Updated guidelines for treatment of aspergillosis

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New guidelines of IDSA for treatment of aspergillosis

- Walsh, Anaissie, Denning et al. Treatment of Aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America. *Clinical Infectious Diseases 2008;46:327-60*.
  - Replaces old guidelines published in 2000
  - Presents guidelines for management of 3 major forms of aspergillosis
    - Invasive aspergillosis
    - Chronic forms of aspergillosis
    - Allergic forms of aspergillosis
  - The quality of evidence for treatment is scored according the standard system used in other IDSA guidelines

Grading systems for the quality of evidence

Category, Grade	Definition
Strength of recommendation	
A	**Good evidence**
B	**Moderate evidence**
C	**Poor evidence**
Quality of evidence	
I	**≥ 1 properly randomized controlled trial**
II	**≥ 1 well-designed clinical trial without randomization (case-control, multicenter studies**
III	**Opinions of respected authorities (clinical experience, descriptive studies)**

Standard definitions for IA (*EORTC and Infectious Diseases Mycosis Study Group, Ascioglu et al. CID 2002;34*)

- 3 levels of certainty for clinical and epidemiological research
- For immunocompromised patients
  - Proven IA:
    - Histopathological documentation
    - Positive culture from sterile site
  - Probable IA → relatively high degree of certainty
    - Host factors: immunosuppression
    - Clinical manifestations (symptoms, signs and radiological features
    - Microbiological evidence
      - **Positive culture from BAL-fluid or sputum, positive cytology**
      - **Non-culture based methods (galactomannan antigen)**

Nephrotoxicity of D-AmB (I)

- *Wingard et al. CID 1999*: Retrospective study (5 centers in USA)
  - 239 immunocompromised patients
    - Allogeneic HSCT 30 %
    - Autologous HSCT 7 %
    - Solid organ transplantation 26 %
    - Hematological malignancy 37 %
  - Confirmed or suspected IPA ja D-AmB (median 20 days)
  - Creatinine doubled in 53 % of patients
    - Risk factors: duration of AmB therapy, baseline creatinine
    - Mean time to doubling of creatinine 7 days

Nephrotoxicity of D-AmB (II)

- Risk of nephrotoxicity
  - Creatinine > 2.5 mg/dl (> 220 µmol/l) in 29 % of all patients
    - **allogeneic HSCT 33 %**
    - **autologous HSCT 47 %**
    - **SOT 36 %**
    - **Other hematological patients 20**
- Hemodialysis in 15 % of all patients
    - **allogeneic HSCT 20 %**
    - **autologous HSCT 19 %**
    - **SOT 18 %**
    - **Other hematological patients 7 %**

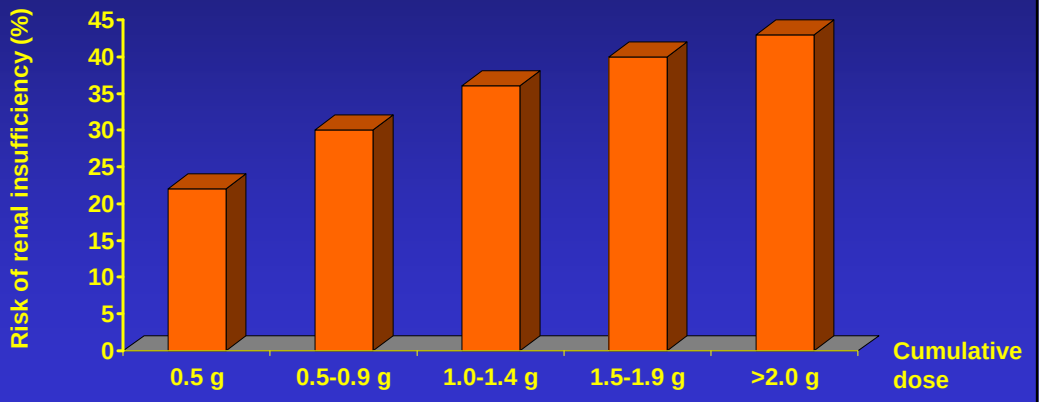
Nephrotoxicity of D-AmB (III)

