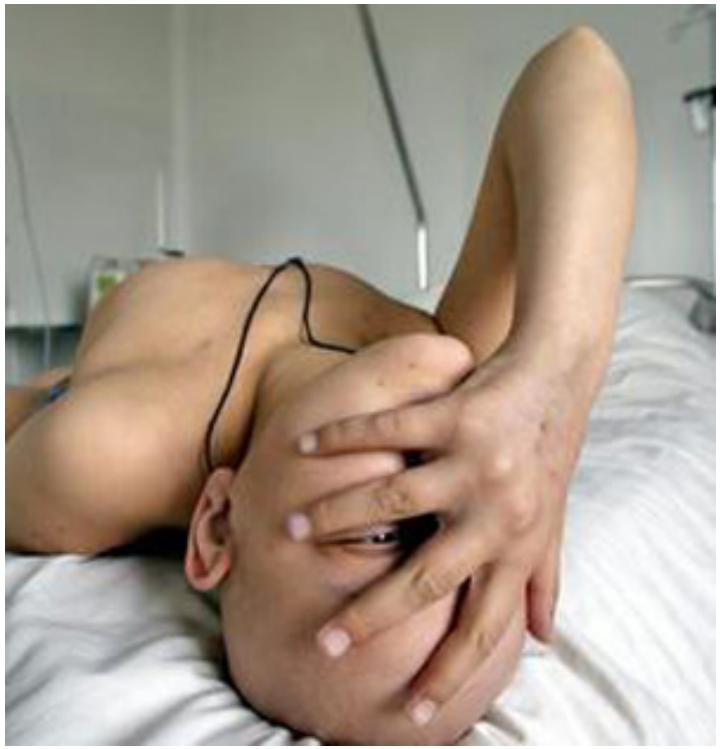

Management of invasive fungal infections (IFI)

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Conflicts of interests:

I collaborate with:

Astellas, Gilead, Novartis, MSD, Pfizer, TEVA

- Risk populations for IFI
- Epidemiology
- Management of IFI
  - *Candida*
  - *Aspergillus*
- Futur?

INCREASE IN FUNGAL INFECTIONS: WHY?

- **Better diagnosis**
- **More broadspectrum antibiotics**
- **Higher age of patient population**
- **More complex interventions (e.g.transplants)**
- **More intensive cytotoxic therapy**
- **More immunosuppressive therapy**
- **Less mortality from other causes**
- **More high risk patients**

Sources and Sites of Fungal Infection in Neutropenic Patients

Aspergillus
- Air conditioning
- Construction
- Re-activation
- Raw vegetables

Candida
- Skin
- Mucosal surfaces
- Re-activation
- Indwelling catheter

Inhalation

Skin barrier

GI tract

Inhalation

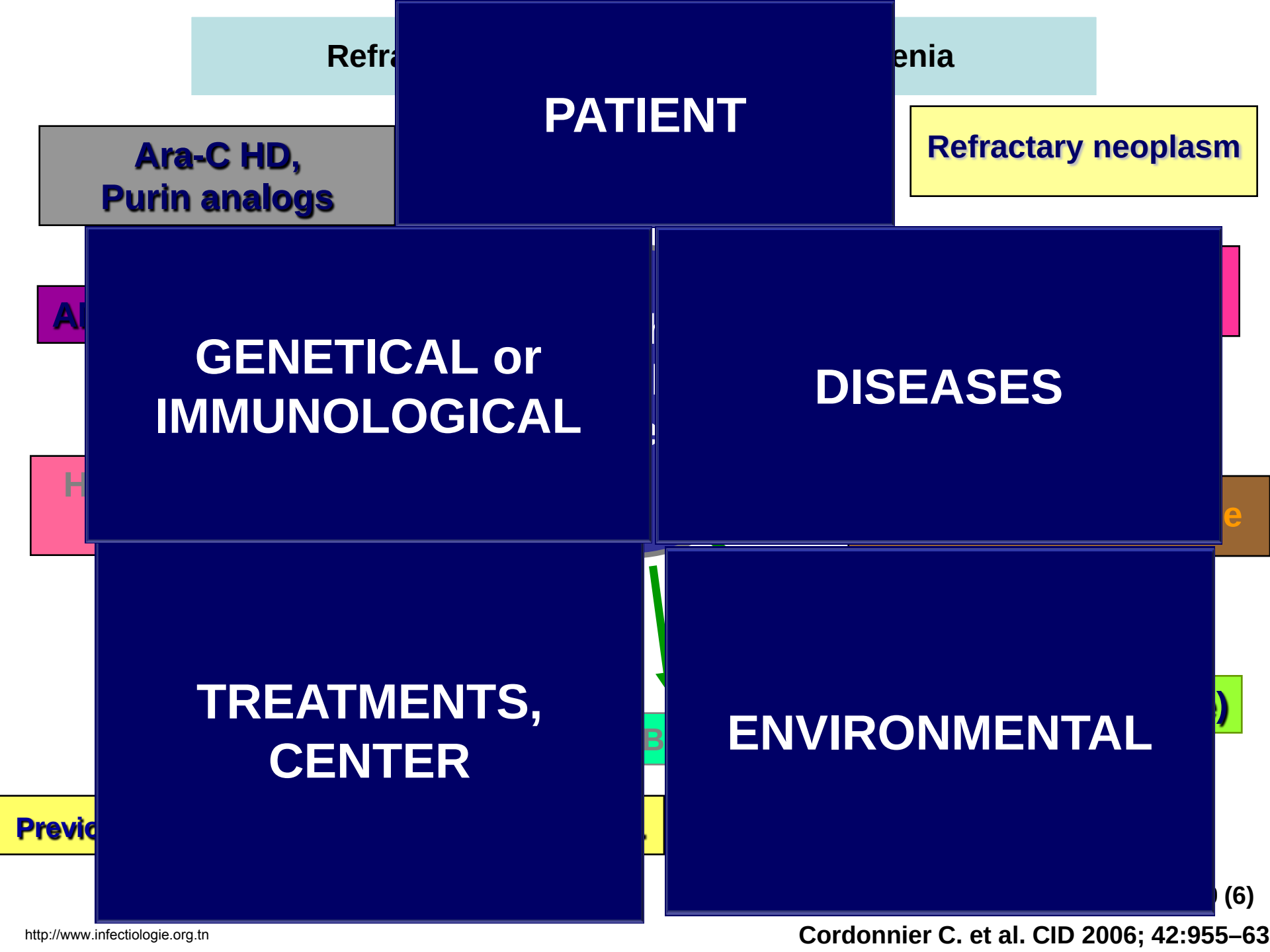
GI tract

Emerging fungi

Mucor, Cryptococcus, Fusarium
- Plants
- Pepper
- Animal droppings

Trichosporon
- Mucosal surfaces
- Skin

Saccharomyces



Cordonnier C. et al. CID 2006; 42:955–63

Genetical factors

Table 1 Genetic association studies implicating specific markers for IFI risk in SCT recipients

Genetic marker tested[Ref]	*SCT population/study design ethnicity*	*IA risk*	*Biological plausibility*	*Comments*
SNP in TLR2, TLR3, TLR4, TLR9 haplotypes in SCT recipients and their unrelated donors[51]	336 allo-SCT recipients IA in 33/336 (9.8%) FLU prophylaxis (d0–d75) in 90% Retrospective analysis IA assessed in 6 and 36 months Discovery study→ Validation study Mostly Caucasians. (Seattle, USA)	TLR4 S3 and S4 haplotypes in donors: 6.6-fold increased risk, association only in MUD SCT (discovery phase) Only TLR4 S4 in validation study: 2.49-fold increased risk	TLRs are receptors in immune cells that detect fungal PAMPs	Frequency of TLR4 S4 haplotype in 6% of donors. CMV, GVHD were also independent predictors Concomitant absence of CMV seropositivity and TLR4 S4 haplotype may define a subgroup at very low IA risk
SNPs in TLR1, TLR4, TLR6 in SCT recipients and their donors[55]	127 allo-SCT recipients (22 with IA) Retrospective analysis No data on follow-up, type of prophylaxis Mostly Caucasians. (NY, USA)	No association between donor SNP and IA risk TLR1239G or TLR1734A and TLR6745 marginally increased (OR 1,3) IA risk	As above	Specificity of association is unclear (e.g., relationship with CMV, RSV, GVHD) not addressed, TLRs also sense bacterial PARMs
CXC10 polymorphisms, CXR10 serum levels, SNP in 18 immune relevant genes[54]	81 allo-SCT recipients with IA 58 allo-SCT recipients without IA No information about prophylaxis, follow-up, accuracy of IA diagnosis Mostly Caucasians	Three SNPs of CXC10 (rs1554013, rs4257674, rs3921) were associated with increased IA risk, CXR10 serum levels were lower in SCT recipients with IA	Stimulation of immature DC by *Aspergillus* augmented CXC10 expression in patients with WT CXC haplotype	Specificity of association is unclear (e.g., relationship with CMV, RSV, GVHD) not addressed

SNP in human plasminogen gene of SCT recipients and donors[48]	236 allo-SCT recipients 96% received FLU prophylaxis Retrospective analysis Mostly Caucasians (Duke, NC, USA)	Homozygous for Asp472 Asn: 5.6-fold increased risk Heterozygous: 3-fold increased risk Donor SNP: no increased risk	Plasminogen binds to swollen conidia and hyphae of *Aspergillus*	Increased IA risk seen after day 40 and persistent for 1 year Possible association with improved outcome of SCT recipients with IA
MBL alleles in recipients and donors, low MBL levels (<400 ng/mL)[49]	131 allo-SCT recipients Incidence of fungal pneumonia: 35% (day 0–75 post-SCT) Retrospective analysis, no information on prophylaxis Mostly Caucasians	No association between MBL genotype and IA in both donors and recipients but low MBL serum levels increased no risk for fungal pneumonia by 4, 4	MBL ligands mannan of various fungi	Low MBL was also correlated with sepsis, viral reactivation No association with GVHD risk. Issues with selection of cases and controls
SNP in dectin-1[52]	142 allo-SCT and 138 donors FLU prophylaxis Retrospective analysis Mostly Caucasians (Dutch)	Dectin Y238X polymorphisms increased risk for *Candida* colonization (OR 11, 9)	Dectin-1 is a global pattern recognition receptor for fungi This SNP was associated with impaired cytokine production	No increased risk for candidiasis (effect of fluconazole?) or IMIs Gene dose effect seen with the polymorphism
IL-10 promotor polymoprphisms[53]	120 hematology patients, 124 controls, IA in 59/120 pts Neutropenia in 71% no information about SCT recipients prophylaxis Mostly Caucasians (Spanish)	IL-101082 (AA) genotype was associated with increased resistance to IA (OR 4, 5)	Unclear IL-10 overexpression down regulates Th1 response and is associated with poor survival in murine IA	Specificity issues Issues with selection of cases and controls
IL-1α, IL-1b, IL1Ra polymorphisms[50]	110 hematology patients and 148 healthy controls Retrospective analysis No information on prophylaxis IA incidence 59/110 Mostly Caucasians	VNTR-2/- 889C/S11T haplotypes: increased risk for IA VTR-2/- 889C/-511C haplotype: increased resistance to IA	Unknown	Some IL-1 gene cluster polymorphisms were associated with higher *Aspergillus* galactomannan titers Issues with selection of cases and controls
TNF-a, TNF-R polymorphisms[56]	122 hematology patients, 124 age-matched controls Retrospective analysis No information about prophylaxis Mostly Caucasians (Spanish)	VNTR-322 allele was associated with increased IA risk	TNF is a key mediator for immune responses against fungii	Issues with selection of cases and controls TNF serum levels did not differ between IA patients and controls

Abbreviations: CXC10 = chemotactic cytokine CXC10; FLU = fluconazole; IA = invasive aspergillosis; IFIs = invasive fungal infections; IMIs = invasive mold infections; MBL = mannose-binding lectin; MUD = matched unrelated donor; PAMP = pathogen-associated molecular patterns; RSV = syncytial respiratory virus; SNP = single-nucleotide polymorphism; TLR = toll-like receptor; TNF-R = TNF receptor.

- decreased production IL-10 (haplotype AAC) 9-fold lower risk of developing IFI compared with controls
- various polymorphism in TLRs (2, 4, 1, 6) are though to be allied to an increased risk of IFD
- polymorphisms in the plasminogen gene and the mannose-binding lectine gene have bee linked with increased incidence of IFI

Environmental risk factors

Risk factors related to diseases and procedures

Table 2. Environmental risk factors

Risk factor	Reference(s)
Seasonal incidence	18,19
Weather variation	18,19
temperature	18,19
rainfall	18,19
humidity	18
wind speed	18
Personal habits	20,21
smoking	20
living in countryside	20
fungus exposure	20
type of work (e.g. farmer, agriculture)	21
Exposure outside	20–22
pets	
dusty household	20
construction work	
Exposure inside	6
potted plants	
absence of HEPA-filtered rooms	2,23
water	6

HEPA, high-efficiency particulate air.

Table 2 Hematopoietic stem cell transplant recipients at highest risk for IA and other IMIs

Patients with prolonged preengraftment periods (i.e., cord blood recipients)
Patients with history of IA before SCT
Patients receiving haploidentical or T-cell-depleted transplants
Patients with GVHD receiving high doses of steroids (⩾1 mg per kg prednisone equivalent) with or without ATG or TNF blockade (infliximab)
Transplant recipients with active CMV infection or RSV
Patients with active leukemia
Patients who undergo retransplantation
Patients with secondary graft failure
Patients with colonization of certain fungi, such as *Aspergillus*, *Fusarium*, *Zygomycetes*, and *Scedosporium* species and *Candida tropicalis*
Specific risks for mycormycosis
Iron overload
Baseline serum ferritin >1000 ng/mL
3–4+ iron in BM
Iron overload by liver MRI
Diabetes mellitus or chronic hyperglycemia due to corticosteroids
Pre-exposure to *Aspergillus*-active antifungals (e.g. VRC, echinocandins)

Table 1. Stratification of immunocompromised patients in risk categories for invasive fungal disease according to incidence and mortality rates obtained from current literature[2–7,9–11]

Low risk	Intermediate risk	High risk
autologous HSCT	acute lymphoblastic leukaemia	acute myeloid leukaemia (above all in first induction)
Hodgkin's lymphoma	chronic lymphocytic leukaemia	allogeneic HSCT (particularly with cord blood source)
chronic myeloproliferative disorders (CML and Ph− diseases)	lymphoma	heart, lung, liver transplantation
solid cancer	COPD	
myeloma	AIDS	
kidney transplantation	myelodysplastic syndromes	
chronic immunological disease		
systemic lupus erythematosus		

CML, chronic myeloid leukaemia; COPD, chronic obstructive pulmonary disease; Ph−, Philadelphia negative.

http://www.infectiologie.org.tn

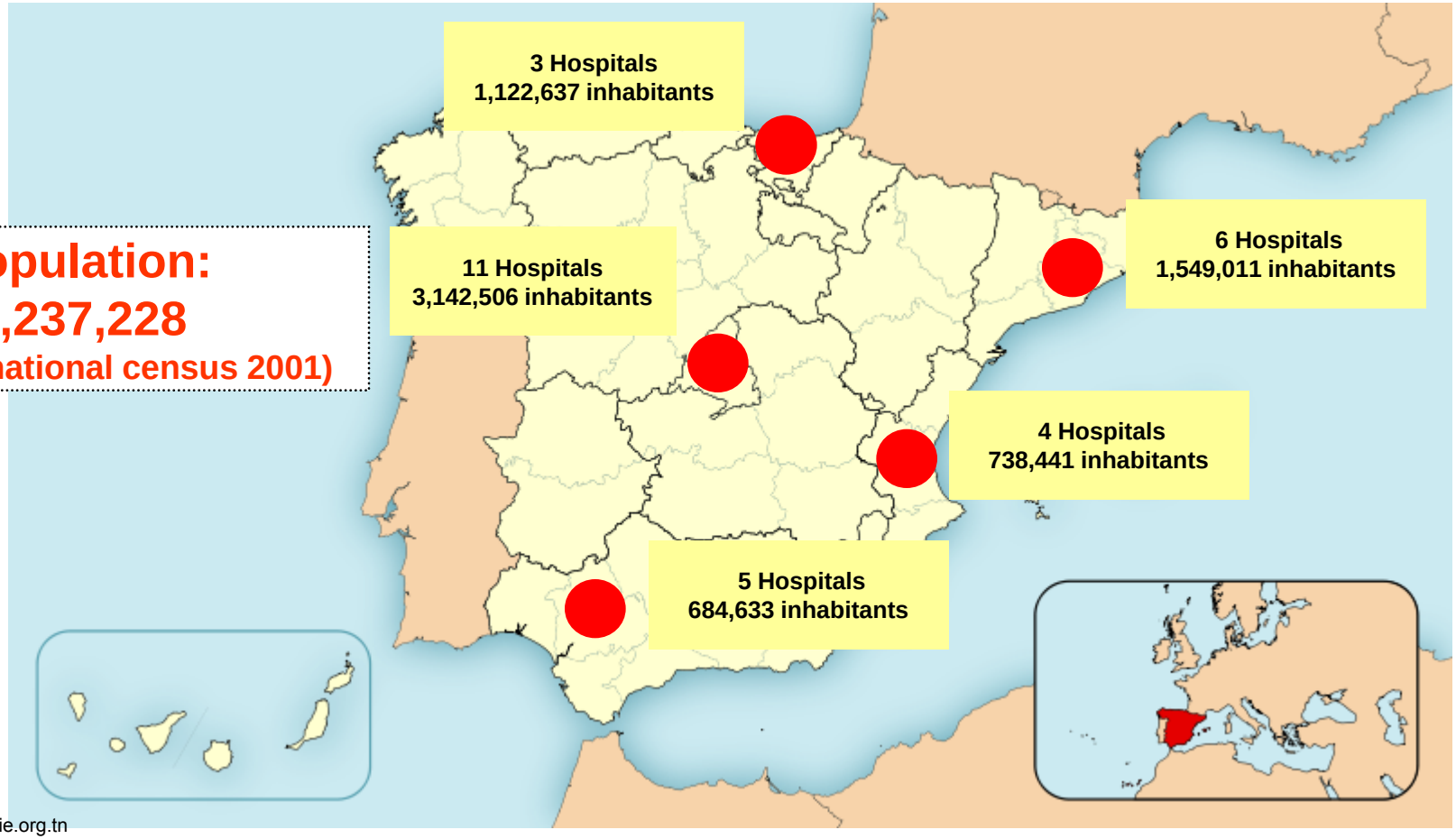
IFI epidemiology around the world

Methods (I)

Study design

- Prospective multicenter **population-based** surveillance on *Candida* BSI (May 2010-April 2011)
- 29 hospitals from **5 areas** of Spain

Population:
7,237,228
(last local national census 2001)

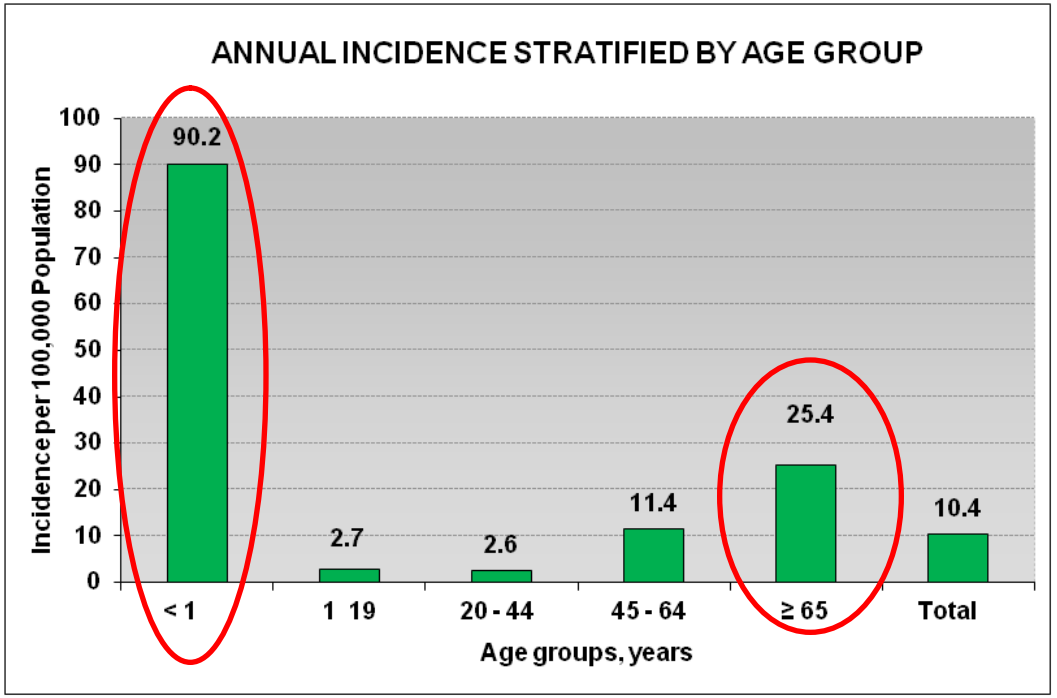


Results

- A total of **752 episodes** in 729 patients were detected.
- 14 cases had two different *Candida* species, resulting in **766 strains**.

