Top 5 papers in clinical mycology

Dirk Vogelaers
Department of General Internal Medicine
University Hospital Ghent

Joint symposium BVIKM/BSIMC and SBMHA/BVMDM

UZ GENT

UNIVERSITEIT GENT

Influenza-associated aspergillosis in critically ill patients

- Multi-center retrospective observational one season study (12.2015-4.2016) in 8 academic tertiary care ICU the Netherlands aimed at describing diagnosis, treatment and outcome of IAA in adults
- PCR confirmed influenza (local microbiology lab registry + national ICU registrations of viral pneumonia and oseltamivir treatment in ICU admitted patients
- Positive PCR for influenza A or B in respiratory sample + new infiltrates on imaging + clinical symptoms (refractory fever or worsening of respiratory insufficiency in spite of more than 3 d of antibiotic therapy, dyspnea, hemoptysis and/or pleural friction rub + mycologic evidence
- Serum galactomannan (GM) more sensitive than expected (17/18 or 94 %); 14/18 pts (78 % BAL culture positive
- In 144 PCR confirmed episodes of influenza pneumonia in ICU high incidence of proven/probable invasive pulmonary aspergillosis using EORTC/MSG criteria (23/144 or 16 %)

(van de Veerdonk et al Am J Resp Crit Care Med 2017; 196 (4): 524-7)

Table 1. Underlying Disease, Influenza Type, *Aspergillus* Diagnosis, Initial Antifungal Therapy, and Outcome of 23 Patients with Influenza-associated Aspergillosis

Patient ID	Sex/ Age (*yr*)	Underlying Disease	Influenza Type	BAL GMI	Serum GMI	BAL Culture	*In Vitro* Susceptibility*	Corticosteroids	Initial Antifungal Therapy	Outcome†
2-1	F/34	None	A, H1N1		5.3		Wild-type and azole resistant	No	Voriconazole	Died (+27)
3-1	M/63	Hypertension, arthrosis	A, NT	1.5		*A. fumigatus*	Wild-type	Yes	Voriconazole + Lip-AmB	Died (+38)
3-3	M/65	FSGS	A, NT	6.5		*A. fumigatus*	Wild-type	No	Lip-AmB	Died (+21)
4-2	M/52	None	A, H1N1	13.6		*A. fumigatus*	Azole resistant	Yes	Voriconazole	Died (+13)
4-3	M/62	Churg-Strauss syndrome	A, NT	4.5	0.2	Negative		Yes	Voriconazole	Died (+12)
4-4	F/61	Kidney transplant	A, NT	11.7		*A. fumigatus*	Wild-type	Yes	Voriconazole	Died (+7)
5-3	M/62	None	A, NT		2.4			Yes	Voriconazole	Died (+11)
5-4	F/67	GPA	A, H1N1	8.3		*A. fumigatus*	Wild-type	Yes	Voriconazole + anidulafungin	Died (+8)
5-5	F/38	None	A, H1N1	2.0	0.9	*A. fumigatus*	Wild-type and azole resistant	Yes	Voriconazole	Died (+16)
5-6	M/53	None	A, NT	7.4	0.1	Negative		Yes	Voriconazole + caspofungin	Died (+43)
7-1	F/60	COPD	A, NT		2.8			Yes	Voriconazole	Died (+31)
7-2	F/67	Nonmalignant hematological disease	A, H1N1	2.8	0.1	Negative		Yes	Voriconazole	Died (+25)
7-3	M/66	GPA	A, NT	6.2	0.1	Negative		Yes	Voriconazole	Died (+27)
7-5	F/80	Churg-Strauss syndrome	A, H1N1		1.2		Wild-type	Yes	Lip-AmB	Died (+17)
2-2	F/53	Hematologic malignancy	A, H1N1	2.9	0.6	*A. fumigatus*	Wild-type	Yes	Voriconazole	Survived
2-3	F/45	Asthma, sinusitis	B	8.6	0.6	*A. fumigatus*	Wild-type and azole resistant	Yes	Voriconazole	Survived
4-1	M/64	None	A, H1N1	10.4		*A. fumigatus*	Wild-type	Yes	Voriconazole	Survived
5-2	M/50	COPD	B		0.6		Wild-type	Yes	Voriconazole	Survived
1-1	M/64	Myelofibrosis	A, NT	11.7		*A. fumigatus*		No	Voriconazole	Survived
6-1	M/70	Hematologic malignancy	A, H1N1	0.1	4.2	*A. fumigatus*	Wild-type	Yes	Voriconazole	Survived
6-2	M/57	Cystic fibrosis	A, H1N1	1.5		*A. fumigatus*	Wild-type	Yes	Voriconazole	Survived
6-3	M/55	None	A, H1N1	2.8		*A. fumigatus*		No	Voriconazole	Survived
7-4	M/65	Kidney transplant	A, NT	1.4	0.6	*A. fumigatus*		No	Voriconazole + micafungin	Survived

Definition of abbreviations: *A. fumigatus* = *Aspergillus fumigatus*; BAL = bronchoalveolar lavage; COPD = chronic obstructive pulmonary disease; FSGS = focal segmental glomerulosclerosis; GMI = galactomannan index; GPA = granulomatosis with polyangiitis; ID = identification number; Lip-AmB = lipid formulation of amphotericin B; NT = not typed.

*In three patients, wild-type and azole-resistant *A. fumigatus* colonies were recovered from culture.

†Parentheses show number of days from diagnosis of influenza.

