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Aspergillus: Invasive and Non-Invasive Infections

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Definitions

What is non-invasive disease?

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Definitions

Colonization

- Isolation of *Aspergillus* spp. from mucocutaneous surface without evidence of invasive, saprophytic, or allergic disease
- Transient passage in the airway
- Genuine long term carriage (benign); patients with localized structural or functional pulmonary deficits
- Marker or precedent to the development of invasive disease
  - Lung transplant recipients: 5.7% develop IA (Singh et al. 2003)
  - PCR detection in allogeneic HCT recipients => IA (Einsele et al. 1998)
- Role of PCR for the definition of colonization? Quantitative PCR?

Modified: Hope et al. Med Mycol 2005

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Definitions

Chronic pulmonary aspergillosis

- Various wordings:
  - pulmonary aspergillosis with cavitation
  - Symptomatic pulmonary aspergillosis
  - Complex aspergilloma
  - Semi-invasive pulmonary aspergillosis
  - Chronic necrotizing pulmonary aspergillosis
- CNPA
  - Slowly progressing cavitary lung disease
  - Chronic respiratory symptoms
  - Presence of precipitating antibodies to *Aspergillus* spp.
  - ? Direct invasion of hyphal elements into the lung parenchyma (subacute non-angioinvasive form of IPA)

Hope et al 2005 Med Mycol

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Definitions

CCPA

- Chronic cavitary pulmonary aspergillosis
- Formation and expansion of mulitple cavities

CFPA

- Chronic fibrotic pulmonary aspergillosis
- Cavitary formation followed by marked fibrotic reactions

Hope et al 2005 Med Mycol

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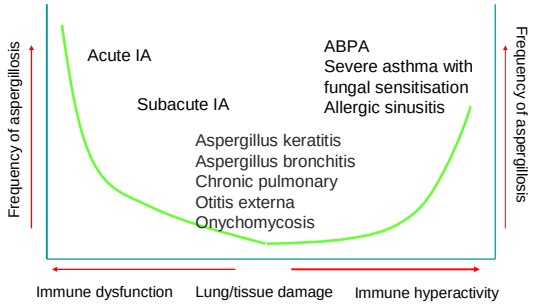
Interaction of *Aspergillus* with the host

A unique microbial-host interaction



After Casadevall & Pirofski, Infect Immun 1999;67:3703

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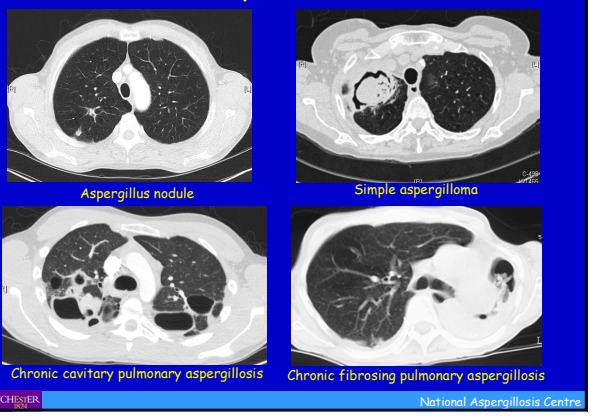
Different patterns of CPA



Aspergillosis burden in Europe

Type of aspergillosis	Predominant risk groups	Risk population size (000's)	Aspergillosis rate	Annual aspergillosis burden (000's)
ABPA	Asthma	35,474	2.5%	887 (248 – 1,242)
	Cystic fibrosis	2		4.3
SAFS	Severe asthmaa	3,547	33%	1,170 (886 – 1,774)
Chronic pulmonary aspergillosis	COPD, TB, sarcoidosis, ABPA, Pneumothorax	>13,600	1-10%	240
Invasive aspergillosis	Myeloid leukaemia, Other haematological HSCT	44 11.4	7%	3.1 3.1 0.8
	COPD hospital admissions	3,600		34
	Solid organ transplantation	30	0.75%	0.25
	Medical ICU	1,100 (all ICU)	2%	22
Total aspergillosis annual burden	All	-	-	**2,364.55**

2,061,300

63,250

ECDC report published February 2013

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What is...

...invasive aspergillosis?

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Angioinvasive Pulmonary Aspergillosis

Pathological findings:

•Vascular invasion by hyphal elements, coagulative necrosis, haemorrhagic infarction. The target lesion (or mycotic sequestrum) and distal wedge shaped areas of pulmonary infarction are classical manifestations of angioinvasion.

Radiographical features:

•Halo sign, air crescent sign, single or multiple pulmonary nodules.

