Infezioni da funghi filamentosi resistenti

SITA
Società Italiana di Terapia Antinfettiva
Antibatterica Antivirale Antifungina

14° CONGRESSO NAZIONALE
GENOVA | 21-22 novembre 2024

Livio Pagano
UOC di Ematologia Geriatrica ed Emopatie Rare

Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Invited Speaker – Consultant – Research grants

Stemline acquired by Menarini group

Jazz Pharmaceuticals

Gentili Oncology

Pfizer

Gilead

Cidara Therapeutics

AstraZeneca

Scynexis

Janssen Pharmaceutical Companies of Johnson & Johnson

Kyowa Kirin

abbvie

moderna

Fungi and Drug Resistance

Clinical resistance is classically defined as persistence or progression of an infection despite the administration of appropriate antimicrobial treatment. The prediction of the clinical outcome for a patient with a mycotic infection is often a difficult question and one in which many factors intervene. The antifungal susceptibility of the fungal isolate is only one of the elements that contribute to clinical resistance; other factors include the pharmacokinetics of the antifungal drug used, host factors, the site of infection, and the fungal pathogen itself. In general, **fungi can be intrinsically resistant to antifungal drugs (primary resistance) or can develop resistance in response to exposure to the drug during treatment (secondary resistance)**

Perea & Patterson, CID 2002

Antifungal drugs prevent topical or invasive fungal infections (mycoses) either by stopping growth of fungi (termed fungistatic) or by killing the fungal cells (termed fungicidal). **These microorganisms successfully develop resistance against conventional drugs that are designed to kill or stop them** from multiplaying. When a fungus no longer responds to antifungal drug treatments and continues to grow, this is known as antifungal drug resistance. **Fungi have an amazing capacity to become resistant to antifungal action**

Houssain et al, Encyclopedia 2022

Defining Breakthrough Invasive Fungal Infection–Position Paper of the Mycoses Study Group Education and Research Consortium (MSG-ERC) and the European Confederation of Medical Mycology (ECMM)

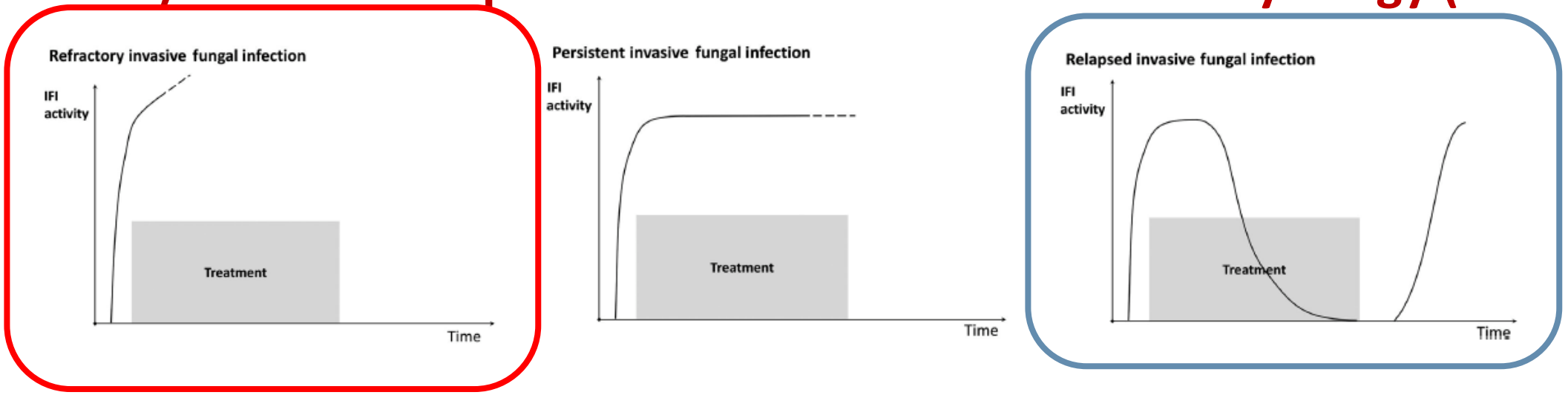


Figure 1.
Treatment Courses of Invasive Fungal Infections

Cornely et al. Mycoses 2019

Defining Breakthrough Invasive Fungal Infection– Position Paper of the Mycoses Study Group Education and Research Consortium (MSG-ERC) and the European Confederation of Medical Mycology (ECMM)

Term	Definition
Persistent IFI	IFI unchanged from baseline, may precede treatment success
Refractory IFI	IFI with worsening or new attributable clinical signs or symptoms or radiological findings attributable to IFI while on treatment
Relapsed IFI	IFI occurring after antifungal treatment discontinuation. IFI is caused by the same pathogen at the same site with or without dissemination
Breakthrough IFI	IFI occurring during exposure to an antifungal drug, including fungi outside the spectrum of activity of an antifungal (treatment emergent IFI is a synonym); The time point of breakthrough IFI is the first attributable clinical sign or symptom, mycological findings or radiological feature; The period of breakthrough IFI depends on the pharmacokinetic properties of the antifungal evaluated

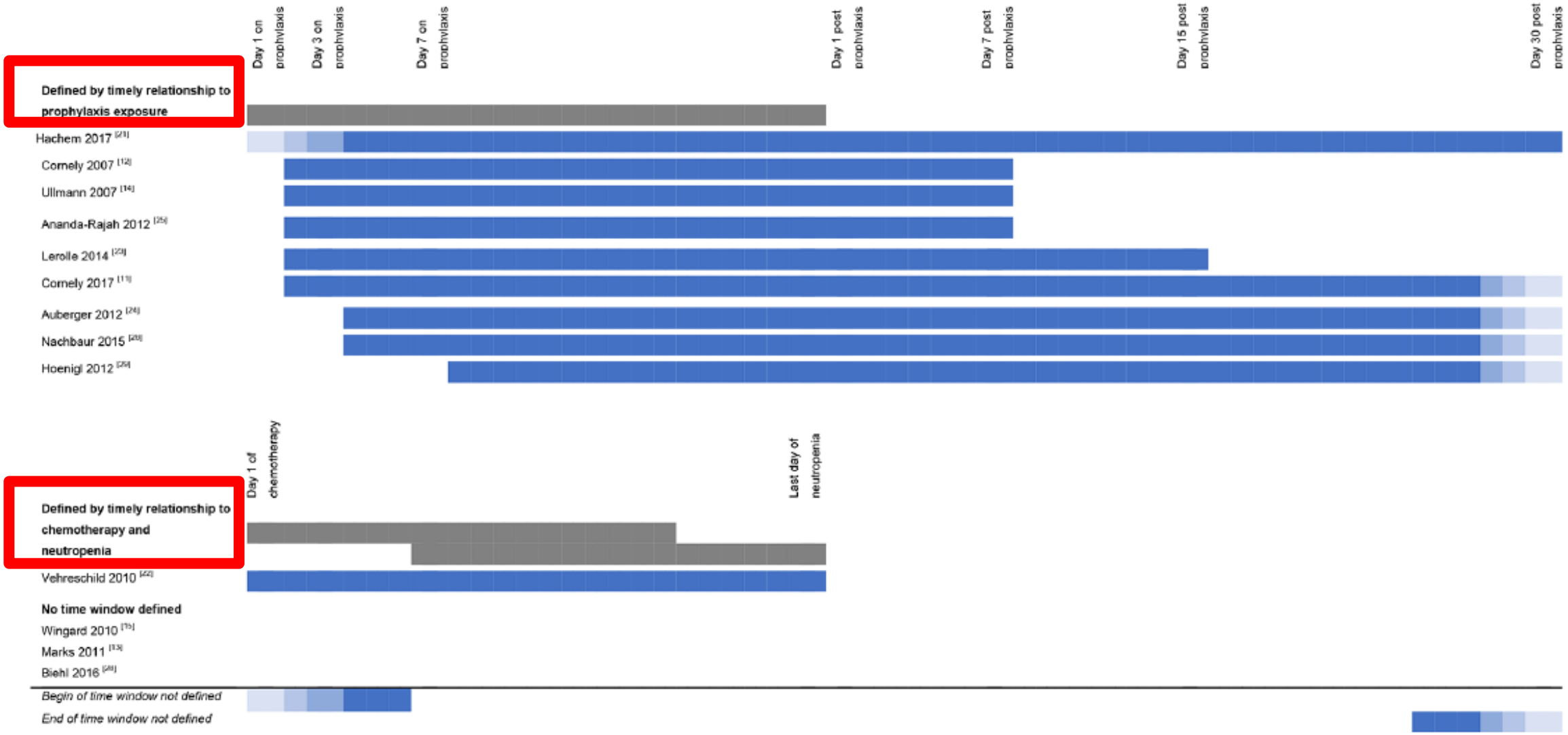
Cornely et al. Mycoses 2019

Consensus guidelines for the diagnosis and management of invasive aspergillosis, 2021

Clinical context	Definition
Primary IA	IA in a patient not exposed to a mould-active antifungal at presentation or within the last 7 days; first-line therapy is appropriate
Breakthrough IA	IA which occurs during exposure to an antifungal drug (given as either antifungal prophylaxis or treatment)
Refractory IA	Progression of disease, with worsening or new clinical symptoms, signs, or radiological features attributed to IA as a result of failure to respond to anti-*Aspergillus* antifungal treatment[†]

Douglas et al. Int Med J 2021

Breakthrough or refractory IFDs are quite similar?