- Usually concomitant CyA or other nephrotoxic medications
- Risk of hemodialysis, when creatinine > 2.5 (10 days cAmB)
  - **Stem cell transplantation** **>90 %**
  - **Other hematological patients** **35 %**
- Risk of hemodialysis, when creatinine > 2.0 (10 days of cAmB)
  - **Stem cell transplantation** **50 %**

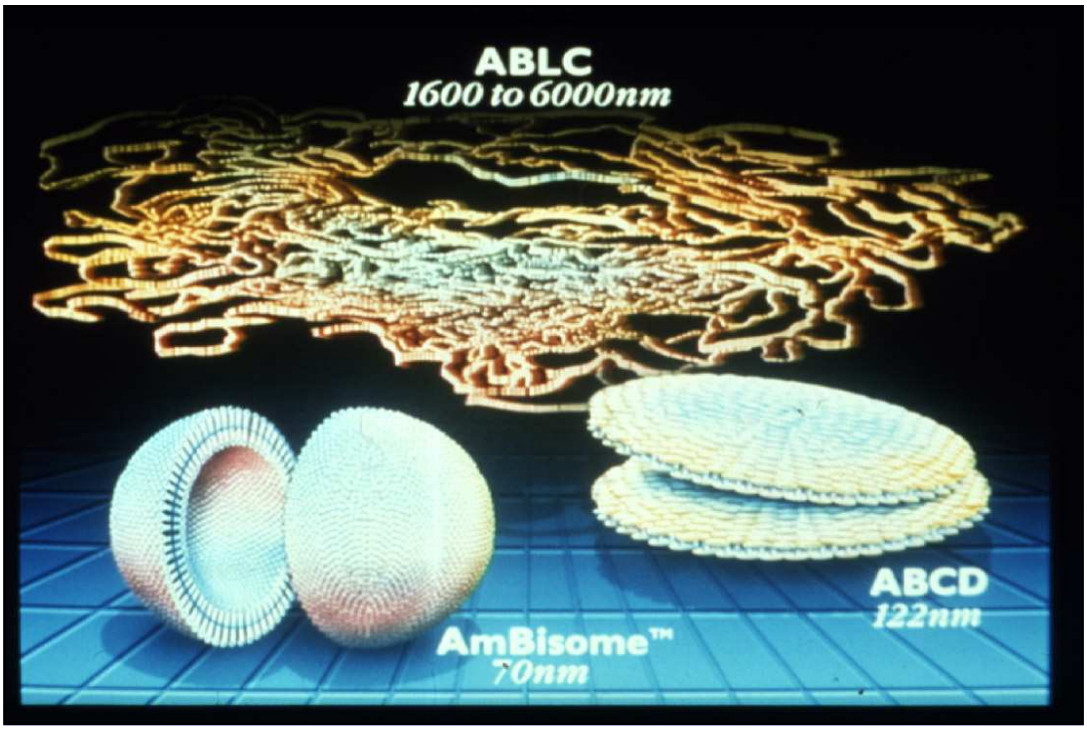
Nephrotoxicity of D-AmB (IV)

707 courses of D-AmB 1993-1997 (Boston) (*Bates et al. CID 2001*)

- **HSCT** **25 %**
- **Hematological malignancy** **21 %**
- **Surgical patient** **16 %**