Clinical setting:

•Prolonged and profound neutropenia

Direct evidence:

•*Aspergillus* spp. (culture/histology) from lung biopsy *Aspergillus* spp. (culture/histology) from contiguous site [PCR from lung biopsy (especially in the context of tissue infarction and necrosis)].

Indirect evidence:

•Proven/probable IA at non-contiguous site *Aspergillus* spp. (culture/ cytology) from respiratory tract Specimen. Positive GM (x2) from blood. Positive GM from respiratory tract specimena, [Positive PCR from blood][Positive PCR from respiratory tract specimen]

Hope et al 2005 Med Mycol

Non-Angioinvasive Pulmonary Aspergillosis

Pathological features:

•No evidence of vascular invasion, pyogranulomatous inflammatory infiltrate, inflammatory necrosis, cavitation (occasionally a mixed histological picture may be observed)

Radiological features:

•Non-specific abnormalities including air-space disease, nodular infiltrates and cavitation

Clinical setting:

•Non-neutropenic individuals, including corticosteroid therapy, non-neutropenic HSCT, GVHD, HIV/AIDS, CGD and SOT. Some chronic forms of pulmonary aspergillosis with progressive pulmonary cavitation and the presence of precipitating antibodies to *Aspergillus* spp. are characterised by tissue invasion

Direct evidence:

•*Aspergillus* spp. (culture/histology) from lung biopsy or contiguous site

Indirect evidence:

•Proven/probable IA at non-contiguous site *Aspergillus* spp. (culture/ cytology) from respiratory tract specimen, Positive GM from blood or respiratory tract specimen (Precipitating antibodies in CPA forms)

Hope et al 2005 Med Mycol

Bringing the worlds together

Some more data and...
...guidelines

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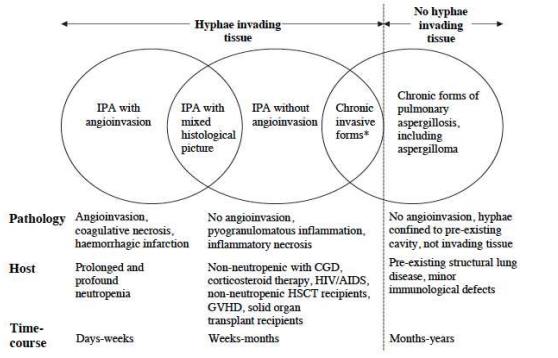
The spectrum of aspergillosis of the lower respiratory tract



Pathology	Angioinvasion, coagulative necrosis, haemorrhagic infarction	No angioinvasion, pyogranulomatous inflammation, inflammatory necrosis	No angioinvasion, hyphae confined to pre-existing cavity, not invading tissue
Host	Prolonged and profound neutropenia	Non-neutropenic with CGD, corticosteroid therapy, HIV/AIDS, non-neutropenic HSCT recipients, GVHD, solid organ transplant recipients	Pre-existing structural lung disease, minor immunological defects
Time-course	Days-weeks	Weeks-months	Months-years

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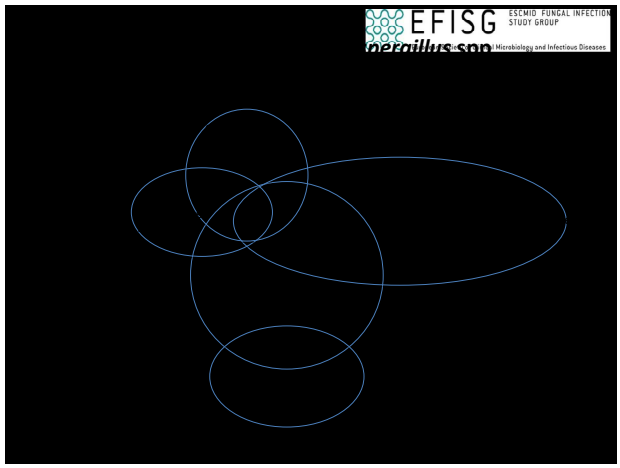
Hope et al 2005 Med Mycol



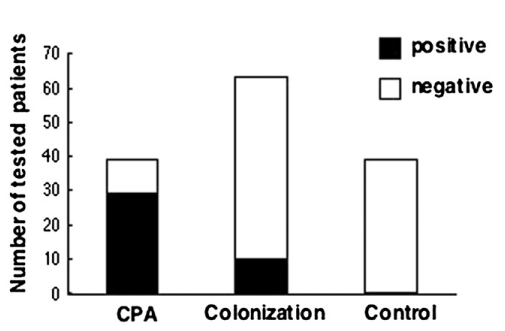
Underlying diseases in patients with CPA (%)