Cornely et al. Mycoses 2019

Breakthrough invasive fungal infections: Who is at risk?

TABLE 2 Host and iatrogenic risk factor for breakthrough invasive fungal infection (bIFI) in patients with haematologic malignancies

Host and nosocomial factors/studies (yeast to mould)	Acute leukaemia	Neutropenia	Systemic corticosteroids	Mucositis	Central venous catheters	Broad-spectrum antibiotics
Krcmery et al JAC 1998[81] (41 yeast bIFI; 38 controls)	39% of bIFI vs 5% of control ($P < .001$)	Absent in 34% of bIFI vs 61% of control ($P < .02$)	NS	34% in bIFI vs 13% in controls ($P < .05$)	100% in bIFI vs 87% in controls ($P < .02$)	Quinolone prophylaxis; 59% bIFI vs 16% controls ($P < .001$)
Ozun et al CID 2001[22] (49 bIC vs 430 other IC)	AML 69% with bIC vs 29% others ($P < .001$)	88% bIC vs 41% others ($P < .001$)	67% biC vs 35% others ($P = .003$)	NA	NS	98% bIC vs 82% other ($P = .006$)
Puig-Asensio et al CMI 2015[102] (35 bIC vs 202 other IC)	Leukaemia 43% for biC vs 5% others ($P < .001$)	37% bIC vs 5% others ($P < .001$)	NS	27% bIC vs 6% other IC ($P < .001$)	94% bIC vs 79% others ($P = .03$)	NS
Kim et al Med Mycol. 2018[34] (21 yeast bIFI vs 28 other yeast IFI)	62% biFI vs 25% others ($P = .005$)	86% bIFI vs 43% ($P < .01$)	NS	NA	100% bIFI vs 82% others ($P = .06$; NS)	NS
Nucci et al Eur J Clin Micr Inf Dis 2002[20] (29 bIC vs 241 other IC)	NA	OR 9.14; 95% CI 3.30-25.27 ($P < .001$)	OR 3.17; 95% CI 1.31-7.70 ($P < .001$)	NA	NA	OR 2.93; 95% CI 1.13-7.61 ($P = .03$)
Pasqualotto et al J Infect 2006[35] (20 break through candidemia vs 171 with other candidaemia)	NA	NS	NS	15% bIC vs 2% other IC ($P = .027$)	NS	NA
Breda et al Med Mycol 2018[36] (27 bIC vs 121 other IC)	HSCT 59% bIC vs 2% other IC ($P < .001$)	74% bIC vs 6% other IC ($P < .001$)	56% biC vs 30% other IC ($P = .011$)	63% bIC vs 2% other IC ($P < .001$)	NS	NS
Hoenigl et al JAC 2012[103] (44 mould bIFI; 14 yeast bIFI; 116 controls)	NS	>10 d 60% vs 25% ($P < .001$)	>14 d 31% vs 8% ($P < .001$)	NA	NA	NA
Cornely et al JAC 2008[101] (26 bIFI including 18 caused by *Aspergillus*, 1 *Candida* and 8 probable with unknown pathogen; 217 without/possible bIFI)	85% newly diagnosed AML vs 60% ($P = .016$)	OR 1.043 for bIFI per additional day ($P < .001$)	NS	23% vs 11% ($P = .08$; NS)	NS	Higher number of antibiotics administered in those with bIFI ($P = .019$)

Abbreviations: bIFI, breakthrough invasive fungal infection; CI, confidence interval; IC, invasive candidiasis; NA, not applicable; NS, non-significant; OR, odds ratio.

Jenks et al. Mycoses 2020

Breakthrough invasive fungal diseases in acute myeloid leukemia patients receiving mould active triazole primary prophylaxis after intensive chemotherapy: An Italian consensus agreement on definitions and management

Full-paper articles on MA-PAP with azoles and echinocandins in AML patients submitted to intensive chemotherapy were searched on Pubmed for relevant English language publications from 2007 through May 2019. Overall, 30 articles fulfilled the predefined eligibility criteria for the literature review.

Antifungal drug (n.studies)	N. Of courses	N (%) Proven/probable Br-IFDs	N. (%) aspergillosis	N. candidosis	N.mucormycosis	N. fusariosis	N. trichosporon/geotrichum	Other	N. (%) Possible Br-IFD	Total N. (%) Br-IFD
Posaconazole (23)	3269	137 (4.3)	99 (3.0)	19	6	2	4	7	341 (10.4)	478 (14.6)
Voriconazole (5)	501	16 (3.2)	11 (2.2)	0	3	0	0	2	49 (9.8)	65 (10.8)
Itraconazole (8)	843	54 (6.4)	39 (4.6)	10	0	2	1	2	125 (14.8)	179 (21.2)
Echinocandin (7)	432	31 (7.2)	14 (3.2)	8	0	1	3	5	22 (5.1)	53 (12.3)
Total N. (%) (30)	5045	238 (4.7)	167 (3.3)	32 (0.6)	8 (0.16)	5 (0.1)	8 (0.16)	23 (0.46)	537 (10.6)	775 (15.4)

Girmenia et al. Med Mycol 2019

Antifungal prophylaxis in newly diagnosed AML patients– Adherence to guidelines and feasibility in a real life setting

- 90 AMLs undergoing induction-chemotherapy between 2011 and 2014
- 75.5% of the 90 patients received posaconazole prophylaxis. All but 8 patients received the recommended dosage.
- A total of 77.95% on prophylaxis had serum galactomannan measured twice weekly.
- Overall, 16.17% of patients had prophylaxis discontinued and started empirical antifungal treatment in the absence of diagnostic criteria for IFI.
- The breakthrough IFI rate was 36.7% (proven, probable and possible) with 7.35% of infections being classified as proven or probable.

