria**
  - **Acute or subacute clinical deterioration (cough, wheeze, and other pulmonary symptoms) not explained by another etiology**
  - **IgE in serum elevated ( 1,000 IU/mL)**
  - **Immediate cutaneous reactivity to Aspergillus or presence of serum IgE antibody to *A fumigatus***
  - **Precipitating antibodies to *A fumigatus* or serum IgG antibodyto *A fumigatus***
  - **New or recent abnormalities on chest radiograph or chest CT scan that have not cleared with antibiotics and standard physiotherapy Classic diagnostic criteria**

Stevens DA et al. Clin Infect Dis 2003; 37(suppl):S225–S264



## Allergic Bronchopulmonary Aspergillosis Diagnostic Criteria in CF

- **Minimal diagnostic criteria**
  - **Acute or subacute clinical deterioration (cough, wheeze, andother pulmonary symptoms) not explained by another etiology**
  - **Total serum IgE levels  500 IU/mL. If total IgE level is 200–500 IU/mL, repeat testing in 1–3 mo is recommended**
  - **Immediate cutaneous reactivity to Aspergillus or presence of serum IgE antibody to *A fumigatus***
  - **One of the following:**
    - **precipitins to *A fumigatus* or demonstration of IgG antibody to *A fumigatus*; or**
    - **new or recent abnormalities on chest radiography (on chest radiography or chest CT scan that have not cleared with antibiotics and standard physiotherapy)**

Stevens DA et al. Clin Infect Dis 2003; 37(suppl):S225–S264

## Allergic Bronchopulmonary Aspergillosis Staging

| Stage | Description | Clinical Picture | Radiologic Findings | Immunologic Features |
|---|---|---|---|---|
| I | Acute phase | Usually symptomatic, fever, weight loss, wheeze | Normal or presence of radiologic opacities | IgE > 1,000 IU/mL, raised specific IgG/IgE and precipitins to *A fumigatus* |
| II | Remission | Asymptomatic | Generally normal or significant resolution of radiologic opacities from the acute phase | Usually 35–50% decline in IgE levels by 6 wk to 3 mo; we give additional label of "complete remission" if the patient did not have any additional ABPA exacerbations over the next 3 mo after stopping steroid therapy |
| III | Exacerbation | Symptomatic as in acute phase | Transient or fixed pulmonary opacities | Doubling of IgE levels from baseline |
| IV | Glucocorticoid-dependent ABPA | Symptomatic | Transient or fixed pulmonary opacities | Two groups can be identified: one in whom IgE levels do not rise but require steroids for asthma control (glucocorticoid-dependent asthma); the other in whom steroids are required to continually suppress the disease activity (glucocorticoid-dependent ABPA) |
| V | End-stage (fibrotic) ABPA | Symptomatic, findings of fixed airway obstruction, severe pulmonary dysfunction, type II respiratory failure, cor pulmonale | Evidence of bronchiectasis, pulmonary fibrosis, pulmonary hypertension | Serum IgE levels and specific immunoglobulins do not become normal in most patients, and even these patients can have frequent exacerbations |

Agarwal R et al. Chest 2006; 130:442–448



## Allergic Bronchopulmonary Aspergillosis Therapy

- **Oral glucocorticoids**
  - **Regime 1 (Greenberger PA. J Allergy Clin Immunol 2002; 110:685– 692)**
    - **Prednisolone, 0.5 mg/kg/d, for 1–2 wk, then on alternate days for 6–8 wk**
    - **Taper by 5–10 mg every 2 wk and discontinue**
    - **Repeat the total serum IgE concentration and chest radiograph in 6 to 8 wk**
  - **Regime 2 (Agarwal R et al. Chest 2006; 130:442–448)**
    - **Prednisolone, 0.75 mg/kg, for 6 wk, 0.5 mg/kg for 6 wk**
    - **Taper by 5 mg every 6 wk to continue for a total duration of at least 6 to 12 mo**
    - **Total IgE levels are repeated every 6 to 8 wk for 1 yr to determine the baseline IgE concentrations**
- **Follow-up and monitoring**
  - **Medical history and physical examination, chest radiograph, and measurement of total IgE levels every 6 wk**
    - **A 35% decline in IgE level signifies satisfactory response to therapy**
    - **Doubling of the baseline IgE value can signify a silent ABPA exacerbation**
- **If the patient cannot be tapered off prednisolone, the disease has evolved into stage IV.**
  - **Management should be attempted with alternate-day prednisone with the least possible dose**
  - **Prophylaxis for osteoporosis: oral calcium and bisphosphonates**
  - **Oral itraconazole**
    - **Dose: 200 mg bid for 16 wk then once a day for 16 wk**



## Allergic Bronchopulmonary Aspergillosis Therapy

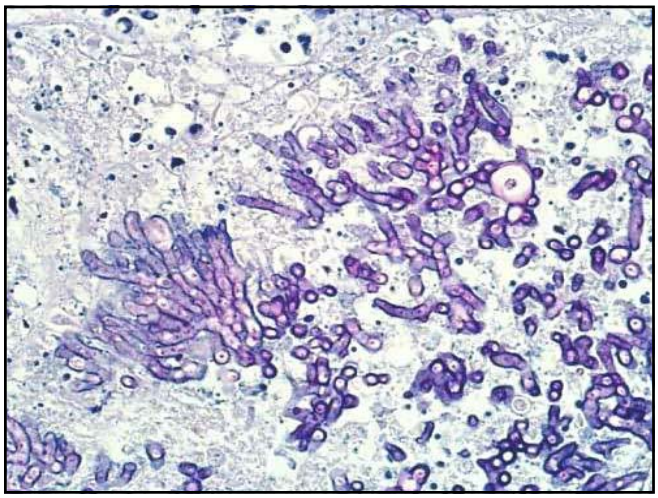
- ***Inhaled Corticosteroids (ICS)***
  - **Small case studies suggest some benefit of ICS**
  - **a double-blind multicenter placebo-controlled trial in 32 patients suggested no superiority over placebo**
  - **use ICS only for the control of asthma once the oral prednisolone dose is reduced to 10 mg/day**

Report to the Research Committee of the British Thoracic Association. Br J Dis Chest 1979; 73:349–356

## Allergic Bronchopulmonary Aspergillosis Alternative Therapies

- **Antifungal Therapy**
  - **Inhaled amphotericin**
  - **Voriconazole**
- **Anti IgE Therapy**
  - **Omalizumab**





# Antifungal stewardship: aspergillosis

Malcolm Richardson PhD, FSB, FRCPath
Mycology Reference Centre Manchester
The National Aspergillosis Centre,
University Hospital of South Manchester,
and University of Manchester, UK

## Financial disclosure

- Astellas Pharma
- Gilead Sciences Europe Ltd
- Gilead UK
- Pfizer UK
- Cephalon
- MSD/Schering-Plough

## Antifungal stewardship

- Stewardship team
- Core strategies
  - Prospective audit with intervention and feedback
  - Formulary restriction and pre-authorisation
- Supplemental strategies
  - Education
  - Guidelines and care pathways
  - De-escalation therapy
  - Dose optimisation
  - IV to PO switching
  - Computer-based surveillance

## Laying the groundwork

- Evaluate current stewardship analysis
- Development of a stewardship website
- Implementation of real-time surveillance system
- Business plan