Acute renal failure developed to 30 % of patients, Severe renal failure in 13 %



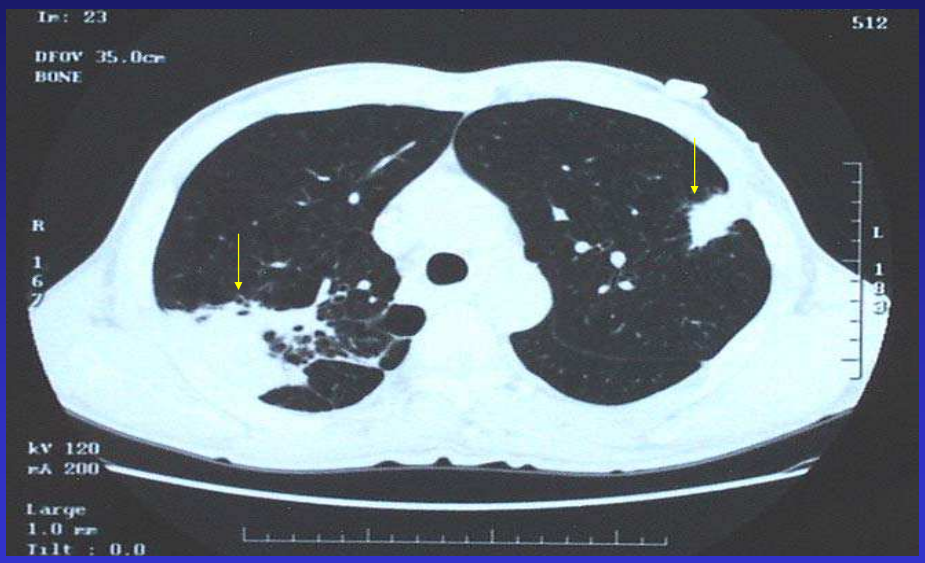
Antifungal agents

- Antifungals with activity against Aspergillus species:
  - AmB deoxycholate (D-AmB)
  - Lipid formulations of AmB (LFAB)
    - L-AmB (*Ambisome*)
    - ABLC (*Abelcet*)
    - ABCD (*Amphocil*)
  - Broad spectrum triazoles
    - Itraconazole
    - Voriconazole
    - Posaconazole
  - Echinocandins
    - Caspofungin
    - Micafungin ?
    - Anidulafungin ?

Invasive aspergillosis (IA)

- Only few randomised trials on the treatment available
- Risk groups:
  - **Prolonged neutropenia**
  - **Allogeneic hematopoietic stem cell transplantations (chronic GVHD)**
  - **Solid organ transplantations (lung, liver)**
  - **Patients with high-dose corticosteroid therapy**
- Invasive pulmonary aspergillosis (IPA) the most common form
  - **dissemination to critical organs (CNS)**
- High mortality (***Denning CID 1996;23***)
  - **Acute leukemia** **50-60%**
  - **Allogeneic HSCT** **80-90%**
  - **CNS aspergillosis** **~100%**
- Difficult diagnosis
  - **CT (*Caillot et al. J Clin Oncol 1997;15*)**
  - **Galactomannan antigen (serum, BAL-fluid)**

Invasive pulmonary aspergillosis



Treatment of IPA (I)

- Key recommendations:
  - Strongly suspected IA → Early initiation of antifungal therapy (A I)
  - Primary therapy → Voriconazole (in most patients) (A I)
    - **L-AmB alternative (A I)**
  - Salvage therapy (confirmed dg)
    - **LFAB (A II)**
    - **Posaconazole (B II)**
    - **Itraconazole (B II)**
    - **Caspofungin (B II)**
    - **Micafungin (B II)**
    - **Antifungal combination possible alternative (B II)**
  - Routine administration of combination therapy for primary therapy is not recommended (B II)
    - **Absence of a well-controlled prospective clinical trials**