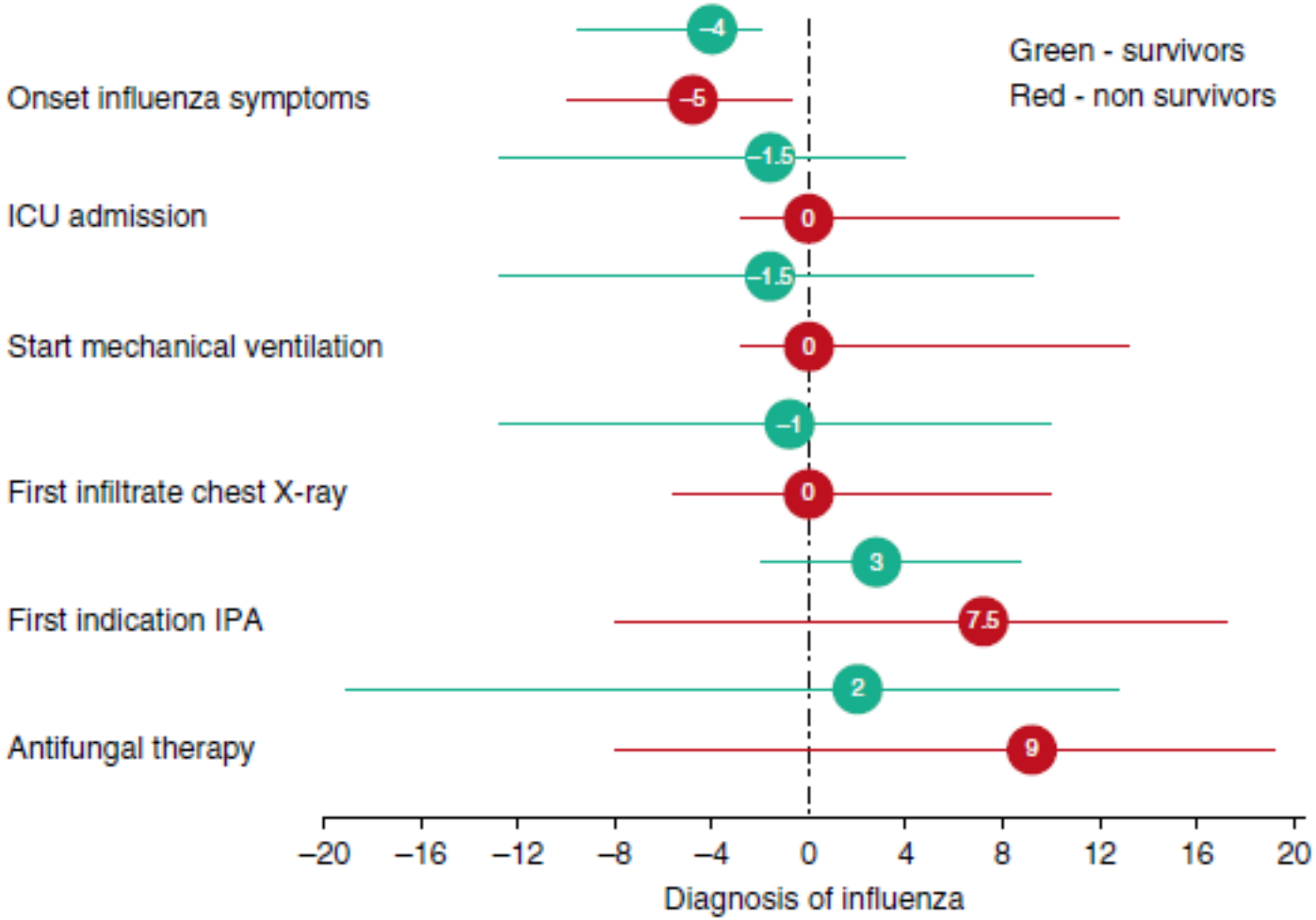
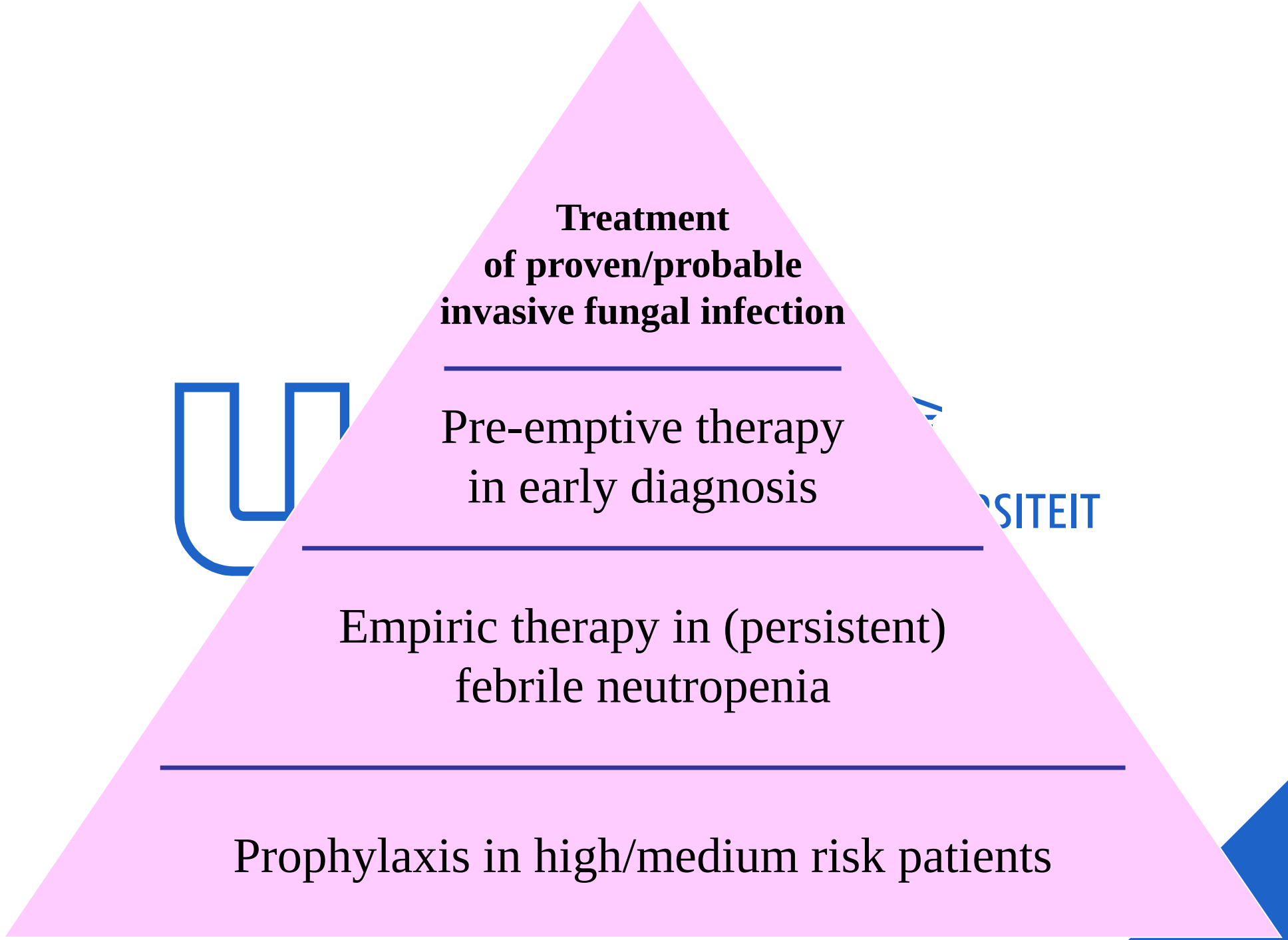


Figure 1. The median and range time to event from influenza diagnosis for survivors and nonsurvivors. The *x-axis* shows the number of days from diagnosis of influenza, with confirmed diagnosis at Day 0. ICU = intensive care unit; IPA = invasive pulmonary aspergillosis.

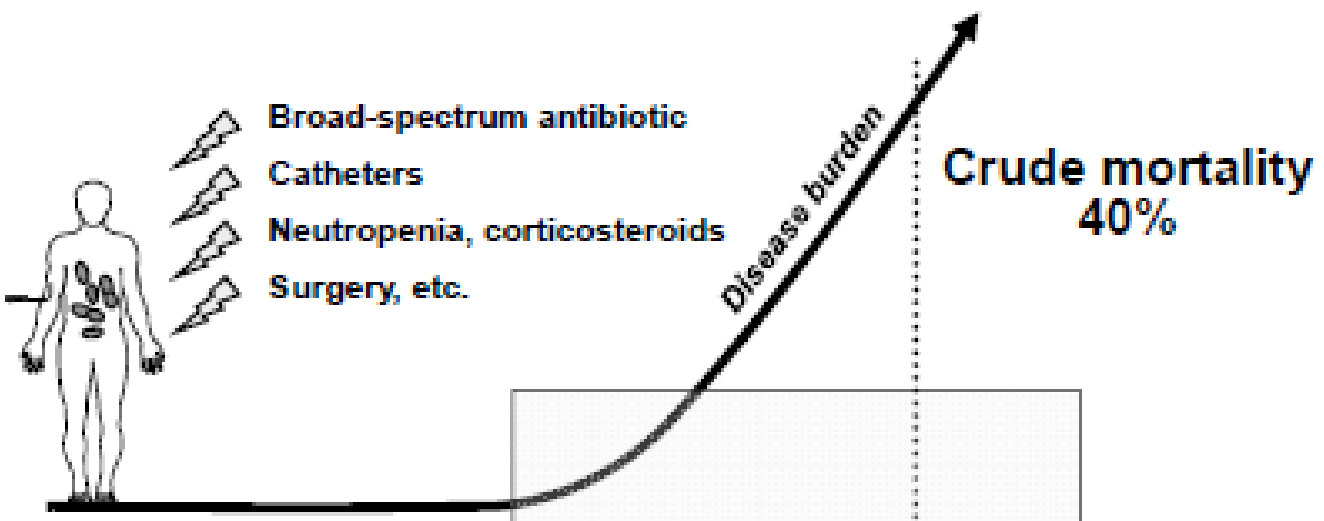
Influenza-associated aspergillosis in critically ill patients

- Also occurring in previously healthy adults: additional risk factor in non-neutropenic pts, adding to liver cirrhosis, COPD GOLD III-IV,….
- In 144 PCR confirmed episodes of influenza pneumonia in ICU high incidence of proven/probable invasive pulmonary aspergillosis using EORTC/MSG criteria (23/144)
- Early event
- Early diagnosis and treatment after admission associated with lower mortality
- Raises the question of prophylaxis

(van de Veerdonk et al Am J Resp Crit Care Med 2017; 196 (4): 524-7)


Treatment
of proven/probable
invasive fungal infection
Pre-emptive therapy
in early diagnosis
Empiric therapy in (persistent)
febrile neutropenia
Prophylaxis in high/medium risk patients

Various stages of treatment of invasive candidiasis



Slide provided by RE Lewis

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, *Candida* Colonization, and Multiple Organ Failure

The EMPIRICUS Randomized Clinical Trial

Jean-Francois Timsit, MD, PhD; Elie Azoulay, MD, PhD; Carole Schwebel, MD, PhD; Pierre Emmanuel Charles, MD, PhD; Muriel Cornet, PhamD; Bertrand Souweine, MD, PhD; Kada Klouche, MD, PhD; Samir Jaber, MD, PhD; Jean-Louis Trouillet, MD, PhD; Fabrice Bruneel, MD; Laurent Argaud, MD, PhD; Joel Cousson, MD; Ferhat Meziani, MD, PhD; Didier Gruson, MD, PhD; Adeline Paris, PharmD; Michael Darmon, MD, PhD; Maité Garrouste-Orgeas, MD, PhD; Jean-Christophe Navellou, MD; Arnaud Foucrier, MD; Bernard Allaouchiche, MD, PhD; Vincent Das, MD; Jean-Pierre Gangneux, PharmD, PhD; Stéphane Ruckly, MSc; Daniele Maubon, MD, PhD; Vincent Jullien, PharmD; Michel Wolff, MD, PhD; for the EMPIRICUS Trial Group

Empirical micafungin treatment in adults with ICU acquired sepsis, Candida colonization and multiple organ failure

- To determine whether empirical micafungin reduces invasive fungal infection free survival at day 28
- Multicenter double-blind placebo controlled study of 260 non-neutropenic, non-transplanted, critically ill pts with ICU-acquired sepsis + multiple Candida colonization + multiple organ failure + exposure to antibiotics (7,2012-2,2015 in 19 French ICU
- Empirical 100 mg micafungin (n = 131) vs placebo (n = 129)
- Primary endpoint: 28 d survival without proven IFI
- Secondary endpoints
  - New proven fungal infections
  - Survival at day 28 and 90
  - Organ failure
  - Serum (1,3)-beta-D glucan level evolution
  - Incidende of VAP

