
# Diagnostica e terapia dell'aspergillosi invasiva nel paziente ematologico

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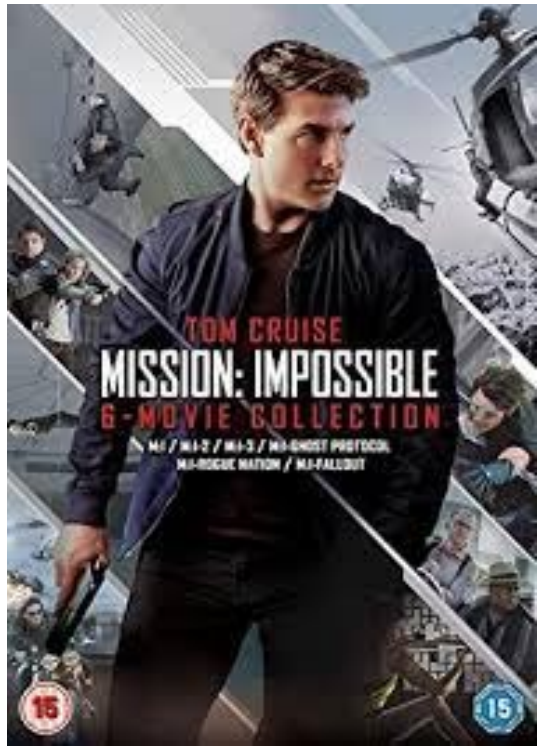
OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

# DISCLOSURES

Lecture or board meeting, grants to my institution
None related to this presentation

- Allovir
- bioMerieux
- Gilead
- Janssen
- Moderna
- Mundipharma
- Pfizer

# ID consult on IFD in hematology




- Why it may feel like mission impossible?

1. Haematology specialists may be more knowledgeable than ID in IFD in haematology/HSCT
2. They care deeply about their patients … and they do not accept that infection might lead to death
3. Clinical signs and symptoms might be very limited
4. Definite diagnosis is difficult due to limited feasibility and sensitivity of biopsy …
5. Once you put your foot down but make a mistake – regaining the trust is not easy ….

# Specifics of IFD in haematology

## Prophylaxis

High rate (>6-8%) of IMI **in certain patient groups but not in others, thus anti-mould prophylaxis strongly recommended in certain groups**

Breakthrough IFD present, also due to persistent immune deficit

Ascioglu S, *et al. Clin Infect Dis*. 2002;34(1):7–14; De Pauw B, *et al. Clin Infect Dis*. 2008;46(12):1813–21; Donnely JP, *et al. Clin Infect Dis.* 2020;71(6):367–76; Maertens JA et al J Antimicrob Chemother. 2018 Dec 1;73(12):3221-3230; Stemler et al. Ann Hematology 2020 Jul;99(7):1429-1440; Fleming et al. Intern Med J 2014 Dec; 44(12b):1283-97; Girmenia et al. Biol Blood Marrow Transplant. 2014 Aug;20(8):1080-8

# Anti-fungal prophylaxis

**Table 1** Established risk groups for IFD and recommended antifungal prophylaxis coverage in adults

| Risk level | Risk groups | Recommended prophylaxis† | Sol |
|---|---|---|---|
| High risk >10% incidence of IFD | Neutrophil <0.1 × $10^9$/L for >3 weeks or <0.5 × $10^9$/L for >5 weeks (e.g. allogeneic HSCT)<br>Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 × $10^9$/L for >1 week<br>Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks<br>Unrelated, mismatched or cord blood allogeneic HSCT<br>GVHD – extensive or severe<br>AML – induction/reinduction<br>ALL – induction/reinduc<br>MDS | First line:<br>Posacona<br>Alternate<br>Voric | |
| B II (context dependent; level I evidence in setting of alloHSCT) | Low risk, less than 5% incidence of IFD | Autologous HSCT,<br>for mucositis<br>Allogene<br>neutrop<br>Lym | |
| No prophylaxis B II | Very low risk, less than 5% incidence of IFD<br>No mucositis | | |