Voriconazole as primary therapy

- Voriconazole superior to D- AmB
  - Randomized, prospective trial (*Herbrecht et al. NEJM 2002; 347*)
    - **VORI 6 mg/kg x 2 → 4 mg/kg BID IV for 7 days → 200 mg BID**
    - **D- AmB 1.0-1.5 mg/kg/d IV**
    - **Successful outcome 53 % vs 32 %**
    - **Survival at 12 weeks 71 % vs 58 %**
    - **Fewer severe drug related adverse events**
- Efficacy in pediatric patients (*Walsh et al. PediatrInfect Dis J 2002;21*)
    - **IPA refractory to conventional antifungal therapy**
    - **response rate 43 %**
- Efficacy in adults (*Denning et al. CID 2002;34*)
    - **IPA refractory to conventional antifungal therapy**
    - **response rate 48 %**

Controlled, prospective studies in IA

Article	Year	Patients	Dose (mg/kg)	No.	Outcome	
Ellis et al. CID	1998	Neutropenia, aspergillosis	L-AmB 4 mg L-AmB 1 mg	87	48 % 64 %	
Herbrecht et al. NEJM	2002	Proven or probable aspergillosis	Vori 4 mg BID/ D-AmB 1-1.5 mg	277	53 % 32 %	} p=0.02
Bowden et al. CID	2002	Proven, probable and possible aspergillosis	ABCD 6 mg D-AmB 1 mg	174	17 % 23 %	
Cornely et al. CID	2007	Proven or probable aspergillosis	L-AmB 10 mg L-AmB 3 mg	201	46 % 50 %	

Treatment of IPA (II)

- Key recommendations (con't)
  - Patient intolerant or refractory to voriconazole
    - **AmB-formulation**
    - **LFAB's as effective as D-AmB, less nephrotoxic (*Bowden et al. CID 2002;35, Leenders et al. Br J Haematol 1998;103, Walsh et al. CID 1998;26*) → Response rate ~ 40 %**
  - Salvage therapy
    - **Caspofungin → Response rate ~ 40 % (*Maertens et al. CID 2004;39*)**
      - **Higher responses in IPA ~ 50 %**
      - **Low nephrotoxicity**
    - **Itraconazole → Response rate from 39 % (oral therapy) to 52 % IV**
      - **Measurement of serum levels (> 250 ng/ml) B II**
      - **Not recommended in voriconazole failure B II (same mechanism of action)**
    - **Posaconazole → Response rate 42 % (*Walsh et al. CID 2007;44*)**

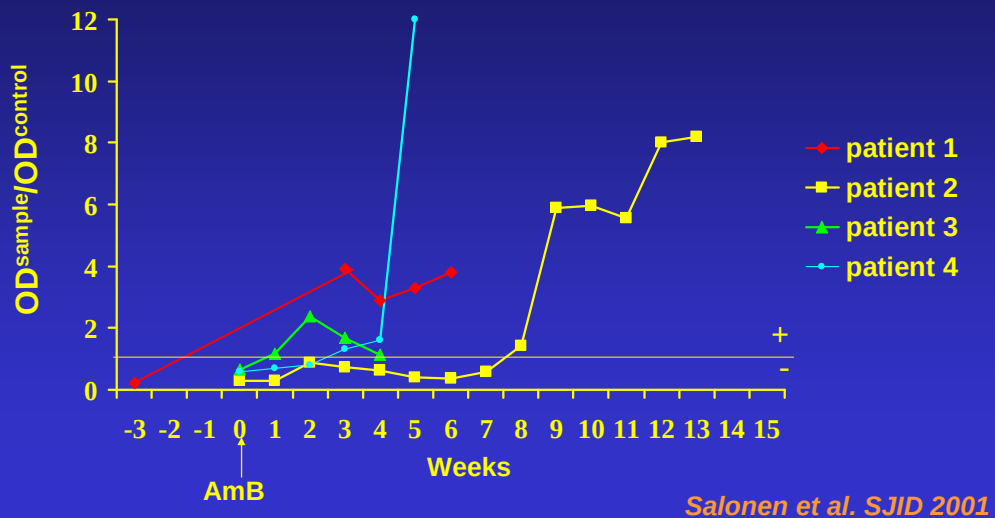
Treatment of IPA (III)