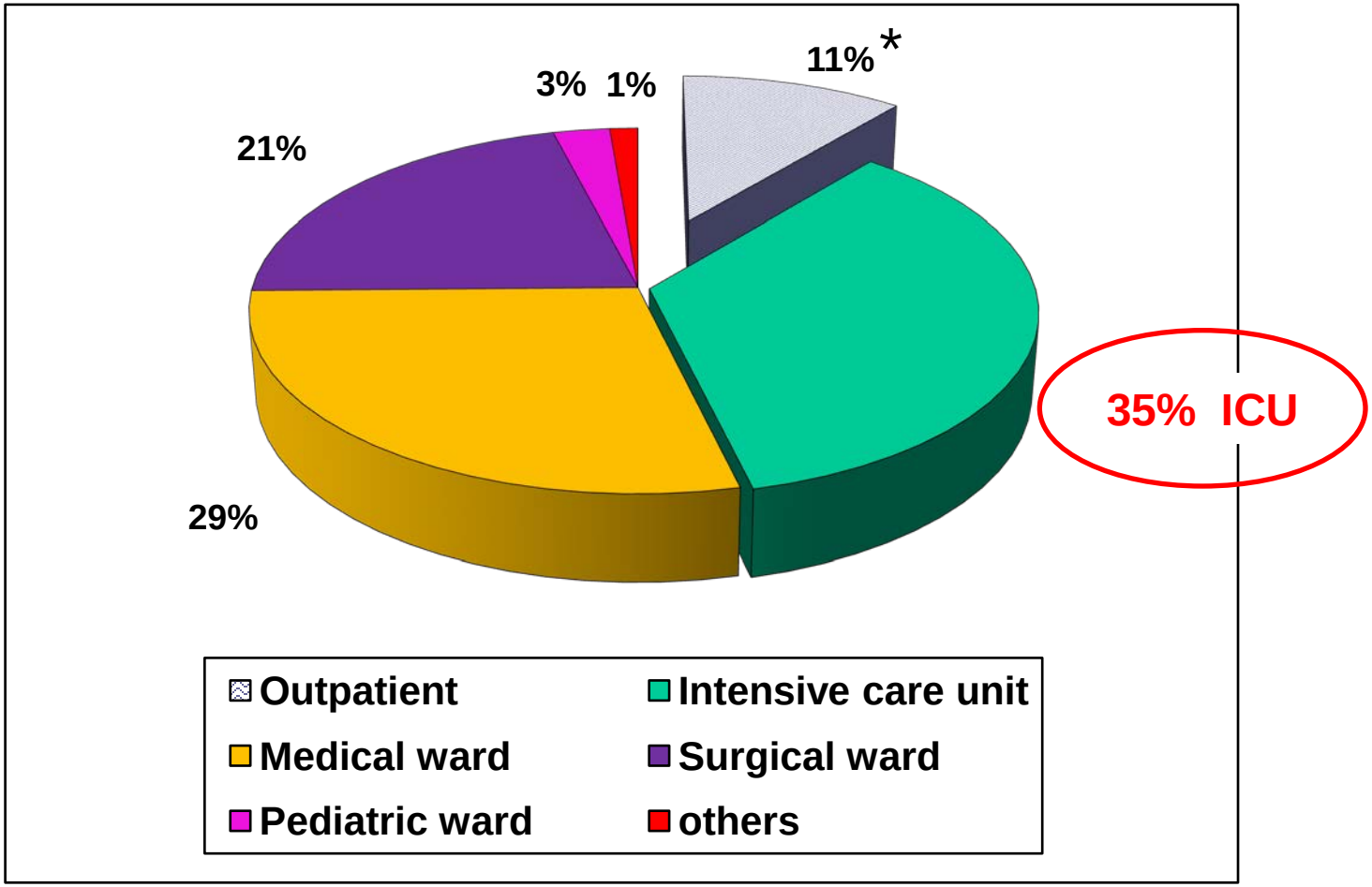
Annual incidences :

- **10.4** episodes/10^5 habitants
- 0.78 episodes/10^3 admissions
- 1.2 episodes/10^4 patient-days.



Results

- **Location of patients at time of candidemia**



* **<u>Outpatient</u>**: Cases with positive blood culture either **prior or at ≤ 2 days** of hospitalization

- **Demographic characteristics and clinical data of candidemia**

Characteristics	Number (%)
Male	442 (58.8)
Median age (range)	62 (0-102)

Source of infection	
Primary	447 (59.4)
Secondary	303 (40.6)
Definite catheter-related	248 (33)
Urologic tract	33 (4.4)
Abdominal	22 (2.9)
Others	2 (0.3)

Co-morbidities	
Malignancy	284 (37.8)
Renal failure	194 (25.8)
Diabetes	160 (21.3)
Transplant patients	45 (6)
Neutropenia	43 (5.7)
Cirrhosis	33 (4.4)
HIV infection	16 (2.1)

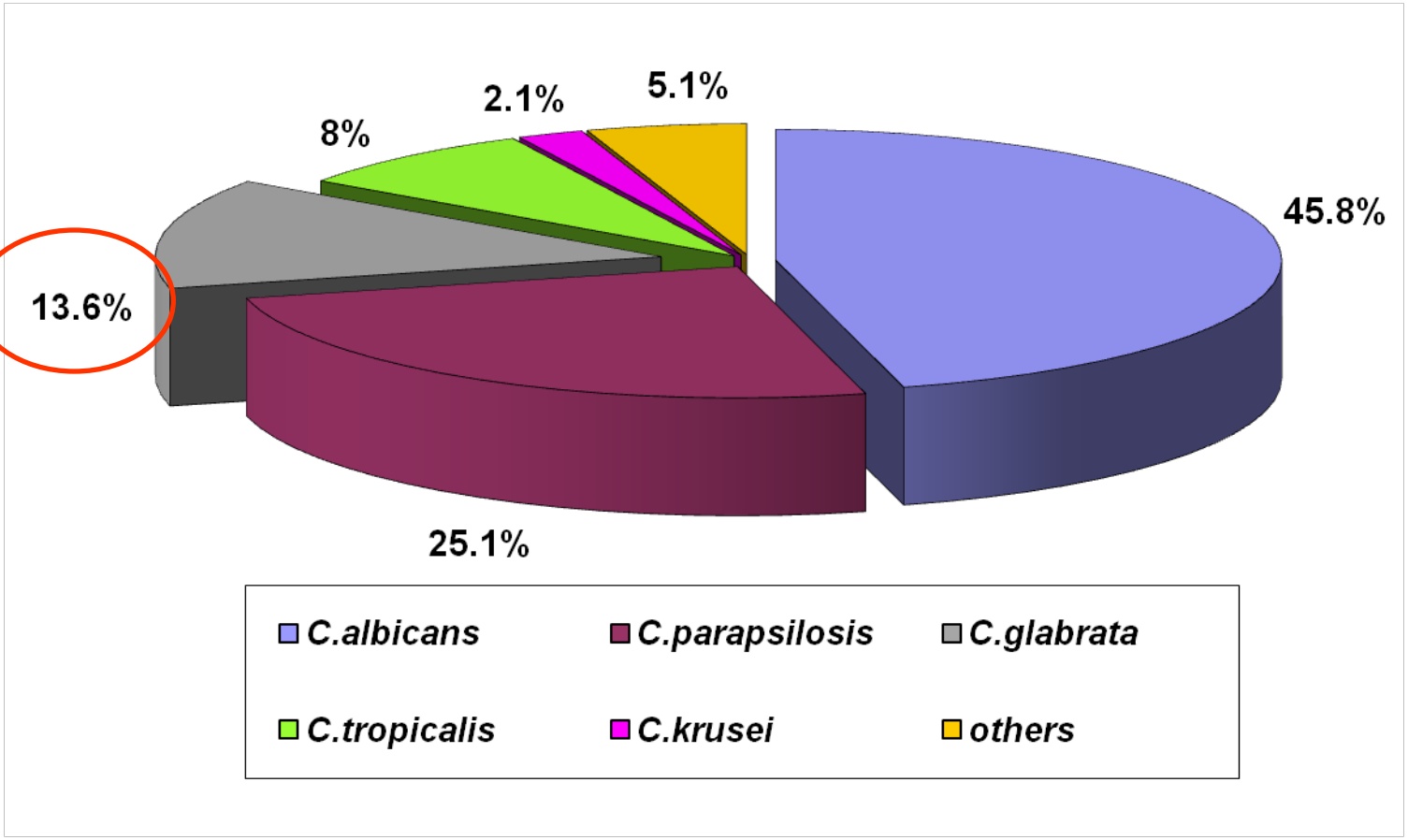
- Conditions known to be associated with candidemia

Risk Factors*	
Prior antibiotic therapy	698 (92.8)
Central venous catheter	574 (76.3)
Surgery in previous 3 months	385 (51.2)
Total parenteral nutrition	352 (46.8)
Prior *Candida* colonization	287 (38.2)
Prior immunosupressive medication	253 (33.6)
Prior antifungal therapy	182 (24.2)
Fluconazole	121 (16.4)

* Within the preceding month, unless otherwise indicated

Results

- **Distribution of *Candida* species**



54.2% of non-*albicans* species

Microbiological results

- Antifungal susceptibility (available data on 650 isolates)

Species	Number (%)	No. Resistant to Fluconazole (%)	No. S-DD to Fluconazole (%)
C. albicans	289 (44.4)	6 (2)	2 (0.7)
C. parapsilosis	178 (27.4)	12 (6.7)	4 (2.25)
C. glabrata	89 (13.7)	52 (58.4)	37 (41.6)
C. tropicalis	45 (6.9)	3 (6.6)	3 (6.6)
C. krusei	15 (2.3)	15 (100)	0
C. guillermondii	9 (1.4)	4 (44.4)	1 (11.1)
C. lusitaniae	9 (1.4)	2 (22.2)	0
C. famata	4 (0.6)	1 (25)	2 (0.5)
C. Kefyr	3 (0.5)	0	0
C. lypolitica	3 (0.5)	1 (33.3)	0
Others	6 (0.9)	0	2 (33.3)
All incident isolates	650 (100)	96 (14.8)	51 (7.8)

S-DD: susceptible dose-dependent

Predictors of mortality

- **225 (29.9%)** patients died within 30 days after onset of candidemia
  -98 (13%) within 7 days

Predictors of **early mortality** (3-7 days)

variable	OR (CI 95%)	P value
Pitt score ≥ 2	3.4 (1.36-8.35)	0.009
C.krusei	4.5 (1.09-18.6)	0.037
CVC removal within 48 h*	0.43 (0.19-0.94)	0.034

CVC: central venous catheter.
***** 554 cases with CVC and primary/catheter-related candidemia

Predictors of **late mortality** (8-30 days)

variable	OR (CI 95%)	P value
Liver cirrhosis	7.52 (1.75-32.3)	0.007
Intubation	3.4 (1.74-6.67)	< 0.001
Recurrent episode	4.37 (1.2-15.9)	0.025
Persistent candidemia (> 6 days)	2.03 (1.02-4.05)	0.043

Conclusions

- Overall **annual incidence** of Candida BSI in Spain is **10.4 cases/10^5 population**. Annual incidence varied widely depending on patients age group.
- Overall mortality is high (nearly 30% within 30 days).
- On multivariable analysis, the presence of Pitt score ≥ 2 and *C.krusei* candidemia significantly increased the risk for early mortality.
- Catheter removal is critical in preventing early mortality in patients with candidemia.
- Variables associated with clinical illness (cirrhosis, intubation, recurrent episode) and poor control of infection (persistent candidemia) were related to late mortality.
- Overall rates of fluconazole resistance (14.8%) has increased in relation to previous Spanish reports, probably due to an increase in *C.glabrata* and new EUCAST breakpoints.

Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database

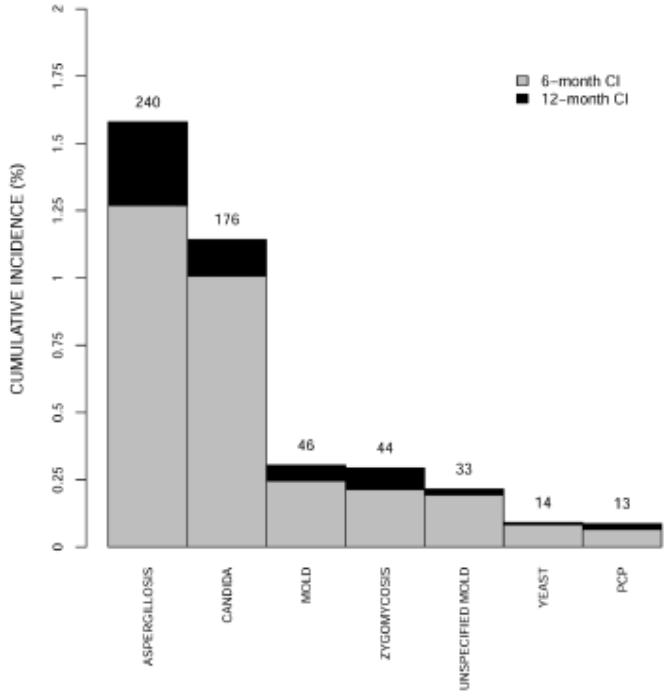
• CID 2010:50 (15 April) •

- ✓23 transplant centers-16200 HSCT
- ✓983 IFI/875HSCTrecipients:
- ✓IA (43%) > IC (28%) > Z (8%)
- ✓Within 60 days neutropenia and GVHD
- ✓Median onset 61d and 99d (C and A)
- ✓Overall 1-year survival:

Candida (33.6%)> Zygomycosis (28%)> Aspergillosis (25.4%) >Fusarium (6.3%)

12 months CI of any IFI: 3.4%

12 months cumulative incidence based on first IFI (cases per 100 transplants):, 8.1 MMRD, 7.7 for URD and 5.8 MRD, 1.2 autologous



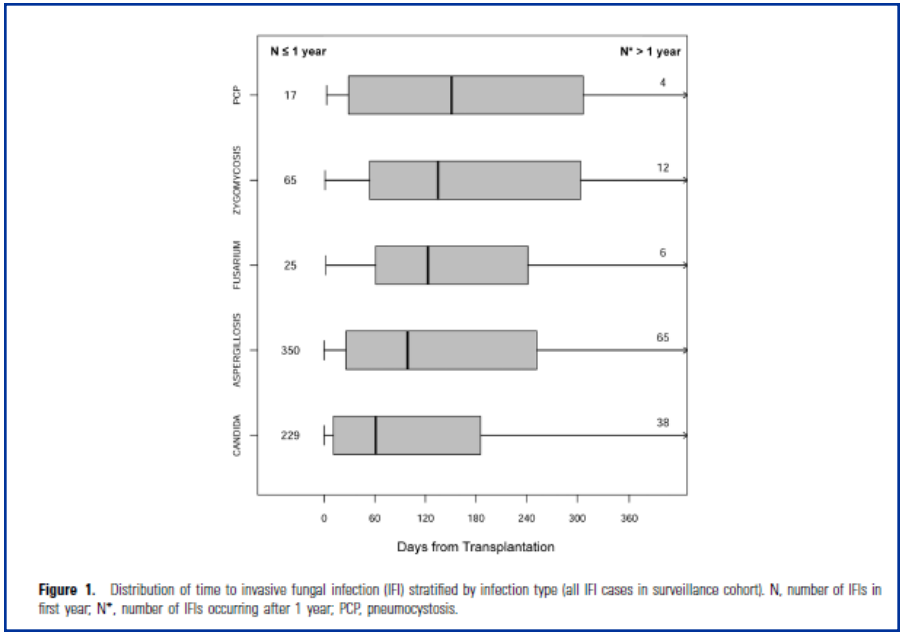


Figure 1. Distribution of time to invasive fungal infection (IFI) stratified by infection type (all IFI cases in surveillance cohort). N, number of IFIs in first year; N*, number of IFIs occurring after 1 year; PCP, pneumocystosis.

Fungal Infections in Recipients of Hematopoietic Stem Cell Transplants: Results of the SEIFEM B-2004 Study—Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne

CID 2007:45 (1 November) • 1161

3228 p (1249 allo/1979 autol)

IFI in 121p (overall incidence 3.7%): 91 molds (2.8%) and 30 (0.9%) yeast.

98 episodes (7.8%) occurred among 1249 allo

Aspergillus(86) > *Candida* spp. (30)

Attributable mortality rate 65.3% (72.4% allogenic vs 34.7% autologous)

Attributable mortality rate for *Aspergillosis* was 72.1% (77.2% allogenic vs 14.3% autologous)

Attributable mortality rate for *Candida* 50% (57.1% allogenic vs 43.8% autologous)

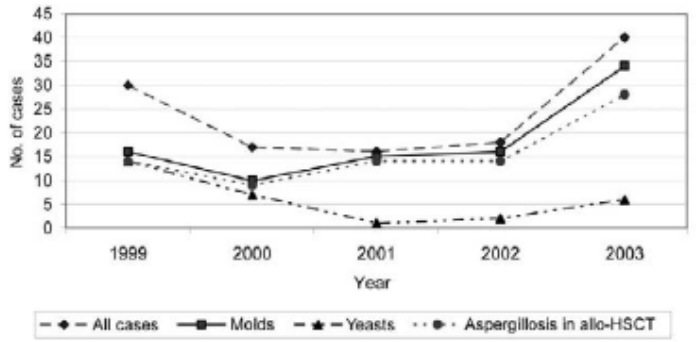


Figure 1. Annual incidence of invasive fungal infections—in particular, of invasive aspergillosis in allogenic hematopoietic stem cell transplant (allo-HSCT) recipients—during the study period.

Table 4. Incidence of invasive fungal infection and attributable mortality rate (AMR) among recipients of allogenic hematopoietic stem cell transplants from different types of donors.

Transplant donor	No. (%) of patients	No. of cases	No. of deaths
Matched, related			
Patients, cases, or deaths	747 (60)	69	49
Incidence or AMR, % (95% CI)[a]	...	9.2 (7.3–11.5)	71 (59.5–80.8)
Mismatched, related			
Patients, cases, or deaths	181 (14)	6	5
Incidence or AMR, % (95% CI)[a]	...	3.3 (7.3–11.5)	83 (40.9–99.2)
Matched, unrelated			
Patients, cases, or deaths	321 (26)	23	17
Incidence or AMR, % (95% CI)[a]	...	7.1 (7.3–11.5)	74 (53.4–88.7)
Total			
Patients, cases, or deaths	1249 (100)	98	71
Incidence or AMR, % (95% CI)[a]	...	7.8 (7.3–11.5)	72 (63.0–80.6)

[a] Rate is the incidence for no. of cases and AMR for no. of deaths.

Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005–2007)

O. Lortholary[1,2,3], *Clin Microbiol Infect*

TABLE I. Risk factors for invasive aspergillosis and underlying diseases of the 393 adult patients of the study

Risks factors/underlying diseases	*n* (%)
Acute leukaemia	136/393 (34.6)
Acute myeloid leukaemia	90/136 (66.2)
Acute lymphoid leukaemia	21/136 (15.4)
Myelodysplasia	9 (6.6)
Acute transformation	16 (11.8)
Allogeneic HSCT	84/393 (21.4)
Acute myeloid leukaemia	28 (33.3)
Acute lymphoid leukaemia	18 (21.4)
Myelodysplasia	4 (4.8)
Acute transformation	7 (8.3)
Lymphoma	13 (15.5)
Chronic lymphoid leukaemia	3 (3.6)
Multiple myeloma	5 (6.0)
Aplasia	3 (3.6)
Others	3 (3.6)
Chronic lymphoproliferative disorders	85/393 (21.6)
Lymphoma	42 (49.4)
Chronic lymphoid leukaemia	26 (30.6)
Multiple myeloma	13 (15.3)
Others	4 (4.7)
Solid organ transplantation	34/393 (8.7)
Heart	7 (20.1)
Lung	7 (20.1)
Liver	9 (26.5)
Kidney	11 (32.4)
Solid tumours	17/393 (4.3)
Broncho-pulmonary and others	6 (35.3)
Others	11 (64.7)
Systemic inflammatory diseases	18/393 (4.6)
Vasculitis	5 (27.8)
Inflammatory rheumatism	3 (16.7)
Glomerulonephritis	2 (11.1)
Others	8 (44.4)
Chronic respiratory diseases	9/393 (2.3)
Chronic obstructive pulmonary disease	2 (22.2)
Pulmonary fibrosis	4 (44.4)
Asthma	2 (22.2)
Others	1 (11.1)
None of the above risk factors	10/393 (2.5)

For patients with AL, IA occurred for 68% (93/136) of them during the induction phase of chemotherapy, for 27% during consolidation and for 5% during palliative care. For the 85 non-allografted patients with chronic lymphoproliferative disorders, IA occurred for 27% (23/85) during the induction phase, for 67% (57/85) during malignancy relapse/non-control, and for 6% (5/85) during palliative care. The time interval between allogeneic HSCT and the occurrence of IA was <40 days, ≥40–100< and ≥100 days for 16 (19%), 11 (13%) and 57 (68%) patients, respectively. IA occurred in the first 12 weeks following heart transplantation (6/7) and at least 100 days after surgery for the other transplant procedures (18/27).

Localization of IA was mostly pulmonary (365/393, 92.9%), either isolated (324/393, 82%) or associated with other localizations (41/393, 10%) that consisted mainly of sinus (n = 18) and central nervous system (CNS, n = 20) involvement. Isolated extrapulmonary aspergillosis was documented in 28 patients (8%) and consisted of sinusitis (n = 11) and/or CNS localizations (n = 9).

424 cases- 0,271 cases/1000 admissions

305 hematological patients (77.6%)

Acute leukaemia: 68% induction-27% consolidation

Chronic Lymphoproliferative disorders: 67% relapses or no control

Allo-HSCT incidence 8.1% (84/1043)

68% (>100d),13% (40-100d).

TABLE 2. Characteristics, diagnostic means, treatment and outcome according to risk factors/underlying diseases in the 393 cases of invasive aspergillosis of the study

	Acute leukaemia (n = 136)	Allogeneic HSCT (n = 84)	Chronic lympho-proliferative disorders (n = 85)	Solid organ transplantation (n = 34)	Solid tumours (n = 17)	Systemic inflammatory diseases (n = 18)	Chronic respiratory diseases (n = 9)	Others (n = 10)	p[a]
Mean age (years) (95% CI)	55 (53–58)	44 (41–47)	59 (56–62)	54 (50–58)	58 (51–65)	62 (55–70)	63 (52–73)	55 (44–66)	$<10^{-3}$
Male, n	77 (56.6%)	56 (66.7%)	53 (62.4%)	25 (73.5%)	15 (88.2%)	6 (33.3%)	7 (77.8%)	5 (50%)	0.016
Proven IA	20 (14.7%)	11 (13.1%)	6 (7.1%)	7 (20.6%)	6 (35.3%)	4 (22.2%)	1 (11.1%)	5 (50.0%)	0.004
CT scan and chest X-ray, No. of patients examined	124 (91.2%)	71 (84.5%)	66 (77.7%)	26 (76.5%)	9 (52.9%)	13 (72.2%)	9 (100%)	6 (60%)	$<10^{-3}$
CT signs recorded in those with pulmonary IA (%)									
Nodule	104/121 (86.0%)	56/65 (86.2%)	51/65 (78.5%)	15/23 (65.2%)	5/9 (55.6%)	10/13 (76.9%)	8/9 (88.9%)	3/5 (60.0%)	0.075
With halo sign	19/121 (15.7%)	6/65 (9.2%)	8/65 (12.3%)	2/23 (8.7%)	4/9 (44.4%)	2/13 (15.4%)	3/9 (33.3%)	3/5 (60.0%)	0.008
With cavitation	66/121 (54.6%)	28/65 (43.1%)	18/65 (27.7%)	10/23 (43.5%)	0/9	2/13 (15.4%)	2/9 (22.2%)	0/5	$<10^{-3}$
Other signs	17/121 (14.1%)	9/65 (13.9%)	14/65 (21.5%)	8/23 (34.8%)	4/9 (44.4%)	3/13 (23.1%)	1/9 (11.1%)	2/5 (40.0%)	0.075
Serum positive for galactomannan detection, No. 2 positive sera/No. 2 sera tested	92/134 (68.7%)	56/81 (69.1%)	27/67 (40.3%)	8/31 (25.8%)	4/8 (50%)	4/11 (36.4%)	0/5	6/8 (75%)	$<10^{-3}$
Direct examination, No. positive/No. tested (%)	46/95 (48.4%)	30/66 (45.5%)	40/76 (52.6%)	23/34 (67.7%)	13/17 (76.5%)	14/18 (77.8%)	7/9 (77.8%)	9/10 (90%)	0.005
Positive culture, No. positive/No. tested (%)	50/95 (52.6%)	45/66 (68.2%)	67/76 (88.2%)	32/34 (94.1%)	15/17 (88.2%)	18/18 (100%)	9/9 (100%)	10/10 (100%)	$<10^{-3}$

	Acute leukaemia	Allogeneic HSCT	Chronic lympho-proliferative disorders	Solid organ transplantation	Solid tumours	Systemic inflammatory diseases	Chronic respiratory diseases	Others	p
Antifungal treatment, No. of patients treated	134	82	69	34	15	17	7	9	0.501
Voriconazole alone	74	31	44	14	11	7	5	4	
Caspofungin alone	16	14	10	6	2	2	0	0	
L-AmB alone	7	8	4	4	0	3	1	1	
Voriconazole + Caspofungin	10	9	2	4	0	0	0	3	
Voriconazole + L-AmB	4	4	3	2	0	1	0	0	
Caspofungin + L-AmB	8	4	3	1	0	1	0	0	
Others[b]	15	12	3	3	2	3	1	1	
Death within 90 days	51/135 (37.8%)	47/84 (56.0%)	35/83 (42.2%)	10/34 (29.4%)	10/15 (66.7%)	10/18 (55.6%)	4/9 (44.4%)	7/10 (70%)	0.019

L-AmB, lipid formulation of amphotericin B.

[a]The comparisons are carried out among the eight groups by use of the χ^2 test or Fisher's exact test for categorical variables, and the t-test for continuous variables.

[b]Others included amphotericin B deoxycholate (n = 16), posaconazole (n = 7), itraconazole (n = 3) alone or in combination with two or three drugs including voriconazole (six cases), caspofungin (seven cases) or L-AmB (three cases).

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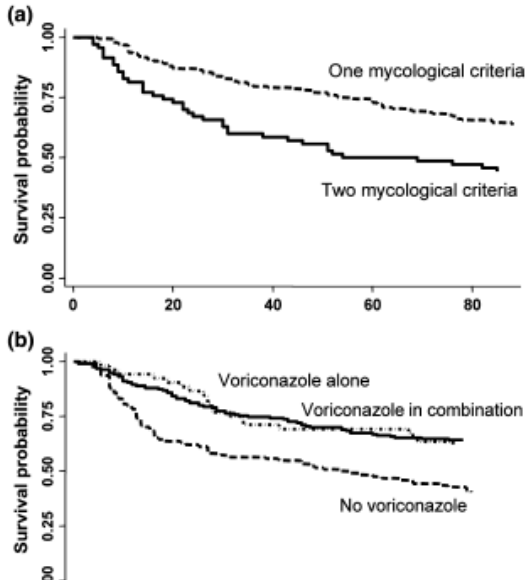


Independent factors related to morlality: age, 2GMag+ and + culture, CNS involvement, pleural effusion

Decreased mortality:

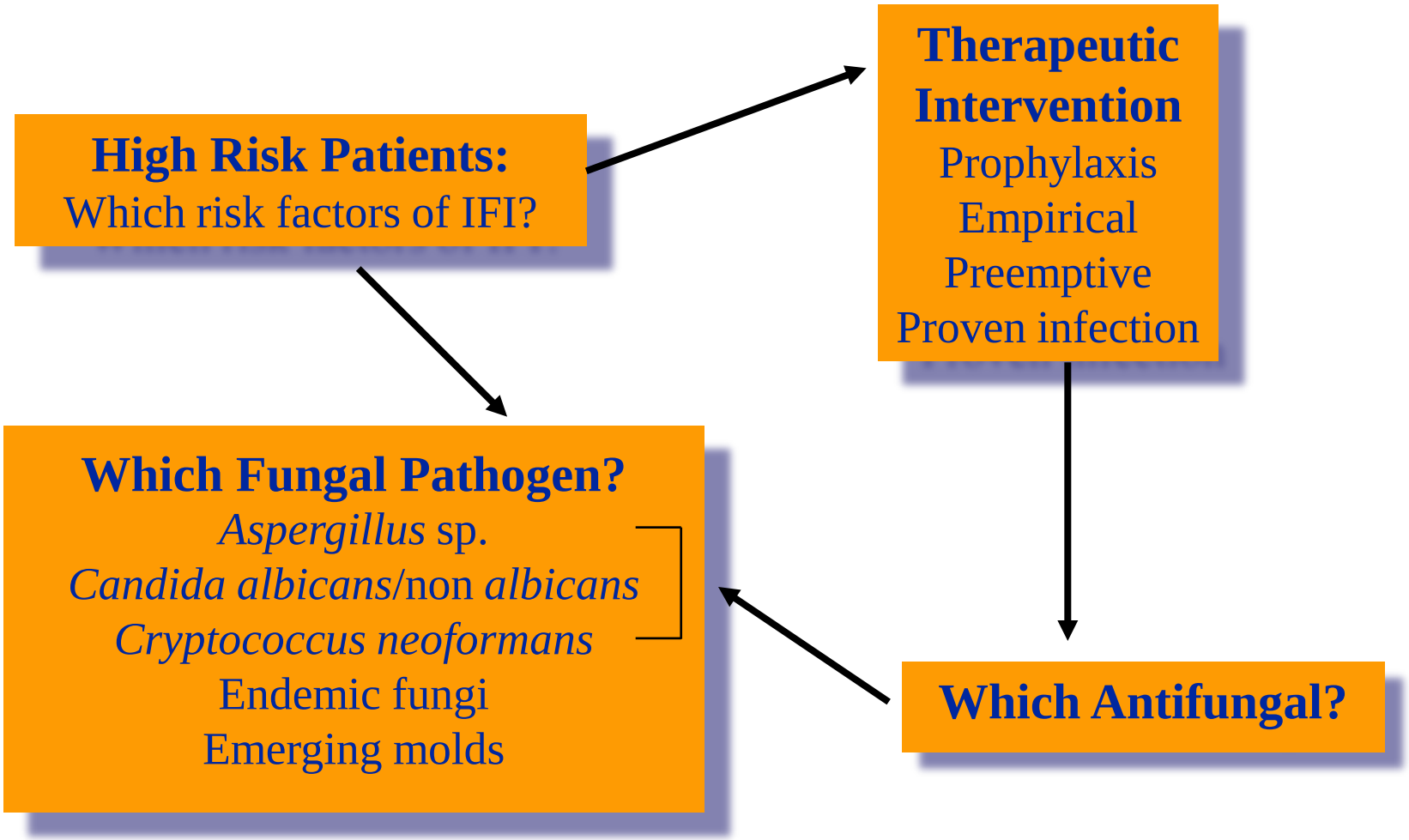
- *Presence of nodule and voriconazole use*

12w. Mortality allo-HSCT 56%,AML 37.8%.

TABLE 3. Parameters associated with deaths within 90 days after the diagnosis of IA for the 388/393 adult patients for whom the outcome was available

	Univariate analysis			Multivariate analysis	
Parameters	No. deaths (n = 214)	Deaths before day 90 (n = 174)	p	OR (95% CI)	p
Gender male	135/214 (63.1%)	106/174 (60.9%)	0.675		
Median age (IC 95%)	52.5 (50.5–54.5)	55.7 (53.5–58.0)	0.034	1.02 (1.00–1.03)	0.034
Underlying risk factors					
Acute leukaemia	84 (38.3%)	51 (29.3%)	0.018		
Allogeneic graft	37 (17.3%)	47 (27.0%)			
Lymphoid disorders	48 (22.4%)	35 (20.1%)			
Solid organ transplantation	24 (11.2%)	10 (5.8%)			
Solid tumours	5 (2.3%)	10 (5.8%)			
Systemic	8 (3.7%)	10 (5.8%)			
Chronic respiratory	5 (2.3%)	4 (2.3%)			
Others	3 (1.4%)	7 (4.0%)			
Positive culture and positive galactomannan on ≥2 serum samples	29/150 (19.3%)	39/109 (35.8%)	0.004	1.72 (1.07–2.74)	0.023
Central nervous system involvement	10/214 (4.7%)	19/174 (10.9%)		2.01 (1.04–3.90)	0.039
Pleural effusion	34/189 (18.0%)	55/132 (41.7%)	$<10^{-3}$	2.38 (1.53–3.70)	$<10^{-3}$
Presence of nodule, halo sign and/or cavitation	155/197 (78.7%)	97/164 (59.2%)	$<10^{-3}$		
Initial antifungal treatment including voriconazole	150/198 (75.8%)	89/164 (54.3%)	$<10^{-3}$	0.53 (0.34–0.82)	0.005

Decisive Moments in Management of Patients with IFI



Adapted O. Lortholary

Antifungal spectrum

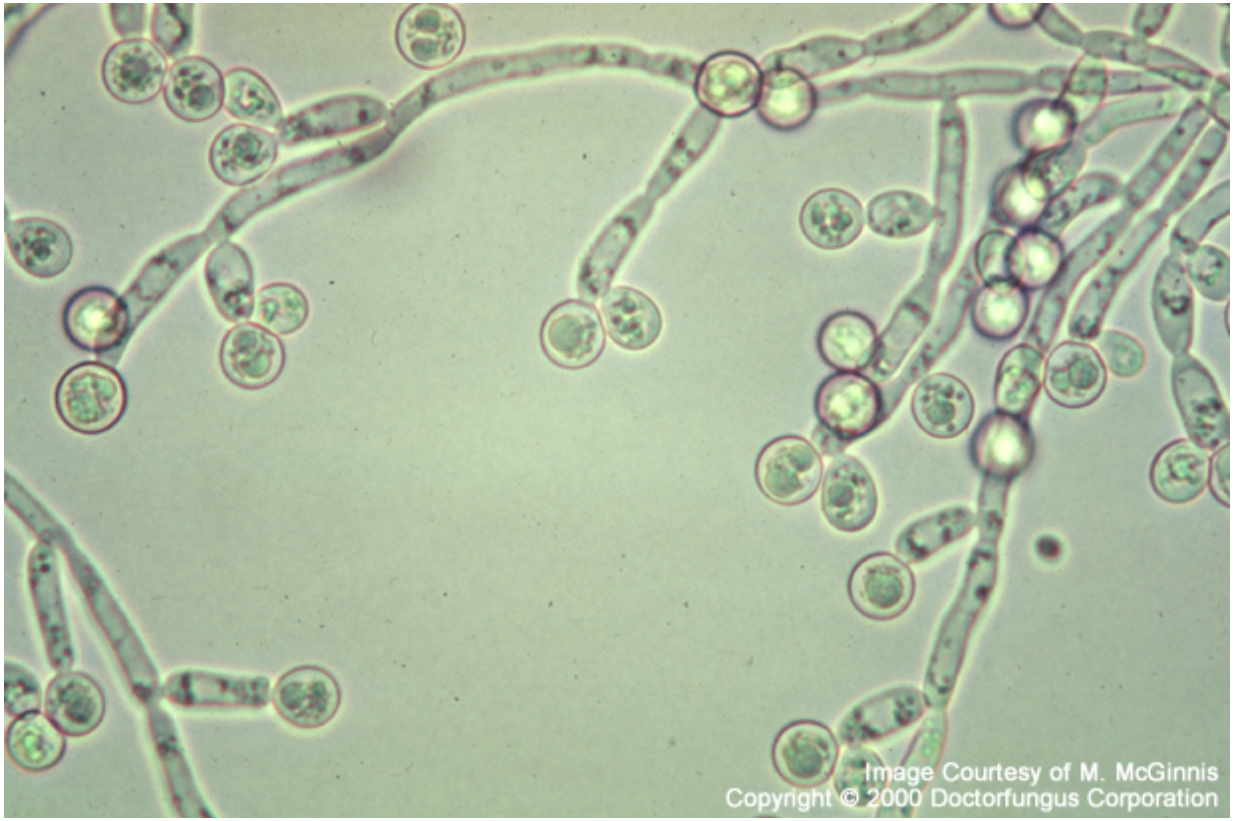
	Polyenes	*Fluco*	*Itraco*	*Vorico*	*Posaco*	*Candins*
C albicans	+	+	+	+	+	+
C krusei	+	-	-	+	+	+
C glabrata	+	-	-	+	+	+
Cryptococcus	+	+	+	+	+	-
Aspergillus	+	-	+	+	+	+
Zygomycetes	+	-	-	-	+	-
Fusarium	+/-	-	-	+/-	+/-	-

Antifungals pharmacodynamics

Class	Conc dep	Time dep	PAE	*Aspergillus*	*Candida*
Triazoles	/	AUC/MIC	long	**Cidal**	**Static**
Polyenes	C_{max}/MIC	/	long	**Cidal**	**Cidal**
Echinocandins	C_{max}/MIC	/	long	**Static**	**Cidal**

**Effect on biofilm: echinocandins>>liposomal amphotericine B

Factors to keep in mind before choosing an antifungal drug



Invasive candidiasis

Table 2. Summary of recommendations for the treatment of candidiasis.