(Timsit et al, JAMA, 2016: 316 (15): 1555-64)

Figure 1. Flow of EMPIRICUS Patients From Eligibility Assessment to Primary Analysis

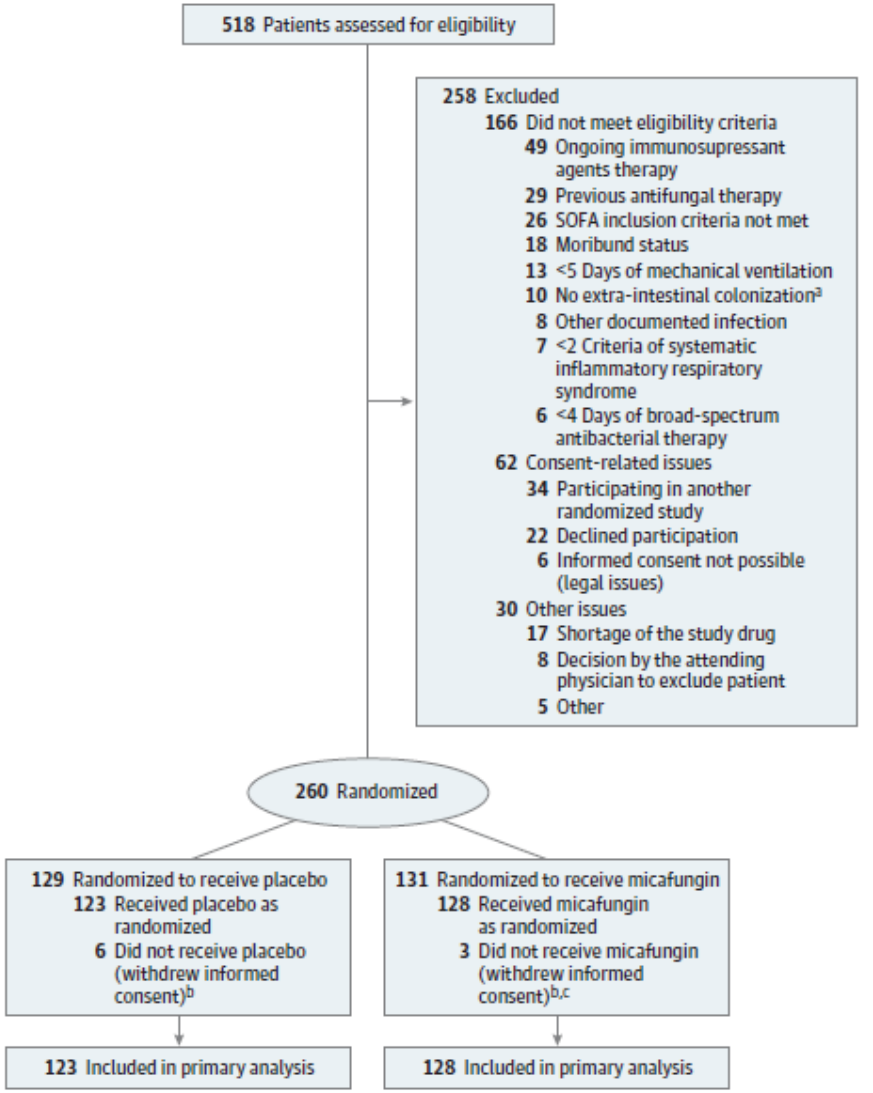
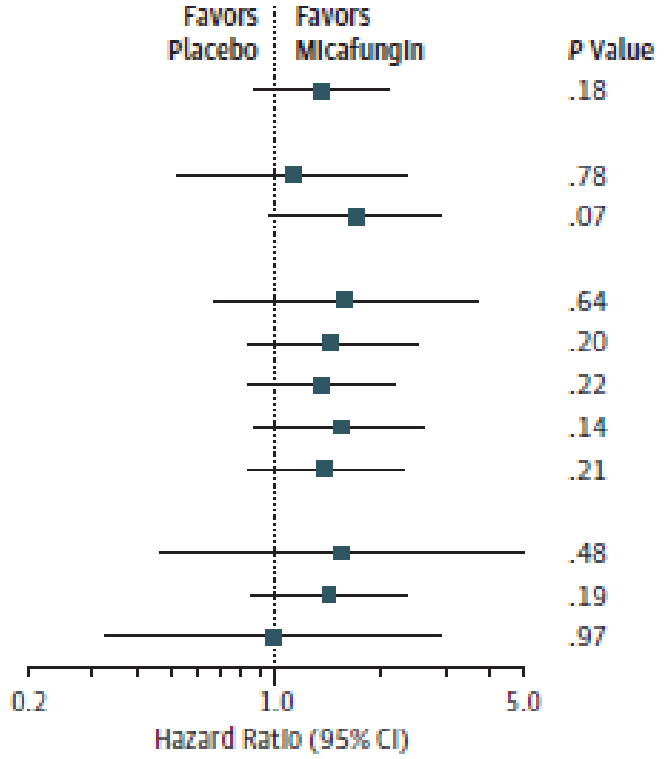


Figure 2. Comparison of Fungal Infection–Free Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	P Value
All patients	87	128	74	123	1.35 (0.87-2.08)	.18
SOFA score						
≤8	51	66	52	68	1.11 (0.53-2.33)	.78
>8	36	62	22	55	1.69 (0.96-2.94)	.07
Admission category						
Surgical	22	34	16	31	1.56 (0.67-3.70)	.64
Medical	65	94	58	92	1.43 (0.83-2.50)	.20
Colonization Index ≥0.5[a]	68	101	58	99	1.35 (0.84-2.17)	.22
Corrected colonization Index ≥0.4[b]	52	76	45	80	1.52 (0.87-2.63)	.14
Candida score ≥3	64	96	47	85	1.37 (0.83-2.27)	.21
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	14	25	1.52 (0.47-5.00)	.48
>80	58	91	47	84	1.41 (0.85-2.33)	.19
≤80	29	37	27	39	0.98 (0.30-2.94)	.97



JAMA October 18, 2016

Figure 3. Comparison of Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	P Value
All patients	90	128	86	123	1.04 (0.64-1.67)	.88
SOFA score						
≤8	53	66	58	68	0.79 (0.32-1.96)	.62
>8	37	62	28	55	1.28 (0.71-2.27)	.42
Admission category						
Surgical	23	34	23	31	0.97 (0.36-2.63)	.96
Medical	67	94	63	92	1.23 (0.69-2.22)	.48
Colonization Index ≥0.5[a]	70	101	70	99	0.93 (0.54-1.59)	.78
Corrected colonization Index ≥0.4[b]	54	76	56	80	1.02 (0.56-1.89)	.94
Candida score ≥3	66	96	58	85	0.95 (0.55-1.67)	.87
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	17	25	0.96 (0.27-3.33)	.95
>80	61	91	58	84	0.98 (0.55-1.75)	.96
≤80	29	37	28	39	0.85 (0.27-2.63)	.78

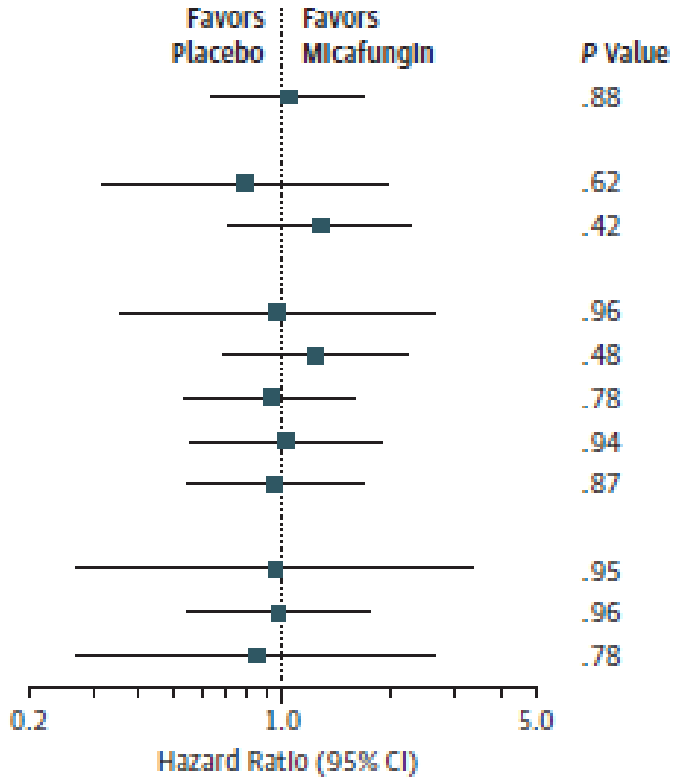


Table 2. Proven Invasive Fungal Infection at Inclusion and 28-Day Follow-up[a]