- Key recommendations (con't)
  - Treatment of break through IA in the context of mould-active prophylaxis
    - **Switch to another class (B III)**
  - Reversal of immunosuppression is important for successful outcome
    - **e.g. withdrawal or reduction of dosage of corticosteroids (A III)**
    - **Recovery from neutropenia**
  - Surgical resection of pulmonary lesions (B II)
    - **Lesions contiguous with great vessels or pericardium**
    - **Hemoptysis from a single cavitary lesion**
    - **Invasion of the chest wall**
    - **Single lesion prior intensive chemotherapy (HSCT)**

Treatment of IPA (IV)

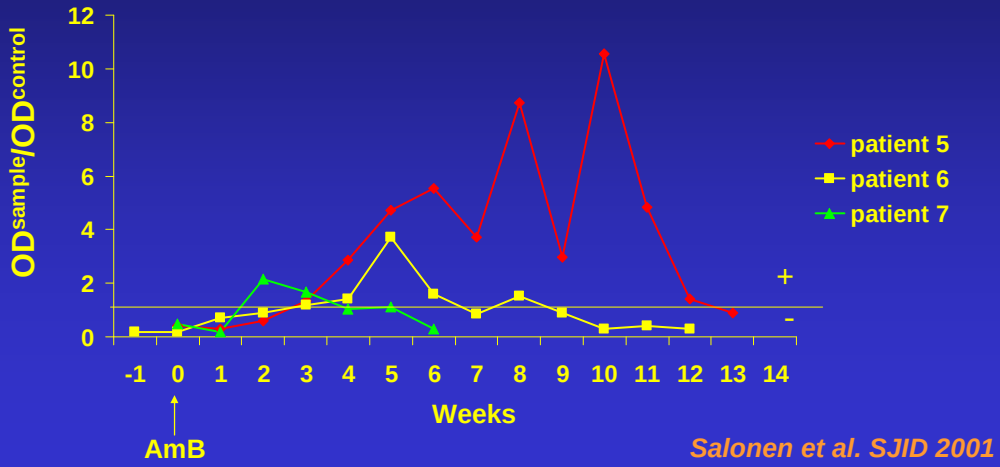
- Key recommendations (con't)
  - Secondary prophylaxis
    - **Successfully treated IPA and subsequent immunosuppression**
  - Duration of therapy
    - **minimum 6 weeks**
    - **throughout the immunosuppression and until the lesions have resolved**
  - Therapeutic monitoring
    - **CT at regular intervals (frequency ?)**
    - **Serial monitoring of galactomannan Ag promising, but still investigational → resolution of antigenemia not sufficient as sole criterion for discontinuation of therapy (B III)**

Monitoring galactomannan Ag during AmB therapy of 4 neutropenic patients with lethal IPA



Salonen et al. SJID 2001

Monitoring galactomannan Ag during AmB therapy of 3 neutropenic patients with IPA who survived



Salonen et al. SJID 2001

Treatment of IPA (V)

- Key recommendations (con't)
  - Impact of *Aspergillus* species
    - ***A. terreus*** **resistant to AmB → Azole therapy preferred**
    - **Itraconazole resistance reported (*A. fumigatus*) → Antifungal susceptibility testing in the context of prior azole therapy**
  - Colony-stimulating factors
    - **Persistent neutropenia → poor outcome**
    - **Patients with prolonged neutropenia may benefit from the addition of G-CSF or GM-CSF (B III)**
    - **IFN-γ in patients with chronic granulomatous disease (B III)**
  - Chronic immunosuppression
    - **Continuation of antifungal therapy throughout the duration of immunosuppression → more favorable outcome**

Other forms of invasive aspergillosis (I)