Condition or treatment group	Therapy		
	Primary	Alternative	Comments
Candidemia			
Nonneutropenic adults	Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily or an echinocandin[a] (A-I). For species-specific recommendations, see text.	LFAmB 3–5 mg/kg daily; or AmB-d 0.5–1 mg/kg daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses, then 200 mg (3 mg/kg) bid (A-I)	Choose an echinocandin for moderately severe to severe illness and for patients with recent azole exposure. Transition to fluconazole after initial echinocandin is appropriate in many cases. Remove all intravascular catheters, if possible. Treat 14 days after first negative blood culture result and resolution of signs and symptoms associated with candidemia. Ophthalmological examination recommended for all patients.
Neutropenic patients	An echinocandin[a] or LFAmB 3–5 mg/kg daily (A-II). For species-specific recommendations, see text.	Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses then 200 mg (3 mg/kg) bid (B-III)	An echinocandin or LFAmB is preferred for most patients. Fluconazole is recommended for patients without recent azole exposure and who are not critically ill. Voriconazole is recommended when additional coverage for molds is desired. Intravascular catheter removal is advised but is controversial.

CID 2009; 48 (1 mars)

Targeted Treatment of Candidaemia – 1 of 2

ECCMID GUIDELINES

Recommendation	SoR	QoE	Reference	Comment
Amphotericin B, deoxycholate	D	I	Anaissie CID 1996 Rex NEJM 1994 Philips EJCMID 1995 Mora-Duarte NEJM 2002 Ullmann CID 2006 Bates CID 2001	
Amphotericin B, liposomal	B	I	Kuse Lancet 2007 Dupont Crit Care 2009	Similar efficacy as micafungin higher toxicity than micafungin
Amphotericin B, lipid complex	C	II_a	Anaissie ICAAC 1995 (abstract) Ito CID 2005	
Amphotericin B, colloidal dispersion	D	II	Noskin CID 1998	Mostly immunocompromised patients (HCT, haem/onc or SOT) rather than ICU patients
Anidulafungin	A	I	Reboli NEJM 2007	Broad spectrum, resistance rare, local epidemiology, *C. parapsilosis, C. krusei*, Fungicidal Safety profile less drug-drug interactions than caspofungin
Caspofungin	A	I	Mora-Duarte NEJM 2002 Pappas CID 2007	
Micafungin	A	I	Kuse Lancet 2007 Pappas CID 2007	direct quote of EMA warning refer to legal department of ESCMID

HCT: haematopoietic stem cell transplantation, SOT: solid organ transplantation

http://www.escmid.org

Targeted Treatment of Candidaemia – 2 of 2

Recommendation	SoR	QoE	Reference	Comment
Fluconazole	B	I	Anaissie CID 1996 Rex NEJM 1994 Rex CID 2003 Philips EJCMID 1995 Reboli NEJM 2007 Tuil CCM 2003 (abstract) Abele-Horn Infect 1996 Leroy CCM 2009 Gafter-Gvili Mayo Clin Proc 2008	Limited spectrum Inferiority to anidulafungin (rem. especially in the subgroup with high APACHE scores), C. parapsilosis
Itraconazole	D	II_a	Tuil CCM 2003 (abstract)	
Posaconazole	D	III	No reference found	PO only
Voriconazole	B	I	Kullberg Lancet 2005 Ostrosky EJCMID 2003 Perfect CID 2003	Limited spectrum compared to echinocandins Drug-drug interactions IV in renal impairment; Need for TDM
Efungumab + lipid-associated amphotericin B	D	II	Pachl CID 2006	
Amphotericin B deoxycholate + fluconazole	D	I	Rex CID 2003	Increased risk of toxicity in ICU patients No survival benefit Efficacious, but toxic
Amphotericin B deoxycholate + 5-fluorocytosine	D	II	Abele-Horn Infect 1996	
other two-drug combinations	D	III	Leroy CCM 2009	

Treatment (Dose) of invasive disease/candidemia in Neutropenia/HCT
Intervention: success incl survival

Agent	Rec	Duration	References
Fluconazole	BII_t		Rex NEJM 1994, Anaissie CID 1996, Anaisssie Am J Med 1996 (Caution regarding resistance) Because of old data, FLUC should rather be considered as a step-down treatment option.
Itraconazole	DIII		Only one abstract in non-neutropenics published 2003 in CCM (O. Tuil & Y. Cohen)
Posaconazole	DIII		One case report in non neutropenic (Anstead GM Med Mycol 2006)
Voriconazole *	CII_t		Kullberg Lancet 2005, Ostrosky-Zeichner EurJCMID 2003
Anidulafungin	BII_t		Riboli NEJM 2007 (<3% neutropenia)
Micafungin	AII_t		Kuse Lancet 2007, Pappas CID 2007 (~10%)
Caspofungin	AII_t		Murate Duarte NEJM 2002, Pappas CID 2007 (~10%)
Liposomal Amphotericin B	BII_t		Kuse Lancet 2007, DuPont CC 2009 (higher tox. than Micafungin)
AmB lipid complex	CIIa		Anaissie ICAAC 2005, Ito CID 2005
AmB colloid dispersion	CIII		Noskin CID 1998
Deoxycholate Amphotericin B +	DII_t		Anaissie CID 1996, Muarte Duarte NEJM 2002, Walsh NEJM 1999, Ullmann CID 2006

As per study design: at least14 days after last BC positivity, recovery from severe neutropenia and resolution of clinical signs including exclusion of endocarditis and endophtalmitis by appropriate examination (Rex NEJM 1994 BII_t,)

Treatment (Combinations) of invasive disease/candidemia in Neutropenia
Intervention: success incl survival

Agent	Rec	Duration	References
Deoxycholate amphotericin B & 5-fluorocytosine	DIII	N/A	Too toxic and erratic PK
Deoxycholate amphotericin B & fluconazole (sequential therapy only)	CII_t	N/A	Rex CID 2003 (study regarding non-antagonism, value in comparison to safer echinocandins unclear, therefore only an option), Kullberg et al (Lancet 2005) studied voriconazole vs. sequential D-AmB and fluconazole No difference in main endpoints; more toxicity in the AmB arm, despite only 3 days AmB median.
Efungumab & lipid formulation of amphotericin	DIII	N/A	Pachl J et al. 2006, flaws in the design of study

Other combinations not studied; expert opinion say combination might be useful in severe deep-seated infections (abdominal infection, CNS, endocarditis) CIII

Documento de consenso

Recomendaciones sobre el tratamiento de la candidiasis invasiva y otras infecciones por levaduras de la Sociedad Española de Enfermedades y Microbiología Clínica (SEIMC). Actualización 2011

Enferm Infecc Microbiol Clin. 2011;29(5):345–361

José María Aguado[a,*], Isabel Ruiz-Camps[b], Patricia Muñoz[c], José Mensa[d], Benito Almirante[b], Lourdes Vázquez[e], Montserrat Rovira[f], Pilar Martín-Dávila[g], Asunción Moreno[d], Francisco Álvarez-Lerma[h], Cristóbal León[i], Luis Madero[j], Jesús Ruiz-Contreras[k], Jesús Fortún[g] y Manuel Cuenca-Estrella[l], Grupo de Estudio de Micología Médica de la SEIMC (GEMICOMED)

Forma	Elección	Alternativa	Comentarios*
Candidemia en neutropénicos	- **CAS** (70 mg de carga y 50 mg/d) o MIC (100 mg/d) **(A-II)** o - **MIC** (100mg/d) **(A-II)** o - **AND** (200 mg de carga y después 100 mg/d) **(A-III)**. o - **AmB-L** (3 mg/Kg/d) **(A-II)**	-FLU (800 mg y pasar a 400 mg/d **(A-II)** - VOR (6 mg/kg/12h durante un día y pasar a 3 mg/Kg/12h) **(A-II)**	-Candina si azoles previos o enfermedad severa. -Fluconazol si no se ha utilizado un azol previamente. -Retirada CVC controvertida - Pasar de candina a fluconazol si es posible* - Tratar 14 días después cultivo negativo y resolución síntomas - Realizar fondo de ojo
Tratamiento empírico en neutropénicos	- AmB-L (3-5 mg/Kg/d) **(A-I)** - CAS (70 mg y después 50 mg) **(A-I)** - VOR (6 mg/kg/12h durante un día y pasar a 3 mg/Kg/12h) **(B-I)**	-FLU (800 mg y pasar a 400 mg/d **(B-I)** - ITRA 200 mg (3mg/Kg) **(B-I)** - MIC (100 mg/d) **(B-II)**	-Si azoles previos o pacientes inestables mejor candina. - Duración no determinada
Candidiasis crónica diseminada	-FLU 400 mg/d en pacientes estables **(A-III)** - AmB-L (3-5 mg/Kg/d) **(A-III)** o - AmB 0.5-0.7 mg/Kg/d si inestable y pasar después a FLU **(A-III)**	Candina y pasar después a FLU **(B-III)**	-Paso a tratamiento oral tras 1-2 semanas de endovenoso - Duración del tratamiento no resuelta, mantenerlo si quimioterapia o TPH

Para *C. glabrata* se prefiere una candina (BIII) o AmB-L (3 mg/Kg), (B-III). Para *C. parapsilosis,* fluconazol (BIII) o AmB-L (BIII). Para *C. krusei*, se recomienda una candina, AmB-L o voriconazol (B-III).

http://www.iimicrobiologie.com

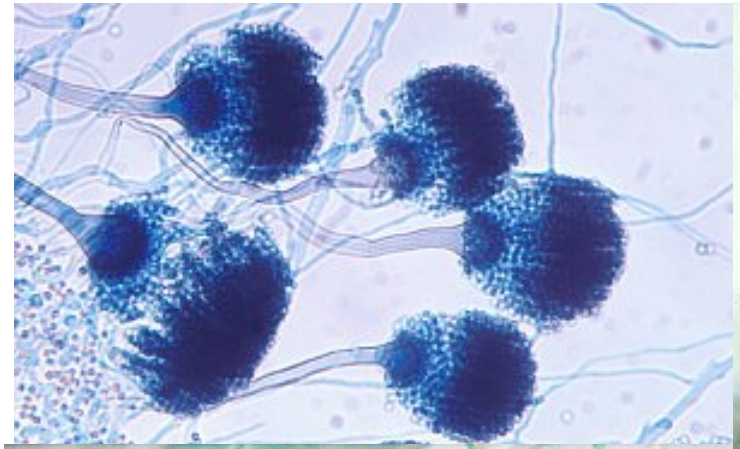
Urinary Tract Infection

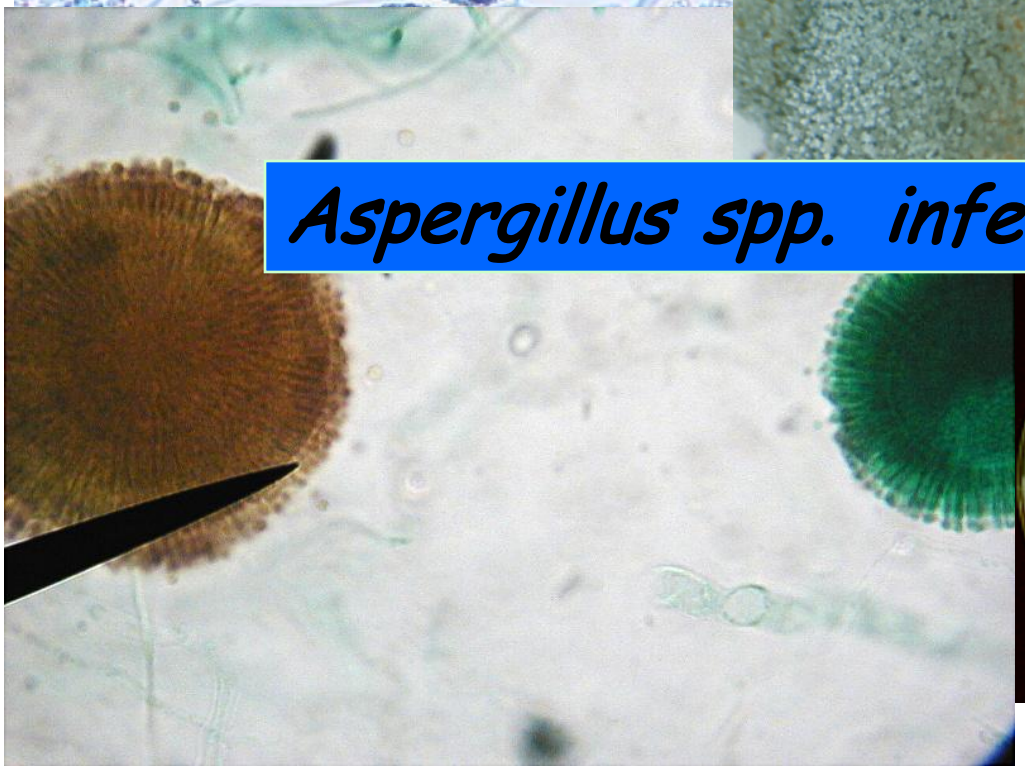
Population	Intention	Intervention	SoR	QoE	Reference
Asymptomatic	Eliminate candiduria	None	A	III	Revankar 2010, Kauffman CID 2000
		Fluconazole 200mg/d d1-d14*	C	I	Sobel CID 2000, Kauffman CID 2000
		Removal of urinary catheter	B	I	Sobel CID 2000
		Amphotericin B bladder irrigation	C	II_r	Tuon IJID 2009, Kauffman CID 2000
Pyelonephritis	Cure	Caspofungin 70/50md/d for 9-28d	C	III	Sobel CID 2007
		Fluconazole +/- 5-fluorocytosine**	A	III	No reference
		Amphotericin B deoxycholate +/- 5-fluorocytosine	A	III	No reference
Cystitis	Cure	Fluconazole	A	III	Sobel CID 2000, Kauffman CID 2000
		Amphotericin B +/- 5-fluorocytosine	B	III	Sobel CID 2000, Kauffman CID 2000
Fungus balls (bezoars)	Cure	Surgical intervention	A	III	Bartone J Urol 1988, Shih Urol 2005

*In pre-operative patients treatment is indicated to suppress candiduria. **if species is susceptible.

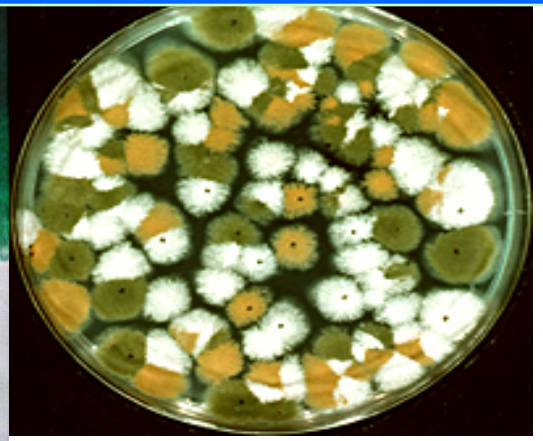
General considerations

- In hematological setting there are few cases of Candidiasis due to the use of fluconazole in prophylaxis
- It is important to know epidemiological data of each center. And deescalate if its possible
  - If *C. glabrata* is isolated use a candin (BIII) or L-AmB (3 mg/Kg) (B-III).
  - If *C. parapsilosis,* FLU is the treatment of choice (BIII) or L-AmB as alternative (BIII).
  - If *C. krusei*, use a candin, L-AmB or VOR (B-III).
- At the moment echinocandins are the best treatment to begin a treatment in candidemia before knowing the species.
- Keep in mind effect on the biofilm





Aspergillus spp. infections

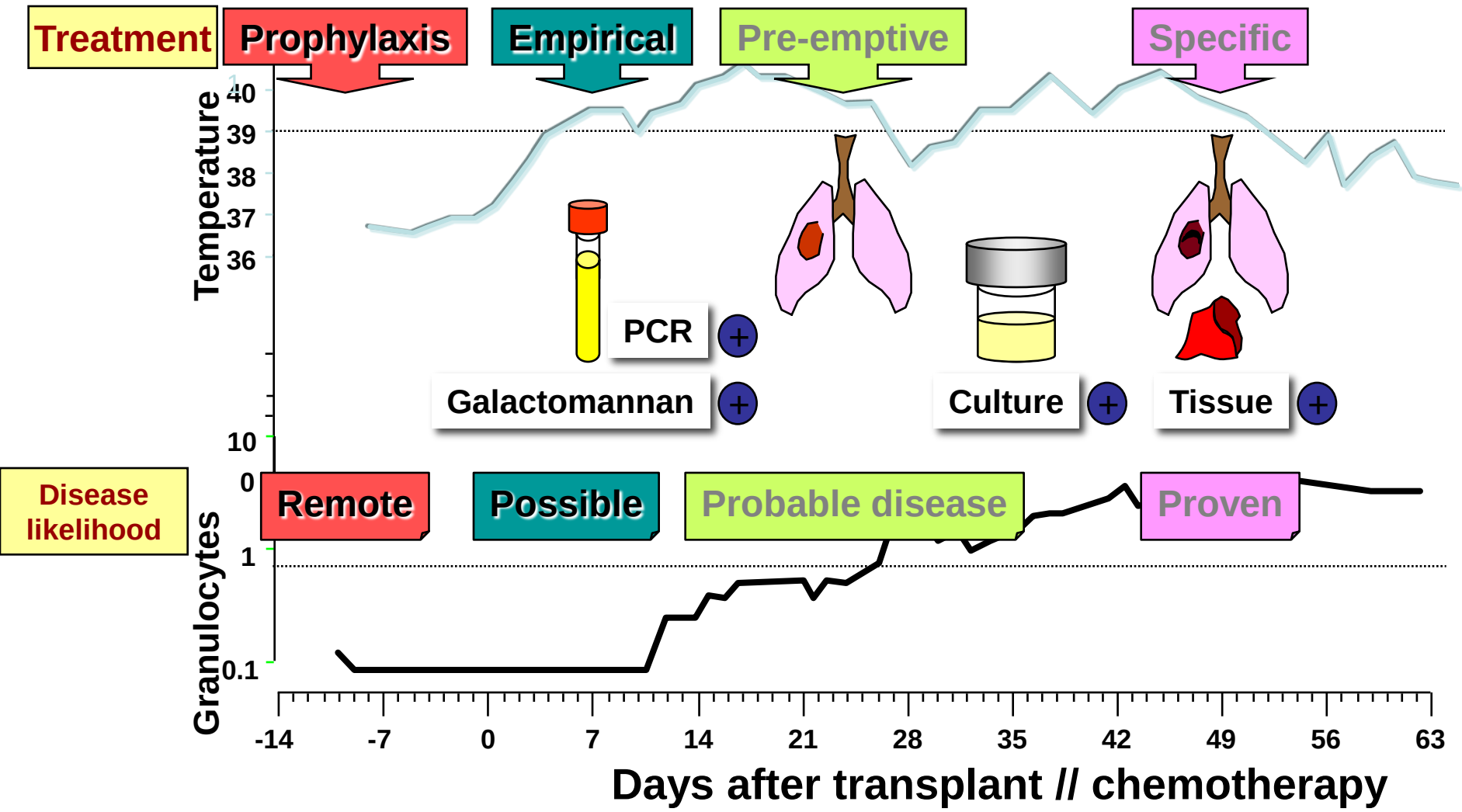


	Aspergillosis	Fusariosis	Zygomycosis	Scedosporiosis	Phaeohy-phomycosis
Clinical picture	Fever, cough, pleuritic chest pain	Similar to aspergillosis + metastatic skin lesions (70%)	Similar to aspergillosis	Similar to aspergillosis; *S. prolificans*: metastatic skin lesions	Similar to aspergillosis
Radiologic pattern	Angioinvasion, nodules +/- halo sign	Similar to aspergillosis	Similar to aspergillosis, >10 nodules and pleural effusion more frequent	Similar to aspergillosis	Similar to aspergillosis
Blood culture	Negative	Positive (60%)	Negative	*S. prolificans*: positive (70%)	May be positive
Serum galactomannan	Sensitivity 70%; specificity 92%. Good at ruling out the diagnosis	Positive results reported in *F. solani* and *F. oxysporum*	Negative	Negative	Positive results reported with some species
Serum 1,3-beta-D-glucan	Positive	Positive	Negative	May be positive	May be positive