## Antimicrobial stewardship

- 36 published studies on effect of antimicrobial stewardship
  - No studies on antifungal stewardship
  - Majority looked at drug costs
  - Few looked at more objective PATIENT outcomes
- One consistent trend:
  - Largest effect associated with education of prescribers

## Core strategies

- Prospective audit
  - Clinical pharmacists
  - Clinical specialists
- Formulary restrictions
  - Pre-printed order forms
  - Infectious disease consultation required
  - Location, laboratory service, age, indication

## Primary goal of antifungal stewardship

- Primary goal:
  - Optimise clinical outcomes while minimising unintended consequences of antifungal use, including:
    - Toxicity
    - Selection of pathogenic fungi
    - Emergence of resistance
- Secondary goal:
  - Reduction of healthcare costs without adversely impacting on quality of care

## ANTIFUNGAL SURVEILLANCE TEAM

- Core members:
  - ID consultant
  - ID pharmacist
  - Mycologists/Microbiologists
  - IT specialists
  - Infection Control professionals
  - Hospital epidemiologists

## Antifungal stewardship

- Supplementary elements:
  - Education
  - Guidelines and clinical pathways
  - Antifungal cycling
  - ?combination therapy
  - Streamlining and de-escaltion of therapy
  - Dose optimisation
  - Parenteral to oral switching

## Key statement

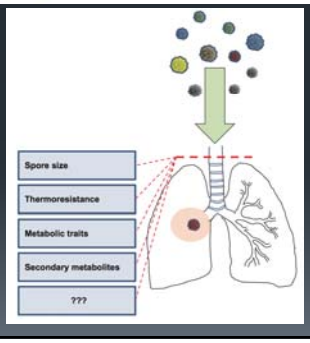
"The mycology laboratory plays a critical role by providing patient-specific culture data to optimise individual therapy and by assisting infection control efforts"

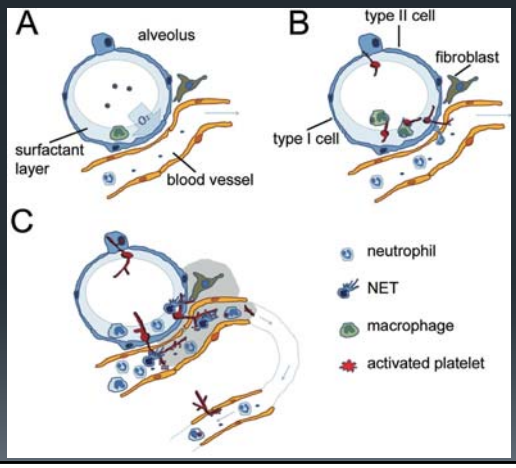
- An understanding of local epidemiology
- Provision of unit-specific antibiograms
- Provision of current antifungal susceptibility data

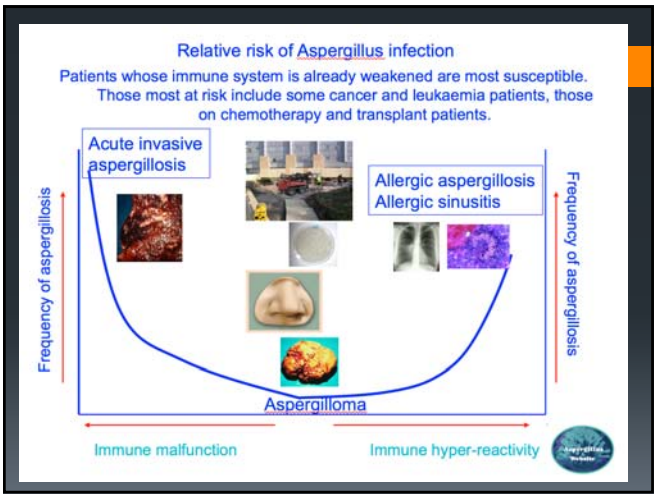
Cellular Microbiology (2010) 12(11), 1535–1543 doi:10.1111/j.1462-5822.2010.01517.x
First published online 16 September 2010

Microreview

***Aspergillus fumigatus*: contours of an opportunistic human pathogen**






## IA: correlates of overall mortality

- Allogeneic haematopoietic stem cell or solid organ transplantation
- Progression of underlying malignancy
- Prior respiratory disease
- Corticosteroid therapy
- Renal impairment
- Low monocyte count
- Dissemination of aspergillosis
- Diffuse pulmonary lesions
- Pleural effusion
- Proven or probable aspergillosis

*Nivoix et al. 2008*

## Invasive aspergillosis-treatment

- Conventional amphotericin B 1.0-1.5 mg/kg/day
- Lipid formulations of amphotericin B (≥ 5 mg/kg/day) in patients who are intolerant of or refractory to conventional amphotericin B
  - Considered first line by many experts
- Other options:
  - IV itraconazole, IV voriconazole, or caspofungin acetate alone +/- voriconazole
- Augmentation of host response: GCSF, GM-CSF +/- granulocyte transfusions-reduce steroids
- Voriconazole 200 mg q12h in stabilized patients
  - Mortality in persistently neutropenic patients > 85%

## Analysis of azole antifungal iv to po programme: MUSC medical centre

- Objectives
  - Evaluate the success of the current process for conversion of IV to PO therapy for both fluconazole and voriconazole
  - Determine what the impact on anti-fungal therapy costs has been since the IV to PO conversion programme was introduced in 2003

## Analysis of azole antifungal iv to po programme: MUSC medical centre

- Retrospective utilisation data for IV and PO fluconazole and voriconazole
- IV to PO ratios calculated
  - Quarterly
  - January 2003 to October 2007
- Institution specific prices used to calculate cost savings
- Programme saved $3,710 per 1000 patient days since 2003
- Total savings = $1.8 million

## Statement

"If we are to avoid excessive preemptive or empirical treatment, it is very important to improve diagnosis"

*Kohno CID 2008*

# Richardson M. - Antifungal stewardship for *Aspergillus*

## Empiric vs preemptive antifungal therapy for high-risk, febrile neutropenic patients

- 293 pts expected neutropaenia ≥10d GM screening x2/w
- E: Rx if persistent fever PE: Rx if clinical/imaging signs or positive GM (≥1.5)
- Endpoint = proportion pts alive d14 post neutrophil recovery

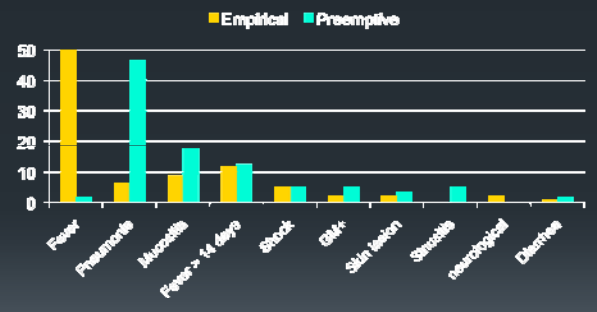
| | E (150) | PE (143) | |
|---|---|---|---|
| Survival (ITT) | 146 (97.3%) | 136 (95.1%) | diff -2.2%* |
| IFI (all) | 4 (2.7%) | 13 (9.1%) | p<0.05 |
| IFI during induction | 3/78 | 12/73 | P<0.01 |
| IFI related mortality | 0 | 3 (2.1%) | p = 0.11 |
| AFT | 66% | 46% (delayed) | p<0.001 |