- Tracheobronchial aspergillosis
  - **Heart-lung and lung transplantations, HSCT**
  - **Site of anastomosis in trachea**
  - **No pulmonary infiltrates in initial stages → bronchoscopy**
  - **Initial therapy Voriconazole (B II)**
  - **LFAB to avoid nephrotoxicity in transplant patients (B III)**
- Chronic necrotizing pulmonary aspergillosis (CNPA)
  - **Slowly progressive inflammatory destruction of lung tissue**
  - **Underlying chronic lung diseases**
  - **Low grade immunosuppression (prolonged corticosteroid therapy)**
  - **Long term orally administered itraconazole (B III)**
  - **Less published information for use of voriconazole**

CNS aspergillosis

- CNS aspergillosis
  - **Dissemination from pulmonary focus or direct extension from paranasal sinuses**
  - **Aggressive diagnostic and therapeutic intervention in patients with IPA and signs of neurological deficits or abnormalities in CT or MRI**
    - **Galactomannan antigen in CSF**
  - **Voriconazole primary recommendation (penetration to CNS) A II**
  - **Alternative therapy: Itraconazole, Posaconazole, LFAB's (B III)**
    - **Intolerance or refractory to voriconazole**
  - **Surgical resection**
    - **Surgery combined with Voriconazole (*Schwartz et al. Blood 2005;106*) → favorable response in 35 %**

Other forms of invasive aspergillosis (II)

- Invasive sinonasal aspergillosis (**randomised trials lacking**)
  - **Combination of surgery and antifungal therapy**
  - **Microbiologically confirmed diagnosis → Voriconazole (B III)**
  - **Rhinonasal zygomycosis resistant to VORI and ITRA !!!**
  - **AmB-formulation, if etiological organism is unknown (A III)**
- Single organ extrapulmonary IA
  - **Uncommon, limited data on the treatment**
  - **Voriconazole for primary therapy B III (based on the randomized study comparing D-AmB and VORI, *Herbrecht et al. NEJM 2002*)**

Other forms of invasive aspergillosis (III)

- Endocarditis
  - **IDU**
  - **Embolic complications (large vegetations) and valvular decompensation**
  - **Antifungal therapy alone rarely successful**
  - **Valvular replacement surgery and antifungal therapy B III (Voriconazole, alternative LFAB) → Risk of recurrent infections**
  - **Minimum 6 weeks, consider lifelong therapy with triazole**
- Osteomyelitis and septic arthritis
  - **Haematogenous dissemination, traumatic inoculation or contamination during surgery**
  - **Combined medical and surgical intervention B III**
  - **Voriconazole or LFAB (B II), minimum for 6-8 wks (immunocompetent)**
  - **Long-term suppressive therapy (Itraconazole)**

Other forms of invasive aspergillosis (IV)

- Endophtalmitis and keratitis
  - **Sight threatening infections**
  - **Hematogenous dissemination (IDU) or direct inoculation by trauma**
  - **Direct ophtalmoscopic examination and culture of vitreous humor**
  - **AmB IV + Intravitreal AmB + vitrectomy (B III) in endophtalmitis**
  - **Voriconazole alternative regimen**
  - **Topical AmB and systemic antifungal therapy in keratitis (B III)**
- Cutaneous aspergillosis
  - **Hematogenous dissemination or enviromental contamination of wound**
  - **Surgical revision and antifungal therapy**
  - **Voriconazole or L-AmB (A I), POSA, ITRA or CASPO (B II)**
- Renal aspergillosis
  - **Nephrostomy reduce complications of obstruction**
  - **All available antifungal penetrate renal parenchyma**
  - **Antifungals not excreted into the pelvis of kidney → AmB instillation**

Dosing of antifungals in invasive aspergillosis

Antifungal agent	Dosage	Comments
Voriconazole	6 mg/kg BID→ 4 mg/kg BID IV (1 day)	Oral dosage: 200 mg BID Pediatric: 5-7 mg/kg BID
Itraconazole	200 mg BID IV →200 mg daily IV (2 days)	Dosage depends on formulation
Posaconazole	200 mg QID → 400 mg BID	Change dosing after clinical stabilization
D-AmB	1 mg/kg/d IV	
L-AmB	3-5 mg/kg/d IV	
ABLC	5 mg/kg/d IV	
ABCD	3-4 mg/kg IV	
Caspofungin	70 mg → 50 mg QD IV	Pediatric: 50 mg/m^2