ole
nate agents:
Itraconazole

Treatment for solid org

**Table 3.** ECIL recommendations on primary antifungal prophylaxis in adult patients with AML and MDS undergoing intensive remission-induction chemotherapy[a]

| Antifungal agent | Grading | Comments |
|---|---|---|
| Posaconazole oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1 | A-I | Recommended if baseline incidence of mould infections is high. Given the increased absorption of the tablet, it is likely that the need for therapeutic drug monitoring will become restricted to specific populations (e.g. severe mucositis). |
| Fluconazole 400 mg q24h | B-I | Only recommended if the incidence of mould infections is low. Fluconazole may be part of an integrated care strategy together with a mould-directed diagnostic approach. |
| Itraconazole oral solution 2.5 mg/kg q12h | B-I | Recommended if baseline incidence of mould infections is high. May be limited by drug–drug interactions or patient tolerability. It is recommended to monitor serum drug concentrations. |
| Voriconazole 200 mg q12h | B-II | Recommended if baseline incidence of mould infections is high. It is recommended to monitor serum drug concentrations. |
| All echinocandins | C-II | Insufficient data on efficacy and tolerability. |
| Liposomal amphotericin B | C-II | Insufficient data on dose, frequency and duration, as well as on efficacy and tolerability. |
| Lipid-associated amphotericin B | C-II | Insufficient data on dose, frequency and duration, as well as on efficacy and tolerability. |
| Aerosolized liposomal amphotericin B (10 mg twice weekly) | B-I | Only when combined with fluconazole 400 mg q24h. |
| Amphotericin B deoxycholate | A-II against | |
| Aerosolized amphotericin B deoxycholate | A-I against | |

[a]Primary antifungal prophylaxis might be considered during intensified consolidation therapy (see text).

Fleming S et al. *Intern Med J* 2014;44:1283–1297; Teh et al. *Intern Med J* 2021.