* Lower 95% CI -5.9% within non-inferiority margin of -8%

Cordonnier CID 2009;48: 1052-4

20

## Reasons for starting antifungal therapy




*Cordonnier Clin Infect Dis 2009; 48: 1042-1051*


Medical Mycology April 2011, 49(Suppl. 1), 548–553 informa

Original Article

**Primary diagnostic approaches of invasive aspergillosis – molecular testing**

STÉPHANE BRETAGNE

*Groupe hospitalier Chenevier-Mondor, APHP, Laboratoire de Parasitologie-Mycologie, Créteil; Institut Pasteur, Centre National de Référence de Mycologie et des Antifongiques, Paris; and Université Paris Est-Créteil, Créteil, France*

- Key points: Use of PCR to guide antifungal chemotherapy
  - Ultimate goal: diagnosis and management of patients with IA
  - Investigation of the impact of PCR for guiding pre-emptive antifungal therapy: initial studies:
  - Millon *et al*. 2005
  - Hebart *et al*. 2009:
  - Hummel *et al*. 2010

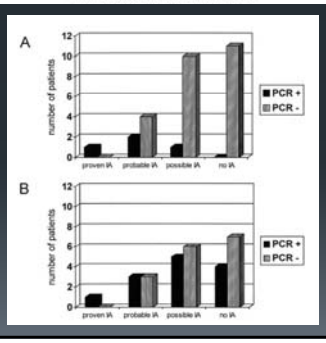
# Richardson M. - Antifungal stewardship for *Aspergillus*

JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 2005, p. 5097–5101 Vol. 43, No. 10
0095-1137/05/$08.00+0 doi:10.1128/JCM.43.10.5097–5101.2005


## Use of Real-Time PCR To Process the First Galactomannan-Positive Serum Sample in Diagnosing Invasive Aspergillosis

Laurence Millon,[1]* Renaud Piarroux,[1] Eric Deconinck,[2] Claude-Eric Bulabois,[2] Frédéric Grenouillet,[1] Pierre Rohrlich,[2] Jean-Marc Costa,[3,4] and Stéphane Bretagne[4]

*Laboratoire de Parasitologie-Mycologie[1] and Service d'Hématologie Clinique,[2] CHU Jean Minjoz, 25030 Besançon; Laboratoire de Biologie Moléculaire, Hôpital américain de Paris, Neuilly;[3] and Laboratoire de Parasitologie-Mycologie, Hôpital Henri-Mondor AP/HP and Université Paris 12, 94010 Créteil,[4] France*




European Journal of Haematology 85 (164–169)

ORIGINAL ARTICLE

## *Aspergillus* PCR testing: results from a prospective PCR study within the AmBiLoad trial

Margit Hummel[1], Birgit Spiess[1], Oliver A. Cornely[2], Martin Dittmer[3], Handan Mörz[1], Dieter Buchheidt[1]

[1]II. Medizinische Klinik, Klinikum Mannheim, University of Heidelberg, Mannheim; [2]Klinik I für Innere Medizin und Zentrum für Klinische Studien (CIKNO706), University of Cologne, Cologne; [3]Gilead Sciences GmbH, Munich, Germany

**Table 2** PCR results in the EORTC/MSG subgroups

| | Proven | Probable | Probable (CT) | Possible | noIA |
|---|---|---|---|---|---|
| Patients, *n* | 7 | 23 | 29 | 31 | 1 |
| Samples per patient; median (range) | 3 (2–7) | 6 (1–12) | 5 (2–14) | 3 (1–19) | 1 |
| Total no. of samples investigated by PCR | 27 | 149 | 166 | 116 | 1 |
| Samples giving positive PCR results, *n* (%) | 4 (15%) | 17 (11%) | 12 (7%) | 10 (9%) | 0 |
| Samples giving negative PCR results, *n* | 23 | 132 | 154 | 106 | 1 |
| Patients with positive PCR results, *n* (%) | 3 (43%) | 9 (39%) | 9 (31%) | 8 (26%) | 0 |
| Patients with more than one positive PCR result, *n* | 1 | 5 | 2 | 2 | 0 |
| Patients with negative PCR results, *n* | 4 | 14 | 20 | 23 | 1 |

Conclusion: The sensitivity of PCR testing is limited during antifungal therapy

Bone Marrow Transplantation (2009) 43, 553–561

www.nature.com/bmt

ORIGINAL ARTICLE

## A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allo-SCT

H Hebart[1], L Klingspor[2], T Klingebiel[3], J Loeffler[4], J Tollemar[5], P Ljungman[6], H Wandt[7], K Schaefer-Eckart[7], HJ Dornbusch[8], C Meisner[9], C Engel[9], N Stenger[1], T Mayer[1], O Ringden[10] and H Einsele[4]

- Allogeneic stem cell transplant recipients:
  - Group A: PCR-based pre-emptive group (*n* = 198)
  - Group B: empirical treatment with liposomal amphotericin B (*n* = 211)
- Group A: 12 proven IFD
- Group B: 16 proven IFD
- Better survival until day 30 when close PCR monitoring was performed (mortality 1.5 vs. 6.3%; *P* = 0.015)
- No difference at day 100

# Richardson M. - Antifungal stewardship for *Aspergillus*

ORIGINAL ARTICLE

**A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allo-SCT**

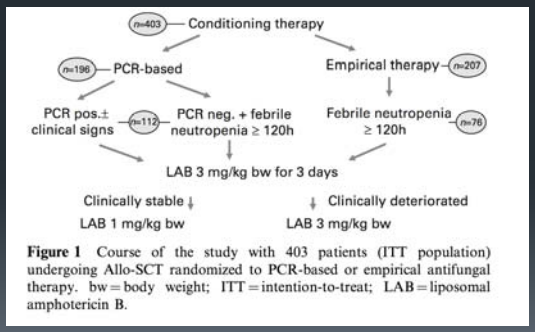



**Figure 1** Course of the study with 403 patients (ITT population) undergoing Allo-SCT randomized to PCR-based or empirical antifungal therapy. bw = body weight; ITT = intention-to-treat; LAB = liposomal amphotericin B.

PCR-based liposomal amphotericin B treatment after SCT
H Hebart et al

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**Table 2** Treatment with liposomal amphotericin B in 403 patients (ITT population) undergoing Allo-SCT randomized to PCR-based or empirical antifungal therapy

| *Treatment with liposomal amphotericin B* | *Group A (PCR-based treatment) (n = 196)* | | | *Group B (empirical treatment) (n = 207)* | | |
|---|---|---|---|---|---|---|
| | *All treatments* | *Until day 30* | *After day 30* | *All treatments* | *Until day 30* | *After day 30* |
| Patients treated[a] | 112 (57.1) | 89 | 23 | 76 (36.7) | 64 | 12 |
| Start of treatment (days after SCT; mean) | 21.0 | 11.4 | 57.6 | 19.5 | 11.2 | 63.3 |
| Treatment courses | 162 | 103 | 59 | 93 | 69 | 24 |
| Dose reduction at day 4 | 80 | 49 | 31 | 47 | 34 | 13 |
| No dose reduction at day 4 | 79 | 54 | 25 | 46 | 35 | 11 |
| Dose unknown | 3 | 0 | 3 | 0 | 0 | 0 |
| Total amount of liposomal amphotericin B given (median (mean; mg/kg)) | | 18.1 (29.2) | | | 19.5 (22.9) | |

Abbreviation: ITT = intention-to-treat.
[a]Number (%).