Chronic and saprophytic forms of aspergillosis

- Aspergilloma (fungus ball), chronic pulmonary aspergillosis (CCPA)
  - **1 or more pulmonary cavities with serum aspergillus-AB's**
  - **Underlying pulmonary disease (TB, sarcoidosis, emphysema)**
  - **Complications: Hemoptysis, pulmonary fibrosis, IA**
  - **Clinical and radiological diagnosis**
  - **Surgical resection of single aspergilloma (difficult surgical procedure)**
  - **Antifungal therapy has limited activity → Important for CCPA**
  - **Broad spectrum triazoles (perhaps lifelong) B III**
- Aspergillus otomycosis
  - **Saprophytic process of external auditory canal (*A. niger*)**
  - **Pruritus, pain, discharge and hypoacusis**
  - **Risk groups: Diabetes, hypogammaglobulinemia, chronic eczema, use of corticosteroids**
  - **Topical therapy with boric or acetic acid (C III)**
  - **Orally administered broad spectrum triazoles (no published studies)**

Allergic forms of aspergillosis (I)

- Allergic bronchopulmonary aspergillosis (ABPA)
  - **Hypersensitivity disease in the lungs**
  - **Response to Aspergillus spp causes inflammatory airway destruction**
  - **Symptoms and findings:**
    - **Episodic bronchial obstruction**
    - **eosinophilia**
    - **scratch test reactivity to aspergillus**
    - **precipitating AB's to aspergillus**
    - **elevated IgE**
    - **pulmonary infiltrates**
  - **Combination of corticosteroids and itraconazole (A I) → reduction of corticosteroid dose, increases intervals between courses, improves pulmonary function**
  - **"corticosteroid sparing agent"**

Allergic forms of aspergillosis (II)

- Allergic aspergillus sinusitis
  - **Similar histopathological features with ABPA**
  - **Affects sinuses**
  - **Patients have history of astma**
  - **Immediate cutaneous reactivity to Aspergillus spp in 60 %**
  - **Elevation of total IgE in 85 %**
  - **Aspergillus precipitins in 85 %**
  - **Treatment:**
    - **Endoscopic drainage in patients with obstructive symptoms C III**
    - **Itraconazole C III**
    - **Systemic or nasal corticosteroids C III**

Aspergillus prophylaxis

- Selection of population for prophylactic strategy remains a challenge
- Antifungal prophylaxis with posaconazole (A I)
  - **HSCT patients with GVHD *(Ullmann et al. NEJM 2007;356)***
  - **Acute myelogenous leukemia and MDS *(Cornely et al NEJM 2007;356)***
    - **Superior to fluconazole and itraconazole**
    - **Which subpopulations would benefit most ??** → Further investigation needed !
- Itraconazole may be effective (B I)
  - **Dose-limiting toxicity and erratic bioavailability problems**
- Micafungin may be effective in HSCT patients ***(van Burik et al. CID 2004; 39)***
  - **Superior to fluconazole**
  - **Small number of break through infections**
- Secondary prophylaxis in confirmed, successfully treated IA

Conclusions

- Voriconazole has replaced AmB-formulations as the primary therapy for invasive aspergillosis
- There are only few comparative, randomized prospective studies available
- Voriconazole is superior to D-AmB in efficacy and safety
- Other antifungals active against aspergillus have not been compared face to face
- There are many unanswered questions in diagnosis, treatment and prevention
- In certain forms of aspergillosis is needed surgical treatment
- Combination of itraconazole and corticosteroids benefit patients with allergic forms of aspergillosis


Thank you !