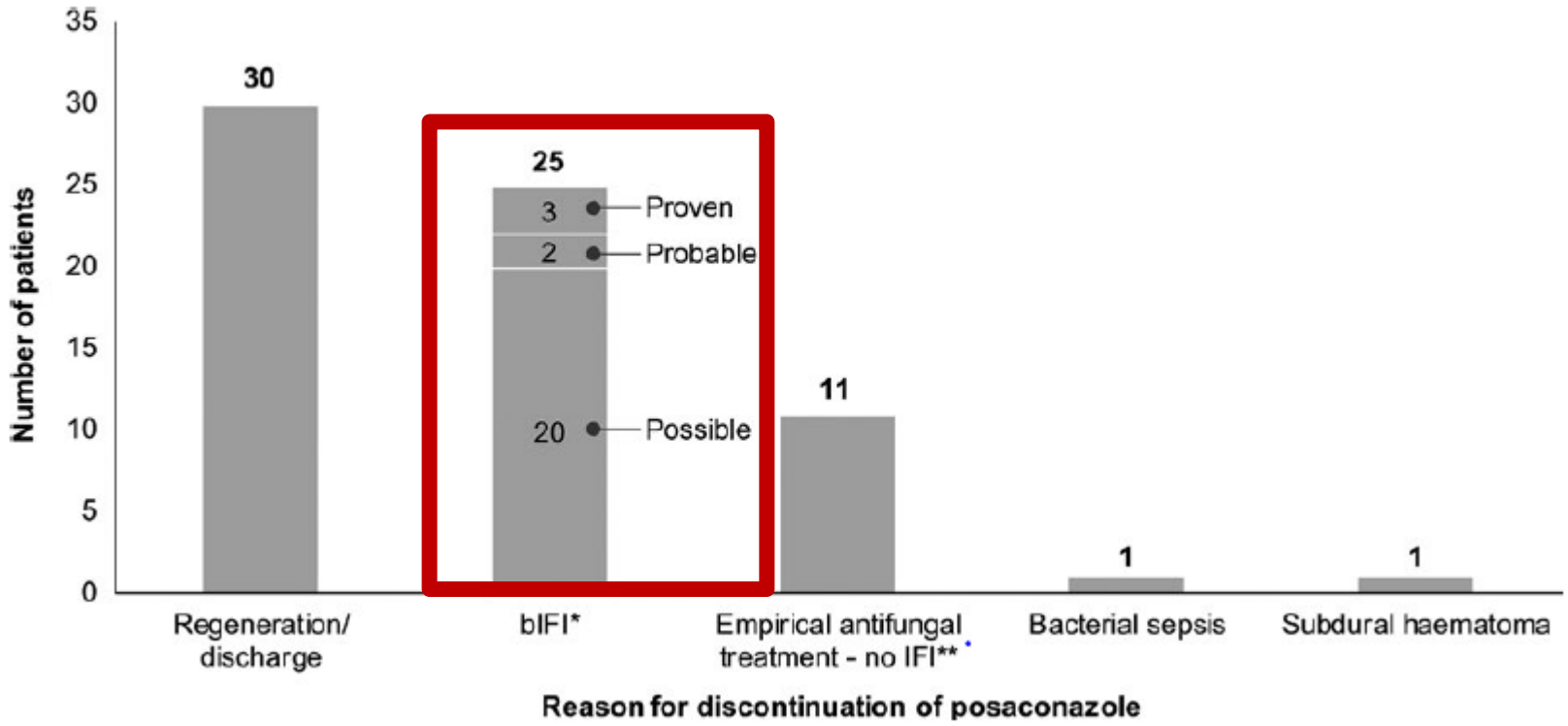


FIGURE 1 Reasons for discontinuation of posaconazole prophylaxis. **bIFI* breakthrough invasive fungal infection. ***IFI* invasive fungal infection

Berking et al, Mycoses 2017

Invasive Mold Infections in Allogeneic Hematopoietic Cell Transplant Recipients in 2020: Have We Made Enough Progress?

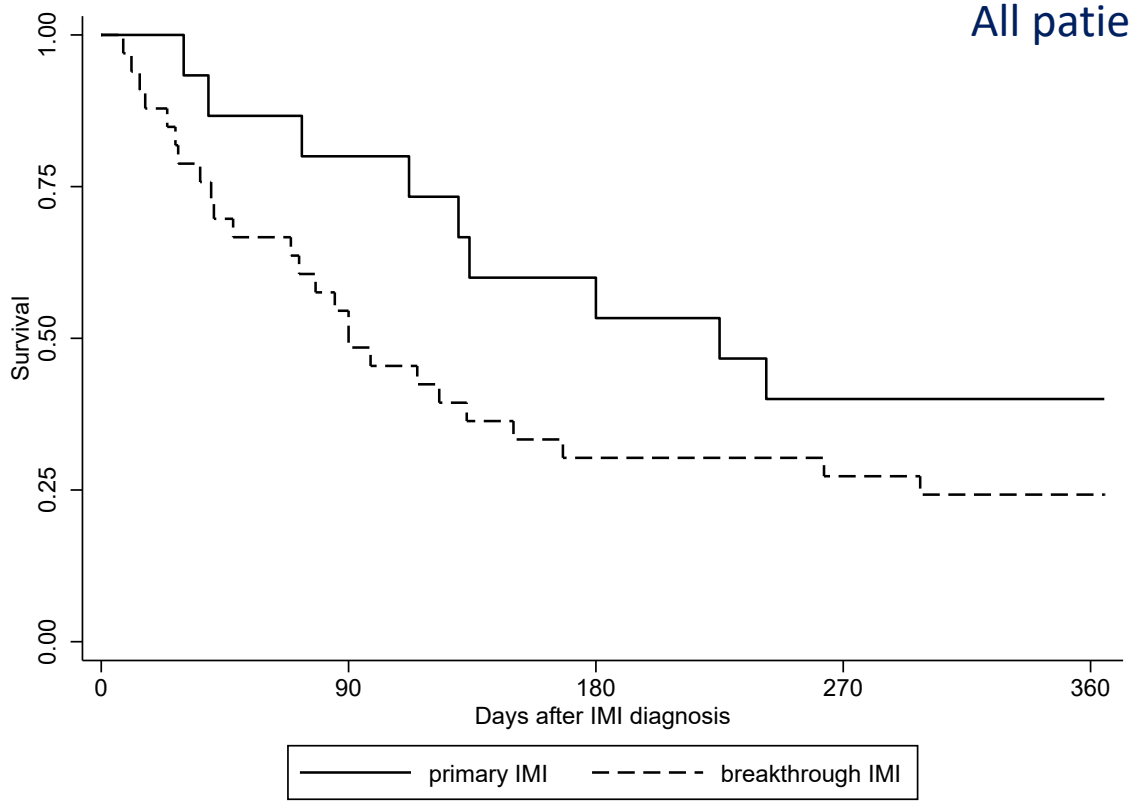
Between 2010-2019
Among 515 allo-HSCT

- 51 molds in 48 patients (9.7%)
- 34 aspergillosis
- 8 mucormycosis
- 8 other molds

35/51 (68.6%) Br-IMI

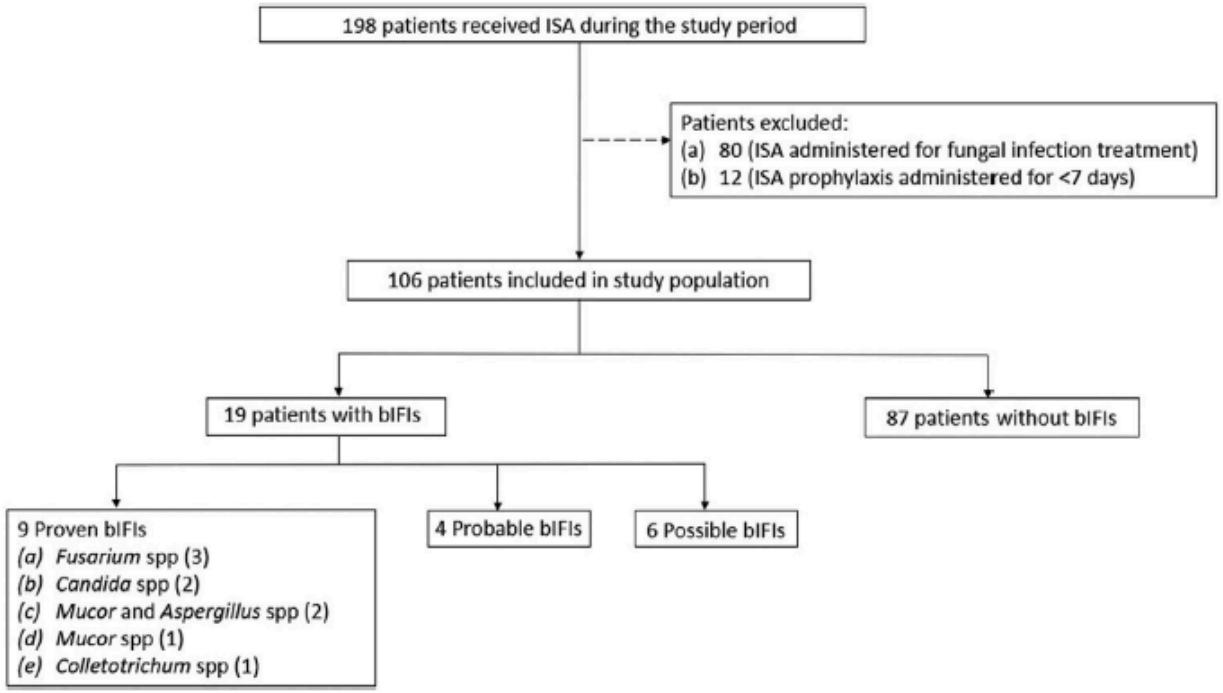
- 22 aspergillosis
- 13 non-aspergillosis