Marcia Garnica and Marcio Nucci

É. Azoulay (ed.), *Pulmonary Involvement in Patients with Hematological Malignancies*,
DOI: 10.1007/978-3-642-15742-4_27, © Springer-Verlag Berlin Heidelberg 2011

THERAPEUTIC STRATEGIES



Created by P.Donnelly

Anticipated treatment

- High resolution CT
- Galactomanan
- Beta-glucan
- PCR

Precocious diagnosis

⇓

Less tisular invasion

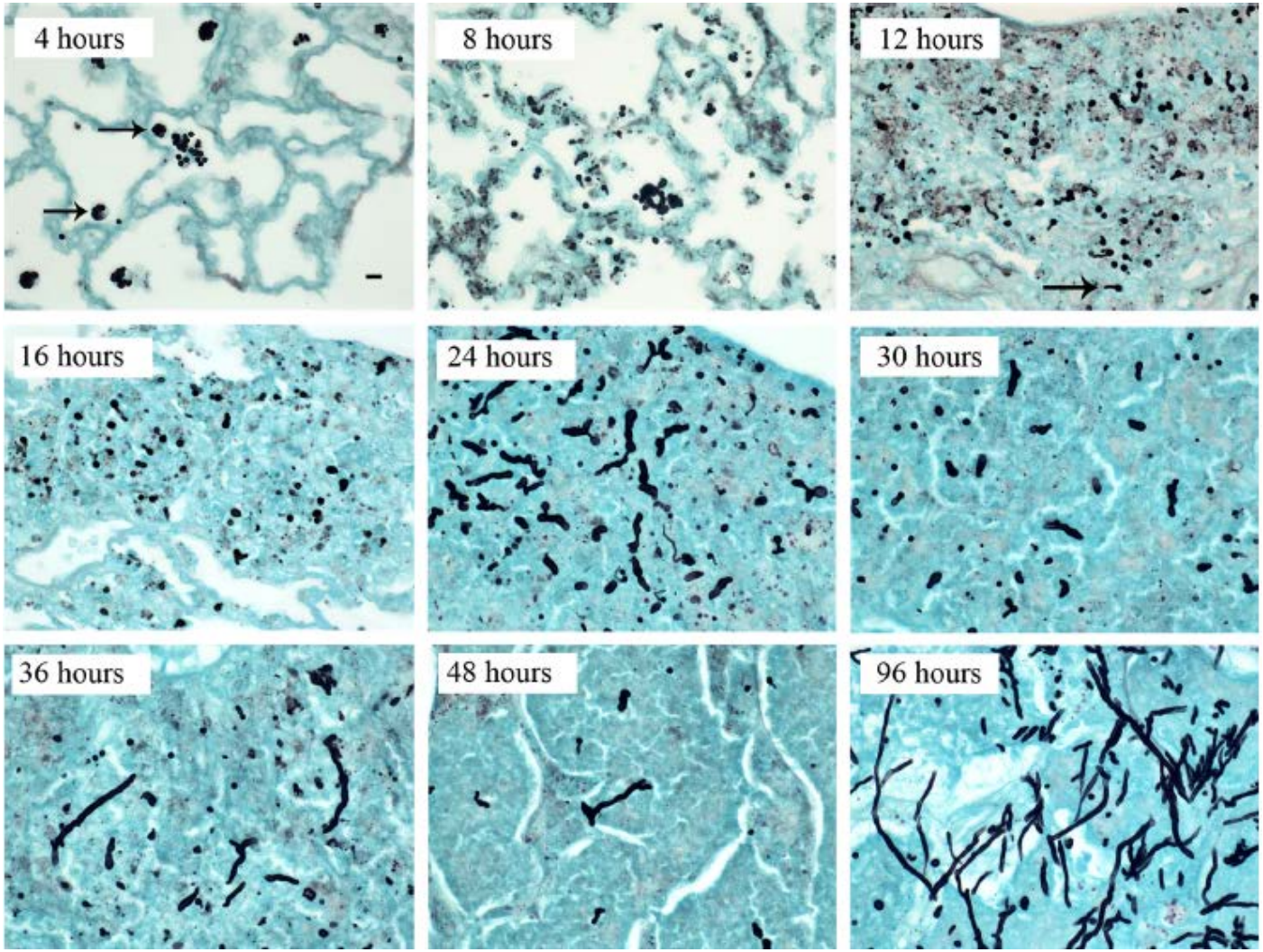
⇓

Higher antifungal efficacy

The Initial 96 Hours of Invasive Pulmonary Aspergillosis: Histopathology, Comparative Kinetics of Galactomannan and (1→3)-β-D-Glucan, and Consequences of Delayed Antifungal Therapy[▽]

William W. Hope,[1,2]* Vidmantas Petraitis,[2,3,4] Ruta Petraitiene,[2,3,4] Tamarra Aghamolla,[3] John Bacher,[5] and Thomas J. Walsh[2,4]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2010, p. 4879–4886



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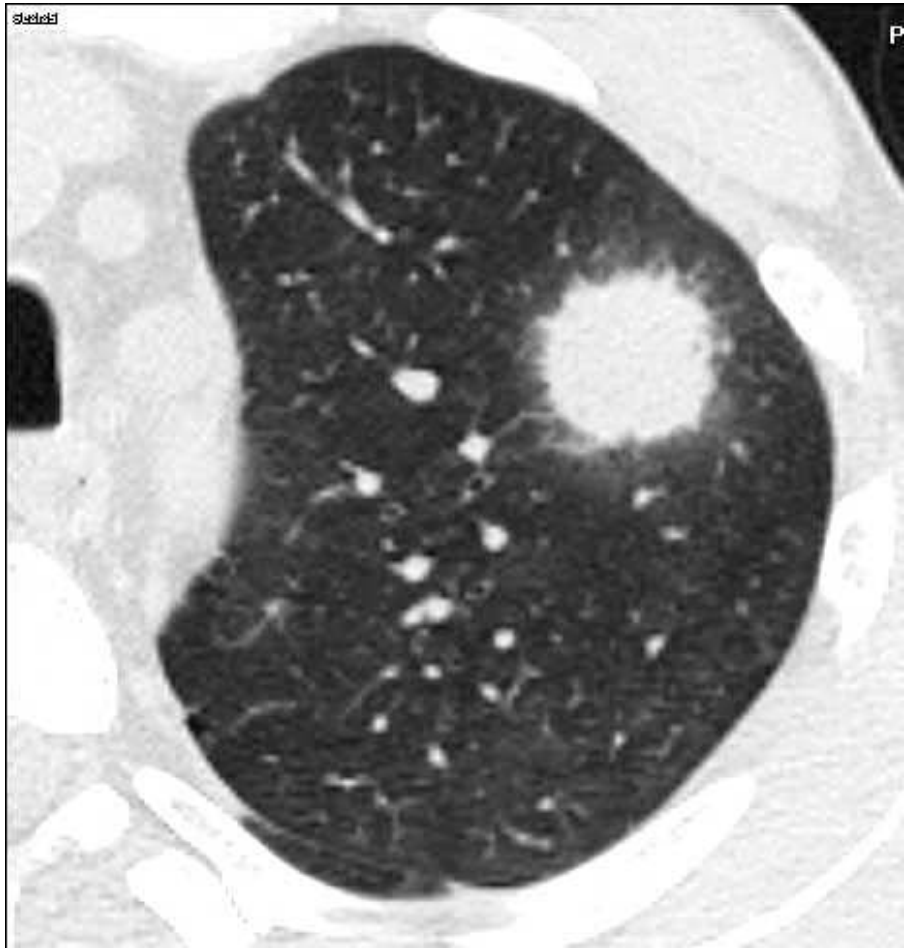
Halo sign



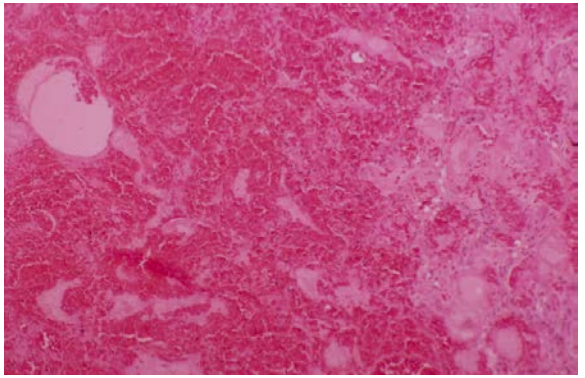


Table 5. Recommendation and quality of evidence of IDSA, ECIL, DGHO and Australian guidelines in the adult hematology/oncology setting for antifungal agents in first-line therapy of invasive aspergillosis.

	Primary Therapy			
	ECIL 2009 §	IDSA 2008	DGHO 2008	Australia 2008
Voriconazole	AI	AI	AI	Recommended
L-AmB	BI	AI	AII	Alternative
ABLC	BII	–	–	–
Caspofungin	CII	–	–	–
Itraconazole	CIII	–	–	–
d-AmB	DI	–	EI	Alternative
Posaconazole	–	–	–	–
Micafungin				–
Combination therapy*	DIII	BII	–	–
Surgery	CIII	BIII	BIII	–

ECIL: European Conference on Infections in Leukemia; IDSA: Infectious Diseases Society of America; DGHO: German Society of Hematology and Oncology
§Update ECIL-3 2009
*Caspofungin + L-AmB or Caspofungin + Voriconazole; no data about AmB (any formulation) + azole
– not reported for primary therapy

Strength of recommendation

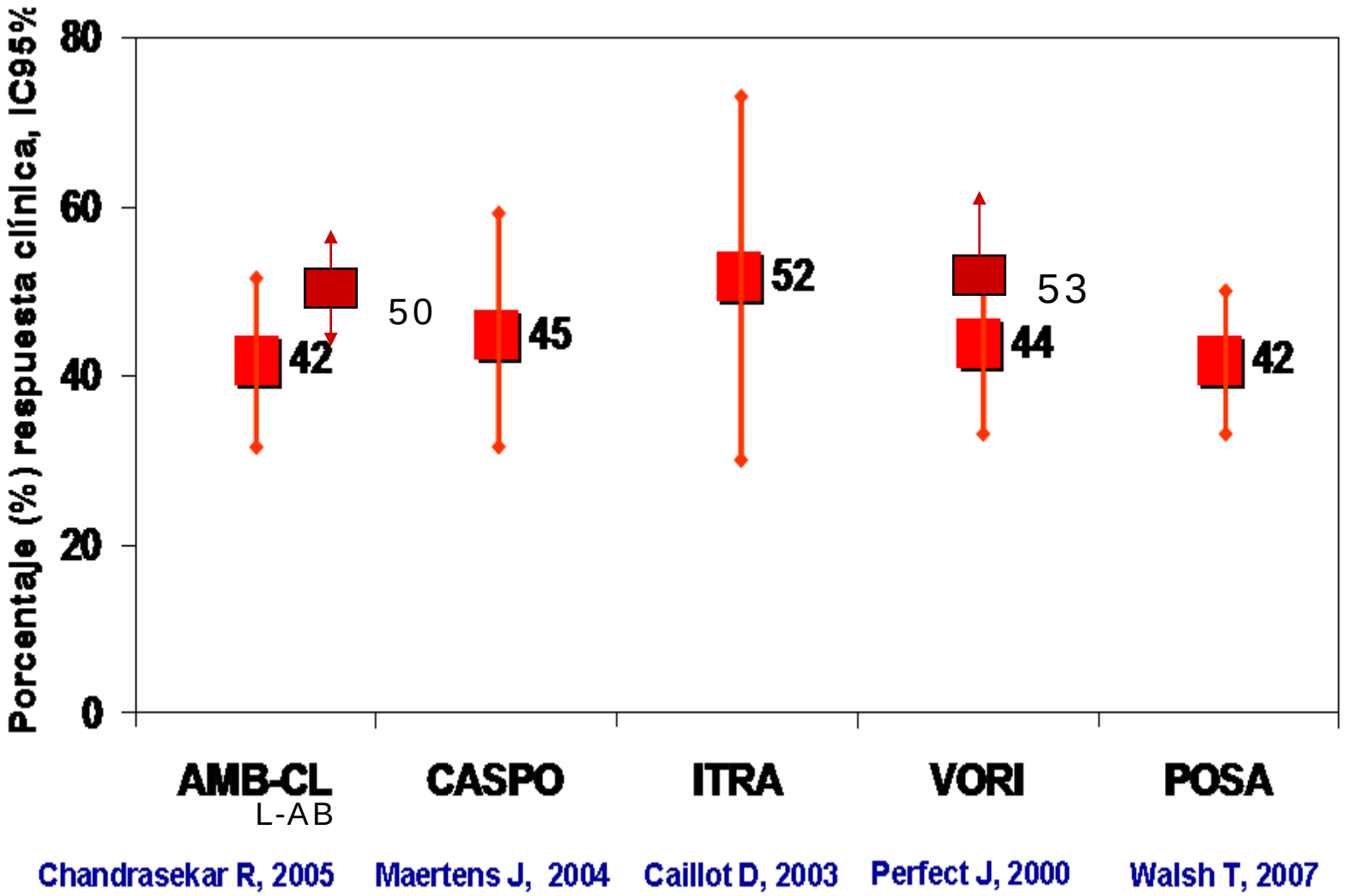
A Good evidence to support a recommendation for use
B Moderate evidence to support a recommendation for use
C Poor evidence to support a recommendation for use
D Moderate evidence to support a recommendation against use
E Good evidence to support a recommendation against use

Quality of evidence

I Evidence from at least 1 properly randomized, controlled trial
II Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time series; or from dramatic results of uncontrolled experiments
III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
N.B: IDSA and DGHO guidelines, using the same criteria, censored strength of recommendation D and E

http://www.infectiologie.org.tn

IA: response to first line therapy



IA: efficacy of combinations in first line and rescue therapy

Reference	Treatments	Study Design	Population (n)	Overall Response (%)	Overall Survival (%)
Kontoyiannis et al.[50]	Caspo+L-AmB	Retrospective	48	42	–
Aliff et al.[51]	Caspo+L-AmB	Retrospective	30	60	–
Marr et al.[52]	Vori Caspo+Vori	Prospective	31 63		
Maertens et al.[53]	Caspo+1 other mold-active AF agent	Prospective	16 Caspo+Amb[a] 37 Caspo+triazoles[b]	49	55
Caillot et al.[54]	L-AmB+Caspo High doses L-AmB	Prospective	15 15	67 27	100 80
Kontoyiannis et al.[55]	L-AmB Itra+L-AmB	Retrospective	101 11	10 0	66 64
Denning et al.[56]	Mica alone Mica combi	Prospective	34[c] 191[d]	44 34	42
Raad et al.[57]	Posa L-AmB L-AmB +Caspo	Retrospective	53 52 38	40 8 11	60 35 32
Lellek et al.[58]	Caspo+posa	Retrospective	31	77	87

[a] 14 HM+1 solid tumor+1 corticosteroids.
[b] 31 HM+1 solid organ transplant+5 corticosteroids.
[c] 23 HM+5 solid organ transplants+1 HIV/AIDS+5 others.
[d] 161 HM+6 solid tumors+8 solid organ transplants+3 COPD+5 HIV/AIDS+8 others.

CLINICAL PROTOCOL

A PROSPECTIVE, RANDOMIZED TRIAL COMPARING THE EFFICACY OF ANIDULAFUNGIN AND VORICONAZOLE IN COMBINATION TO THAT OF VORICONAZOLE ALONE WHEN USED FOR PRIMARY THERAPY OF PROVEN OR PROBABLE INVASIVE ASPERGILLOSIS

PROVEN IA	PROBABLE IA	POSSIBLE IA
Histopathologic, cytopathologic, or direct microscopic examination of a needle aspiration or biopsy specimen showing hyphal forms with evidence of associated tissue damage (either microscopically or as an infiltrate or lesion by imaging) **OR** Recovery of *Aspergillus* species by culture from a sample obtained by a sterile procedure from a normally sterile and clinically or radiographically abnormal site consistent with an infectious disease process, excluding BAL, cranial sinus cavity, and urine	<u>One host factor</u> i.e. recent history of neutropenia, allogeneic HSCT, treatment with T-cell immune suppressants, prolonged corticosteroid use, inherited severe immunodeficiency **AND** <u>One clinical criterion</u> i.e. evidence of lower respiratory, tracheobronchial, sinonasal, ophthalmologic, or CNS disease **AND** <u>One microbiological criterion</u> i.e. cytology, direct microscopy, culture, detection of antigen or cell wall constituents (See Appendix for comprehensive list of criteria)	<u>One host factor</u> **AND** <u>One clinical criterion</u> (See Appendix for comprehensive list of criteria) **NOTE:** Subjects enrolled with possible IA will be required to have a proven or probable diagnosis established within 7 days of enrollment

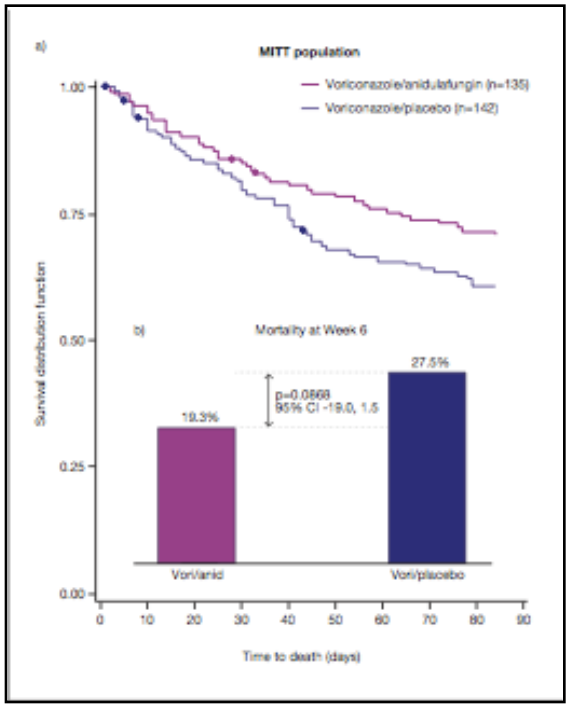
RANDOMIZATION

Week 1	Voriconazole IV bid + Blinded Anidulafungin placebo IV qd	Voriconazole IV bid + Blinded Anidulafungin IV qd
	After an initial week of IV voriconazole, the investigator has the option to switch the patient to PO voriconazole	
Week 2	Voriconazole IV or PO bid + Blinded Anidulafungin placebo IV qd	Voriconazole IV or PO bid + Blinded Anidulafungin IV qd
	The investigator will determine whether the patient should continue on combination therapy or switch to monotherapy for weeks 3 and 4	
Weeks 3 & 4	Voriconazole IV or PO bid + Blinded Anidulafungin placebo IV qd **OR** Voriconazole IV or PO bid monotherapy*	Voriconazole IV or PO bid + Blinded Anidulafungin IV qd **OR** Voriconazole IV or PO bid monotherapy *

**Patients who are switched to voriconazole monotherapy must demonstrate improvement in presenting clinical signs and symptoms and stable or improved radiographic response.*

For the final two weeks of treatment, all patients will receive open-label voriconazole monotherapy. Patients who have not responded to treatment by this time should be placed on alternative therapy.

Weeks 5 & 6	Voriconazole IV or PO bid monotherapy	Voriconazole IV or PO bid monotherapy



Reduction in mortality at 6-12w

No primary end-point

PROGRESSION?

Subjective

Dynamic CT evolution

Immune reconstitution Syndrome

The Impact of the Host on Fungal Infections

John R. Perfect, MD

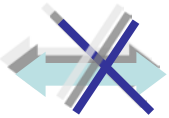
The American Journal of Medicine (2012) 125, S39–S51

THE AMERICAN JOURNAL of MEDICINE®

Immune reconstitution inflammatory syndrome (IRIS)

- New appearance or worsening of clinical or radiologic manifestations consistent with an inflammatory process.
- Symptoms occurring during receipt of appropriate antifungal therapy that cannot be explained by a newly acquired infection.
- Negative results of cultures or stable or reduced biomarkers for the initial fungal pathogen during the diagnostic workup for the inflammatory process.