**Table 3** Incidence of IFIs in 403 patients (ITT population) after SCT according to treatment groups and treatment with liposomal amphotericin B

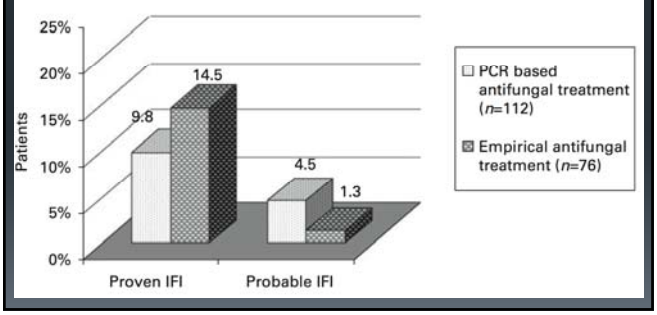
| | *Randomized to PCR testing (n = 196)* | | | *Randomized to empirical therapy only (n = 207)* | | |
|---|---|---|---|---|---|---|
| | *Patients* | *Proven IFI* | *Probable IFI* | *Patients* | *Proven IFI* | *Probable IFI* |
| Total | 196 | 12 | 4[a] | 207 | 16 | 1 |
| With Amph therapy | 112 | 11 | 4[a] | 76 | 12 | 1 |
| No Amph therapy | 84 | 1 | 0 | 131 | 4 | 0 |

Abbreviations: Amph = amphotericin; IFI = invasive fungal infections.
[a]one patient with a probable and a proven IFI was counted as proven.

Conclusion: "This study was not able to show a benefit on the reduction of IFI in allo-SCT by the use of PCR

ORIGINAL ARTICLE

**A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allo-SCT**



# Richardson M. - Antifungal stewardship for *Aspergillus*

## Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients

R A Barnes,[1] P L White,[2] C Bygrave,[3] N Evans,[4] B Healy,[2] J Kell[4]

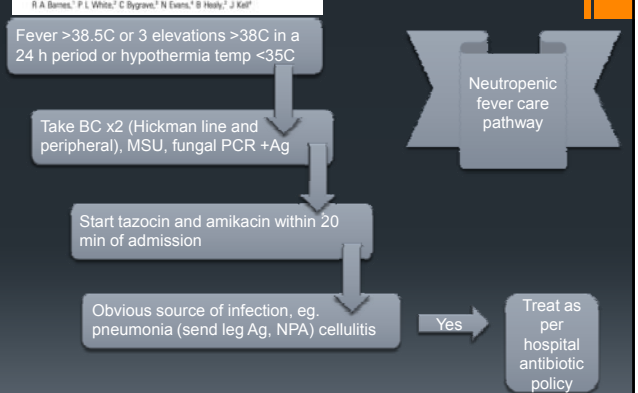
### Take home messages:

- Biomarkers (antigen and nucleic acid detection) can be used to screen for invasive fungal disease in high-risk patients
- The high negative predictive value of these assays enables *Aspergillus* infections to be ruled out and makes empirical antifungal therapy unnecessary
- No excess morbidity or mortality was seen inpatients in whom empiric antifungal treatment was withheld
- This targeted approach is safe and allows more rational use of antifungal drugs
- Substantial savings in antifungal drug expenditure

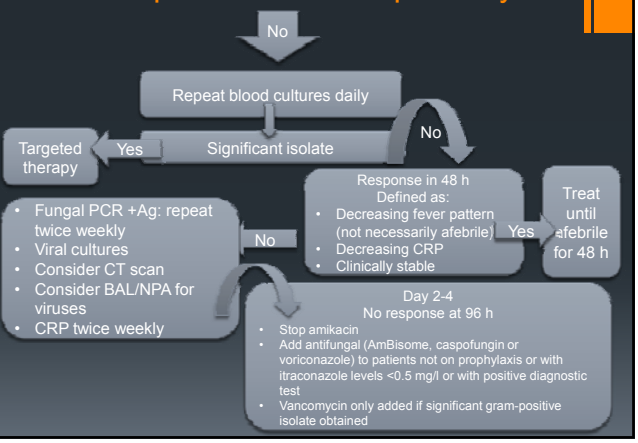
*Barnes et al. J. Clin Pathol 2009*

Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients

R A Barnes,[1] P L White,[2] C Bygrave,[3] N Evans,[4] B Healy,[2] J Kell[4]




## Neutropenic fever care pathway

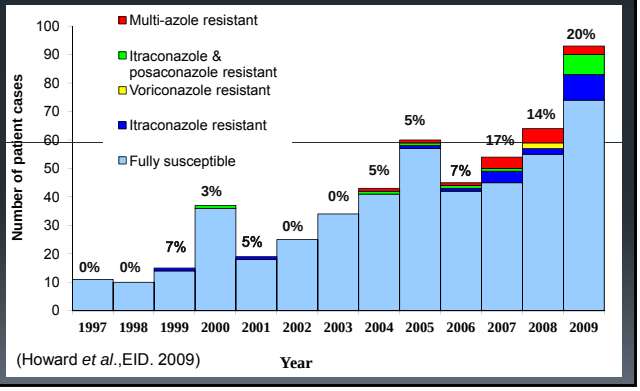


Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients

## Diagnostic test positivity does correlate with clinical signs


## *The frequency of resistance will dictate which antifungal to use*


## Azole resistance frequency in *A. fumigatus* by patient 1997 – 2009




(Howard *et al.*,EID. 2009)

# Richardson M. - Antifungal stewardship for *Aspergillus*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2010, p. 4545–4549 Vol. 54, No. 11
0066-4804/10/$12.00 doi:10.1128/AAC.00692-10


## Environmental Study of Azole-Resistant *Aspergillus fumigatus* and Other Aspergilli in Austria, Denmark, and Spain

Klaus Leth Mortensen,[1]* Emilia Mellado,[2] Cornelia Lass-Flörl,[3] Juan Luis Rodríguez-Tudela,[2] Helle Krogh Johansen,[4] and Maiken Cavling Arendrup[5]

*Mycology Unit, Department of Microbiological Surveillance and Research, Statens Serum Institut, Copenhagen, Denmark[1]; Servicio de Micología, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Spain[2]; Division of Hygiene and Medical Microbiology, Innsbruck Medical University, Innsbruck, Austria[3]; and Department of Clinical Microbiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark[4]*