	Smith	Others
Classical tuberculosis	17	31-81
Atypical tuberculosis	16	?
ABPA	14	12
COPD/emphysema	33	42-56
Pneumothorax	17	12-17
Lung cancer survivor	10	?
Pneumonia	22	9-12
Sarcoidosis (stage II/III)	7	12-17
Thoracic surgery	14	8-11
Rheumatoid arthritis	4	2
Asthma / SAFS	12	6-12
Ankylosing spondylitis	4	2-11
None	1	15

MANCHESTER

Smith, Eur Resp J 2011;37:865

CPA: Clinical Characteristics and Prognosis



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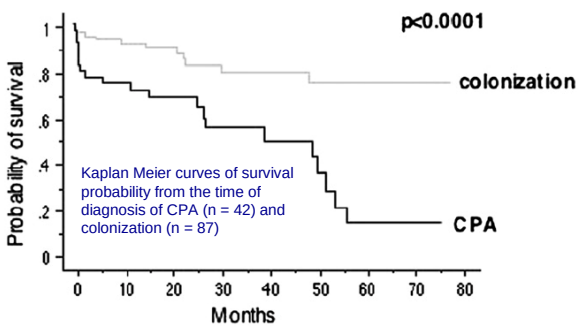
Ohba et al. Respir Med 2012

CPA: Clinical Characteristics and Prognosis



Kaplan Meier curves of survival probability from the time of diagnosis of CPA (n = 42) and colonization (n = 87)

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Ohba et al. Respir Med 2012

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CPA: Clinical Characteristics and Prognosis

Mortality predictive factors in patients with CPA using univariable analysis

	Odds ratio	95%CI	*p* value
Sex(male)	0.455	0.101–2.049	0.3052
Age	0.991	0.936–1.048	0.7405
Body mass index	1.858	1.132–3.047	0.0142
TB	1.833	0.374–8.986	0.4548
NTM	0.952	0.200–4.539	0.9512
C-reactive protein	0.876	0.757–1.014	0.0766
Albumin	6.515	1.408–39.147	0.0165
β–D glucan	0.990	0.975–1.006	0.2210
Aspergillus antigen	1.284	0.679–2.425	0.4420
Therapy (Yes)	0.237	0.044–1.280	0.9430

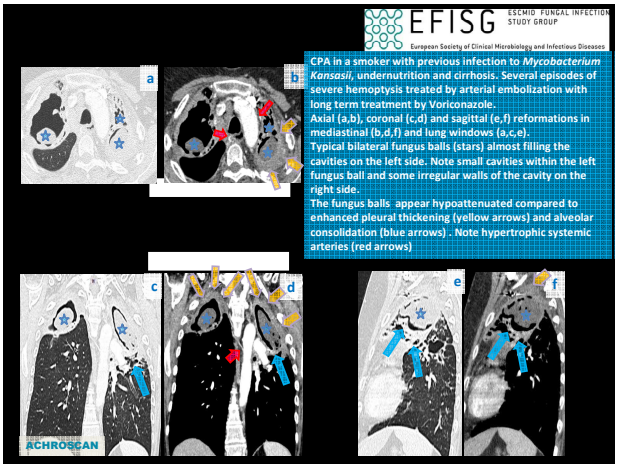
Ohba et al. Respir Med 2012

CPA: Clinical Characteristics and Prognosis

Neither univariate nor multivariate analysis indicated that antifungal therapy significantly affected survival

	Odds ratio	95%CI	*p* value
Age	0.959	0.868–1.058	0.4022
Body mass index	1.973	1.101–3.533	0.0223
C-reactive protein	0.897	0.757–1.064	0.2114
Therapy(Yes)	0.247	0.019–3.181	0.2835

Ohba et al. Respir Med 2012



Diagnostic Criteria for Chronic Necrotizing Pulmonary Aspergillosis

Clinical:

•Chronic pulmonary or systemic symptoms (>1 month), including at least one of weight loss, productive cough, or hemoptysis. No overt immunocompromising conditions (e.g., hematological malignancy, neutropenia, organ transplantation). No dissemination.

Radiographical:

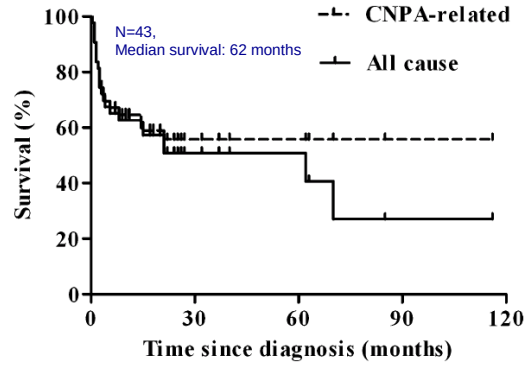
•Cavitary pulmonary lesion with evidence of paracavitary infiltrates. New cavity formation, or expansion of cavity size over time.