ECIL, Maertens JA et al J Antimicrob Chemother. 2018 Dec 1;73(12):3221-3230

# Breakthrough IFD

Usually approx. 3%, up to 12% in some cohorts

Pathogens: rare moulds and azole-resistant *Aspergillus* species

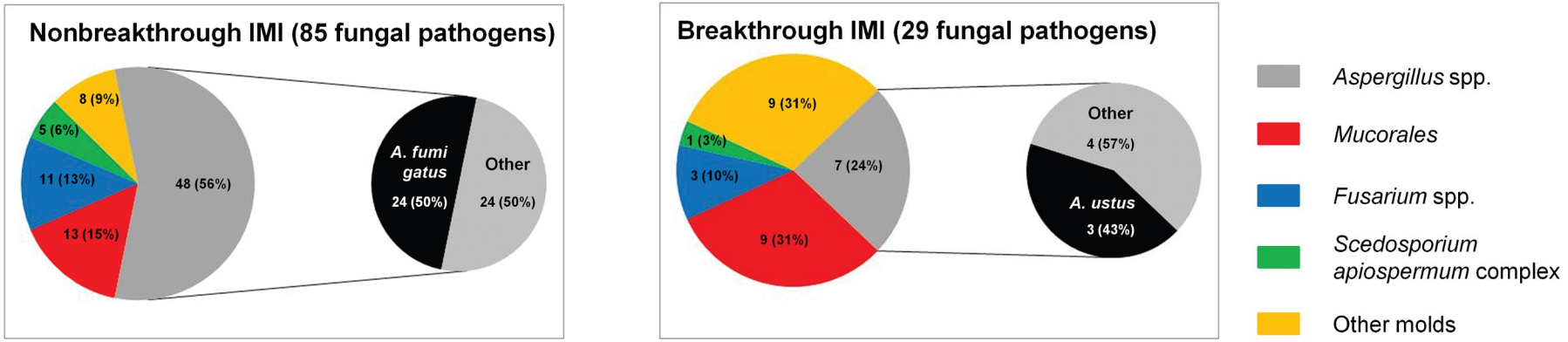



**Figure 1.** Distribution of fungal pathogens in breakthrough and nonbreakthrough invasive mold infections.

Lamoth F et al. *Clin Infect Dis* 2017;64(11):1619–1621; Cornely et al. N Engl J Med. 2007 Jan 25;356(4):348-59; Ullmann et al. N Engl J Med. 2007 Jan 25;356(4):335-47; Winston et al. Biol Blood Marrow Transplant 2011 Apr;17(4):507-15; Auberger et al. J Antimicrob Chemother 2012 Sep;67(9):2268-73; Pagano et al. Clin Infect Dis 2012 Dec;55(11):1515-21; Lerolle et al. Clin Microbiol Infect 2014 Nov;20(11):O952-9; Corzo-Leon et al. Mycoses 2015 Jun;58(6):325-36; Biehl et al. J Antimicrob Chemother 2016 Sep;71(9):2634-41; Kuster et al. Transpl Infect Dis 2018 Dec;20(6):e12981; Fisher et al. JAMA. 2019 Nov 5;322(17):1673-1681.

# Specifics of IFD in haematology

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| Prophylaxis | High rate (>6-8%) of IMI in certain patient groups but not in others, thus anti-mould prophylaxis strongly recommended in certain groups<br>Breakthrough IFD present, also due to persistent immune deficit |
| Diagnosis | EORTC/MSG diagnostic criteria available for 20 years and updated, but not developed for daily clinical practice (e.g. bronchoinvasive aspergillosis – unclassified) |

Ascioglu S, *et al. Clin Infect Dis*. 2002;34(1):7–14; De Pauw B, *et al. Clin Infect Dis*. 2008;46(12):1813–21; Donnely JP, *et al. Clin Infect Dis.* 2020;71(6):367–76; Maertens JA et al J Antimicrob Chemother. 2018 Dec 1;73(12):3221-3230; Stemler et al. Ann Hematology 2020 Jul;99(7):1429-1440; Fleming et al. Intern Med J 2014 Dec; 44(12b):1283-97; Girmenia et al. Biol Blood Marrow Transplant. 2014 Aug;20(8):1080-8

# 20 years of diagnosing invasive mould infections in the immunocompromised

- Risk factors + suggestive clinical presentation

EORTC/MSGERC criteria: 2002, 2008 and **2019** developed for **clinical research in the immunocompromised** at risk of IFD

- Probability levels of having invasive fungal infection:
  - **Proven** Histopathologic, cytopathologic, or direct microscopy in biopsy or culture from a sterile site
  - Probable Presence of Host factor + Clinical criterion + Mycology criterion
  - Possible Presence of Host factor + Clinical criterion

**Host factor**

- Recent neutropenia
- HSCT incl. GvHD, **haematological malignancy, SOT**
- Steroids (≥0.3 mg/kg for ≥3 weeks in the past 60 days)
- **Other T-cell immunosuppressants**
- B-cell immunosuppressants
- Inherited severe immunodeficiency

+

**Clinical criteria**

- Dense, well-circumscribed lesion(s) with or without a halo sign
- Air crescent sign
- Cavity
- **Reverse halo sign**
- **Wedge-shape and segmental or lobar consolidations**

+

**Mycology criteria**

- Direct microscopy, or **culture** in non-sterile samples (BAL, sputum, aspirate)
- **Indirect tests**
  - **GM**
    - Single serum GM ≥ 1.0
    - BAL GM ≥ 1.0
    - Single serum/plasma: ≥0.7 and BAL fluid ≥0.8
  - ***Aspergillus* PCR**
    - Plasma/serum/whole blood **2** or more consecutive PCR tests positive
    - BAL fluid 2 or more duplicate PCR tests positive
    - At least 1 PCR test positive in plasma/serum/whole blood and 1 PCR test positive in BAL fluid

BAL, bronchoalveolar lavage; GM, galactomannan; GvHD, graft-versus-host disease; HSCT, haematopoietic stem-cell transplantation; IFD, invasive fungal disease; PCR, polymerase chain reaction. Ascioglu S, et al. *Clin Infect Dis* 2002;34:7–14; De Pauw B, et al. *Clin Infect Dis* 2008;46:1813–21; Donnelly JP, et al. *Clin Infect Dis* 2020;71:1367–76.