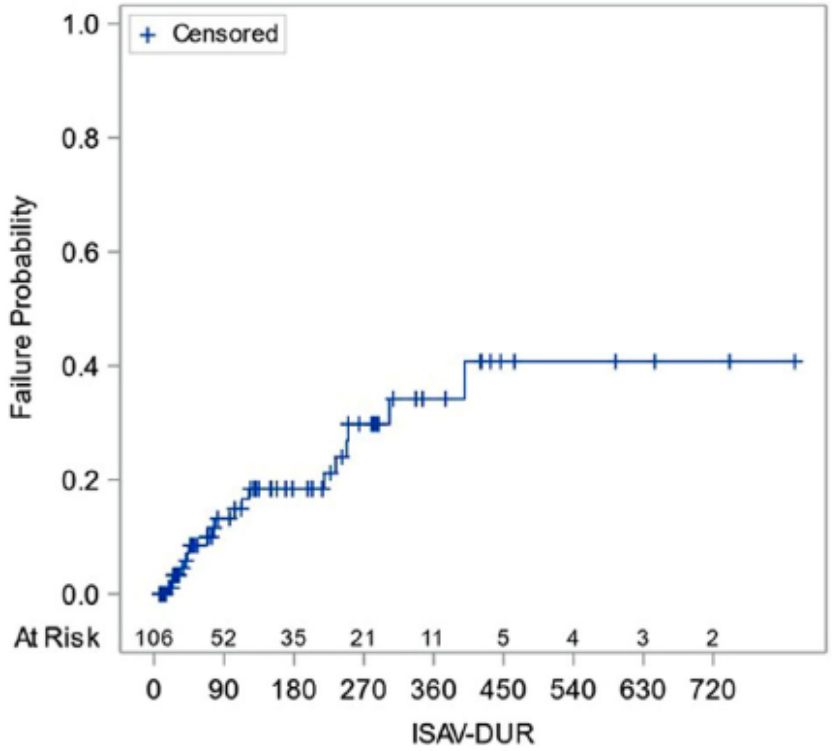
All patients performed mold-active antifungal prophylaxis



Roth et al. OFID 2021

Breakthrough invasive fungal infections on isavuconazole prophylaxis in hematologic malignancy & hematopoietic stem cell transplant patients





ISA prophylaxis was associated with a significant cumulative incidence of bIFIs. Despite the appealing side-effect and drug-interaction profile of ISA, clinicians must be vigilant about the potential risk for bIFIs

Khatri et al. Transpl Infect Dis 2023

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2019, 57, S127–S137
doi: 10.1093/mmy/myy091
Review Article

Review Article

Breakthrough invasive fungal diseases in acute myeloid leukemia patients receiving mould active triazole primary prophylaxis after intensive chemotherapy: An Italian consensus agreement on definitions and management

Corrado Girmenia[1,*], Alessandro Busca[2], Anna Candoni[3], Simone Cesaro[4], Mario Luppi[5], Anna Maria Nosari[6], Livio Pagano[7], Giuseppe Rossi[8], Adriano Venditti[9] and Franco Aversa[10]

Causes of Breakthrough Fungal Infection

Pharmacological causes

1) Non-compliance of patient to the oral primary prophylaxis
2) Insufficient intestinal adsorption and/or inadequate TDM.
3) Drug-drug interaction resulting in subtherapeutic fungal drug concentrations.
4) Br-IFD in a compartment with insufficient antifungal drug concentration (brain parenchyma, cerebrospinal fluid, vitreous body, paranasal sinuses, ischemic and/or necrotic tissues).
5) Br-IFD due to pathogens resistant to the prophylactic antifungal drug.
6) Colonization by fungal pathogens of central venous catheter/lines or other devices.

Girmenia et al. Med Mycol 2019

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Causes of Breakthrough Fungal Infection

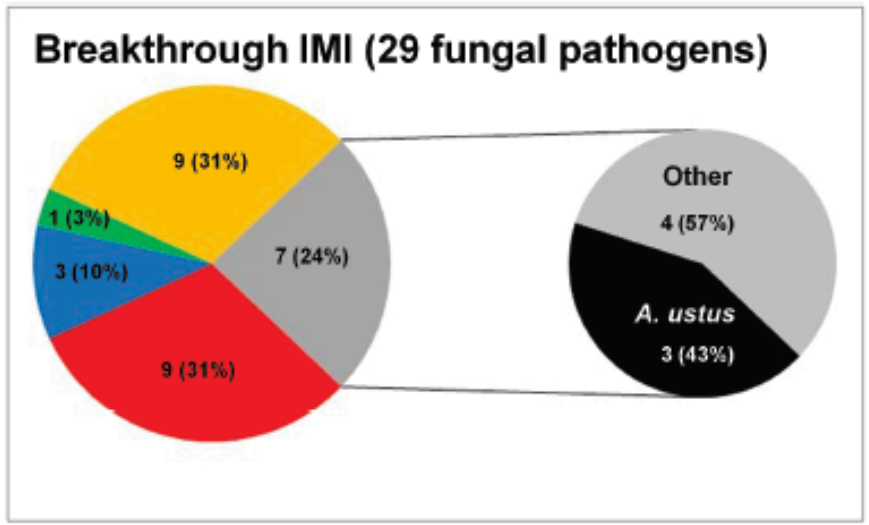
Microbiological causes

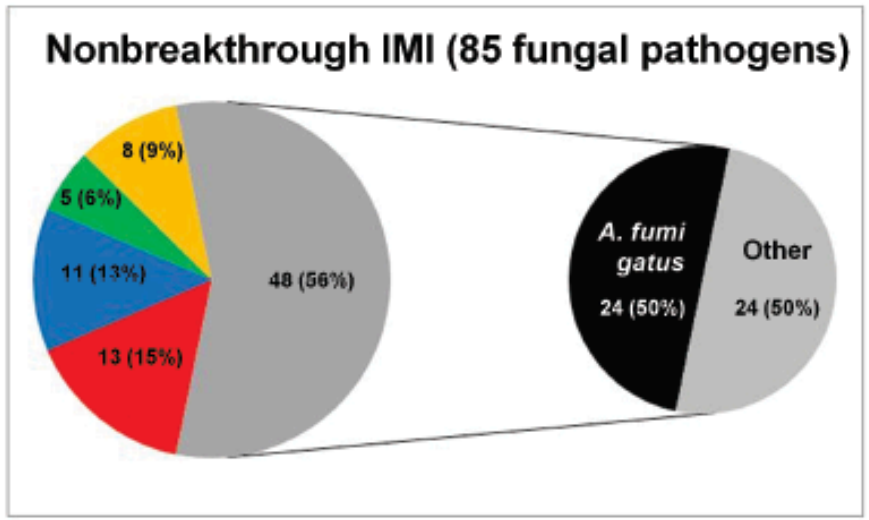
1) Non-compliance of patient to the oral MA-PAP.
2) Insufficient intestinal adsorption and/or inadequate TDM.
3) Drug-drug interaction resulting in subtherapeutic fungal drug concentrations.
4) Br-IFD in a compartment with insufficient antifungal drug concentration (brain parenchyma, cerebrospinal fluid, vitreous body, paranasal sinuses, ischemic and/or necrotic tissues).
5) Br-IFD due to pathogens resistant to the prophylactic antifungal drug.
6) Colonization by fungal pathogens of central venous catheter/lines or other devices.

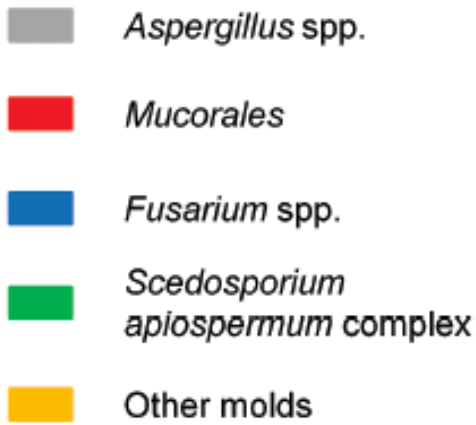
Girmenia et al. Med Mycol 2019

Changing Epidemiology of Invasive Mold Infections in Patients Receiving Azole Prophylaxis

Lamoth et al CID 2017







Both during posaconazole or voriconazole prophylaxis.

Results:

- **More non-*Aspergillus* infections**
- **Among *Aspergillus* higher percentuage of *A. ustus***

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What is an appropriate diagnostic strategy?

For a diagnosis of IFD in AML patients we need:

- Microbiology
  - Colonization
  - Blood cultures
  - Respiratory specimens (sputum, BAL, nasal swab)
    - Microscopic exam
    - Culture
    - Galactomannan (GM)
  - Fungal antigens: GM, Crypto, BDG??,
  - PCR:??
- Imaging
  - TC (EORTC-MSG diagnostic criteria)
  - Ultrasonography
- Fundus oculi
- Diagnostic surgery

The use of GM assay during MA-PAP

- Invasive Aspergillosis (IA) is the most common IFD in AML patients
- >80% of cases of IA are diagnosed at a probable level thanks to serum GM.
- Lower performance of the sensitivity and specificity of the GM assay,during MA-PAP have been hypothesized.
- Is it useful to use GM assay during MA-PAP?

Radiological diagnosis of pulmonary IFD during MA-PAP

- Does MA-PAP modify the radiological findings of pulmonary Br-IFDs?
- Should the standard EORTC-MSG radiological diagnostic criteria be used also in patients receiving MA-PAP?