Laboratory:

•Elevated levels of inflammatory markers (C-reactive protein or erythrocyte sedimentation rate). Either a positive serum Aspergillus precipitin test or isolation of *Aspergillus* spp from the pulmonary or pleural cavity. Exclusion of other pulmonary pathogens with similar disease presentation, including mycobacteria and endemic fungi, using appropriate cultures and serological tests.

Modified:
Nam et al. Int J ID 2010, Zmelli et al. QJM 2007, Denning CID 2003

Treatment Outcomes of Chronic Necrotizing Pulmonary Aspergillosis



Nam et al. Int J ID 2010

Chronic Cavitary Pulmonary Aspergillosis

- Presence of multiple aspergilloma in multiple thick walled cavities with or without presence of underlying parenchymal and pleural fibrosis, both with no or little tissue invasion by *Aspergillus* spp..

In Contrast: **CNPA (subacute IPA)**

- Mild immune-suppression
- Formation of pulmonary cavities
- Cavitary consolidation
- Nodules with or without a fungal ball
- Evidence of invasive by *Aspergillus* spp.

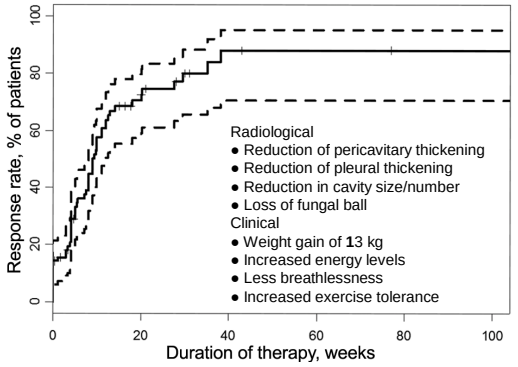
CCPA Therapy: Clinical outcomes of patients after 6 months.

	Itraconazole (n = 17)	Control (n = 14)	P value
Overall response			
Improved	13 (76.5)	5 (35.7)	0.02
Failed	4 (33.5)	9 (64.3)	
Clinical response			
Improved	6 (35.2)	1 (7.1)	0.016
Stable	7 (41.2)	4 (28.6)	
Worsened	4 (23.6)	9 (64.3)	
Radiological response			
Present	4 (23.6)	0	0.01
Stable	9 (52.8)	5 (35.7)	
Progressive	4 (23.6)	9 (64.3)	

All values are in number (percentage) unless otherwise stated.
After additional 6 months: 53% 20%

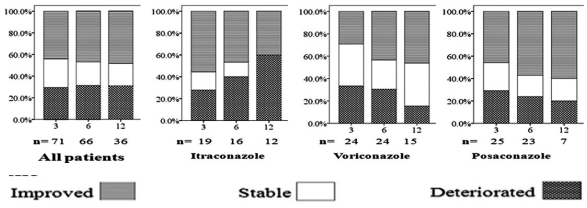
Agarwal et al 2013 Mycoses

CPA Treatment: Posaconazole



Felton et al. CID 2010

CPA: Changes in clinical status for patients who continuously were on the same antifungal therapy



Al-Shair et al. 2013 CID

Oral triazole therapy for CPA

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European Society of Clinical Microbiology and Infectious Diseases

Preliminary results

Population	Intention	Intervention	SoR	QoE	Reference	Comment
CPA patients with progressive disease	Control of infection	Itraconazole Start 200mg BID, adjust with TDM	A	II	Agarwal, 2013; De Buele, 1998, Dupont, 1990; Campbell, 1991; Tsubura, 1997; Denning, 2003; Nam, 2009; Al-shair, 2013	No data to indicate which agent is preferable.
		Voriconazole Start 150-250mg BID, adjust with TDM	A	II	Saito, 2009; Cadranel, 2012, Jain, 2006; Sambatakou, 2006; Camuset, 2007; Philippe, 2009; Al-shair, 2013	Voriconazole preferred for SIA/CNPA and patients with fungal balls to minimise risk of resistance
		Posaconazole Start 400mg BID	B	II	Felton, 2010;	