	No. (%)			
	All Patients (N = 251)	Micafungin (n = 128)	Placebo (n = 123)	Absolute Difference (95% CI)
No. of invasive fungal infections from inclusion to day 28[b]				
≥1	27 (11)	12 (9)	15 (12)	2.82 (−5.0 to 10.8)
2	3 (1)	0	3 (2)	2.44 (−0.9 to 6.9)
Invasive fungal infections by species at inclusion	12 (5)	8 (6)	4 (3)	3.00 (−2.7 to 8.9)
Candida albicans	7 (50)	4 (44)	3 (60)	15.6 (−31.3 to 53.7)
Candida glabrata	5 (36)	4 (44)	1 (20)	24.4 (−25.1 to 57.7)
Candida tropicalis	1 (7)	0	1 (20)	20.0 (−14.1 to 62.5)
Aspergillus fumigatus	1 (7)	1 (11)	0	11.0 (−36.2 to 82.4)
No. of invasive fungal infections at follow-up (day 28)[b]				
≥1[c]	19 (8)	4 (3)	15 (12)	9.1 (2.5 to 16.3)
2	2 (1)	0	2 (2)	1.6 (−1.5 to 5.7)
Invasive fungal infections by species				
Candida albicans	13 (59)	3 (75)	10 (55)	19.4 (−29.7 to 49.4)
Candida glabrata	2 (9)	0	2 (9)	11.1 (−38.5 to 32.8)
Candida parapsilosis	3 (14)	0	3 (14)	16.7 (−33.5 to 39.2)
Candida inconspicua	1 (4)	1 (25)	0	25.0 (−2.0 to 69.9)
Trichosporon[d]	2 (9)	0	2 (11)	11.1 (−38.5 to 32.8)
Aspergillus fumigatus	1 (4.5)	0	1 (6)	5.6 (−43.7 to 25.8)

Empirical micafungin/preemptive antifungal therapy for prevention of invasive candidiasis following gastrointestinal surgery for intra-abdominal infection

- “Established” indication for prophylactic fluconazole in high risk abdominal surgery (recurrent anastomotic leakage, multiple antibiotic exposure…)

- Exploratory, randomized, double-blind, placebo-controlled trial comparing micafungin 100 mg/d to placebo in ICU patients requiring surgery for intra-abdominal infection, both community-acquired and nosocomial
- Exclusion criteria: systemic antifungal within 14 days before study drug/ documented IC at randomization/ expected survival less than 48 hrs
- In full-analysis set 124 placebo- and 117 micafungin treated patients

(Knitsch et al. CID 2015; 61 (11): 1671-8)

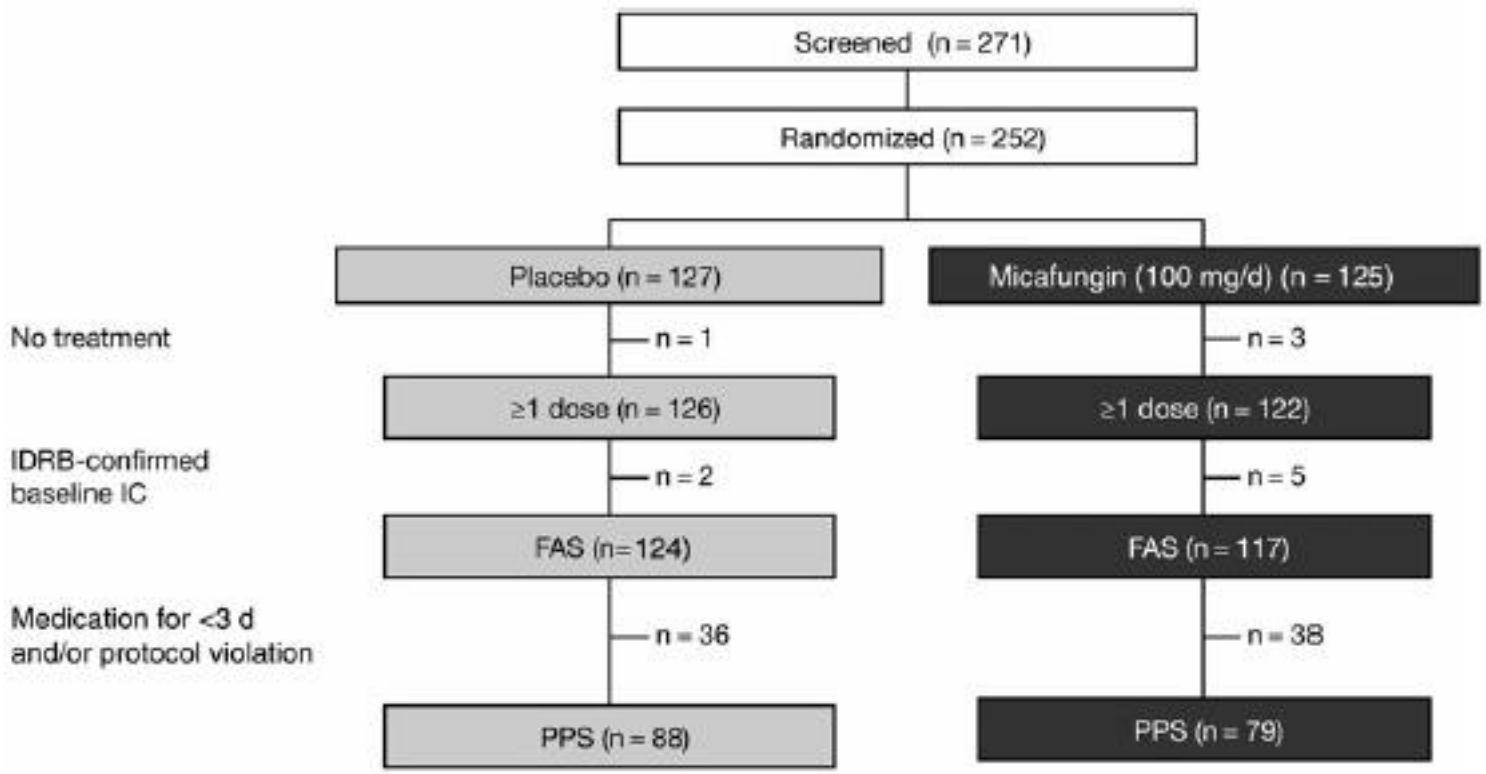


Figure 1. Patient flow through the study. In the full analysis set (FAS), 30.7% of patients had either violated the protocol (10.4% had received concurrent antifungal agents and 12.9% were outside the drug study window) or had received treatment for <3 days (11.6%). Abbreviations: IC, invasive candidiasis; IDRB, independent data review board; PPS, per-protocol set.

Table 2. Incidence of Invasive Candidiasis in the Full Analysis Set and Per-Protocol Set for All Patients

IC Incidence	Patient With IC/Total Patients, No. (%)		
	Placebo	Micafungin[b]	Treatment Difference (Micafungin – Placebo), % (95% CI)
All patients (FAS)			
IDRB-confirmed IC	11/124 (8.9)	13/117 (11.1)	2.24 (–5.52 to 10.20)
Investigator-confirmed IC[a]	20/121 (16.5)	16/116 (13.8)	–2.74 (–11.92 to 6.56)
Any-confirmed IC[a]	20/120 (16.7)	17/115 (14.8)	–1.88 (–11.24 to 7.58)
All patients (PPS)			
IDRB-confirmed IC	5/88 (5.7)	5/79 (6.3)	0.65 (–7.17 to 8.95)

Abbreviations: CI, confidence interval; FAS, full analysis set; IC, invasive candidiasis; IDRB, independent data review board; PPS, per-protocol set.

[a] FAS was modified according to who assessed for IC at baseline. Any-confirmed IC includes IC confirmed by IDRB and/or investigator.

[b] Micafungin 100 mg/d.

CID 2015:61 (1 December)

Table 4. End of Treatment Events (Full Analysis Set)

Reason for EOT	EOT Events, No. (%)	
	Placebo (n = 124)	Micafungin (n = 117)[b]
IDRB-confirmed IC	11 (8.9)	13 (11.1)
No IDRB-confirmed IC,	113 (91.1)	104 (88.9)
Sufficient improvement	78 (62.9)	75 (64.1)
Alternative antifungal therapy	8 (6.5)	5 (4.3)
Death	1 (0.8)	5 (4.3)
Other reasons for EOT[a]	25 (20.2)	18 (15.4)
Maximum 6-wk treatment	1 (0.8)	1 (0.9)

Abbreviations: EOT, end of treatment; IC, invasive candidiasis; IDRB, independent data review board.

[a] Other reasons include investigator-confirmed IC, adverse events, lack of efficacy, and protocol violation.

[b] Micafungin 100 mg/d.