TABLE 2. Results of primary plating, EUCAST susceptibility testing, and Cyp51A amino acid substitution and *cyp51A* gene promoter alteration determination for four azole-resistant *A. fumigatus* isolates

| Sample isolate | Growth of *A. fumigatus* by primary plating on azole agar[a] | | | | MIC (mg/liter; Madrid/Copenhagen) determined by EUCAST | | | Cyp51A alterations |
|---|---|---|---|---|---|---|---|---|
| | ITC (4 mg/liter) | VRC (1 mg/liter) | POS (0.5 mg/liter) | Control (no antifungal) | ITC | VRC | POS | |
| R13 | – | + | – | + | >8/>4 | 4/4 | 0.5/1 | TR/L98H[b] |
| T11 | + | – | + | + | >8/>4 | 4/4 | 0.5/2 | TR/L98H |
| T18 | + | – | – | + | >8/>4 | 4/4 | 0.5/0.5 | TR/L98H |
| T22 | + | – | – | + | >8/>4 | 4/2 | 0.5/0.25 | TR/L98H |
| CM-237[d] | – | – | – | + | 0.25/ND[c] | 0.5/ND | 0.06/ND | None (wild type) |

[a] Subcultured isolates from all four sites were able to grow in all three azole-containing wells. ITC, itraconazole; VRC, voriconazole; POS, posaconazole.
[b] TR/L98H, tandem repeat of 34 bp in promoter region and substitution of leucine with histidine at codon 98.
[c] ND, not determined.
[d] CM-237, azole-susceptible *A. fumigatus* strain.

## High-frequency Triazole Resistance Found In Nonculturable *Aspergillus fumigatus* from Lungs of Patients with Chronic Fungal Disease

**David W. Denning,[1,2,3] Steven Park,[4] Cornelia Lass-Florl,[5] Marcin G. Fraczek,[2,3] Marie Kirwan,[1,2] Robin Gore,[2] Jaclyn Smith,[2] Ahmed Bueid,[2] Caroline B. Moore,[3] Paul Bowyer,[3] and David S. Perlin[3,6]**

[1]National Aspergillosis Centre, [2]School of Translational Medicine, University of Manchester, Manchester, UK, [3]Mycology Reference Centre, Manchester Academic Health Science Centre, University Hospital of South Manchester, Manchester, UK, [4]Public Health Research Institute, New Jersey Medical School-UMDNJ, Newark, New Jersey, and [5]Department für Hygiene, Mikrobiologie und Sozialmedizin, Medizinische Universität Innsbruck, Innsbruck, Austria

**Table 2. Interrelationship Between Azole Therapy, Sampling Time, and Frequency of Azole Resistance Marker Detected**

| | Number of patients with azole resistance marker/total tested (%) | | | | |
|---|---|---|---|---|---|
| | Sample collected on azole therapy | | | | |
| Azole treatment experience | Itra | Vori | Posa | None | Totals |
| Azole naive | – | – | – | 2/3 (67) | 2/3 (67) |
| Itra only | 2/5 (40)[a] | – | – | 2/2 (100)[a] | 4/7 (57) |
| Posa only | – | – | 1/4 (25)[a] | 0/1 (0) | 1/4 (25) |
| Itra + vori | 1/1 (100) | 2/4 (50) | - | 2/2 (100) | 5/7 (71) |
| Itra + Posa | – | – | 1/2 (50) | – | 1/3 (33) |
| Itra + vori + posa | – | – | 3/5 (60)[a] | – | 3/5 (40) |
| Totals | 3/6 (50) | 2/4 (50) | 5/11 (45) | 6/8 (75) | 16/29 (55) |

**NOTE.** Itra indicates itraconazole; vori, voriconazole; posa, posaconazole.
[a] M220 mutation ($n = 4$).

# Munoz - Antifungal stewardship for other fungal pathogens


## Classification of fungus

**According to their morphology after the visualization in the clinical microbiology laboratory**

| Yeasts | Molds | Dimorphic |
|---|---|---|
| *Candida* | *Aspergillus* | *Histoplasma* |
| *Cryptococcus* | Mucorales | *Coccidioides* |
| Other | *Scedosporium* | *Paracoccidioides* |
| | *Fusarium* | *Blastomyces* |
| | Other | *Sporothrix* |

## Other yeasts

- Basidiomicetos
  - *Cryptococcus* spp
  - Malassezia (*furfur* and others)
  - *Rhodotorula* spp
  - *Trichosporon* spp
  - *Sporobolomyces salmonicolor*
- Ascomicetos (Besides *Candida* spp)
  - *Saccharomyces cerevisiae*
  - *Geotricum* (*candidum* y *capitatum*)
  - *Yarrowia lipolytica*

# Munoz - Antifungal stewardship for other fungal pathogens

## Emerging opportunistic yeast infections.

*Miceli et al. Lancet Infect Dis 2011 (feb)*

- **Trichosporon**
  - 2º cause of fungemia in oncohematology (after Candida spp)
  - *T. asahii, T.asteroides, T.cutaneum, T.inkin, T. mucoides, T.ovoides (T. beigelii)*
  - Commensal flora
  - Leukemia, AIDS, burn, valvulopathy
  - Resistance to Anfot-B and echinocandins
- **Rhodotorula**
  - Cryptococcaceae. Asia-Pacífic
  - Sepsis-catéter, sepsis grave, endocarditis en inmunodeprimidos
  - HIV, BMT, Abdominal surgery, cirrhsis,burns, autoinmune disease
- **Criptococcus non-neoformans**
  - HIV, cancer and transplant
- **Geotrichum, Hansenula, Malassezia y Saccharomyces**
  - Severe immunosuppressed
- **Diagnostic difficulties: Blood culture, 1-3 β-D glucan**

## MOLDS

| Septated hypha | | Non-septated hypha |
|---|---|---|
| **Dematiaceous molds** | **Hyaline molds** | **Mucorales** |
| *Fonsecaea* | *Aspergillus* | *Rhizopus* |
| *Phialophora* | *Penicillium* | *Mucor* |
| *Cladosporium* | *Scopulariopsis* | *Rhizomucor* |
| *Cladophialophora* | *Acremonium* | *Absidia* |
| *S. apiospermum* | *Fusarium* | *Apophysomyces* |
| *S. prolificans* | *Verticillium* | *Saksenaea* |
| *Bipolaris* | *Glioclaudium* | *Cunninghamella* |
| *Exophiala* | *Paecilomyces* | *Syncephalastrum* |
| *Alternaria* | | |
| *Chaetomium* | | |

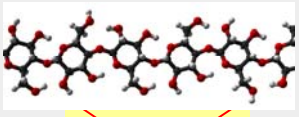
## Emerging molds in SOT

- Prospective, multicenter study
- 20 patients (18 LT, 2 HT) in 2 years
  - *A. fumigatus* (11)
  - Other (9)
    - *1 A. terreus*
    - 2 Zygomycetes (*Mucor*, *Rhizopus*)
    - 3 Hyalohyphomycetes (*S. apiospermum*, *S. prolificans*, *Fusarium*)
    - 2 Phaeohyphomycetes (*C. bantiana*, *P. romeroi*)
    - 1 not identified

Husain, .. Muñoz,.. Singh. CID 2003

## B-1,3-d-glucan

- Candidiasis
- Aspergillosis
- Fusariosis
- Scedosporiosis
- *Pneumocystis*



~~Criptococcosis~~

~~Mucormycosis~~

Pickering. J Clin Microbiol 2005

Odabasi. Clin Infect Dis 2004

Ostrosky-Zeichner. Clin Infect Dis 2005

## Mucormycosis

## Mucor: European Registry

Zygomycosis in Europe: Analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007