Girmenia et al. Med Mycol 2019

Diagnosis of Breakthrough Fungal Infections in the Clinical Mycology Laboratory: An ECMM Consensus Statement

Jenks et al. J Fungi 2020

Diagnosis of Breakthrough Infections Caused by Molds

The diagnosis of breakthrough mold infections is challenging, as all diagnostic tests have reduced sensitivity in samples obtained during treatment or prophylaxis with mold-active antifungals.

- Culture, microscopy, and antifungal susceptibility testing are essential particularly for infections other than IA.
- Cultures of the lower respiratory tract are mostly preferred, although blood cultures may be positive in some cases. Blood invasive procedures to obtain a biopsy and definite proof of bIFI should be considered.
- A negative fungal culture does not rule out a b-mold infection, given the low sensitivity of culture in this setting.
- Despite reduced sensitivities, antigen-based diagnostics, such as GM (in BALF and serum) and BDG (in serum only), or newer assays, such as LFA and LFD (both in BALF or serum), have important roles for diagnosing breakthrough IA when the degree of clinical suspicion is high
- Not recommend using these tests for screening in patients on mold-active prophylaxis or treatment, a combination of multiple antigen-based diagnostics, conventional diagnostics, PCR-based assays, and novel diagnostic markers can help to diagnose breakthrough mold infections.
- Many of the available antigen-based diagnostics such as GM or the LFA and the LFD tests are specific for IA and very few other mold infections such as fusariosis, a negative test results do not automatically rule out a breakthrough mold infection, but instead should raise the suspicion for mucormycosis or another rare mold as a potential causative pathogen.

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What is the appropriate diagnostic strategy during MA-PAP to detect br-IFD?

For a diagnosis of IFD in AML patients we need:

- Microbiology
  - Colonization
  - Blood cultures
  - Respiratory specimens (sputum, BAL, nasal swab)
    - Microscopic exam
    - Culture
    - Galactomannan (GM)
  - Fungal antigens: GM, Crypto, BDG??,
  - PCR:??
- Imaging
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Girmenia et al. Med Mycol 2019

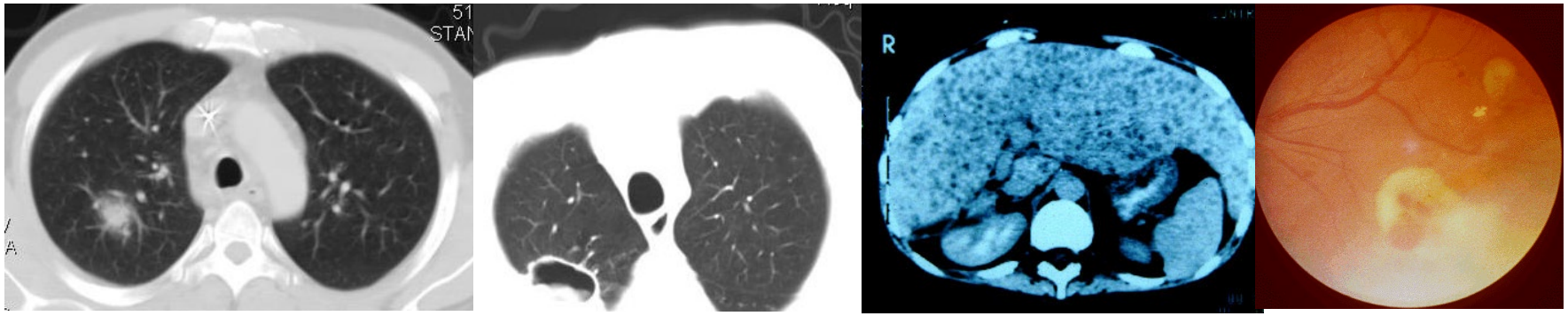
Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

Donnelly et al, CID 2020

Probable IFD : possible IFD + microbiology (GM, BDG, Culture)

Possible IFD

- dense, well-circumscribed nodular lesion(s) with or without a halo sign,
- air-crescent sign,
- cavity for pulmonary infections
- target-like abscesses (bull's eye lesions) in liver or spleen
- progressive retinal exudates on ophthalmologic examination



Pulmonary fungal infections in patients with acute myeloid leukaemia: is it the time to revise the radiological diagnostic criteria?

Characteristic at diagnosis	Group A (n = 49)	Group B (n = 24)	P
Sex, no. of male (%)	31 (63.3)	14 (58.3)	0.8
Age, median years (range)	53 (24–73)	54 (30–72)	0.9
Type of chemotherapy, no. of cases (%)			
First induction	37 (75.5)	17 (70.1)	0.7
Consolidation	6 (12.2)	2 (8.3)	
Re-induction/salvage therapy	6 (12.2)	5 (20.1)	
Microbiological diagnosis			
Aspergillus	46 (93.9)	19 (79.2)	0.1
Mucormycetes	0	3 (12.5)	0.03
Geotrichum capitatum	1 (2.2)	2 (8.3)	0.2
Aspergillus plus Mucormycetes	1 (2.2)	0	1
Aspergillus plus *G. capitatum*	1 (2.2)	0	1
Posaconazole prophylaxis, no. of cases (%)	21 (42.9)	10 (41.7)	1

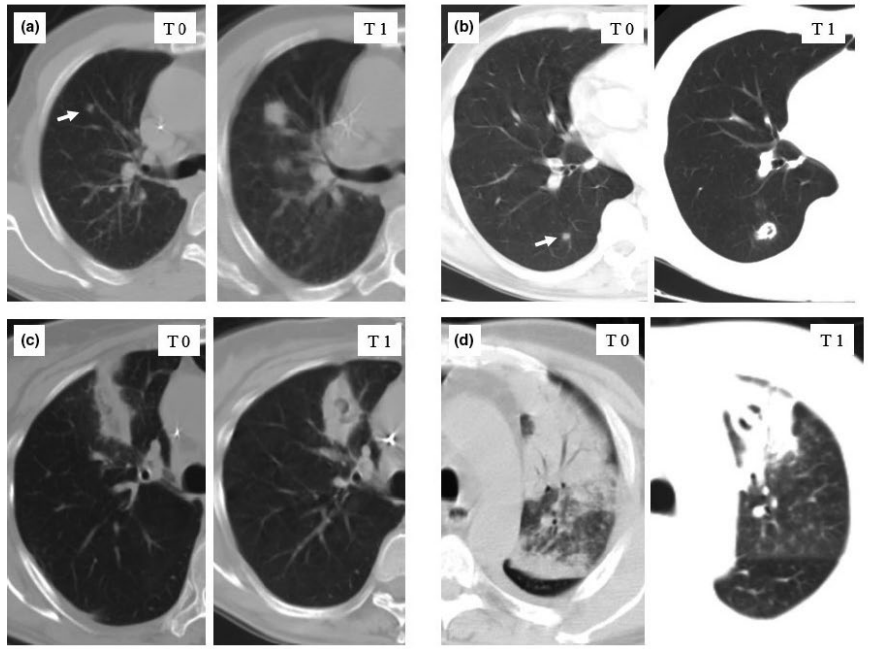


Figure 1 Cases of pulmonary fungal infections with aspecific radiological findings at first documentation (T0) and evolution in specific radiological findings at re-evaluation (T1). (a) A micronodular lesion at T0 (arrow) and a nodular lesion at T1 (day +5). (b) A micronodular lesion at T0 (arrow) and an air crescent sign lesion at T1 (day +8). (c) A consolidation at T0 and an air crescent sign lesion at T1 (day +9). (d) A mass with air bronchogram at T0 and a cavity lesion at T1 (day +11).

Maccioni et al. Mycoses 2016

Chest CT scans are frequently abnormal in asymptomatic patients with newly diagnosed acute myeloid leukemia

CT findings, *N* (%)	Baseline CT (*N* = 145)	Pneumonia[b] (*N* = 47)	No pneumonia (*N* = 98)	Significance (*p* value)[c]
Unspecified opacity	75 (51.7)	27 (57.4)	48 (49.0)	.3778
Odule	71 (49.0)	31 (66.0)	40 (40.1)	.0074
Linear opacity[a]	69 (47.6)	25 (53.2)	44 (44.9)	.3784
Ground glass opacity	26 (17.9)	18 (38.3)	8 (8.2)	<.0001
Atelectasis	26 (17.9)	11 (23.4)	15 (15.3)	.2533
Pleural effusion	27 (18.6)	14 (29.8)	13 (13.3)	.0226
Consolidation	17 (11.7)	14 (29.8)	3 (3.1)	<.0001
Emphysema	16 (11.0)	8 (17.0)	8 (8.2)	.1552
Bronchial dilatation	6 (4.1)	2 (4.3)	4 (4.1)	.5954
Bronchiectasis	4 (2.8)	2 (4.3)	2 (2.0)	>.9999

[a]Linear opacity includes septal thickening and reticulations.
[b]Pneumonia is defined as statement of 'pneumonia' on consultant radiologists' report.
[c]Comparison of CT findings in scans with summary statement suggesting pneumonia (*n* = 47) versus all other baseline scans (98).