TDM required for itraconazole and voriconazole or desirable for posaconazole

28

Alternative intravenous therapy for CPA

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Preliminary results

Population	Intention	Intervention	SoR	QoE	Reference	Comment
CPA patients with progressive disease, who fail, are intolerant of triazoles or have triazole resistance	Control of infection	Micafungin 150mg/d	B	II	Kohno, 2011; Kohno, EJCMID 2013; Saito, 2009; Kohno, 2011; Kohno , 2004; Izumikawa, 2007; Yasuda, 2009; Nam, 2009	
		Amphotericin B deoxycholate 0.7-1.0mg/kg/d	C	III	Denning, 2003	
		Liposomal AmB 3mg/kg/d	B	IIa	Newton, 2014	
		Caspofungin 50-70mg/d	C	IIa	Kier, 2014; Kohno ECCMID 2013	

29

Local cavity therapy for CPA

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Preliminary results

Population	Intention	Intervention	SoR	QoE	Reference	Comment
CPA with aspergilloma, unwilling or unable to take oral therapy, multi-azole resistance and inoperable	Control of infection	Instillation of amphotericin B deoxycholate into cavity	C	II	Giron, 1998; Kravitz, 2013	Experimental

30

Duration of antifungal therapy for CPA

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Preliminary results

Population	Intention	Intervention	SoR	QoE	Reference	Comment
CPA patients on antifungal therapy	Control of infection, arrest of pulmonary fibrosis, prevention of haemoptysis, improved quality of life.	6 mo antifungal therapy	B	II	Agarwal, 2013: Yoshida, 2012; Nam, 2010: Felton, 2010; Camuset, 2007: Jain, 2006: Cadranel, 2012	Optimal duration of therapy in CPA is unknown, indefinite suppressive therapy may be appropriate in selected patients
		Long term antifungal therapy, depending on status and drug tolerance	C	III	Felton, 2010; Camuset, 2007; Jain, 2006; Cadranel, 2012	
Subacute IA/CNPA	Cure	6 mo	B	II	Camuset, 2007 Cadranel, 2012	

31

Surgically Treated Cases of CPA

Author/year	Period	No. patients/No. operated	Operative mortality	Operative mortality in simple aspergilloma	Operative mortality in complex aspergilloma
Battaglini [13] 1985	1972-1983	15/15	13.3%	0	18.1%
Daly [21] 1986	1953–1984	53/53	22.6%	4.7%	34.3%
Shirakusa [11] 1989	1979–1987	24/35	0	0	0
Massard [6] 1992	1974–1991	63/63	9.5%	0	10.0%
Regnard [22] 2000	1977–1997	87/89	5.6%	0	6.2%
Akbari [9] 2005	1985–2003	60/65	3.3%	0	4.3%
Lejay [23] 2011	1998-2009	33/33	0	0	0
Chen [20] 2012	1975-2010	256/262	1.17%	0	1.9%
Current series	1996-2011	30/33	0	0	0

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Farid et al 2013 J Cardioth Surg

Indications for surgery in CPA

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Preliminary results

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Simple/single aspergilloma	Cure and prevention of life-threatening haemoptysis	Lobectomy or any other segmental resection	A	II	Daly, 1986; Regnard, 2000; Kim, 2005; Pratap, 2007; Brik, 2008; Muniappan, 2014; Farid, 2013; Chen, 2012; Nacera, 2012; Lejay, 2011; IDSA 2008	Ratio risks/benefits = define surgical risk assessment scale Patients should be seen in centres with experience of aspergillosis surgery
		Video-assisted thoracic surgery (VATS)	B	II	Chen, 2014; Muniappan, 2014.	May require conversion to thoracotomy
CCPA refractory to medical management (including multi-azole resistance) with antifungal treatment and/or life-threatening haemoptysis.	Improved control of disease, possibly cure	Careful risk assessment, followed by lobectomy or pneumonectomy	A	II	Kim, 2005; Farid, 2013 (others)	Prior embolization as a temporizing procedure
		Thoracoplasty with simultaneous cavernostomy and muscle transposition flap	C/D	III	Grima, 2008 Igai , 2012	Highly experienced surgical team required

Follow up of Aspergillus nodule and after resection surgery

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Preliminary results

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Aspergillus nodule not treated with antifungal therapy	To identify progression early and/or carcinoma of lung if multiple lesions	3-6 mos clinical follow up with (low dose) imaging, inflammatory markers and Aspergillus IgG/precipitins	A	III	Farid, 2013; Muldoon, 2014	Not necessary if entire single nodule resected
Post-lobectomy/pneumonectomy	To detect recurrence early	3-6 mos then 6 monthly for 3 years with inflammatory markers and Aspergillus IgG/precipitins	A	III	Farid, 2013.	No predictors of recurrence yet described. Full re-evaluation if consistent increase in Aspergillus IgG titres.