# EORCT/MSG 2019 Clinical criteria for pulmonary IMI

Nodule +/-halo sign

Air crescent sign

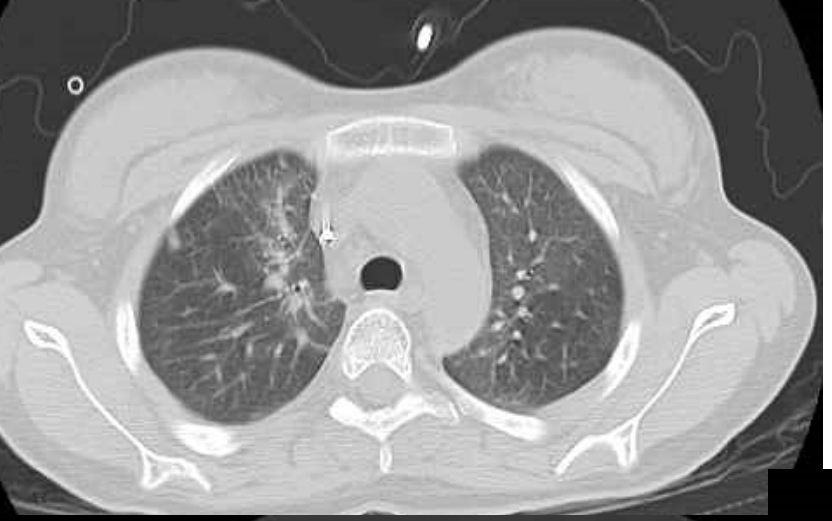
Cavity

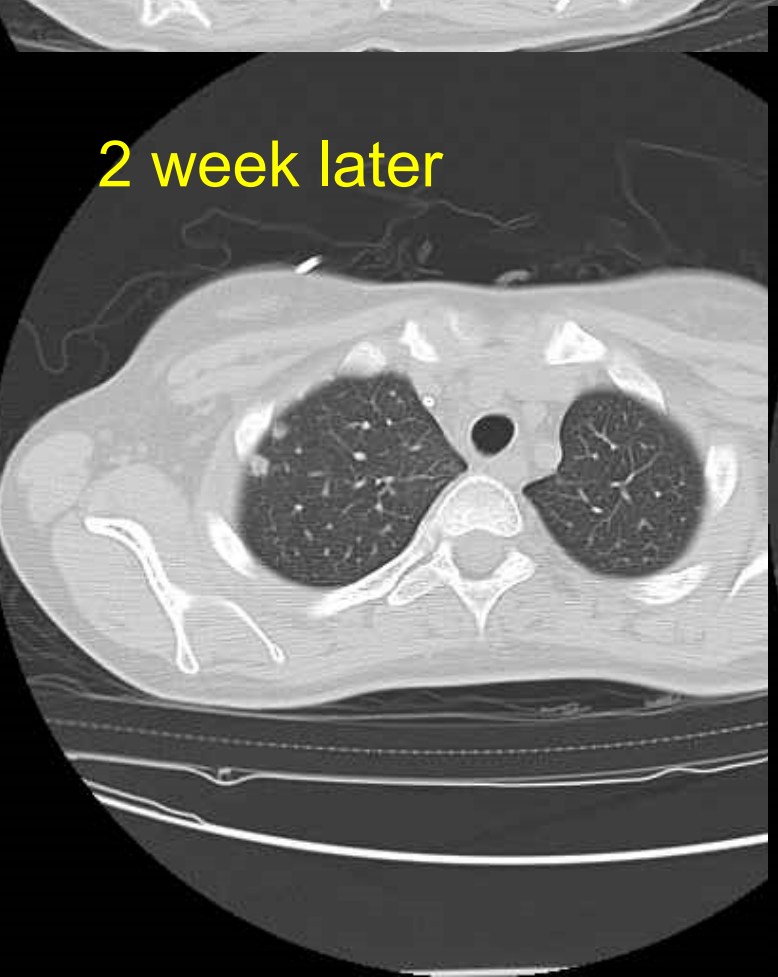

Wedge-shape and segmental or lobar **consolidations**

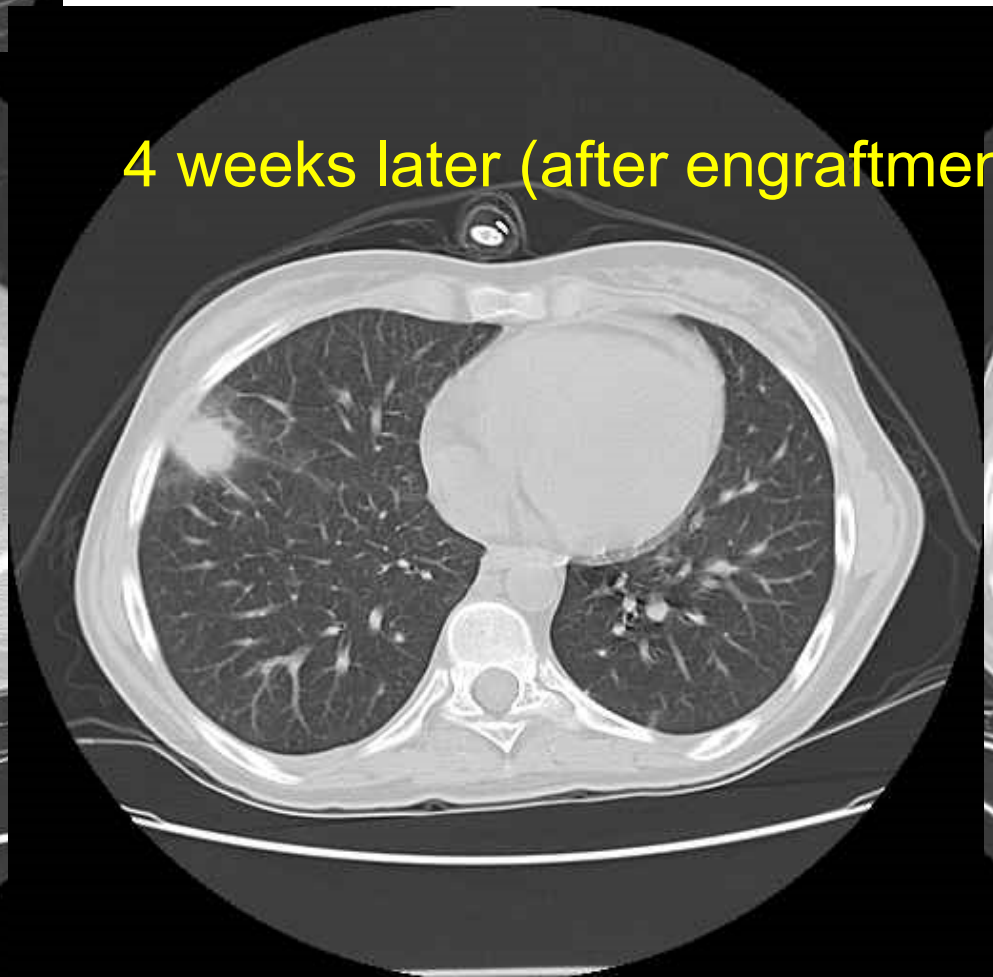
**Reverse halo sign**

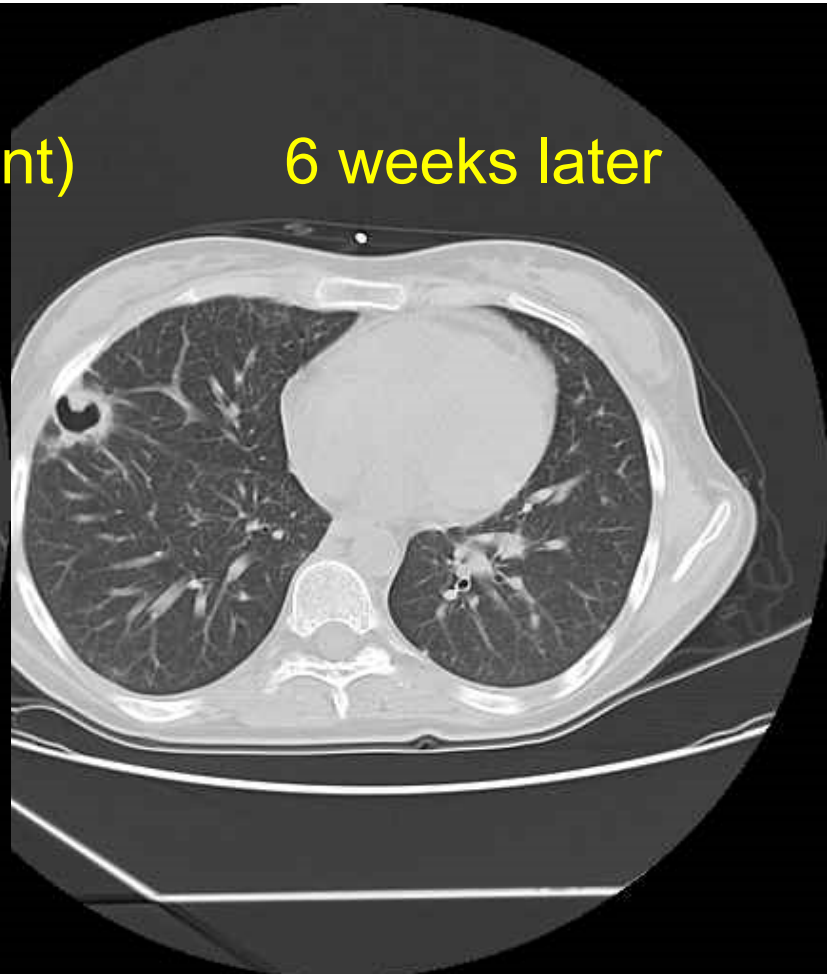
# with the wisdom of hindsight

19 yo female with SAA undergoing second alloHSCT
Long term neutropenia, no mould active prophylaxis
GM screening positive 0.6





# EORTC/MSGERC criteria were designed for clinical trials and epidemiology

## Not for everyday clinical decisions

**Table 1.** Patterns of invasive fungal disease in pratice, based on 2008 EORTC-MSG criteria.

| | A | B | C | | | | D | E |
|---|---|---|---|---|---|---|---|---|
| | - | - | I | II | III | IV | - | |
| Radiological signs and clinical symptoms | No | Persistent febrile neutropenia | No | Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria) | | Radiological signs on CT (dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or cavity) | | Not considered necessary |
| Mycology results | Negative | Negative | Positive biomarker or microscopy or culture | Negative | Positive biomarker or microscopy or culture | Negative | Positive biomarker or microscopy or culture | Positive tissue or specimen from a sterile site |
| Clinical evidence of IFD | No | No | No | No | No | Yes | Yes | Yes |
| Mycological evidence of IFI | No | No | Yes | No | Yes | No | Yes | Yes |
| Final diagnosis | Unclassified | | | | | Possible IMD | Probable IMD | Proven IMD |

blood 2012 119: 1831-1837
Prepublished online October 18, 2011;
doi:10.1182/blood-2011-04-351601