Working Group on Zygomycosis
European Confederation of Med. Mycol.
2005-2007
230 cases. 15 countries

Skiada A. Clin.Microb.Infect.2011

# Munoz - Antifungal stewardship for other fungal pathogens

## Mucor: European Registry

| Underlying condition | No. of patients (% |
|---|---|
| Acute myeloid leukemia | 49/102 (48) |
| Acute lymphoblastic leukemia | 22/102 (22) |
| Non-Hodgkin lymphoma | 11 /102 (11) |
| Myelodysplastic syndrome | 6/102 (6) |
| Other | 12/102 (12) |
| Hematopoietic stem cell transplantation**** | 21 (9) |

| Underlying condition | No. of patients (% |
|---|---|
| Other malignancies | 11 (5) |
| Solid organ transplantation | 10 (4) |
| Diabetes mellitus | 39 (17) |
| Trauma | 39 (17) |
| Burn | 7 (3) |
| HIV/AIDS | 4 (2) |
| Aplastic anemia | 4 (2) |
| Other***** | 9 (4) |

8% Inmunocompetent

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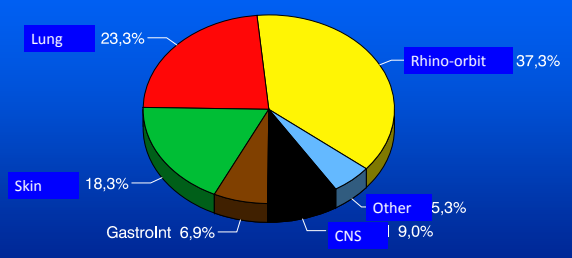
## Mucormycosis 929 cases

**Disseminated 23%**




Roden MM. C.I.D. 2005

## Mucormycotina: European Registry

Species

| Species | N of cases |
|---|---|
| Rhizopus | 58 (34%) |
| ~~Mucor~~ | ~~33 (19%)~~ |
| Lichtheimia | 32 (19%) |
| Cunninghamella | 8 (5%) |
| Apophysomyces elegans | 2 (1%) |
| Saksenae species | 1 |

Skiada A. Clin.Microb.Infect.2011

## Incidence of Mucormycosis:

### A nationwide study:

JOURNAL OF CLINICAL MICROBIOLOGY, June 2007, p. 2051–2053 Vol. 45, No. 6
0095-1137/07/$08.00+0 doi:10.1128/JCM.02473-06


Impact of Zygomycosis on Microbiology Workload: a Survey Study in Spain[▽]

Marta Torres-Narbona, Jesús Guinea,* José Martínez-Alarcón, Patricia Muñoz, Ignacio Gadea, and Emilio Bouza as a representative of the MYCOMED Zygomycosis Study Group

*Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain*

**50 hospitals in Spain**

**14,069,094 inhabitants**

## Incidence of Mucormycosis:

**Year 2005**

**Samples for fungal detection 187.031**

**78 patients with 1 or more isolates**

**6 were clear cases of Mucormycosis**

**(7.7%; CI95% 1,8-13,6)**

**Incidence in Spain:**

**0.43 cases/1,000,000 inhabitants**

Torres-Narbona M. J.Clin.Microb. 2007

## Mucor: Review of treatment

Curr Infect Dis Rep (2010) 12:423–429
DOI 10.1007/s11908-010-0129-9

Recent Advances in the Treatment of Mucormycosis

Brad Spellberg · Ashraf S. Ibrahim

Early diagnosis
Control of the underlying disease
Surgery
Antifungal treatment

Spellberg B. Curr.Infect.Dis.Rep.

## *In vitro activity*

| Fármaco | $CMI_{50}$ | $CMI_{90}$ | Comentario |
|---|---|---|---|
| Anfotericina B | 0.125 | 1 | Actividad |
| Posaconazol | 0.25 | 1 | Actividad |
| Ravuconazol | 0.5 | 2 | Variable |
| Itraconazol | 0.5 | 8 | Variable |
| Voriconazol | 16 | 32 | Resistencia |
| Caspofungina | >8 | >8 | Resistencia |
| Flucitosina | >256 | >256 | Resistencia |

Dannaoui E. J Antimicrob Chemother 2003

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2008, p. 1396–1400 Vol. 52, No. 4
0066-4804/08/$08.00+0 doi:10.1128/AAC.01512-07


In Vitro Antifungal Activities of Isavuconazole (BAL4815), Voriconazole, and Fluconazole against 1,007 Isolates of Zygomycete, *Candida*, *Aspergillus*, *Fusarium*, and *Scedosporium* Species▽

Jesús Guinea,[1,2]* Teresa Peláez,[1,2] Sandra Recio,[1] Marta Torres-Narbona,[1] and Emilio Bouza[1,2]

*Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain,[1] and CIBER de Enfermedades Respiratorias (CIBER RES CD06/06/0058)[2]*

| Isolate group (n) | Voriconazole MIC-0, MIC-1 | | | | Isavuconazole activity | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MIC-0, MIC-1 | | | | MFC | | |
| | GM | 90% | 50% | Range | GM | 90% | 50% | Range | 90% | 50% | Range |
| Zygomycetes[a] | | | | | | | | | | | |
| *Mucor* (21) | | >16, >16 | >16, 16 | 2->16, 2->16 | | 16, 8 | 2, 1 | 1->16, 0.25->16 | >16 | 8 | 2->16 |
| *Rhizopus* (12) | | >16, >16 | 8, 8 | 8->16, 4->16 | | 16, 4 | 1, 0.5 | 1->16, 0.5->4 | >16 | 4 | 1->16 |
| *Absidia* (6) | | | | 16->16, 4->16 | | | | 1->16, 0.5->8 | | | 4->16 |
| *Cunninghamella* (4) | | | | 16->16, 8->16 | | | | 2->16, 0.5->8 | | | 16->16 |
| *Syncephalastrum* (2) | | | | 4->16, 2->16 | | | | 0.25->8, 0.125->4 | | | 1->16 |
| Overall (45) | | >16, >16 | >16, 16 | 2->16, 2->16 | 3.364, 1.506 | 16, 8 | 2, 1 | 0.25->16, 0.125->16 | >16 | 4 | 1->16 |
| *S. apiospermum* (16) | | 1, 0.5 | 0.5, 0.25 | 0.25->8, 0.125->4 | | 4, 2 | 4, 1 | 0.5->8, 0.06->8 | >16 | 8 | 2->16 |
| *S. prolificans* (6) | | | | 16->16, 4->8 | | | | >16, 4->16 | | | >16 |
| Overall (22) | 1.438, 0.571 | >16, 8 | 0.5, 0.25 | 0.25->16, 0.125->8 | 5.040, 1.257 | >16, 8 | 4, 1 | 0.5->16, 0.06->16 | >16 | >16 | 2->16 |
| *Fusarium* spp. (20) | 7.727, 3.605 | 16, 8 | 4, 4 | 1->16, 1->8 | 16.564, 11.314 | >16, >16 | 16, 16 | 1->16, 2->16 | >16 | >16 | 4->16 |

[a] Activities are given for the most clinically relevant genera of Zygomycetes and overall. All values are expressed as micrograms per milliliter. GM, geometric mean. For the two azoles against *Fusarium* spp., *Scedosporium* spp., and Zygomycetes, the MIC end point was defined as the lowest concentration that produced complete inhibition of growth (MIC-0). We also calculated MIC-1, defined as the lowest concentration that produced slight growth or approximately 25% of that of the growth control.