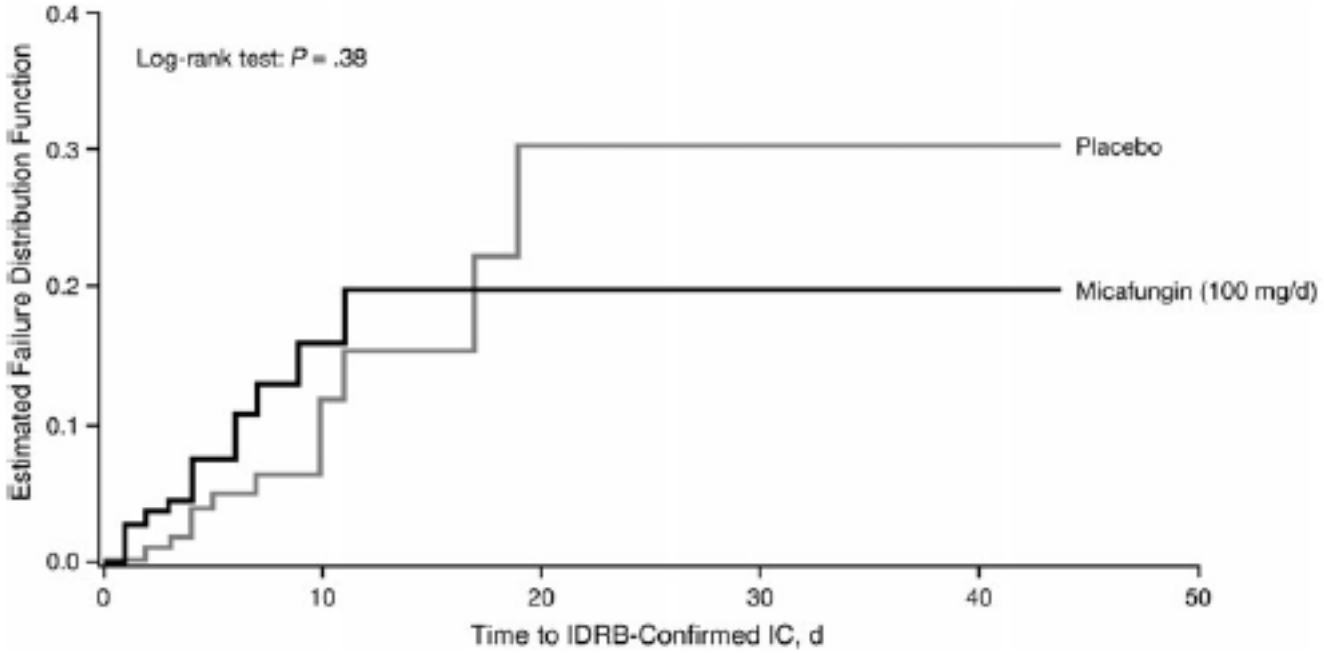


Figure 2. Kaplan–Meier failure curves of time to independent data review board (IDRB)-confirmed invasive candidiasis (IC) (full analysis set).

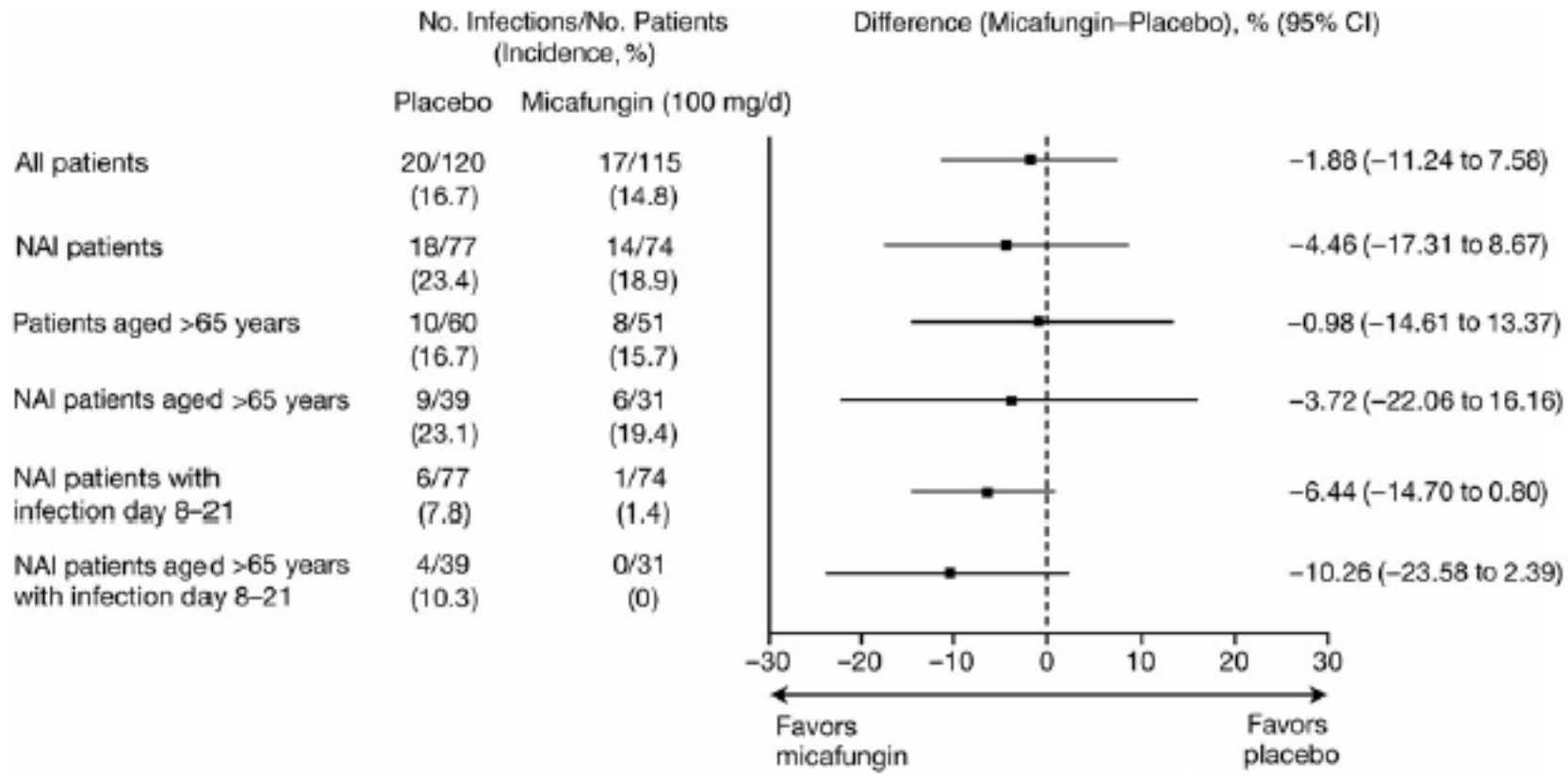


Figure 3. Incidence of confirmed cases of invasive candidiasis (IC) by higher-risk subgroups (full analysis set, modified according to who assessed for IC at baseline; cases were confirmed by independent data review board and/or investigator). Abbreviations: CI, confidence interval; NAI, nosocomially acquired infection.

Empirical micafungin/preemptive antifungal therapy for prevention of invasive candidiasis following gastrointestinal surgery for intra-abdominal infection

- Exploratory, randomized, double-blind, placebo-controlled trial comparing micafungin 100 mg/d to placebo in ICU patients requiring surgery for intra-abdominal infection
- In full-analysis set 124 placebo- and 117 micafungin treated patients
- **No differences in**
  - **Incidence of invasive candidiasis (IC): 8,9 % for placebo vs 11,1 % for micafungin (difference 2,24 %; 95 % confidence interval – 5,52 to 10,20)**
  - **In median time to IC**
  - **With positive (1,3)-beta-D-glucan 3.36 higher likelihood (95 % CI 1,01-13,29) to have confirmed IC**
- **No evidence that preemptive echinocandin is effective even in high-risk surgical ICU group with intra-abdominal infections**
- Overall low number of IC events

(Knitsch et al. CID 2015; 61 (11): 1671-8)

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Galia Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Misun Lee, Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew J Ullmann

Isavuconazole vs vorico for primary treatment of invasive mould disease (SECURE)

- Phase 3 double-blind, global multicentre, comparative group study in pts with suspected invasive mould disease
- Stratification by geographical region, allogeneic hematopoietic stem stell Tx, active malignant disease at baseline
- Isa 200 mg IV tid on d 1-2, followed by IV or po OD vs vorico 6 mg/kg IV bid d 1, 4 mg/kg IV d 2, followed by IV 4 mg/kg bid or po 200 mg bid from d 3 onwards
- Non-inferiority of primary efficacy endpoint of all-cause mortality from first dose of study drug to d 42; ITT = at least one dose using a 10 % non-inferiority margin
- Assessment of safety

(Johan Maertens et al Lancet 2016; 387: 760-69)