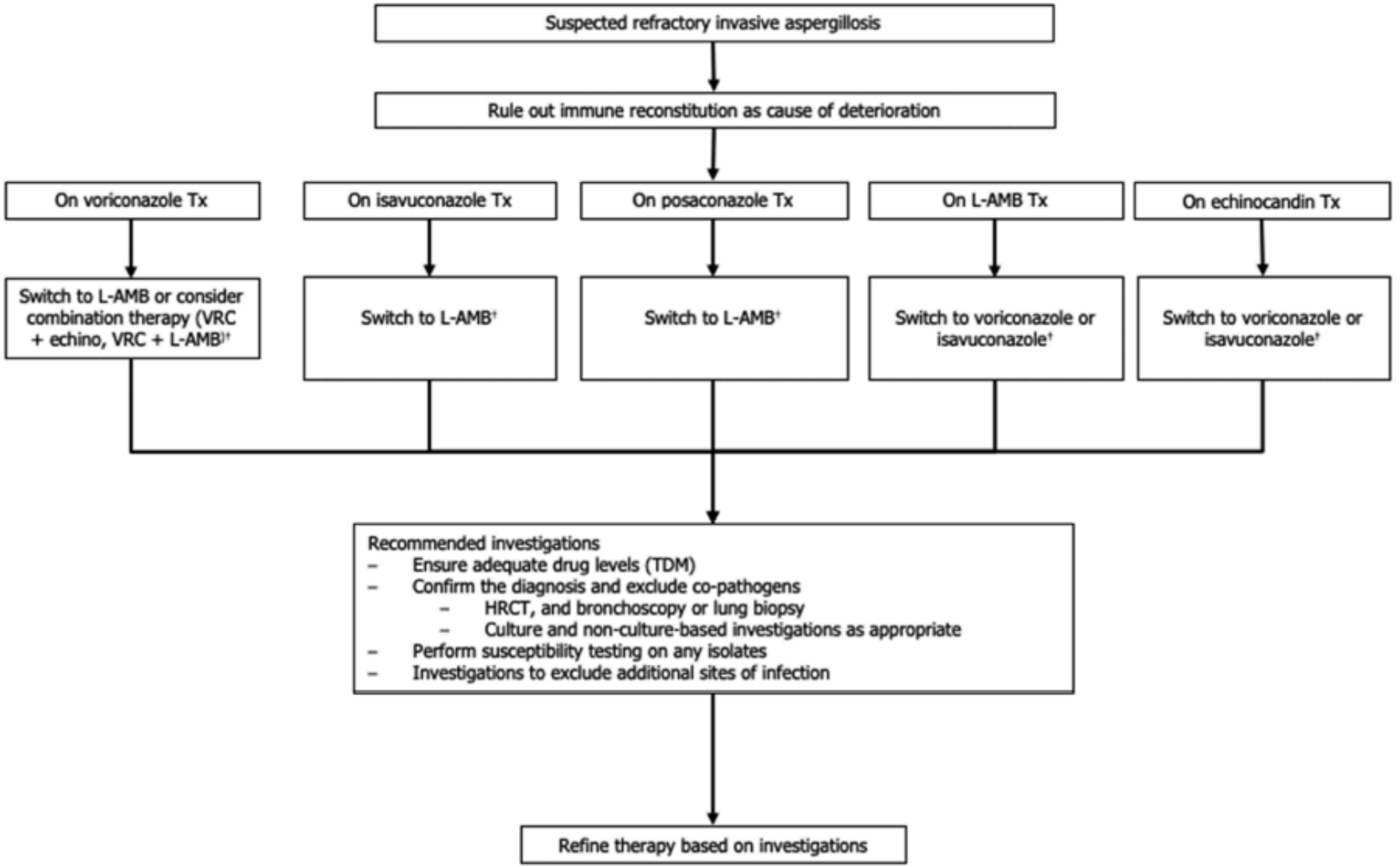
The study demonstrates that a large majority of asymptomatic AMLs have radiographic pulmonary abnormalities at baseline. The high prevalence of these findings in our asymptomatic population demonstrates that CT findings need to be correlated with the clinical status of the patient and the pretest likelihood of opportunistic infection.

There were no radiographic findings compatible with established major criteria for fungal disease in the baseline studies. Characterization of abnormalities in the radiology report into major or minor criteria for fungal disease should improve assessment and interpretation of the imaging findings

Vallipuran et al. Leuk & Lymphoma 2016

Consensus guidelines for the diagnosis and management of invasive aspergillosis, 2021

REFRACTORY

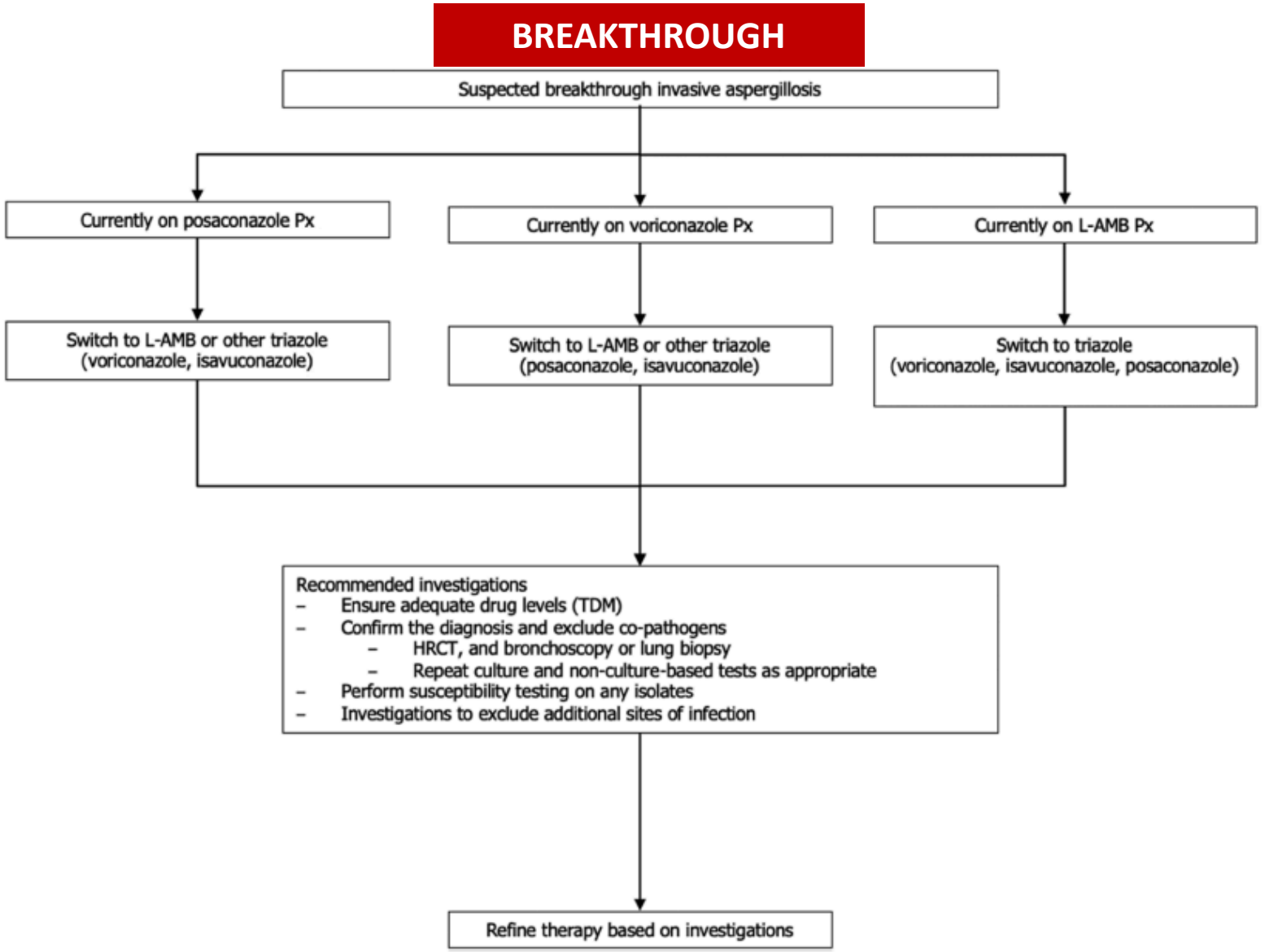


Recommendations

- Switching antifungal class in refractory IA is strongly recommended (Strong recommendation, Level III evidence).
- Combination antifungal therapy and surgical management may also be considered (Moderate recommendation, Level II evidence).
- Document adequate triazole drug levels before declaring refractory IA (Strong recommendation, Level III evidence).