[b] MICs for Zygomycetes were read after 24 h of incubation.

## Mucor: First line monotherapy

Lipidic Amphotericins AmB Deoxicolate

L-AmB >> ABLC >> AmB Deoxicolate

Dose (??) 5-7,5 mg/kg

## Mucor: Anfotericina B

Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Trial Comparing a High–Loading Dose Regimen with Standard Dosing (AmBiLoad Trial)

3 mg/kg = 10 mg/kg
339 patients. Only 5 were Mucormycosis

Cornerly O. C.I.D. 2007

## Mucor: Posaconazole

Active "in vitro" against Mucorales

Difficult to obtain adequate levels at 400mg/bid

Poor results in experimental models

Break through Mucormycosis in patients on posaconazole

Second line treatment for

Cornerly O. C.I.D. 2007

## Mucor: Posaconazole in rescue treatment

REVIEW 10.1111/j.1469-0691.2009.02985.x

Current experience in treating invasive zygomycosis with posaconazole

Effective in 2 series as rescue

Cornely O. C.M.I. 2009

Posaconazole as Salvage Therapy for Zygomycosis

24 cases. Response in 79%

Greenberg RN. A.A.C. 2006

91 cases. Response in 60%

Van Burik JA. C.I.D. 2006

## Mucor: Combinations

Polyenes sinergistic with equinocandins

Polyenes and iron chelators

Triple therapy

(Polyenes+Candins+chelators)

Polyenes + Posaconazole

## Mucor: Combination

Combination Polyene-Caspofungin Treatment of Rhino-Orbital-Cerebral Mucormycosis

Caitlin Reed,[1] Richard Bryant,[2,3] Ashraf S. Ibrahim,[1,3] John Edwards, Jr.,[1,3] Scott G. Filler,[1,3] Robert Goldberg,[2,3] and Brad Spellberg[1,3]

41 cases with Rhino-Orbital Mucor
Polyene + Caspo 100% response (6 cases)
Monotherapy with L-AmB 45% response

Reed C. C.I.D. 2008

## Mucor: Retraso de Anfotericina B

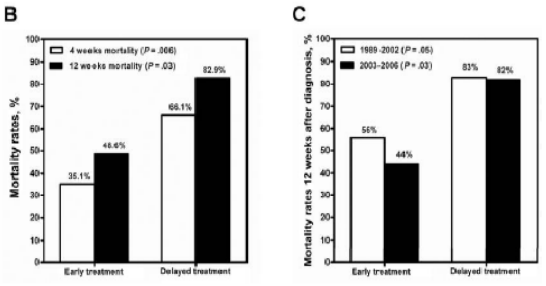
Delaying Amphotericin B–Based Frontline Therapy Significantly Increases Mortality among Patients with Hematologic Malignancy Who Have Zygomycosis

Georgios Chamilos,[1] Russell E. Lewis,[1,2] and Dimitrios P. Kontoyiannis[1,2]
[1]Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas M. D. Anderson Cancer Center, and [2]University of Houston College of Pharmacy, Houston, Texas

Delay to initiate Ampho B increase mortality

Chamilos G. C.I.D. 2008

## Mucor: Delay of Amphotericin B




Chamilos G. C.I.D. 2008

## Mucor: Posaconazole + Amphotericin B

Posaconazole Combined with Amphotericin B, an Effective Therapy for a Murine Disseminated Infection Caused by *Rhizopus oryzae*▽

M. Mar Rodríguez, Carolina Serena, Marçal Mariné, F. Javier Pastor, and Josep Guarro*
*Unitat de Microbiologia, Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, Reus, Spain*

Received 14 May 2008/Returned for modification 25 June 2008/Accepted 28 July 2008

Ampho B alone at 0,8 mg/kg is
Equal to a combination of Ampho B (0,3 mg/kg) + Posaconazole

Murine model

Rodriguez MM. A.A.C. 2008

## Mucor: Posa and Caspo

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2007, p. 3457–3458 Vol. 51, No. 9
0066-4804/07/$08.00+0 doi:10.1128/AAC.00595-07


Synergistic Effect of Posaconazole and Caspofungin against Clinical Zygomycetes▽

In vitro against 12 strains of Mucorales
Combination Posa + Caspo
Sinergisme in all strains
Caspo MIC's in combination remained higher than serum levels

Guembe M. A.A.C. 2007

## Mucor: L-Ampho B + Candins

Combination Echinocandin-Polyene Treatment of Murine Mucormycosis[▽]

Ashraf S. Ibrahim,[1,2]* Teclegiorgis Gebremariam,[1] Yue Fu,[1,2] John E. Edwards, Jr.,[1,2] and Brad Spellberg[1,2]

*Division of Infectious Diseases, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California,[1] and David Geffen School of Medicine at UCLA, Los Angeles, California[2]*

Murine model

L- Ampho B + Micafungin
+ Anidulafungin

Better results
Class effect

Ibrahim AS. A.A.C. 2008

## Mucor: Surgical treatment

Essential for success

Independent variable for better prognosis

No surgery = Worse prognosis

Extension and moment of surgery not well defined

## Mucor: European Registry

Treatment and mortality

| Treatment | N of cases | Mortality |
|---|---|---|
| Medical + surgery | 90 (40%) | 24% |
| Only medical | 102 (46%) | 58% |
| Only surgical | 9 ( 4%) | 44% |
| None | 24 (11%) | 95% |
| All medical | 192 (85%) | 41% |
| Al surgical | 99 (44%) | 26% |

Skiada A. Clin.Microb.Infect.2011

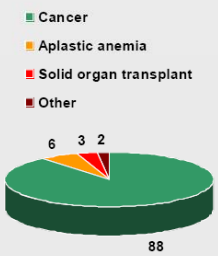
# FUSARIOSIS

## Fusarium

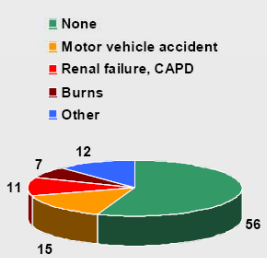
- Soil, water, water biofilms
- Banana-shaped macroconidia
  - Species identification difficult
  - *F. solani (50%), F. oxysporum (20%), F. verticillioides (10%), F. moniliforme(10%)*
- Angioinvasive disease: thrombosis and infarction
  - In tissue: hyaline, septate, acute branching hyphae – hyalohyphomycosis2

## Underlying Diseases in 259 Patients with Fusariosis

**Immunocompromised n=232**




**Immunocompetent n=27**

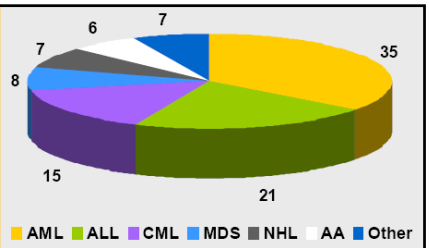



Nucci & Anaissie. Clin Infect Dis 2002;35:909-20

## Fusarium in Hematologic Diseases:

**84 Patients from 12 Centers**

*Mostly acute leukemia not in complete remission with prolonged neutropenia*




- Neutropenia in 83% (median 16 days)
- HSCT in 39%
- 9 of 14 non-neutropenic patients were HSCT recipients
- Use of corticosteroids in 46%