34

New Data on Invasive Aspergillosis

Phase III Trial
Isavuconazole vs Voriconzole

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24th ECCMID Barcelona, Spain 10 - 13 May 2014

A Phase 3, Randomised, Double-blind Trial Evaluating Isavuconazole vs. Voriconazole for the Primary Treatment of Invasive Fungal Disease Caused by *Aspergillus* spp. or Other Filamentous Fungi (SECURE)

Johan Maertens, Thomas Patterson, Galia Rahav, Dimitrios Kontoyiannis, Kieren Marr, Rochelle Maher, Misun Lee, Bernhardt Zeiher and Andrew Ullmann, on behalf of the SECURE Study Group

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Study overview

Study design	Multicentre, randomised, double-blind, non-inferiority, active-controlled, parallel-group, phase 3 trial
Study size	527 patients were randomised
Indication	IFD caused by *Aspergillus* spp. or other filamentous fungi
Primary objective	To assess non-inferiority of isavuconazole compared with voriconazole for all-cause mortality through Day 42 in the intent-to-treat population with a 10% non-inferiority margin (NIM)
Main secondary efficacy endpoint	Overall success rate at end of treatment (EOT), as assessed by a blinded, Independent Data-Review Committee (DRC)

Demographic and Baseline Characteristics (ITT Population)

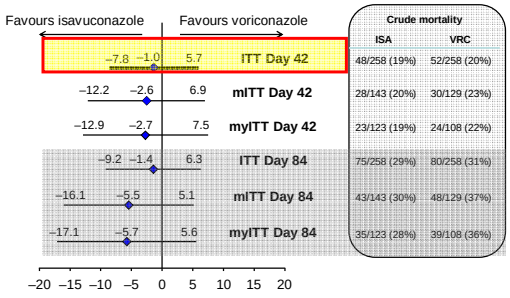
Category	Isavuconazole N = 258	Voriconazole N = 258	Total N = 516
Age, mean ± SD years	51.1 ± 16.2	51.2 ± 15.9	51.1 ± 16.0
Sex, n (%)			
Male	145 (56.2)	163 (63.2)	308 (59.7)
Geographic region, n (%)			
North America	30 (11.6)	28 (10.9)	58 (11.2)
Western Europe	105 (40.7)	107 (41.5)	212 (41.1)
Other	123 (47.7)	123 (47.7)	246 (47.7)
Baseline condition, n (%)			
Haematologic malignancy	211 (81.8)	222 (86.0)	433 (83.9)
Allogeneic BMT/HSCT	54 (20.9)	51 (19.8)	105 (20.3)
Uncontrolled malignancy	173 (67.1)	187 (72.5)	360 (69.8)
Neutropenia	163 (63.2)	175 (67.8)	338 (65.5)
T-cell immunosuppressants	111 (43.0)	109 (42.2)	220 (42.6)

Baseline pathogen (mITT population)

Pathogen Causing IFD[a, b]	Isavuconazole (N = 143)	Voriconazole (N = 129)
Proven/Probable IFD	29 (11.2%) / 114 (44.2%)	36 (14.0%) / 93 (36.0%)
Galactomannan only[c]	71 (49.7%)	68 (52.7%)
Aspergillus spp. only	49 (34.3%)	39 (30.2%)
Aspergillus spp. plus other filamentous fungi	3 (2.1%)	1 (0.8%)
Non-*Aspergillus* spp. only	5 (3.5%)	6 (4.7%)
Filamentous fungi NOS	14 (9.8%)	15 (11.6%)

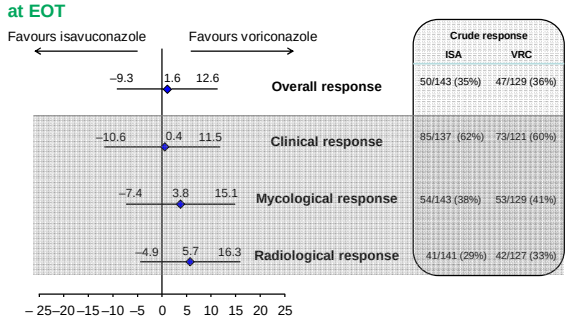
[a]As assessed by the DRC
[b]*Note*, >90% of the mITT population had pulmonary involvement
[c]Serum: 1 value ≥0.7 or 2 serial values ≥0.5 – <0.7; Bronchoalveolar lavage: 1 value ≥1.0