Douglas et al. Int Med J 2021

Consensus guidelines for the diagnosis and management of invasive aspergillosis, 2021

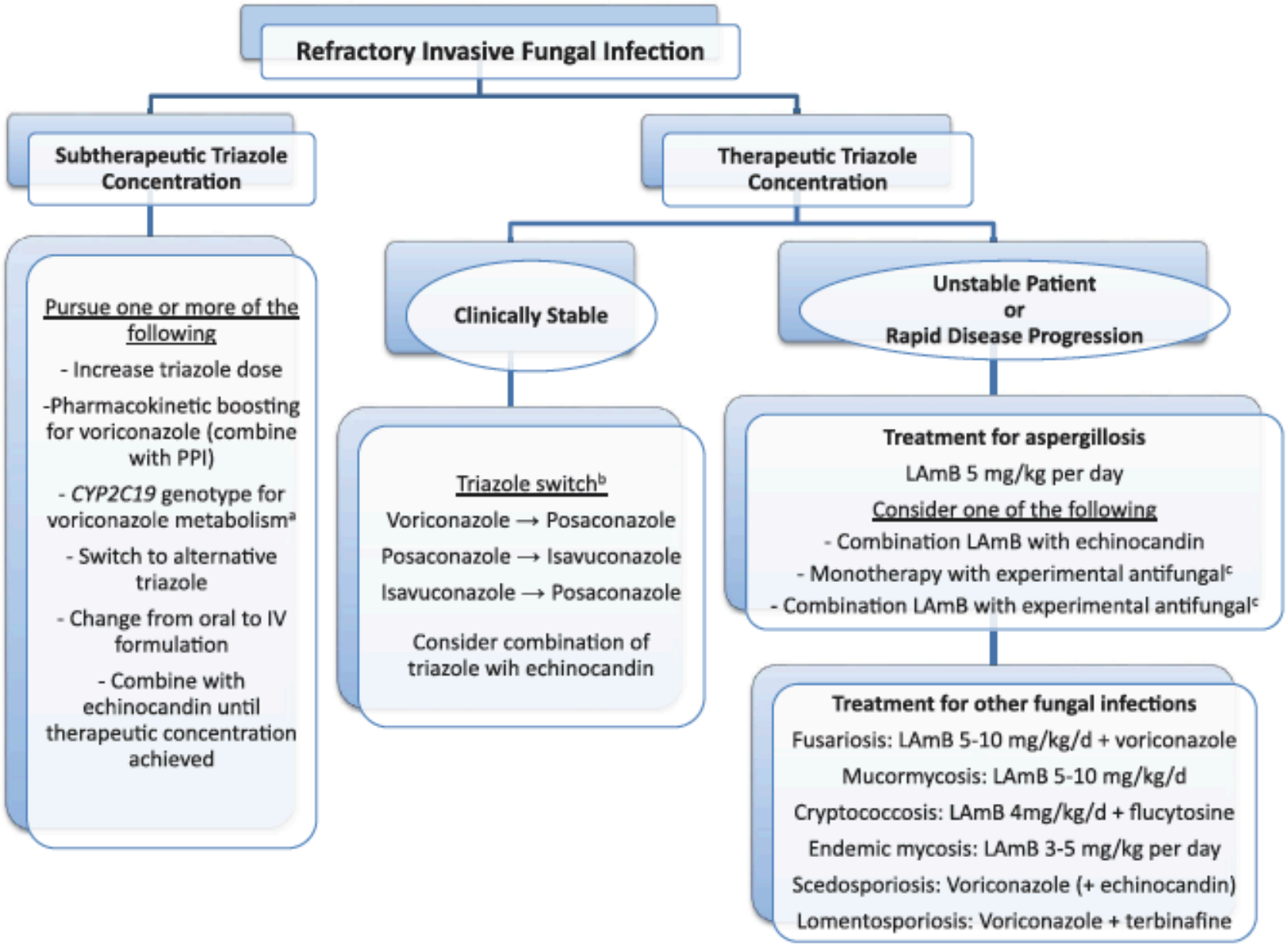


Recommendations

- Verification of adherence to antifungal therapy together with TDM should be performed in suspected breakthrough IA (Strong recommendation, Level III evidence).
- If breakthrough IA occurs on triazole prophylaxis or therapy, a switch to liposomal amphotericin B is strongly recommended (Strong recommendation, Level III evidence).
- If breakthrough IA occurs on liposomal amphotericin B therapy, a switch to voriconazole or isavuconazole is strongly recommended (Strong recommendation, Level III evidence).
- Where possible, definitive treatment targeted towards the specific fungal pathogen and with an agent confirmed to be effective on antifungal susceptibility is strongly suggested (Strong recommendation, Level III evidence).

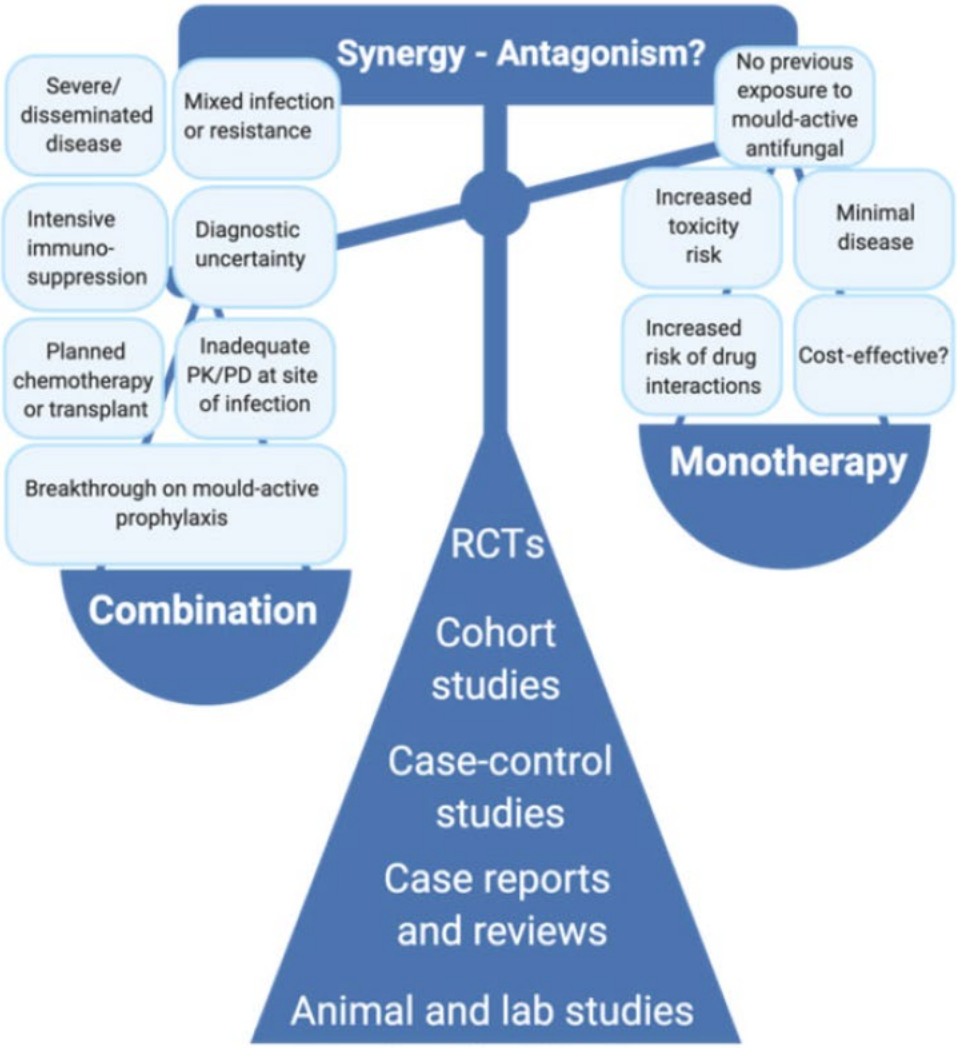
Douglas et al. Int Med J 2021

How do I manage refractory invasive pulmonary aspergillosis



Vergitis et al, CMI 2024

Combination antifungal therapy for breakthrough invasive mould disease in patients with haematological malignancies: when management reasoning eclipses evidence-based medicine