Nucci et al. Cancer 2003;98:315-9

## Clinical presentation

- Refractory fever
- Portals of entry: Lungs, sinuses, catheters, skin
- Skin lesions: 60-80%
  - SOT soft tissues

## Comparative In Vitro Activity against *Fusarium*

| Organism | n | $MIC_{90}$ (µg/mL) POS | VOR | AMB |
|---|---|---|---|---|
| All *Fusarium* | 67 | 32.0 | 32.0 | 32.0 |
| *F solani* | 39 | 32.0 | 32.0 | 32.0 |
| *F oxysporum* | 12 | 4.0 | 32.0 | 16.0 |
| *F moniliforme* | 2* | 1.0 | 1.0 | 1.0–4.0 |
| *Fusarium* spp† | 14 | 16.0 | 16.0 | 2.0 |

*When n < 10, the range of MICs is shown.
†Unspeciated *Fusarium*.

Sabatelli FJ et al. ICAAC 2004. Abstract M-1810.

# Munoz - Antifungal stewardship for other fungal pathogens

## Role of antifungal susceptibility testing in patient management
Graeme Forrest

Table 2 Medically important filamentous fungi susceptibilities to antifungal agents

| | Antifungal therapy | | | | |
|---|---|---|---|---|---|
| Mold species | Itraconazole | Voriconazole | Posaconazole | Echinocandin | Amphotericin B |
| *Aspergillus fumigatus* | S | S | S | S | S |
| *Aspergillus terreus* | S | S | S | S | R |
| *Scedosporium apiospermum* | S | S | S | R | R |
| *Scedosporium prolificans* | R | R[a] | R[a] | R | R |
| *Fusarium solani* | R | S to R | S | R | S |
| Zygomycetes | R | R | S | R | S |

Note: Data compiled from [4**,7,9,38*,41].
[a]Successful therapy has been reported with these agents both individually and with combination antifungal therapy. S, susceptible; R, resistant.

Curr Opin Infect Dis 19:538–543.

## Posaconazole in Animal Infection Models (Survival/Tissue Clearance–CFU)

| Genus | Infection Type | Organ / Outcome | Comparative Activity |
|---|---|---|---|
| *Aspergillus* | Disseminated, pulmonary, CNS | Brain, kidney, liver, lung, spleen | POS* > ITZ and CSP, ≥AMB |
| *Fusarium* | Disseminated | Kidney, liver | POS* ~AMB |
| *Coccidioides* | Disseminated | Liver, lung, spleen | POS* > ITZ and FLZ |
| *Blastomyces* | Pulmonary | Lung | POS* > ITZ and AMB |
| *Candida* | Oral-intragastric, disseminated | Alimentary tract, kidney, spleen | POS > VOR, ≥FLZ, ~AMB |
| *Cladophialophora* | Intracranial | Brain | POS >FLZ |
| *Cryptococcus* | Intracisternal, disseminated, pulmonary | CSF, brain, lung | POS ≥FLZ, >AMB |
| *Histoplasma* | Pulmonary | Lung, spleen | POS* > ITZ, ~AMB |
| *Scedosporium* | Disseminated | Brain, kidney, spleen | POS > ITZ, ~FLZ |
| *Ramichloridium* | Intracranial | Survival, brain | POS > ITZ and AMB |
| *Wangiella* | Disseminated | Survival | POS > ITZ |
| Zygomycetes | Disseminated | Survival, kidney | POS and AMB > ITZ |

Yellow text indicates central nervous system model.
*Posaconazole sterilizes tissue; ~indicates approximate equivalence.

## Posaconazole as Salvage Treatment for Invasive Fusariosis in Patients with Underlying Hematologic Malignancy and Other Conditions

Issam I. Raad,[1] Roy Y. Hachem,[1] Raoul Herbrecht,[2] John R. Graybill,[3] Roberta Hare,[3] Gavin Corcoran,[4] and Dimitrios P. Kontoyiannis[1]

| Characteristic | No. of patients | No. (%) of patients who responded to treatment |
|---|---|---|
| *Fusarium* species as the primary pathogen | | |
| All patients | 21 | 10 (48) |
| Patients with proven infection[a] | 18 | 7 (39) |
| Patients with probable infection[a] | 3 | 3 (100) |
| Age, years | | |
| <18 | 3 | 1 (33) |
| 18–64 | 14 | 6 (43) |
| ≥65 | 4 | 3 (75) |
| Sex | | |
| Female | 13 | 7 (54) |
| Male | 8 | 3 (38) |
| Neutropenia[b] | 8 | 3 (38) |
| Risk factor[c] | | |
| Hematologic malignancy | 16 | 7 (44) |
| Nonhematologic malignancy (breast cancer) | 2 | 0 |
| Hematopoietic stem cell transplant | 6 | 1 (17) |
| Allogeneic | 4 | 1 (25) |
| Autologous | 2 | 0 |
| Solid organ transplant | 2 | 2 (100) |
| Diabetes | 6 | 3 (50) |

CID 2006

# Munoz - Antifungal stewardship for other fungal pathogens

## Posaconazole as Salvage Treatment for Invasive Fusariosis in Patients with Underlying Hematologic Malignancy and Other Conditions

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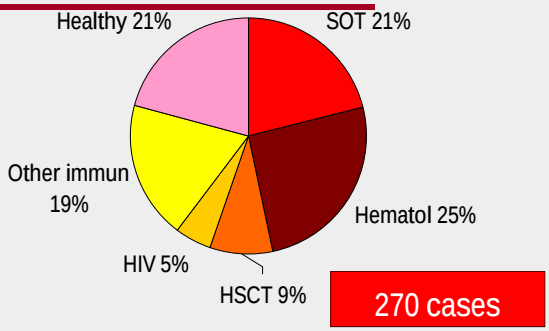
| | | |
|---|---|---|
| Duration of prior antifungal therapy, days | | |
| ≤30 | 18 | 7 (39) |
| 31–60 | 2 | 2 (100) |
| 61–90 | 1 | 1 (100) |
| Enrollment reason | | |
| Refractory or refractory/intolerant to treatment | 17 | 8 (47) |
| Progressing infection[d] | 3 | 2 (67) |
| Intolerant to treatment | 4 | 2 (50) |
| General site of infection | | |
| Pulmonary | 4 | 3 (75) |
| Extrapulmonary | 7 | 4 (57) |
| Disseminated with pulmonary involvement | 3 | 1 (33) |
| Disseminated without confirmed pulmonary involvement | 7 | 2 (29) |

## *Scedosporium* spp.




270 cases

Husain, Muñoz, et al. CID 2005

MAJOR ARTICLE

## *Saccharomyces cerevisiae* Fungemia: An Emerging Infectious Disease

Patricia Muñoz,[1] Emilio Bouza,[1] Manuel Cuenca-Estrella,[2] Jose María Eiros,[1] María Jesús Pérez,[2] Mar Sánchez-Somolinos,[1] Cristina Rincón,[2] Javier Hortal,[3] and Teresa Peláez[1]

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