All-cause mortality at Days 42 and 84 in the ITT, mITT and myITT populations



Adjusted difference (%; 95% CI) between isavuconazole versus voriconazole

DRC Overall, Clinical, Mycological, & Radiological responses (mITT) at EOT



Adjusted difference (%; 95% CI) between isavuconazole versus voriconazole

Safety and tolerability

Overview of treatment emergent adverse events (TEAEs) and death

Safety population	Isavuconazole N = 257	Voriconazole N = 259
Number of subjects ≥1 TEAE, n (%)	247 (96.1)	255 (98.5)
Study drug-related TEAE	109 (42.4)	155 (59.8)*
Serious TEAE	134 (52.1)	149 (57.5)
Study drug-related serious TEAE	28 (10.9)	29 (11.2)
TEAE leading to discontinuation of study drug	37 (14.4)	59 (22.8)*
Study drug-related TEAE leading to discontinuation	21 (8.2)	35 (13.5)
Death	81 (31.5)	87 (33.6)

*Significant difference p<0.05

Safety and tolerability

10 most frequent TEAEs by System Organ Class

System Organ Class	Isavuconazole N = 257	Voriconazole N = 259	p-value
Overall, n (%)	247 (96.1)	255 (98.5)	
Gastrointestinal disorders	174 (67.7%)	180 (69.5%)	
Infections and infestations	152 (59.1%)	158 (61.0%)	
General disorders & admin. site conditions	148 (57.6%)	144 (55.6%)	
Respiratory, thoracic & mediastinal disorders	143 (55.6%)	147 (56.8%)	
Metabolism and nutrition disorders	108 (42.0%)	121 (46.7%)	
Nervous system disorders	95 (37.0%)	89 (34.4%)	
Skin and subcutaneous tissue disorders	**86 (33.5%)**	**110 (42.5%)**	**0.037**
Investigations (abnormal laboratory tests)	85 (33.1%)	96 (37.1%)	
Blood and lymphatic system disorders	77 (30.0%)	82 (31.7%)	
Psychiatric disorders	70 (27.2%)	86 (33.2%)	
Eye disorders	**39 (15.2%)**	**69 (26.6%)**	**0.002**
Hepatobiliary disorders	**23 (8.9%)**	**42 (16.2%)**	**0.016**

Conclusions

- The primary study objective was achieved for 10% NIM:
  - All-cause mortality through Day 42 in the ITT population was 18.6% vs. 20.2% in the isavuconazole and voriconazole groups, respectively
- Additional all-cause mortality analyses demonstrated consistent results
- Fewer patients given isavuconazole than voriconazole experienced hepatobiliary, skin and eye disorder-type TEAEs
- Fewer patients given isavuconazole (42%) than voriconazole (60%) experienced drug-related TEAEs

A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis

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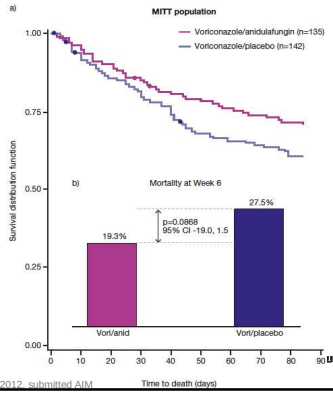
LB 2812

- The primary endpoint was overall survival at 6 weeks in patients with proven or probable IA confirmed by day 7 (modified intent-to-treat population, MITT).
- MITT population:
  - 142 (vori) 135 (combo)

Variable	Voriconazole monotherapy	Combination therapy
Underlying diseases, non-HSCT	97	86
Acute leukaemia	2 (2)	1 (1)
Acute lymphoblastic leukaemia	19 (20)	12 (14)
Acute myeloid leukaemia	43 (44)	47 (55)
Aplastic anaemia	1 (1)	1 (1)
Chronic lymphocytic leukaemia	8 (8)	5 (6)
Chronic myeloid leukaemia	1 (1)	0
Lymphoma	13 (13)	12 (14)
Multiple myeloma	3 (3)	2 (2)
Myelodysplastic syndrome	7 (7)	2 (2)
Myeloproliferative syndrome	0	2 (2)
Non haematological	0	2 (2)
Neutropenic[3] n (%)	86 (61)	77 (57)

Marr K et al ECCMID 2012, submitted AIM

Kaplan-Meier survival curves for the overall MITT using mortality estimates adjusted for randomisation strata.



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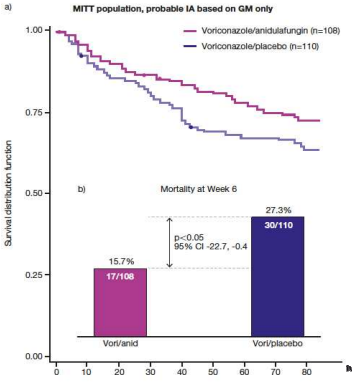
Kaplan-Meier survival curves for the overall MITT using mortality estimates adjusted for randomisation strata.