- Timely diagnosis and treatment of IFI is challenging in patients who develop breakthrough infections while on antifungal prophylaxis.
- Currently, there are no high-quality data on how to best diagnose and treat these infections.
- Pre-emptive use of antifungal combination therapy with frequent re-evaluation with an aimof de-escalation could be justified for many high-risk patients

Garcia Vidal et al. JAC 2020

Olorofim for treatment of mould IFD in patients with limited or no treatment options: Results from a Phase 2b open-label study

(NCT03583164, Study 32)

Maertens et al, AAAM 2024

Study Population

Adult (≥ 18 years of age) patients able to take oral medication

1

Diagnosed (based on 2008 EORTC/MSG criteria) with one of these 4 forms of proven invasive fungal infection

- *Lomentospora prolificans* (LoPro),
- *Scedosporium* spp.,
- *Aspergillus* spp., at any site
- Other olorofim-susceptible fungi (requiring approval)

OR

- **Probable lower respiratory tract (pulmonary) invasive aspergillosis**

2

With **limited or no alternative treatment options:**

- Known or predicted **resistance** of the infecting isolate to all licensed agents.
- **Failure** of available therapy.
- **Intolerance** to available therapy.
- Inability to manage **drug-drug interactions**.
- Inability to produce therapeutic **drug levels**.
- An **IV-only option** (e.g., an amphotericin) has produced a clinical response and a switch to an oral azole for completion of therapy is not feasible

***Key exclusion criteria**: (i) Suspected mucormycosis; (ii) Evidence of hepatic dysfunction (Total bilirubin ≥2 x ULN, Alanine transaminase or aspartate transaminase ≥3 x ULN, or Known cirrhosis or chronic hepatic failure), or (iii) Concomitant administration of inhibitors of human DHODH (teriflunomide and leflunomide)*

Demographics, underlying disease, and causative fungi

Demographics and underlying disease (n = 202 in mITT population)

- 124 men, 78 women
- 18-85 years old (mean 53)
- 71% significantly immunosuppressed[1] (40% hematological malignancy or HSCT)

Fungi

- *Aspergillus* spp. (n = 101)
- *Lomentospora prolificans* (26)
- *Scedosporium* spp. (22)
- *Coccidioides* spp. (41)
- *Scopulariopsis* spp. (6)
- Others (8): *Fusarium, Madurella,*, etc.

a) Hematological malignancy, HSCT (hematopoietic stem cell transplant), solid organ transplant, other malignancy, other immunosuppressive disease
b) Two patients had a dual infection with Scopulariopsis + Aspergillus (n=1) and Scopulariopsis + Lomentospora (n=1); these patients are counted primarily under *Aspergillus* and *Lomentospora*

DRC-adjudicated response rate and all-cause mortality at Day 42 and Day 84 (mITT)

	DRC-adjudicated response rate[1] n (%)		ACM n(%)	
	Day 42	Day 84	Day 42	Day 84
Overall (n = 202)	58 (28.7)	55 (27.2)	23 (11.4)	32 (15.8)
Aspergillus spp. (n = 101)	35 (34.7)	34 (33.7)	18 (17.8)	26 (25.7)
Lomentospora prolificans (n = 26)	11 (42.3)	11 (42.3)	3 (11.5)	3 (11.5)
Scedosporium spp. (n = 22)	8 (36.4)	5 (22.7)	2 (9.1)	2 (9.1)
Scopulariopsis spp. (n = 6)	5 (83.3)	5 (83.3)	0	0
Other Olorofim-susceptible fungi (n = 8)	1 (12.5)	2 (25.0)	0	1 (12.5)
Coccidioides spp. (n = 41)	0	0	0	0

1. EORTC-MSG criteria per Segal 2008 CID

DRC-adjudicated response rate and all-cause mortality at Day 42 and Day 84 (mITT)

% success	DRC-adjudicated response rate[1] n (%)		ACM (%)	
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Coccidioides spp. (n = 41)	0	0	0	0

Reasons for failure at day 42

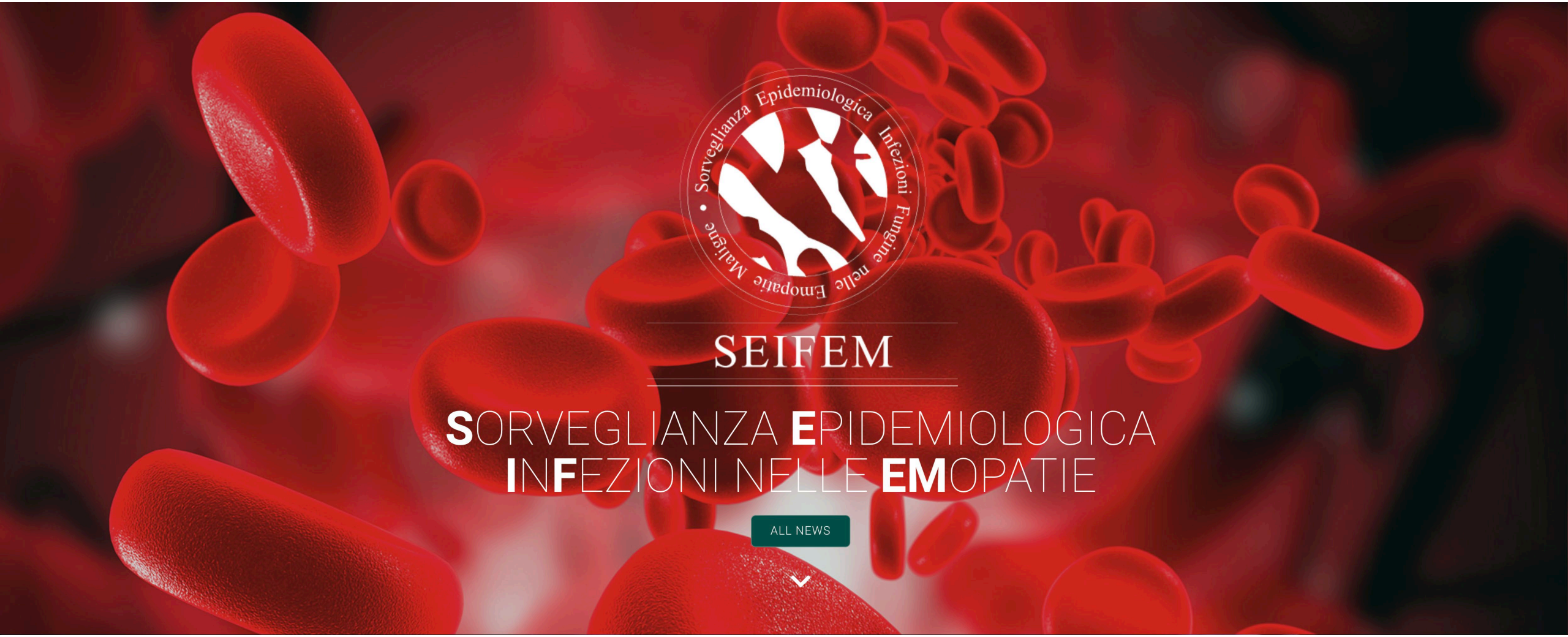
Stable (n=94)
Progression (n=21)
Death (n=24)
Not evaluable (n=0)
Missing data (n=5)

1. EORTC-MSG criteria per Segal 2008 CID

PC945 (opelconazole) nebulizer suspension: Clinical trials

- Opelconazole has successfully completed a phase I clinical trial [1]:
  - Safe and well tolerated by both healthy subjects and subjects with mild asthma;
  - The study also confirmed very slow systemic absorption from the lung.
- Recent case reports showed successful usage as salvage therapy for fungal tracheobronchial disease as well as bronchial anastomotic infection after lung transplantation. [2, 3]
- A phase II study of opelconazole prophylaxis vs antifungal standard of care in lung transplant recipients has finished enrollment (data pending publication). [4]
- A phase III double-blind placebo-controlled trial is currently assessing safety and efficacy of opelconazole in combination with systemic antifungal drugs for the treatment of refractory invasive pulmonary aspergillosis, with enrollment ongoing. [5]
- Since only very small amounts of the compound reach the systemic circulation, inhalation of opelconazole is unlikely to cause any relevant drug-drug interactions despite *in vitro* affinities for the CYP enzyme system. [1, 6]

1. Cass et al, 2021; 2. Pagani et al, 2020. 3.Singh et al, 2022
4. ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT05037851?intr=opelconazole&rank=1
5. ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT05238116?intr=opelconazole&rank=2
6. Hoenigl et al, 2024



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