**The strategy for the diagnosis of invasive pulmonary aspergillosis should depend on both the underlying condition and the leukocyte count of patients with hematologic malignancies**

Anne Bergeron, Raphaël Porcher, Annie Sulahian, Cédric de Bazelaire, Karine Chagnon, Emmanuel Raffoux, Anne Vekhoff, Muriel Cornet, Françoise Isnard, Benoit Brethon, Claire Lacroix, Jean Louis Poirot, Claire Bouges, Francis Derouin, Abdellatif Tazi and Patricia Ribaud

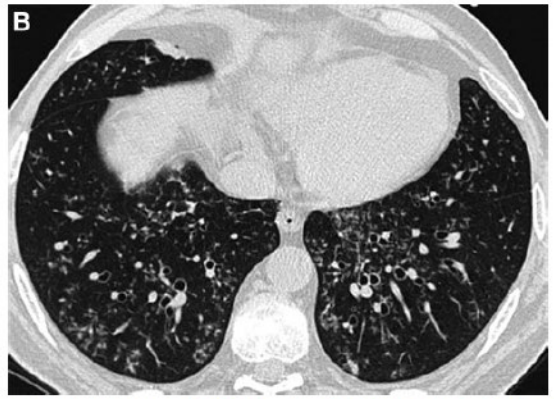



**Figure 1. Lung CT scans from 2 different patients.** (A) Nodule with a halo sign revealing angioinvasive aspergillosis in an AL patient. (B) Centrilobular nodules and tree-in-bud opacities showing airway-invasive aspergillosis in a patient who underwent an allogeneic HSCT.

Maertens et al. Haematologica 2012; Bergeron et al. Blood 2011

# Performance of GM in BAL, the role of cut-off

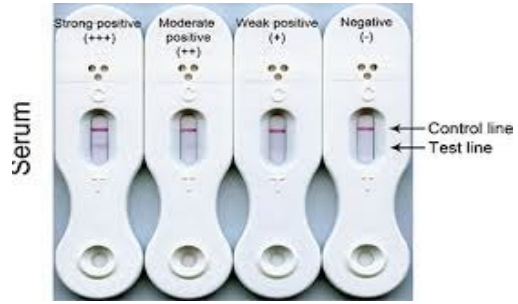
| Cut-off value | No. of participants | Summary estimates (95% CI) | Implications | Quality and Comments |
|---|---|---|---|---|
| dies except one had a high risk of bias in two or more domains. For all studies the concerns regarding applicability were low. | 0.5 ODI (12 studies) 229 with proven or probable IA 894 with possible or no IA | Sensitivity: 0.88 (95% CI 0.75 to 1.00) Specificity: 0.81 (95% CI 0.71 to 0.91) | At a prevalence of 12%, 120 out of 1000 patients will develop proven or probable IA. Of these, 14 will be missed. Of the 880 patients with possible or no IA, 167 will have a false-positive test result and may be unnecessarily treated. Of all 273 patients with a positive test, 106 will indeed have proven or probable IA; of all 727 negative tests, 14 will have IA after all (2%). | All stu |
| develop proven or 2 will have a false-positive d. Of all 156 patients with a roven or probable IA; of all 844 neg- (3%). | 1.0 ODI (11 studies) 177 with proven or probable IA 594 with possible or no IA | Sensitivity: 0.78 (95% CI 0.61 to 0.95) Specificity: 0.93 (95% CI 0.87 to 0.98) | At a prevalence of 12%, 120 out of 1000 patients will probable IA. Of these, 26 will be missed. Of the 880 patients with possible or no IA, 6 test result and may be unnecessarily treate positive test, 94 will indeed have p ative tests, 26 will have IA after all | |
| interpretation and extrapolation of these results has to be | | | Note, the populations and results were very heterogeneous. Therefore, performed with caution. | |

de Heer K, Gerritsen MG, Visser CE, Leeflang MMG. Galactomannan detection in broncho-alveolar lavage fluid for invasive aspergillosis in immunocompromised patients. *Cochrane Database of Systematic Reviews* 2019, Issue 5. Art. No.: CD012399. DOI: 10.1002/14651858.CD012399.pub2.