- HIV receiving ART
- SOT
- Neutropenic host
- Pregnant women
- Anti-TNFa

Th1/Th17  Th2/T_{reg}

Histoplasmosis, IA, cryptococcosis, candidiasis, pneumocystosis

No useful biomarkers or test for diagnosis

PROGRESSION?

Subjective

Dynamic CT evolution

Immune reconstitution Syndrome

Biomarker?

Monitorize AF levels

Low < 1 µg/mL

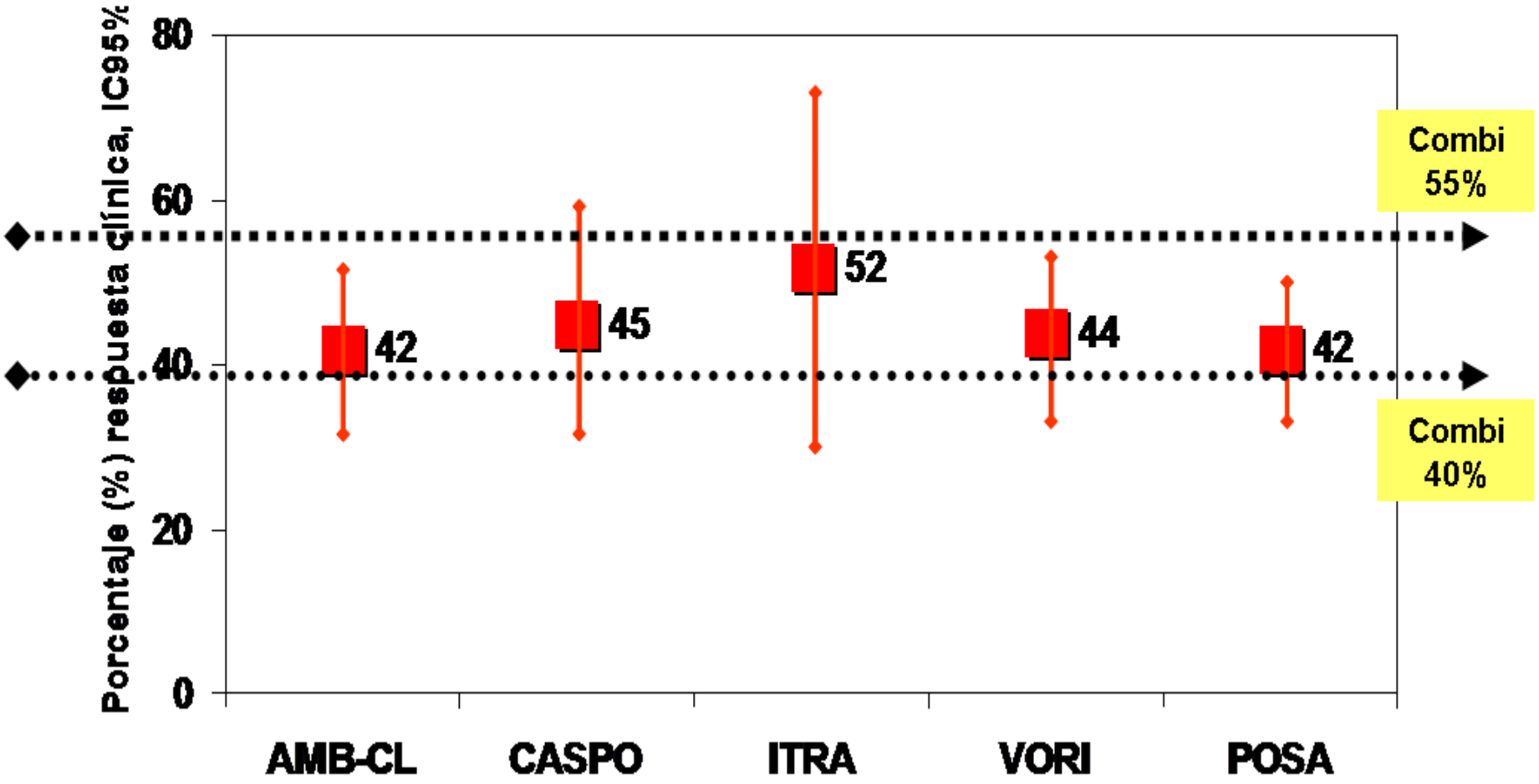
Increase the dose

Add a candin

• Change to a rescue treatment (CAS/Ambisome/Posa o combined)

•Keep in mind another fungi

Invasive aspergillosis: response to rescue treatment in immunocompromised patients



Factors Associated with Mortality in Transplant Patients with Invasive Aspergillosis

31.823 Tx/ 642 casos AI

John W. Baddley,[1,2] David R. Andes,[3] Kieren A. Marr,[4] Dimitrios P. Kontoyiannis,[6] Barbara D. Alexander,[8] Carol A. Kauffman,[9] Robert A. Oster,[1] Elias J. Anaissie,[10] Thomas J. Walsh,[5] Mindy G. Schuster,[11] John R. Wingard,[12] Thomas F. Patterson,[7] James I. Ito,[13] O. Dale Williams,[1] Tom Chiller,[14] Peter G. Pappas,[1] and the Transplant Associated Infection Surveillance Network

Clinical Infectious Diseases 2010; 50(12):1559–1567

Table 1. Characteristics of 415 Hematopoietic Stem Cell Transplant Patients with Invasive Aspergillosis (IA)

Characteristic	Total (n = 415)	Survivors[a] (n = 176)	Nonsurvivors (n = 239)	P[b]
Age, mean ± SD, years	46.9 ± 15.6	47.3 ± 16.9	46.6 ± 14.6	.68
Male sex	260/414 (62.8)	108/176 (61.4)	152/238 (63.9)	.60
White race	343/384 (89.3)	151/163 (92.6)	192/221 (86.9)	.07
Hematopoietic stem cell transplant				
Allogeneic	337/415 (81.2)	131/176 (74.4)	206/239 (86.1)	.002
Matched related[c]	168/337 (49.9)	71/131 (54.2)	97/206 (47.1)	.20
Autologous	78/415 (18.8)	45/176 (25.6)	33/239 (13.8)	
Myeloablative conditioning	288/415 (69.4)	117/176 (66.5)	171/239 (71.6)	.27
Neutropenia[d]	224/415 (54.0)	83/176 (47.1)	141/239 (59.0)	.017
Fever[e]	207/415 (49.9)	84/176 (47.7)	123/239 (51.5)	.45
Graft-versus-host disease[f]	135/337 (40)	48/131 (39)	87/206 (61.1)	.30
Cytomegalovirus disease[g]	104/415 (25.1)	34/176 (19.3)	70/39 (29.3)	.021
Renal insufficiency[h]	118/415 (28.4)	31/176 (17.6)	87/239 (36.4)	<.001
Hepatic insufficiency[i]	86/415 (20.8)	11/176 (6.3)	75/239 (31.4)	<.001
Malnutrition[j]	69/415 (16.6)	19/176 (10.8)	50/239 (20.9)	.006
Diabetes	116/415 (28.0)	43/176 (24.4)	73/239 (30.5)	.17
Early-onset IA[k]	147/401 (36.7)	70/174 (40.2)	77/227 (33.9)	.19
Proven IA (vs probable IA)	113/415 (27.2)	30/176 (17.1)	83/239 (34.7)	<.001
Aspergillus fumigatus	183/415 (44.1)	69/176 (39.2)	114/239 (47.7)	.085
Prednisone use[l]	134/415 (32.3)	64/176 (36.4)	70/239 (29.3)	.13
Methylprednisone use[l]	131/415 (31.6)	37/176 (21.0)	94/239 (39.3)	<.001
Site of IA				
Pulmonary	385/415 (92.8)	166/176 (94.3)	219/239 (91.6)	.29
Central nervous system	25/415 (6.0)	4/176 (2.3)	21/239 (8.8)	.006
Disseminated[m]	66/415 (15.9)	16/176 (9.1)	50/239 (20.9)	.001
Mould-active prophylaxis	115/415 (27.7)	47/176 (26.7)	68/239 (28.5)	.69
Antifungal therapy[n]				
Combination therapy[o]	100/348 (28.7)	41/151 (27.1)	59/197 (29.9)	.57
Voriconazole	158/348 (45.4)	81/151 (53.6)	77/197 (39.1)	.007
Caspofungin	143/348 (41.1)	58/151 (38.4)	85/197 (43.2)	.37
Amphotericin B formulation	144/348 (41.4)	50/151 (33.1)	94/197 (47.7)	.006
Lipid amphotericin B	134/348 (38.5)	49/151 (32.5)	85/197 (43.2)	.042
Amphotericin B	10/348 (2.9)	1/151 (0.7)	9/197 (4.6)	.048
Itraconazole	10/348 (2.9)	5/151 (3.3)	5/197 (2.5)	.75

Table 3. Multivariable Logistic Regression Analysis of Factors Associated with Mortality among 415 Hematopoietic Stem Cell Transplant (HSCT) Patients with Invasive Aspergillosis (IA) and 227 Solid Organ Transplant (SOT) Patients with IA

Model, variable	OR (95% CI)	P[a]
HSCT-specific model		
Age	1.0 (0.99–1.02)	.57
Male sex	1.1 (0.6–1.7)	.82
White race	0.4 (0.2–0.8)	.017
Neutropenia	2.3 (1.4–4.1)	.002
Renal insufficiency	2.2 (1.2–3.8)	.007
Hepatic insufficiency	6.2 (2.8–13.5)	<.001
Early-onset IA	2.2 (1.2–3.8)	.007
Proven IA (vs probable IA)	2.4 (1.4–4.1)	.002
Methylprednisone use	1.9 (1.1–3.2)	.016
SOT-specific model		
Age	1.0 (0.99–1.05)	.11
Male sex	1.7 (0.9–3.3)	.13
White race	0.4 (0.1–1.2)	.11
Hepatic insufficiency	3.9 (1.3–11.8)	.015
Malnutrition	2.3 (1.0–5.1)	.044
Prednisone use	0.4 (0.2–0.8)	.011
CNS disease	6.6 (1.4–29.9)	.015

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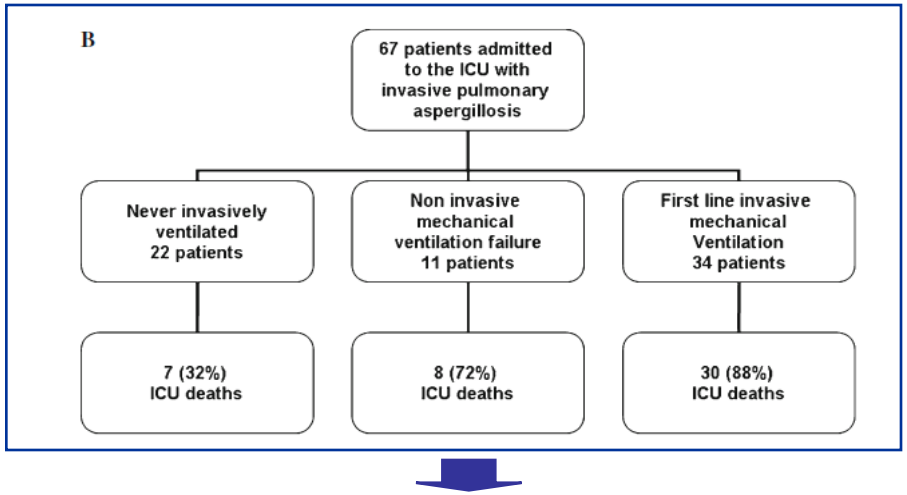
Outcomes of mechanically ventilated hematology patients with invasive pulmonary aspergillosis

Burghi G Intensive Care Med



42 (61%) shock, 21(31%) Ins renal y 17(25%) coma

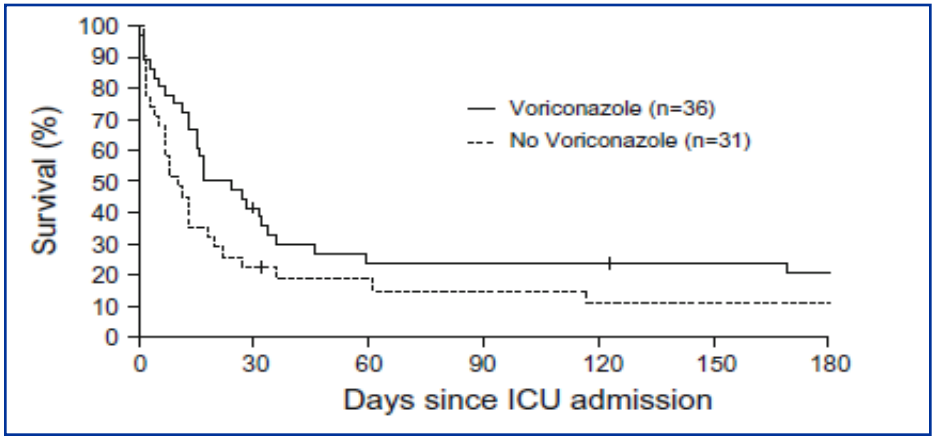


Table 1 Patient characteristics and risk factors associated with mortality

Patient characteristics ($n = 67$)	N (%) or median (IQR)
Male n (%)	44 (66)
Age	47 [39.5–57]
Underlying disease	
Acute myeloid leukemia	19 (28)
Acute lymphoid leukemia	7 (10)
Non-Hodgkin's lymphoma	18 (28)
Hodgkin's disease	1 (1.5)
Chronic lymphocytic leukemia	5 (7.5)
Multiple myeloma	6 (9)
Chronic myeloid leukemia	2 (3)
Other diseases*	9 (13)
Underlying risk factor	
Neutropenia	49 (73)
Allogeneic BMT	14 (21)
Long-term steroids	23 (34)
Respiratory symptoms at presentation	
Fever	60 (90)
Dyspnea	53 (59)
Chest pain	12 (18)
Tachypnea	61 (91)
Cough	27 (40)
Hemoptysis	8 (12)
Extrapulmonary signs	
Shock	42 (63)
Acute kidney injury	21 (31)
Coma	17 (25)
Thrombopenia	7 (10)
Liver failure	6 (9)
Concomitant infection	24 (36)
Chest X-ray ($n = 65$)	
Normal	4 (6.2)
Focal infiltrate	31 (48)
Diffuse infiltrate	30 (46)
Pleural effusion	13 (20)
CT scan ($n = 41$)	
Alveolar condensation	9 (21.9)
Centrolobular nodules	13 (31.7)
Halo sign	15 (36.5)
Excavated lesion	9 (21.9)
Pleural effusion	6 (14.6)
Sinusitis	8/21 (38)
Cerebral aspergillosis	7/27 (26)
Treatment by voriconazole	36 (54)
Length of ICU stay (days)	10 [4–18]
Median survival time	15 [IC 95%: 11–27]
ICU mortality (J30 mortality)	45 (67)
6 months mortality	55 (82)

Empirical treatment

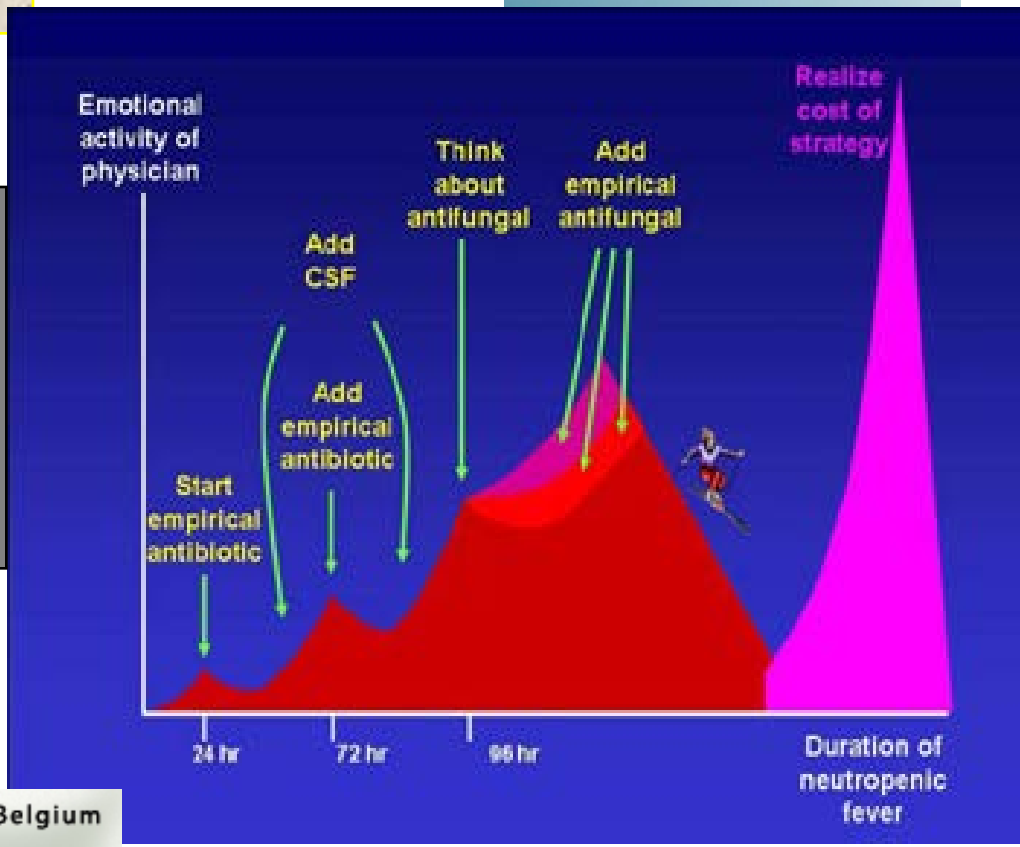
Empirical treatment

Persistent neutropenic fever

Broad spectrum AB. (4-7 day)

Empirical antifungal treatment

- No positive culture
- No biomarker
- Only clinical evidence is fever
- % IFI < 5%??



Dr. Marc A. B. Boogaerts | University Hospital Gasthuisberg, Belgium
Chief of Department Haematology

http://www.infectiologie.org.tn

UPDATE ECIL-3 2009

2009 UPDATE : Antifungal Drugs for Empirical Therapy

BII

Antifungal agent	Daily dose	CDC Grading		
		Level of Recommendation	Evidence for	
			Efficacy	Safety
Liposomal AmB	3 mg/kg	A *	I	I
Caspofungin	50 mg	A *[1]	I	I
ABCD	4 mg/kg	B [2]	I	I
ABLC	5 mg/kg	B [2]	I	I
Itraconazole	200 mg iv	B [1,4]	I	I
Voriconazole	2x 3 mg/kg iv	B [1,3,4]	I	I
NEW: Micafungin	100 mg	B	II	II
AmB deoxycholate	0.5-1 mg/kg	B [2] / D [5]	I	I
Fluconazole	400 mg iv	C [1,4,6]	I	I

* A double-blind, randomized trial comparing caspofungin 50 mg/m² (n=56) with liposomal ampho B 3 mg/kg/d (n=25) (published in abstract form) suggests a provisional grading BII for children ; the constitution of a pediatric group specifically addressing antifungal prophylaxis and therapy in children will be considered for 2011 update of ECIL guidelines

1 No activity against mucorales

2 Infusion-related toxicity (fever, chills, hypoxia)

3 Failed the 10% non-inferiority cut-off when compared with liposomal AmB (and thus not approved by the FDA for this indication), but first-line for aspergillosis, effective therapy for candidiasis, and efficacious for prevention of breakthrough IFI.