Marr K et al ECCMID 2012, submitted AIM

Targeted therapy (IA) : Choice of antifungal agents for first line therapy (I)

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European Society of Clinical Microbiology and Infectious Diseases

Preliminary results

Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Reference	Comment
[1]Neutropenia (non- allo HSCT recipients)	To increase response and survival rate	Voriconazole 2x 6 mg/kg on D1, then 2x 4 mg/kg (oral 400mg bid)	A	I	II_t	II_t	Herbrecht NEJM 2002 Marr ECCMID 2012	C III for start with IV: D III, if mould active azole prophylaxis; TDM*
[2]Allo-HCT (during neutropenia)		Liposomal AmB 3 mg/kg	B	II	II_t	II_t	Cornely CID 2007	
[3]Allo-HCT (w/o neutropenia) or other non-neutropenic patients		Caspofungin 70/50 mg	C	II	II	II	Viscoli JAC 2009 Herbrecht BMT 2010 Cornely AAC 2011	
		Micafungin 100 mg	C	III	III	III	Kohno Scand JID 2004 Denning J Infect 2006 Kontoyiannis TID 2009	
		Itraconazole 200mg q12h iv on D1, then 200 mg/qd	C	III	$II_{t,a}$	$II_{t,a}$	Caillot CID 2001	D III for start with oral, TDM*
*:TDM is discussed in an extra guideline		Isavuconazole 200mg iv tid D1-2, then 200mg qd oral	A	II_a	$II_{t,a}$	$II_{t,a}$	Maertens ECCMID 2014	This is a RCT but not yet peer-reviewed & published

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Targeted therapy (IA : Choice of antifungal agents for first line therapy (II)

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Preliminary results

Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Reference	Comment
[1]Neutropenia (non- allo HCT recipients) [2]Allo-HCT (during neutropenia) [3]Allo-HCT (w/o neutropenia)	To increase response and survival rate	cAmB 1-1.5 mg/kg	D	I	II_t	II_t	Herbrecht NEJM 2002	
		ABLC 5 mg/kg	C	III	III	III	Ito BMT 2005	
		ABCD 4-6 mg/kg	D	I	II_t	II_t	Bowden CID 2002	
		Voriconazole 6/4 mg/kg bid after one week oral possible (300mg bid) + Anidulafungin 200/100 mg	C	II_a	$II_{t,a}$	$II_{t,a}$	Marr ECCMID 2012	No difference compared to voriconazole. This is a RCT but not yet peer-reviewed & fully published; TDM*
*:TDM is discussed in an extra guideline		Other combinations, e.g. cAmB plus 5-FC	D	III	III	III	Caillot Cancer 2007	Efficacy unproven; cAmB plus 5-FC too toxic and PK erratic

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Preliminary results

Definition of patient populations: no GM/(PCR) monitoring & no prophylaxis

Patients at risk with symptoms (e.g. fever)
Minimum diagnostics: (low dose) CT and consider serial serum GM testing

CT and GM negative:
Do not treat

CT or GM positive:
Treat as recommended for fever-driven approach

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Preliminary results

Definition of patient populations: GM/(PCR) monitoring & no prophylaxis

Patients at risk with symptoms (e.g. fever) or positive GM
Minimum diagnostics: (low dose) CT and consider serial serum GM testing

CT negative:
Do not treat, but actively exclude alternative foci (e.g. sinusitis)

CT positive (infiltrates):
Treat as recommended for targeted treatment

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Preliminary results

Definition of patient populations: no GM/(PCR) monitoring, but using prophylaxis

Patients at risk with symptoms (e.g. fever) or positive GM
Minimum diagnostics: (low dose) CT, microbiological sampling (e.g. galactomannan)

CT negative:
Continue prophylaxis, consider TDM, and actively exclude alternative foci (e.g. sinusitis)

CT positive (infiltrate):
Discontinue prophylaxis, consider TDM, and treat as recommended for targeted treatment, but change antifungal class

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Preliminary results

Definition of patient populations: GM/(PCR) monitoring & prophylaxis

Patients at risk with symptoms (e.g. fever) or positive GM/PCR
Minimum diagnostics: (low dose) CT and microbiological sampling

CT negative:
Continue prophylaxis, consider TDM, and actively exclude alternative foci (e.g. sinusitis)

CT positive (infiltrate):
Discontinue prophylaxis, consider TDM, and treat as recommended for targeted treatment, but change antifungal class

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