	Isavuconazole	Voriconazole	Adjusted treatment difference (95% CI)*
All-cause mortality			
ITT population	258	258	
Day 42 all-cause mortality	48 (19%)	52 (20%)	−1·0% (−7·8 to 5·7)
Deaths	45 (17%)	50 (19%)	..
Unknown survival status†	3 (1%)	2 (1%)	..
Day 84 all-cause mortality	75 (29%)	80 (31%)	−1·4% (−9·2 to 6·3)
Deaths	72 (28%)	75 (29%)	..
Unknown survival status†	3 (1%)	5 (2%)	..
mITT population	143	129	
Day 42 all-cause mortality	28 (20%)	30 (23%)	−2·6% (−12·2 to 6·9)
Day 84 all-cause mortality	43 (30%)	48 (37%)	−5·5% (−16·1 to 5·1)
myITT population	123	108	
Day 42 all-cause mortality	23 (19%)	24 (22%)	−2·7% (−12·9 to 7·5)
Day 84 all-cause mortality	35 (28%)	39 (36%)	−5·7% (−17·1 to 5·6)
Possible invasive mould disease	88	108	
Day 42 all-cause mortality	15 (17%)	19 (18%)	−0·5% (−12·3 to 11·2)‡
Day 84 all-cause mortality	24 (27%)	27 (25%)	2·3% (−11·2 to 15·8)‡
DRC-assessed response (mITT population)			
Overall response at EOT§	143	129	
Success	50 (35%)	47 (36%)	1·6% (−9·3 to 12·6)
Complete	17 (12%)	13 (10%)	..
Partial	33 (23%)	34 (26%)	..
Failure¶	93 (65%)	82 (64%)	..
Stable	42 (29%)	33 (26%)	..
Progression	51 (36%)	49 (38%)	..
Clinical response at EOT§	85/137 (62%)	73/121 (60%)	0·4% (−10·6 to 11·5)
Mycological response at EOT§	54/143 (38%)	53/129 (41%)	3·8% (−7·4 to 15·1)
Radiological response at EOT§	41/141 (29%)	42/127 (33%)	5·7% (−4·9 to 16·3)

Lancet 2016; 387: 760–69

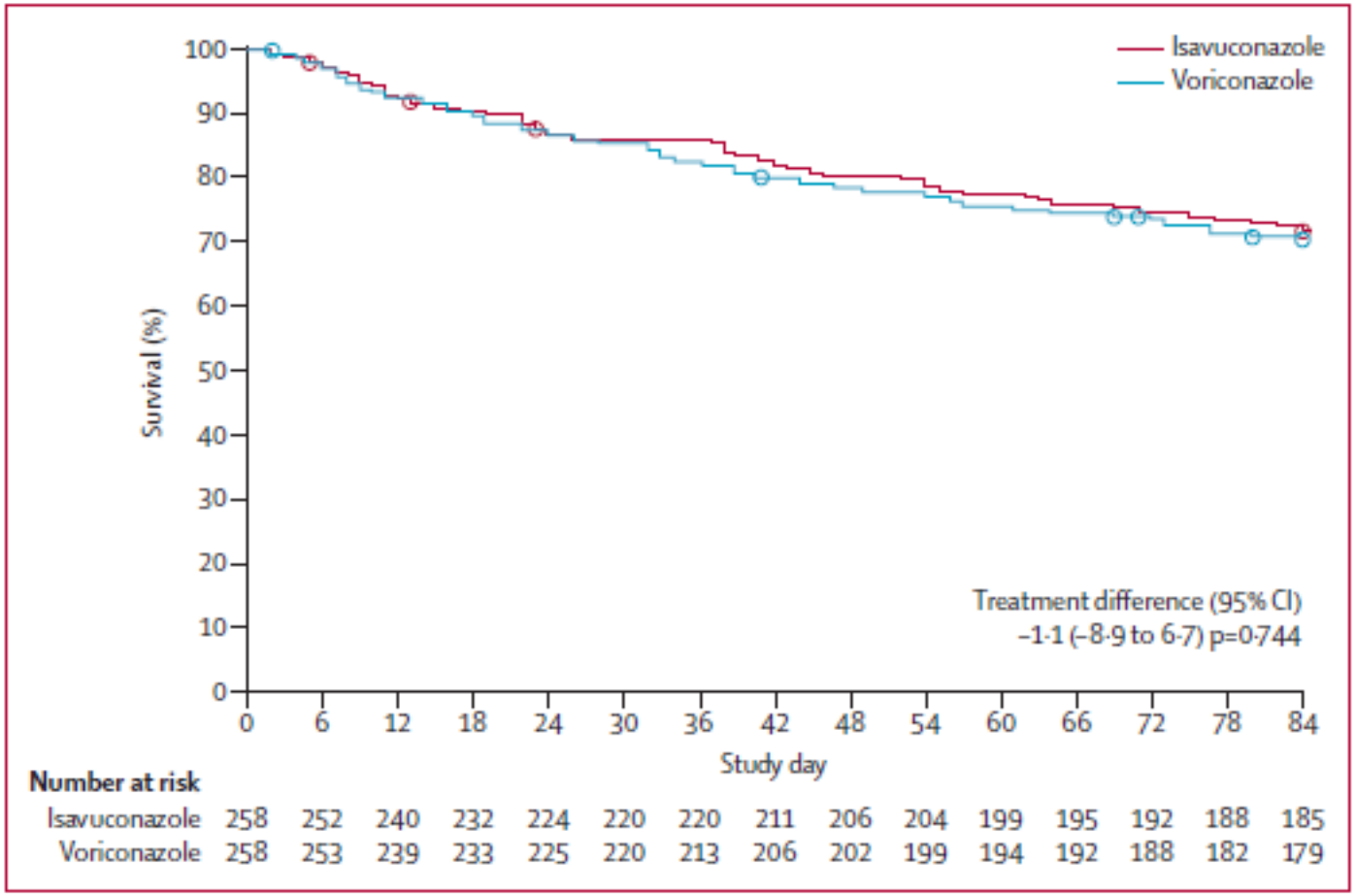


Figure 2: **Survival from first dose of study drug to day 84**
Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

Lancet 2016; 387: 760–69

	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0·122
Gastrointestinal disorders	174 (68%)	180 (69%)	0·705
Infections and infestations	152 (59%)	158 (61%)	0·719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0·658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0·859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0·289
Nervous system disorders	95 (37%)	89 (34%)	0·582
Skin and subcutaneous tissue disorders*	86 (33%)	110 (42%)	0·037¶
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0·357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0·703
Psychiatric disorders†	70 (27%)	86 (33%)	0·151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0·495
Vascular disorders	67 (26%)	77 (30%)	0·378
Renal and urinary disorders	55 (21%)	58 (22%)	0·832
Cardiac disorders	43 (17%)	57 (22%)	0·148
Eye disorders‡	39 (15%)	69 (27%)	0·002¶
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0·526
Hepatobiliary disorders§	23 (9%)	42 (16%)	0·016¶
Immune system disorders	20 (8%)	25 (10%)	0·533
Neoplasms benign, malignant and unspecified	19 (7%)	31 (12%)	0·101
Ear and labyrinth disorders	14 (5%)	13 (5%)	0·846
Reproductive system and breast disorders	8 (3%)	13 (5%)	0·373
Endocrine disorders	5 (2%)	3 (1%)	0·503
Congenital, familial, and genetic disorders	3 (1%)	2 (1%)	0·685
Social circumstances	0	1 (<1%)	>0·999