4 Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class.

5 B in absence of / D in presence of risk factors for renal toxicity (e.g. impaired renal function at baseline, nephrotoxic co-medication including cyclosprin or tacrolimus in allogeneic HSCT recipients, aminoglycoside antibiotics, history of previous toxicity).

6 No activity against *Aspergillus* and other moulds. Not approved by the FDA for this indication.

http://www.infectiologie.org.tn

Empiric treatment in Neutropenia/autologous SCT

ECCMID GUIIDELINES

WHEN: 3 to 4 days of persistent fever in all major trials (AII), not defined for relapsing fever

Dosage & *Intention: morbidity reduction*

Agents // Situation (trial included alloHCT)	Recommendation	References
Liposomal amphotericin B (3mg/kg/d) (Allo= yes)	AI	Walsh NEJM 1999; Prentice Br J Haematol 1997; Wingard CID 2000; Walsh NEJM 2002; Walsh NEJM 2004; Maertens Pediatr Inf Dis J 2010
Caspofungin (70 mg on D1 then 50 mg) (Allo=yes)	AI	Walsh NEJM 2004; Maertens Pediatr Inf Dis J 2010
Amphotericin B colloidal dispersion (4 mg/kg/d) (Allo=yes)	BI	White CID 1998
Amphotericin B lipid complex (5 mg/kg/d) (Allo=yes)	BI	Wingard CID 2000
Itraconazole (200 mg iv Q12h on D1 & D2 then 200 mg iv/d) (Allogeneic HCT=not reported)	BI	Boogaerts Ann Intern Med 2001; Ehninger Onkologie 2007
Voriconazole (2 x 6 mg/kg on D1 then 2x3 mg/kg/d) (Allo=yes)	BI	Walsh NEJM 2002
Fluconazole (400 mg/d) (Allo=not reported)	CI*	Winston Am J Med 2000; Viscoli C, Eur J Cancer. 1996 May;32A(5):814-20.
Amphotericin B deoxycholate (0.5 – 1.0 mg/kg/d) (Allo=yes)	CI	White CID 1998; Walsh NEJM 1999; Boogaerts Ann Intern Med 2001; Ehninger Onkologie 2007
Micafungin (100 mg) (AlloHSCT = yes)	BII	Tamura Leuk Lymphoma 2009; Kubiak Clin Ther 2010
Anidulafungin	No recommendation	No data

Ex
MD
Onl
Lim
For micafungin: Pamela – non comparative trial (dose 50-150 mg) ; Kubiak – 329 pts, retrospective, observational, sequential cohort (dose 100 mg)

Prevention

Guidelines for the prevention of invasive mould diseases caused by filamentous fungi by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

I. Ruiz-Camps[1], J. M. Aguado[2], B. Almirante[1], E. Bouza[3], C. F. Barbera[1], O. Len[1], L. Lopez-Cerero[4], J. L. Rodriguez-Tudela[5], M. Ruiz[6], A. Solé[7], C. Vallejo[8], L. Vazquez[9], R. Zaragoza[10] and M. Cuenca-Estrella[5] GEMICOMED (Medical Mycology Study Group of SEIMC)

1) *Infectious Diseases Department, Hospital de Vall d'Hebron, Barcelona,* 2) *Infectious Diseases Unit, Hospital Doce de Octubre, Madrid,* 3) *Clinical Microbiology and Infectious Diseases Department, Hospital Gregorio Marañón, Complutense University, Madrid,* 4) *Microbiology Department, Hospital Universitario Virgen de la Macarena, Seville,* 5) *Mycology Department, National Centre of Microbiology, Instituto de Salud Carlos III, Majadahonda,* 6) *TELSTAR Project SA, Madrid,* 7) *Lung Transplant and Cystic Fibrosis Unit, Hospital Universitario la FE, Valencia,* 8) *Haematology Department, Hospital Universitario Central de Asturias, Oviedo,* 9) *Haematology Department, Hospital Clínico, Salamanca and* 10) *Intensive Medicine Department, Hospital Universitario Dr Peset, Valencia, Spain*

Clin Microbiol Infect 2011; 17 (Suppl. 2): 1–24

1 Environmental preventive measures.
2 Control measures for hospital infections.
3 Special and additional preventive measures.
4 Preventive measures outside of the hospital.
5 Pharmacological prophylaxis.

Different ways to prevent invasive fungal infection

- Prevention of superficial mucosal colonisation, e.g. mucosal hygiene
- Laminar air flow and HEPA filtration
- Lowering airborne spore levels (construction)
- Avoiding long term indiscriminate antibiotic/steroid usage
- Appropriate catheter care
- Avoiding raw vegetables, beer (Saccharomyces)
- Avoiding animal contacts, animal droppings
- Avoiding plant contamination
- Drugs

Guidelines: who and what?

- Agreement on "who": high-risk patients
- No agreement on specific drug recommendations

- IDSA: Allogeneic SCT with GVHD at high-risk for InvA
  AML or MDS at high risk for InvA
- NCCN: Patients at high/intermediate risk IFI
  Not for all patients; not for low risk patients
- ECIL: Patients with an expected IFI incidence ≥10%
  Acute leukemias, high-risk MDS, SCT (Allo > Auto)

InvA: invasive aspergillosis

Table 2 ECIL 3 Guidelines on antifungal primary prophylaxis in hematology patients (the items in bold italic have been introduced at ECIL 3)

Antifungal drug	*Grading*	*Comments*
Leukemia patients, induction chemotherapy		
Fluconazole (50–400 mg/day)	CI	Azoles should not be used empirically in case of prevoius azole prophylaxis Combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections
Itraconazole oral solution (2.5 mg/kg b.i.d.)	CI	May be limited by drug interactions and/or patient tolerability Azoles should not be used empirically in case of prior azole prophylaxis It is recommended to monitor serum drug concentrations
Posaconazole (200 mg t.i.d.)	AI	Azoles should not be used empirically in case of previous azole prophylaxis It is recommended to monitor serum drug concentrations
Echinocandins IV	Insufficient data	
Polyenes IV	CI	Includes low doses of conventional ampho B and lipid formulations
Aerosolized liposomal ampho B combined with oral fluconazole	***BI***	***The ECIL recommendation for aerosolized amphotericin B deoxycholate is DI***
Allogeneic HSCT recipients, initial neutropenic phase		
Fluconazole (400 mg q.d. i.v. or oral)	AI	Azoles should not be used empirically in case of previous azole prophylaxis Combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections
Itraconazole (200 mg i.v. followed by oral solution 200 mg b.i.d.)[a]	BI	May be limited by drug interactions and/or patient tolerability Azoles should not be used empirically in case of previous azole prophylaxis It is recommended to monitor serum drug concentrations
Posaconazole	No data	
Voriconazole (200 mg b.i.d. oral)	***Provisional AI***	***Grading pending the publication of the full paper***
Micafungin (50 mg q.d. i.v.)	CI	
Polyenes i.v.	CI	Includes low doses of conventional ampho B and lipid formulations
Aerosolized liposomal ampho B combined with oral fluconazole	***BII***	***The ECIL recommendation for aerosolized ampho B deoxycholate is DI***
Allogeneic HSCT recipients, GVHD phase		
Fluconazole (400 mg q.d. i.v. or oral)	CI	Azoles should not be used empirically in case of previous azole prophylaxis
Itraconazole (200 mg i.v. followed by oral solution 200 mg b.i.d.)[a]	BI	May be limited by drug interactions and/or patient tolerability Azoles should not be used empirically in case of prior azole prophylaxis It is recommended to monitor serum drug concentrations
Posaconazole	AI	Azoles should not be used empirically in case of previous azole prophylaxis It is recommended to monitor serum drug concentrations
Voriconazole (200 mg b.i.d. oral)	***Provisional AI***	***Grading pending the publication of the full paper***
Echinocandins i.v.	Insufficient data	
Polyenes i.v.	CI	Includes low doses of conventional ampho B and lipid formulations
Aerosolized liposomal ampho B combined with oral fluconazole	***Insufficient data***	

Abbreviation: ECIL = European Conference on Infections in Leukemia.
[a]In case the i.v. form of itraconazole is not available, the treatment will start with the oral solution, 200 mg b.i.d.

http://www.infectiologie.org.tn

Guidelines for the prevention of invasive mould diseases caused by filamentous fungi by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) I. Ruiz-Camps[1], *Clin Microbiol Infect* 2011; 17 (Suppl. 2): 1–24

TABLE 9. Prophylaxis regimen for filamentous fungi in high-risk patients

Indication	Target population	Antifungal drug	Duration	Observations
Lung transplant patient	All	Liposomal amphotericin B 25 mg or amphotericin B lipid complex 50 mg, in nebulized form, three times weekly until resolution of bronchial suture, once a week from the second to the sixth month, and once a fortnight from the sixth month on	Indefinite	Bronchospasm as a side effect
		Voriconazole 200 mg/12 h orally	Determined by the presence of risk factors, although it is usually administered for a minimum of 4 months	Monitor liver enzymes, voriconazole concentrations, and anticalcineurins
Other solid organ transplant patients	High-risk patients for early IFI: renal clearance techniques, CMV disease, acute liver failure (liver transplant), primary graft failure, re-transplantation	Amphotericin B lipid formulation 2.5–5 mg/kg/day parenterally	Determined by the presence of risk factors	Studies carried out preferably in liver transplant patients
		Itraconazole 400 mg/day orally		Study carried out in heart transplant patients. Monitor anticalcineurin concentrations
		Caspofungin 70 mg/day in the first dose and then continue with 50 mg/day		Study carried out in liver transplant patients. Monitor liver enzymes. In the study, this was administered for 21 days
	High-risk patients for late IFI: chronic rejection, recurrent liver condition VHC (liver transplant), renal clearance techniques	Liposomal amphotericin B 25 mg or amphotericin B lipid complex 50 mg, in nebulized form three times weekly until resolution of bronchial suture, onceal week from the second to the sixth month, and oncea fortnight from the sixth month on		Bronchospasm as a side effect
Chronic granulomatous disease	Patients over 5 years of age	Itraconazole 200 mg/day orally (100 mg/day <13 years or <50 kg of weight)	Indefinite	In the clinical trial, prophylaxis was carried out for 1 year

CMV, cytomegalovirus; IFI, invasive fungal infection; VHC, virus of hepatitis C.

Prophylaxis in hematological patients.
Vall d'Hebron Hospital. Barcelona (Spain)

Posaconazol:

- MAL/MDS induction or rescue (IA)
- Allogenic HSCT + GVHD receiving immunosupressors (IA)
- Umbilical cord transplant

ABL-N+fluconazol 200-400mg/d

- MAL in consolidation
- ALL induction
- Burkitt lymphoma receiving Burkimab treatment.

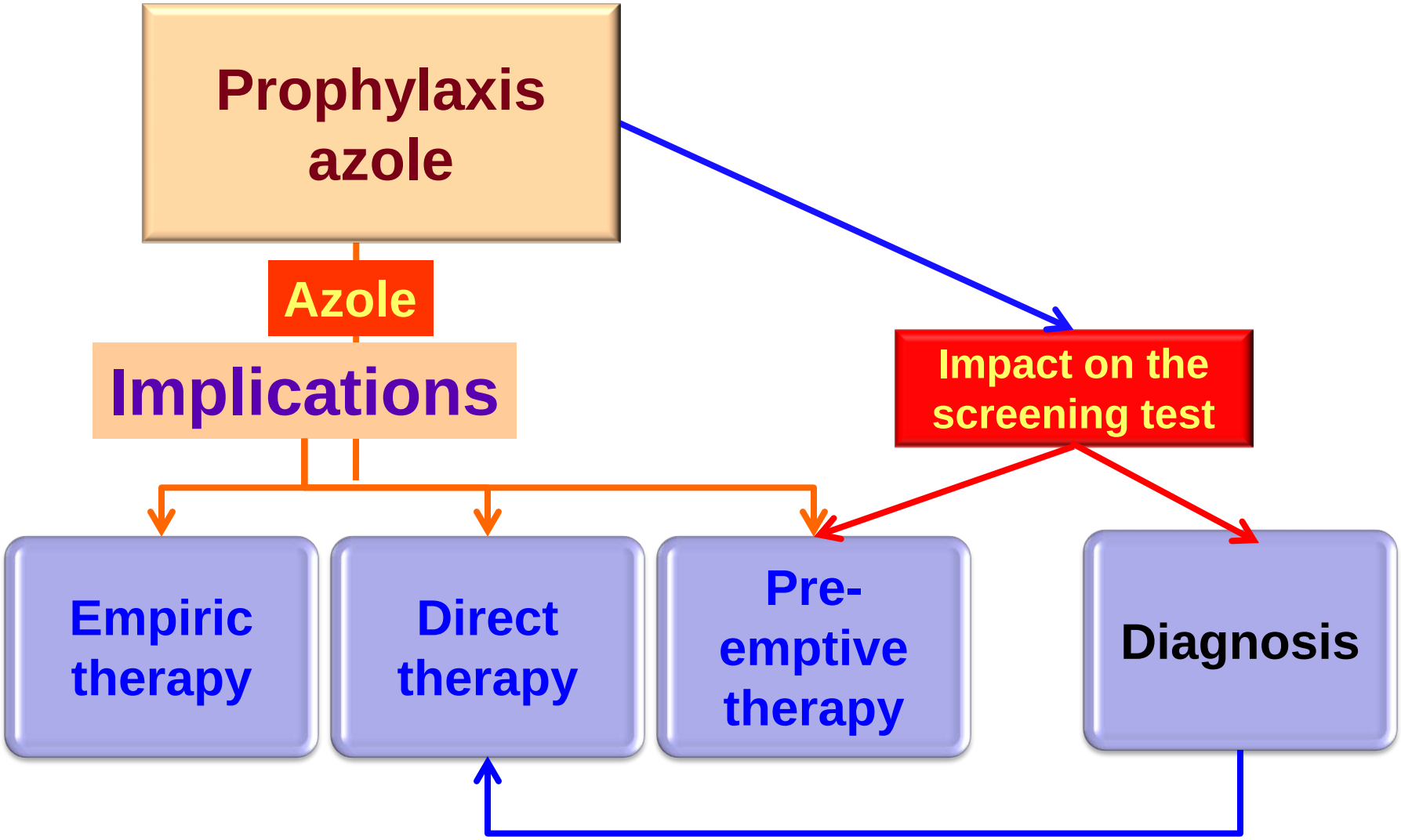
Fluconazol:

- Autologous HSCT
- Allogenic HSCT (TPHperitrasplant)
- ALL in consolidation
- If neutropenia will last >10days (if receiving steroids, mucositis...)

- Dr. Pere Barba
- Dra. I. Ruiz

Febrer 2011

Strategies and IFI incidence interaction



Galactomannan antigenaemia (GM) sensitivity and anti-mould antifungals

42 invasive aspergillosis vs. 269 controls

GM ≥ 0.5	With antifungal*	Without antifungal*	P
Sensitivity	52%	89%	0.02
Specificity	91%	92%	ns
*Antifungal with anti-mould activity			

Anti-mould antifungal drugs:

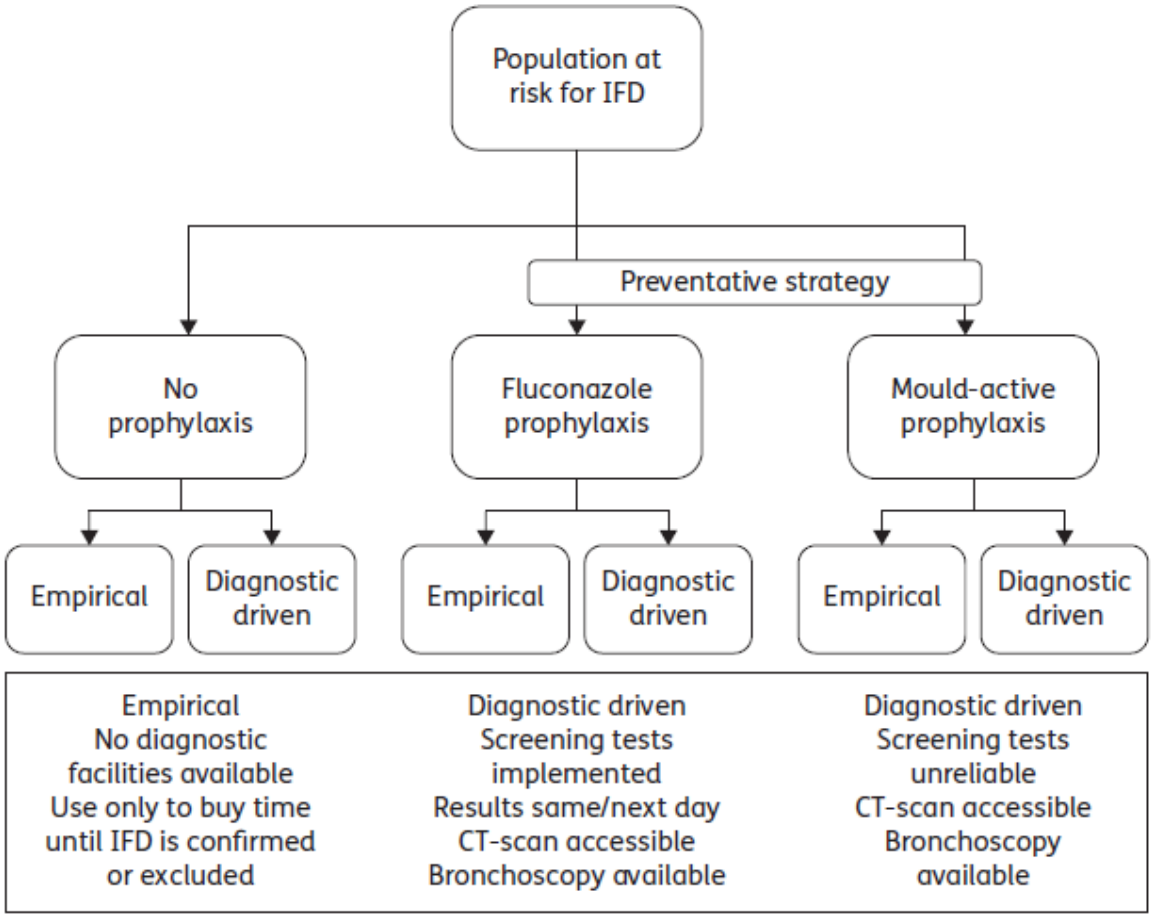
- **Lower the GM sensitivity**
- **Do not change the specificity**

Marr KA. CID 2005;40:1762-9

http://www.infectiologie.org.tn

Optimizing management of invasive mould diseases

Samir Agrawal[1]*, William Hope[2], János Sinkó[3] and Christopher Kibbler[4]



J Antimicrob Chemother 2011; **66** Suppl 1: i45–53

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Why does prophylaxis fail?

- Prolonged neutropenia
  - Refractory leukemia
- Severe immunodeficiency
  - Severe GVHD
- Poor oral intake
  - Drug compliance/ vomiting/mucositis
- Poor drug absorption
  - Diarrhoea/low oral intake
- Drug toxicity

- Exposure (colonization/environment)
  - Local epidemiology
- Resistant fungus
  - Antifungal selection

The Bug

- Pharmacokinetics
  - Route/dose
  - Absorption
  - Metabolism
  - Interactions
  - Levels

Host

IFI Breakthrough

The Drug

What can we do?

- Usually it is not possible to correct Host factors
- Exceptions:
  - catheter removal for yeast infections
  - Neutrophil recovery with CSF
  - Try to decrease immunosuppression

- If we know the bug: administer the appropiate treatment quickly
- If we don't know the bug: empirical changes quickly

The Bug

- Change dose and route
  - Possible for itra/vori
  - Not possible for posaconazole
- Add or switch

Host

IFI Breakthrough

The Drug

Trifilio S et al. BMT. 2007 Sep;40(5):451-6

http://www.infectiologie.org.ch

What do we know?
Reported breakthrough IFI on prophylaxis

Many single-case reports. Problem: what is the denominator?