Lancet 2016; 387: 760–69

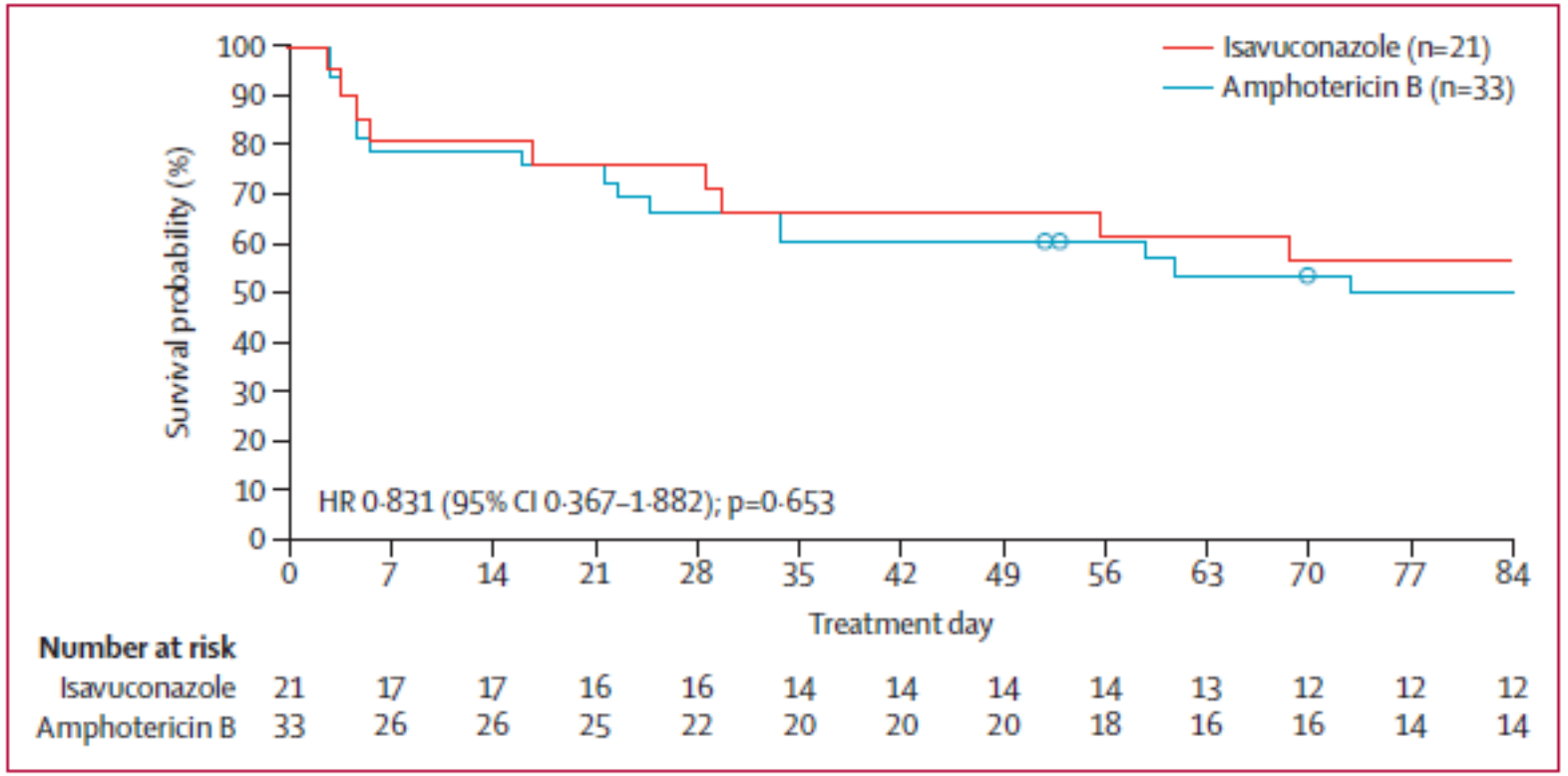


Figure 2: **Kaplan-Meier analysis of patients who received isavuconazole as primary treatment (VITAL) compared with amphotericin B-treated matched controls (FungiScope)**

Hazard ratio (HR) and 95% CI are calculated from a Cox model without covariates. Patients were censored on the day of their last known survival status, represented by the circles.

Lancet Infect Dis 2016;
16: 828–37

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

A.J. Ullmann [1, 62, 63], J.M. Aguado [2, 62, 63], S. Arikan-Akdagli [3, 62, 63], D.W. Denning [4, 5, 6, 63], A.H. Groll [7, 62, 63], K. Lagrou [8, 62, 63], C. Lass-Flörl [9, 62, 63], R.E. Lewis [10, 62], P. Munoz [11, 12, 13, 62, 63], P.E. Verweij [14, 62, 63], A. Warris [15, 62, 63], F. Ader [16, 17, 65], M. Akova [18, 62, 63], M.C. Arendrup [19, 62, 63], R.A. Barnes [20, 63], C. Beigelman-Aubry [21, 65], S. Blot [22, 23, 65], E. Bouza [11, 12, 13, 62, 63], R.J.M. Brüggemann [24, 62], D. Buchheidt [25, 62, 63], J. Cadranel [26, 65], E. Castagnola [27, 62], A. Chakrabarti [28, 63], M. Cuenca-Estrella [29, 62, 63], G. Dimopoulos [30, 65], J. Fortun [31, 62, 63], J.-P. Gangneux [32, 62, 63], J. Garbino [33, 62, 63], W.J. Heinz [1, 62, 63], R. Herbrecht [34, 62], C.P. Heussel [35, 63], C.C. Kibbler [36, 63], N. Klimko [37, 63], B.J. Kullberg [24, 62, 63], C. Lange [38, 39, 40, 65], T. Lehrnbecher [41, 63], J. Löffler [1, 62, 63], O. Lortholary [42, 62, 63], J. Maertens [43, 62, 63], O. Marchetti [44, 45, 62, 63], J.F. Meis [46, 62, 63], L. Pagano [47, 63], P. Ribaud [48], M. Richardson [4, 5, 6, 62, 63], E. Roilides [49, 50, 62, 63], M. Ruhnke [51, 62, 63], M. Sanguinetti [52, 62, 63], D.C. Sheppard [53, 62, 63], J. Sinkó [54, 62], A. Skiada [55, 62, 63], M.J.G.T. Vehreschild [56, 57, 58, 63], C. Viscoli [59, 62, 63], O.A. Cornely [56, 58, 60, 61, 62, 63, 64, *]

- Collaborative effort of European Society for Clinical Microbiology and Infectious Diseases, European Confederation of Medical Mycology and European Respiratory Society
- Multidisciplinary focus on diagnosis and treatment of aspergillosis
- Evidence graded recommendations

Table 1
Strength of recommendation and quality of evidence

Strength of recommendation	**Definition**
Grade A	Societies strongly support a recommendation for use
Grade B	Societies moderately support a recommendation for use
Grade C	Societies marginally support a recommendation for use
Grade D	Societies support a recommendation against use
Quality of evidence	**Definition**
Level I	Evidence from at least one properly* designed randomized, controlled trial (oriented on the primary end point of the trial)
Level II	Evidence from at least one well-designed clinical trial (including secondary end points), without randomization; from cohort or case–controlled analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added index	**Source of Level II evidence**
r	Meta-analysis or systematic review of randomized controlled trials
t	Transferred evidence, i.e. results from different patients' cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	Published abstract presented at an international symposium or meeting

* Poor quality of planning, inconsistency of results, indirectness of evidence etc. would lower the Strength of recommendation.

Table 7
Galactomannan testing in samples other than blood

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Any	To diagnose pulmonary IA	To apply GM test on BAL fluid	A	II	GM in BAL is a good tool to diagnose, optimal cut-off to positivity 0.5 to 1.0	[86,88,411–414]
Any	To diagnose cerebral IA	To apply GM test on cerebrospinal fluid	B	II	No validated cut-off	[415,416]
Any	To detect GM in tissue	To apply GM test on lung biopsies	B	II	Using a cut-off 0.5 resulted in a sensitivity of 90 % and a specificity of 95%; specimens need to be sliced, precondition for doing so is that sufficient material is available; dilution in isotonic saline	[61,417]

Abbreviations: BAL, bronchoalveolar lavage; GM, galactomannan; IA, invasive aspergillosis; QoE, Quality of evidence; SoR, Strength of recommendation.

Table 2
Recommendations for imaging and bronchoalveolar lavage

Population	Intention	Intervention[a]	SoR	QoE	Comment	Ref.
Neutropenia, fever or clinical symptoms of pneumonia, empiric antibiotics failing to achieve defervescence, e.g. FUO	To detect pulmonary infiltrates	Chest CT and thin section multi-detector CT (MDCT)	A	II	Dose optimization recommended	[21,31,35,366]
	To identify vessel occlusion	Chest angio-CT/pulmonary CT angiography	B	II		[24–26]
Haemoptysis	To identify vessel erosion	Chest angio-CT/pulmonary CT angiography	A	II		[367,368]
Any, with infiltrate	To identify possible underlying fungal or other infectious disease	BAL	A	II		[21,49–54]
Any, with infiltrate	To obtain appropriate specimens for microscopy, culture and PCR	CT-guided BAL	A	III		[55,56]

Abbreviations: BAL, bronchoalveolar lavage; CT, computed tomography; FUO, fever of unknown origin; PCR, polymerase chain reaction; QoE, Quality of evidence; SoR, Strength of recommendation.
[a] Diagnostic tests are interventions.

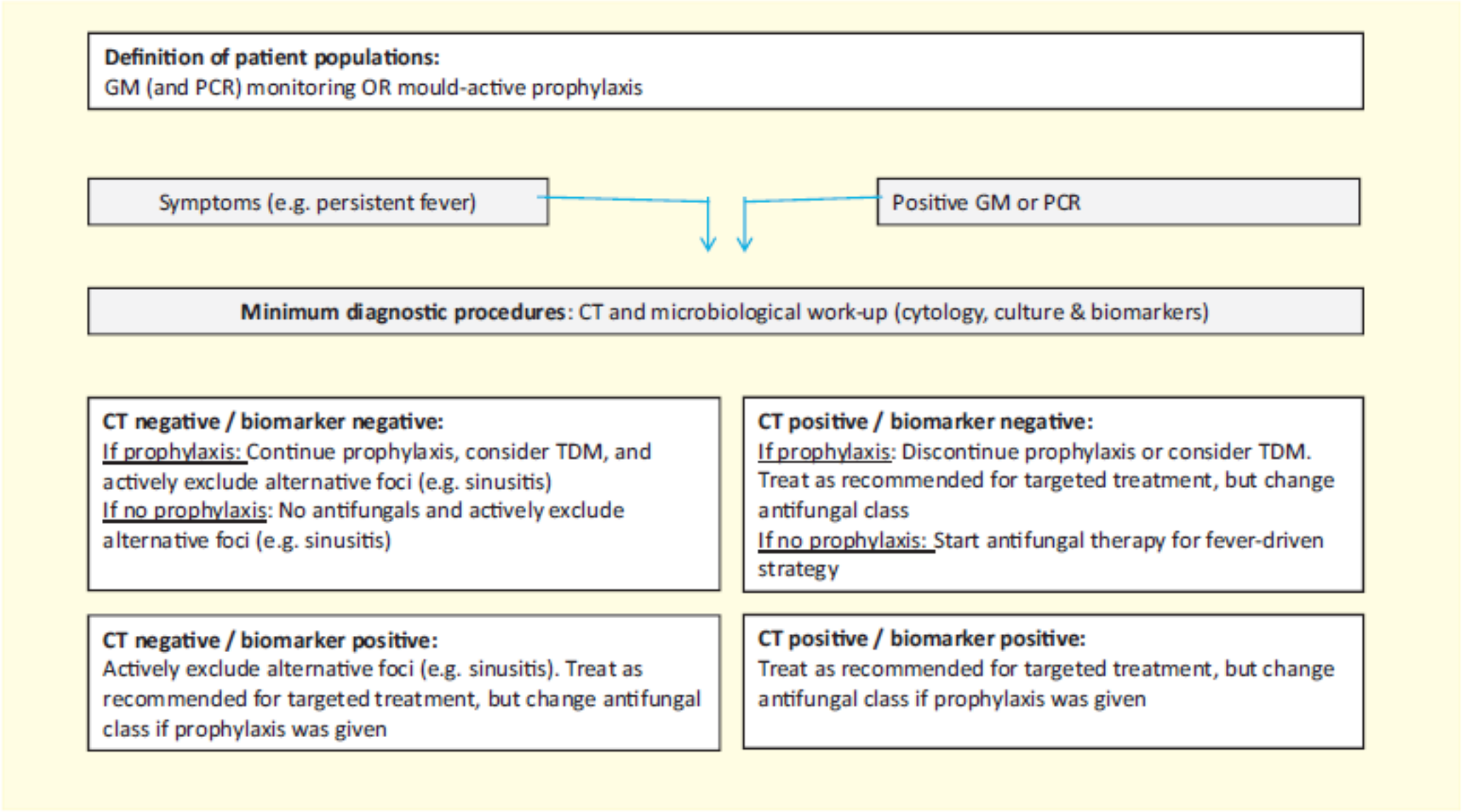


Fig. 1. Management during neutropenia.

Table 29
Fever-driven ('empiric') approach

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
Chemotherapy for haematological malignancies or HSCT, neutropenia <500/μL ≥96 h, fever (>38C), and parenteral broad spectrum antibacterial therapy ≥96 h (some centres consider 48 h)	Reduction in the incidence of IA and/or related mortality	Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	A	I	Caspofungin was associated with a significantly higher rate of survival than L-AmB (subgroup analysis).	[188]
		L-AmB 3 mg/kg	B	I	Less toxicity in comparison to cAmB but more renal toxicity compared with echinocandin	[188,189]
		Voriconazole 6 mg/kg bid IV (oral 400 mg bid) on day 1, then 4 mg/kg bid IV (oral 200–300 mg bid)	B	II	Failed the 10% non-inferiority cut-off when compared with L-AmB, but first-line for aspergillosis. Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class. TDM	[190]
		Itraconazole 200 mg qd iv	C	II	Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class. TDM	[588]
		ABLC 5 mg/kg qd	C	I	Infusion-related toxicity (fever, chills, hypoxia)	[589]
		ABCD 4 mg/kg	C	I	Same as above	[590]
		cAmB 0.5–1 mg/kg qd	D	I	Poor tolerance due to extreme toxicity	[189,342,583,584,588,590]
		Micafungin 100 mg qd	B	II		[591]
		Fluconazole	D	II_r	No activity against *Aspergillus*	[592]

Abbreviations: ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; cAmB, conventional amphotericin B; IV, intravenous; L-AmB, liposomal amphotericin B; QoE, Quality of evidence; SoR, Strength of recommendation; TDM, therapeutic drug monitoring.

Table 27
Targeted therapy of pulmonary disease—first line

Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Comment	Ref.
1] Neutropenia (non-allo HSCT recipients)	To increase response and survival rate	Isavuconazole 200 mg IV tid day 1–2, then 200 mg qd oral	A	I	II_t	II_t	D III, if mould active azole prophylaxis fewer adverse effects than voriconazole	[173,507,564,565]
2] Allo-HSCT (during neutropenia)		Voriconazole 2× 6 mg/kg IV (oral 400 mg bid) on day 1, then 2–4 mg/kg IV (oral 200–300 mg bid)	A	I	II_t	II_t	C III for start with oral; D III, if prior mould active azole prophylaxis; TDM	[170,172,507,566]
3] Allo-HSCT (w/o neutropenia) or other non-neutropenic patients		L-AmB 3 mg/kg	B	II	II_t	II_t		[171]
		Combination of voriconazole 6/4 mg/kg bid (after 1 week oral possible (300 mg bid)) + anidulafungin 200/100 mg	C	I	II_t,	II_t,	No significant difference compared to voriconazole, in GM-positive (subgroup) better survival; TDM	[172,566]
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	C	II	II	II		[567–569]
		Itraconazole 200 mg q12 h IV on day 1, then 200 mg/qd	C	III	$II_{t,a}$	$II_{t,a}$	D III for start with oral, TDM D III, if mould active azole prophylaxis	[507,537]
		AmB lipid complex (ABLC) 5 mg/kg	C	III	III	III		[570]
		Micafungin 100 mg	C	III	III	III		[571–573]
		AmB colloidal dispersion (ABCD) 4–6 mg/kg	D	I	II_t	II_t		[142]
		Conventional AmB 1–1.5 mg/kg	D	I	II_t	II_t		[170]
		Other combinations	D	III	III	III	Efficacy unproven	[574]
Life-threatening haemoptysis	Bridging until neutrophil recovery	Arterial embolization, emergency surgical intervention	B	III	III	III		[575]

Abbreviations: allo-HSCT, allogeneic haematopoietic stem cell transplantation; AmB, amphotericin B; bid, twice daily; GM, galactomannan; IA, invasive aspergillosis; IV, intravenous; qd, once daily; QoE, Quality of evidence; SoR, Strength of recommendation; TDM, therapeutic drug monitoring; tid, thrice daily.

Table 23
Voriconazole therapeutic drug monitoring

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All patients receiving voriconazole treatment for IA	Improve efficacy, safety and compliance	Measure plasma trough level after 2–5 days of therapy or soon after	A	II	Target range of 1–5.5 mg/L	[128–131,133,538–540]
		Repeat plasma trough level	B	II	Repeat during second week of therapy, additional samples as clinically indicated and outlined in the text	[128–131,133,538–540]
All patients receiving voriconazole prophylaxis for IA	Improve efficacy, safety and compliance of prophylaxis	Measure serum trough level after 2–5 days of therapy or soon after, and 4 days after change of dose	A	IIt	As above; most studies investigated voriconazole treatment rather than prophylaxis	[132,541,542]
Patients with IA due to *Aspergillus* strains of reduced azole susceptibility MIC 2 mg/mL	Improve efficacy of treatment for isolates with MIC 2 mg/mL	Measure serum trough level after 2 to 5 days of therapy or soon after and 4 days after change of dose	A	II	Trough >2 mg/L recommended on the basis of PK/PD analysis	[131,543]

Abbreviations: IA, invasive aspergillosis; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; QoE, Quality of evidence; SoR, Strength of recommendation.

Table 24
Posaconazole therapeutic drug monitoring

Population	Intention	Intervention	SoR	QoE	Comments	Ref.
Patients receiving posaconazole suspension for **treatment of IA**	Improve efficacy, compliance	Serum trough level on day 5 of therapy or soon after	A	II	Target level >1 mg/L Gastroresistant tablet or intravenous formulation preferred for most patients, consider switch to tablet or intravenous, if no therapeutic levels with oral suspension Repeat determination as clinically appropriate Prolonged half-life gives similar results for random sampling and true trough samples	[138]
Patients receiving posaconazole suspension for **prophylaxis to prevent IA**	Improve efficacy, compliance	Serum trough level on day 5 of therapy or soon after.	C	II	Target level >0.7 mg/L Adequate tissue concentrations may occur despite serum concentration <0.7 mg/L Repeat determination as clinically appropriate	[136,137,544–547]
Patients receiving posaconazole	Improve safety	Measure serum trough level on day 5 of therapy or soon after	C	III	If treatment failure or toxicity suspected, therapeutic drug monitoring may be indicated in patients receiving gastroresistant tablet or intravenous formulation Posaconazole exposures between 0.5–3.75 mg/L are well studied and considered safe and effective with all three formulations Posaconazole plasma levels above this exposure range may be associated with toxicity	[120,121]

Abbreviations: IA, invasive aspergillosis; QoE, Quality of evidence; SoR, Strength of recommendation.

Table 25
Isavuconazole therapeutic drug monitoring

Population	Intention	Intervention	SoR	QoE	Comment	Ref.
All patients receiving isavuconazole	Improve efficacy safety and compliance	Measure serum trough level on day 5 of therapy or soon after	C	III	Limited data to support routine TDM but may be indicated in the setting of treatment failure, drug interactions, or if toxicity is suspected The long half-life of isavuconazole (130 h) may support the use of TDM in some clinical situations to confirm drug clearance before starting medications metabolized by CYP3A4, especially chemotherapy agents	FDA advisory briefing documents

Abbreviations: FDA, US Food and Drug Administration; QoE, Quality of evidence; SoR, Strength of recommendation; TDM, therapeutic drug monitoring.