	Itra	Posa	Vori	Candin	Amphotericin
Aspergillosis	X	X	X	X	X
Candidiasis	X	X	X	X	X
Trichosporon	XX	X	X	XX	X
Zygomycosis	X / -	X	XX	X	X
S.prolificans		X	X		
Fusarium			X		X

The majority are aspergillosis and candidiasis (in randomized studies)

- Special cases: Zygomycosis and voriconazole
  Trichosporon and echinocandins

Kremery V. *et al.* Chemotherapy 1997;43(5):367-70

What to do when there is a disease progression?

TABLE 4. Tentative recommendations for monitoring of blood levels during antifungal therapy

Drug	Indication	Time of first measurement after start of therapy (days)	Target blood concn[a] (μg/ml) for:	
			Efficacy	Safety
Flucytosine	Routine during first wk of therapy, renal insufficiency, lacking response to therapy	3–5	Peak of >20	Peak of <50
Itraconazole	Routine during first wk of therapy, lacking response, gastrointestinal dysfunction, comedication	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >1 to 2	NA
Voriconazole	Lacking response; gastrointestinal dysfunction; comedication; children; intravenous-to-oral switch; severe hepatopathy; unexplained neurological symptoms/signs	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >1 to 2	Trough of <6
Posaconazole	Lacking response; gastrointestinal dysfunction, therapy with proton pump inhibitors; comedication	4–7	For prophylaxis, trough of >0.5; for therapy, trough of >0.5 to 1.5	NA

[a] Total or bound and unbound drug concentrations. NA, not applicable.

What do we know?
Breakthrough IFI on voriconazole prophylaxis

- Allogeneic SCT. Randomized trial (vori vs fluco) (ASH 07)*
  - Vori (305): 7 IA, 3 *Candida*, 2 zygomycosis

- Increase in zygomycosis incidence (x 3) began before voriconazole was available (Kontoyiannis CID 2000)[2]
- Voriconazole may have amplified a previous tendency

- The majority are candidiasis, aspergillosis and zygomycosis (?)
- Relation with levels: suggested (<2000 ng/ml)

* Unpublished study

1 Trifilio S *et al*. Cancer 2007;40(5):451-6

2 Kontoviannis DP *et al*. CID 2000;30:851-6


FUTURE
PAST
PRESENT

Treatment

Prophylaxis

IFI

Acquired R

Resistant species

Innate R

No TDM

Emergent species

Epidemiological change

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 Rodriguez-Tudela,[2] Helle Krogh Johansen,[4] and Maiken Cavling Arendrup[1]

Antimicrobial Agents and Chemotherapy, Nov. 2010, p. 4545–4549

A single mechanism of azole resistance was shown to predominate in clinical and environmental *Aspergillus fumigatus* isolates from the Netherlands, and a link to the use of azoles in the environment was suggested. To explore the prevalence of azole-resistant *A. fumigatus* and other aspergilli in the environment in other European countries, we collected samples from the surroundings of hospitals in Copenhagen, Innsbruck, and Madrid, flowerbeds in an amusement park in Copenhagen, and compost bags purchased in Austria, Denmark, and Spain and screened for azole resistance using multidish agars with itraconazole, voriconazole, and posaconazole. EUCAST method E.DEF 9.1 was used to confirm azole resistance. The promoter and entire coding sequence of the *cyp51A* gene were sequenced to identify azole-resistant *A. fumigatus* isolates. *A. fumigatus* was recovered in 144 out of 185 samples (77.8%). Four *A. fumigatus* isolates from four Danish soil samples displayed elevated azole MICs (8%), and all harbored the same TR/L98H mutation of *cyp51A*. One *A. lentulus* isolate with voriconazole MIC of 4 mg/liter was detected in Spain. No azole-resistant aspergilli were detected in compost. Finally, *A. terreus* was present in seven samples from Austria. Multi-azole-resistant *A. fumigatus* is present in the environment in Denmark. The resistance mechanism is identical to that of environmental isolates in the Netherlands. No link to commercial compost could be detected. In Spain and Austria, only *Aspergillus* species with intrinsic resistance to either azoles or amphotericin B were found.

Azole resistance in *Aspergillus fumigatus*: a side-effect of environmental fungicide use?

Lancet Infect Dis 2009; 9: 789–95

Paul E Verweij, Eveline Snelders, Gert H J Kema, Emilia Mellado, Willem J G Melchers

Invasive aspergillosis due to multi-azole-resistant *Aspergillus fumigatus* has emerged in the Netherlands since 1999, with 6·0–12·8% of patients harbouring resistant isolates. The presence of a single resistance mechanism (denoted by TR/L98H), which consists of a substitution at codon 98 of *cyp51A* and a 34-bp tandem repeat in the gene-promoter region, was found in over 90% of clinical *A fumigatus* isolates. This is consistent with a route of resistance development through exposure to azole compounds in the environment. Indeed, TR/L98H *A fumigatus* isolates were cultured from soil and compost, were shown to be cross-resistant to azole fungicides, and genetically related to clinical resistant isolates. Azoles are abundantly used in the environment and the presence of *A fumigatus* resistant to medical triazoles is a major challenge because of the possibility of worldwide spread of resistant isolates. Reports of TR/L98H in other European countries indicate that resistance might already be spreading.

http://www.infectiologie.org.tn

Epidemiological changes

Bone Marrow Transplantation (2007), 1–5
© 2007 Nature Publishing Group All rights reserved 0268-3369/07 $30.00
www.nature.com/bmt

ORIGINAL ARTICLE

Breakthrough zygomycosis after voriconazole administration among patients with hematologic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy

SM Trifilio[1], CL Bennett[2,3], PR Yarnold[4], JM McKoy[5], J Parada[6,7], J Mehta[3], G Chamilos[8], F Palella[9], L Kennedy[10], K Mullane[11], MS Tallman[3], A Evens[3], MH Scheetz[1], W Blum[12] and DP Kontoyiannis[13]

Breakthrough Trichosporonosis in Patients with Hematologic Malignancies Receiving Micafungin

Kosei Matsue, Hidetaka Uryu, Mihoko Koseki, Noboru Asada, and Masami Takeuchi
Department of Hematology and Oncolo

Clinical Infectious Diseases 2006; 42:753–7

Candidemia in Patients With Hematologic Malignancies in the Era of New Antifungal Agents (2001-2007)

Stable Incidence But Changing Epidemiology of a Still Frequently Lethal Infection

Species	No. of Patients (%)		
	1988-1992,[17] n=230	1993-2002,[18] n=281	2001-2007, n=173
C. albicans	79 (34)	38 (13)	41 (24)
Non-*albicans* species	139 (60)	227 (81)	129 (75)
C. glabrata	28 (12)	86 (31)	8 (5)
C. krusei	17 (7)	68 (24)	30 (17)
C. parapsilosis	33 (14)	39 (14)	42 (24)
C. tropicalis	53 (23)	27 (10)	37 (21)
C. guilliermondii	2 (1)	4 (1)	4 (2)
C. lusitaniae	3 (1)	3 (1)	2 (1)
Other*	—	—	6 (3)
Mixed *Candida* spp.	12 (5)	16 (6)	3 (2)

**C. kefyr* (1), *Torulopsis famata* (1), and nonspecified non-*albicans Candida* spp. (4).

Breakthrough cryptococcosis in a patient with systemic lupus erythematosus (SLE) receiving micafungin.

Suzuki K. J Infect Chemother. 2008 Aug;14(4):311-4.

Forty-one recent cases of invasive zygomycosis from a global clinical registry

J Antimicrob Chemother 2010; **65**: 296–302

M. J. G. T. Rüping[1], W. J. Heinz[2], A. J. Kindo[3], V. Rickerts[4], C. Lass-Flörl[5], C. Beisel[1], R. Herbrecht[6], Y. Roth[7], G. Silling[8], A. J. Ullmann[9], K. Borchert[10], G. Egerer[11], J. Maertens[12], G. Maschmeyer[13], A. Simon[14], M. Wattad[15], G. Fischer[16], J. J. Vehreschild[1] and O. A. Cornely[1,17]*

Table 1. Underlying conditions, associated mortality and treatment response in 41 patients with invasive zygomycosis

Underlying conditions[a]	*n* (%)	Mortality [*n* (%)]	Favourable response [*n* (%)]
Haematological or oncological malignancy	26 (63.4)	15 (57.7)	15 (57.7)
haematological malignancy	13 (50)	6 (46.2)	10 (76.9)
solid tumour	1 (3.8)	0 (0)	1 (100)
allogeneic HSCT[b]	12 (46.2)	9 (75)	4 (33.3)
Diabetes mellitus	7 (17.1)	4 (57.1)	3 (42.9)
Solid organ transplant	4 (9.8)	0 (0)	4 (100)
Major surgery	4 (9.8)	2 (50)	2 (50)
Intensive care unit	4 (9.8)	2 (50)	2 (50)

Table 2. Sites of infection from 41 patients with invasive zygomycosis

Site of infection	*n*	%
Lungs	24	58.5
Rhino-sinu-orbital region	8	19.5
Soft tissues[a]	8	19.5
Central nervous system	6	14.6
Intestine or peritoneum	5	12.2
Liver or spleen	4	9.8
Kidneys	3	7.3
Biliary tract	1	2.4
Disseminated infection[b]	6	14.6

[a]Including lower extremities ($n=4$), upper extremities ($n=1$), face ($n=2$)

TRANSNET USA: The incidence was 1,7/1000 in 2001 and 6,2/1000 in 2006

Table 3. Causative pathogens identified in 41 patients with invasive zygomycosis

Pathogen	*n* (%)
Mycocladus corymbifer	10 (24.4)
Apophysomyces elegans	1 (2.4)
Conidiobolus spp.	1 (2.4)
Cunninghamella bertholletiae	1 (2.4)
Mucor spp.	5 (12.2)
Rhizomucor spp.	4 (9.8)
Rhizomucor pusillus	2 (50)
Rhizopus spp.	7 (17.1)
Rhizopus homothallicus	1 (14.3)
Rhizopus microsporus	2 (28.6)
Rhizopus oryzae	1 (14.3)
Mucorales (NOS)	12 (29.3)

NOS, not otherwise specified.

Treatments	*n*	*n* (%)	*P*	*n* (%)	*P*
Overall	41	23 (56.1)	NA	21 (51.2)	NA
antifungal Tx only	18	10 (55.6)	NS	9 (50)	NS
surgical Tx only	2	1 (50)	NS	2 (100)	NS
antifungal+surgical Tx	19	13 (68.4)	NS	11 (57.9)	NS
no Tx	2	0 (0)	NS	0 (0)	NS
Empirical Tx	17	9 (52.9)	NS	6 (35.3)	NS
active Tx	7	5 (71.4)	NS	5 (71.4)	0.035
L-AMB	4	3 (75)	NS	3 (75)	NS
POS	2	1 (50)	NS	1 (50)	NS
POS+L-AMB	1	1 (100)	NS	1 (100)	NS
Initial targeted Tx	39	23 (59)	NA	20 (51.3)	NA
active Tx	34	23 (67.6)	0.014	20 (58.8)	NS
L-AMB	17	16 (94.1)	0.012	14 (82.4)	0.004
D-AMB	4	1 (25)	NS	1 (25)	NS
POS	6	4 (66.7)	NS	3 (50)	NS
POS+L-AMB	7	4 (57.1)	NS	2 (28.6)	NS
any AMB[a]	28	17 (60.7)	NS	19 (67.9)	NS

JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2009, p. 379–384
0095-1137/09/$08.00+0 doi:10.1128/JCM.01716-08
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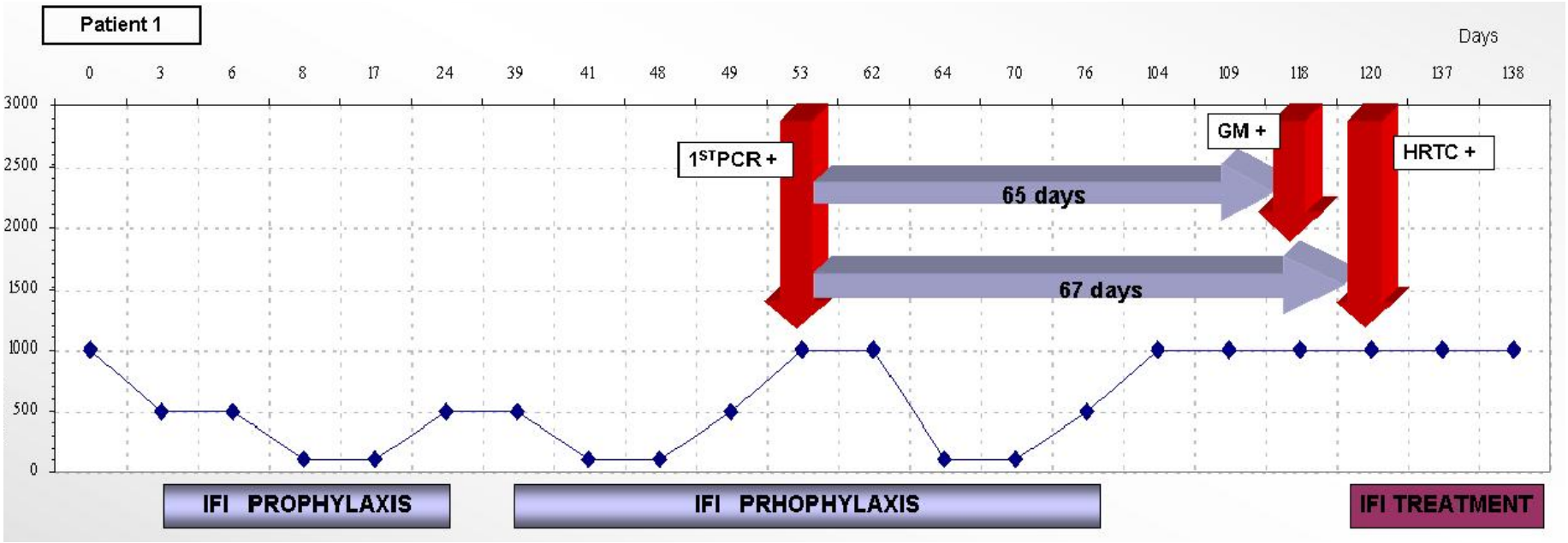
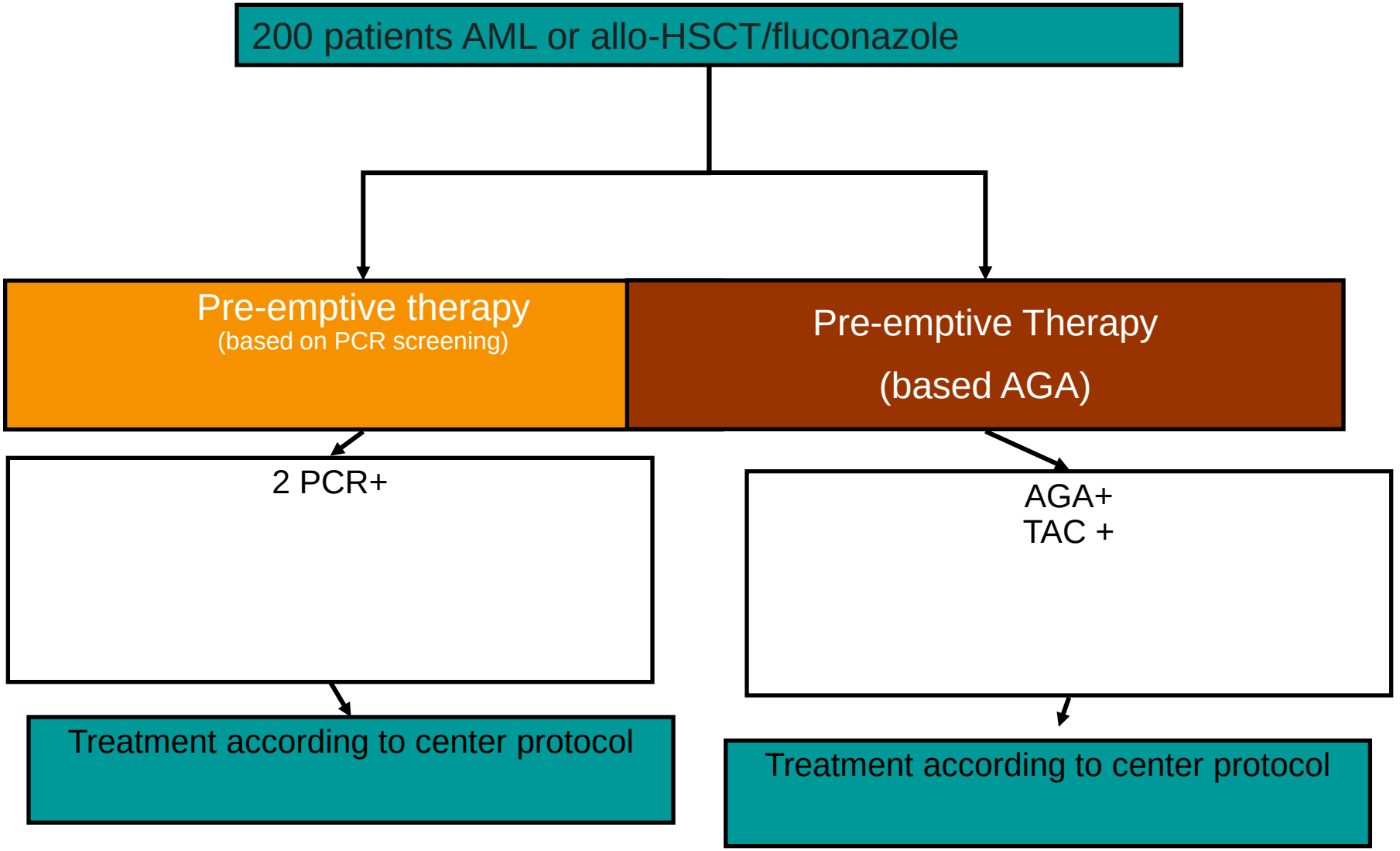
Galactomanano *vs* PCR

Vol. 47, No. 2

Value of Serial Quantification of Fungal DNA by a Real-Time PCR-Based Technique for Early Diagnosis of Invasive Aspergillosis in Patients with Febrile Neutropenia▽

Manuel Cuenca-Estrella,[1]* Yolanda Meije,[2] Carmen Diaz-Pedroche,[2] Alicia Gomez-Lopez,[1] Maria J. Buitrago,[1] Leticia Bernal-Martinez,[1] Carlos Grande,[3] Rafael San Juan,[2] Manuel Lizasoain,[2] Juan L. Rodriguez-Tudela,[1] and Jose M. Aguado[2]




200 patients AML or allo-HSCT/fluconazole
Pre-emptive therapy
(based on PCR screening)
Pre-emptive Therapy
(based AGA)
2 PCR+
AGA+
TAC +
Treatment according to center protocol
Treatment according to center protocol

CONCLUSIONS

1.- Fungal infections are frequent in some risk populations

2.- All antifungal drugs have a role in the managment of IFI

3.- In *Candida* spp. Infection it is important to know the epidemiology of each center to start the proper treatment.

4.- Candins are the empirical treatment of choice in candidiasis before knowing the species.

5.- In IA it is important to diagnose the disease and start the treatment with VOR early.

CONCLUSIONS

6.- Combination therapy could play a role in some patients

7.- In patients undergoing prophylaxis GM test presented a lower sensibility. Keep in mind empirical treatment.

8.- Emerging species and resistant fungi are increasing in frequency

9.- New diagnostic techniques urgently need to be developed

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