# Faster GM results - Towards point-of-care testing

- **Reliable, quantitative «almost» PoC for** BAL fluid (with pre-treatment): **15–25 minutes, two assays available**:[1,2]

1. Aspergillus galactomannan **LFA**
2. Aspergillus-specific **LFD** that detects the mannoprotein antigen secreted by growing Aspergillus with JF5 MAbs




- A 2015 meta-analysis investigated LFD in BAL:[2]
  - Sensitivity: 86% (95% CI: 76–93)
  - Specificity: 93% (95% CI: 89–96)
- Included in the 2018 ESCMID IA guidelines (B II)[3]

- Qualitative/semi-quantitative results were provided initially > optical reader
- Compared with visual readouts, digital readouts provide quantitative results and perform better with BAL (235 samples from HM patients) for both assays – LFA and LFD[1]
- There was a good correlation with traditional GM for LFA5[5]

BAL, bronchoalveolar lavage; GM, galactomannan; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IA, invasive aspergillosis; LFA, lateral flow assay; LFD, lateral flow device.

1. Mercier T et al. *Med Mycol*. 2020; 58:444–452; 2. Pan Z et al. *J Med Microbiol* 2015; 3.Ullmann A et al. *CMI* 2018;24:e1–e38; 4.Jenks et al. Clin Infect Dis 2021;73:e1737–e1744.

# *Aspergillus* PCR: blood and BAL

- Included in some 2018 ESCMID, 2019 EORTC/MSG guidelines
- **In addition to in-house methods, commercial assays are available**
  - For *A. fumigatus* or for several species, not all differentiate between species
  - Some detectsalso **mutations associated with azole-resistance in *A. fumigatus*** ($TR_{34}$/L98H, T289A, Y121F)
- Initial studies: sensitivity 68-94%, specificity 80-98%
- **Recent reports: sensitivity not specificity seems a crucial issue**
  - Sensitivity/specificity  30%/91%; 40%/69%; 65%/100%
- The performance variable, higher in culture positive samples
  - Our experience: sensitivity for proven/probable IA in H
    - 40% with one commercially available assay
    - 92% with another

Ullmann et al. CMI 2018 ; Donnelly et al. CID 2019;  Rath and Steinmann, Front Microbiol 2018, 9:740, doi: 10.3389/fmicb.2018.00740; Wehrle-Wieland et al. Transpl Infect Dis 2018; Mikulska et al. Med Mycol. 2019; Pelzer et al. Med Mycol. 2019; Gangneux et al. J Fungi 2020; Mikulska et al. Medical Mycology, 2019, 57, 987–996; Mikulska et al Mycoses 2022 Apr;65(4):411-418

# Clinical impact of PCR-based Aspergillus and azole resistance detection in invasive aspergillosis. A prospective multicenter study. Unexpected lessons

- Prospective study in the Netherlands and Belgium
- Evaluated the clinical value of the multiplex AsperGenius®PCR in hematology patients from 12 centers
- This PCR detects the most frequent cyp51A mutations in *A. fumigatus* conferring azole-resistance
- **Inclusion: patients with a CT-scan showing a pulmonary infiltrate and BAL within 48h (=possible IA)**
- The primary endpoint - antifungal treatment failure in patients with azole-resistant IA
- 323 patients enrolled (32% alloHSCT), complete mycological and radiological information available in 94% (276/323)
- **Probable IA – 36% (99/276)**
- PCR testing in BAL in 91% (293/323): **positive in 40% (116/293), with *A. fumigatus* DNA in 30% (89/293)**
- The resistance PCR was conclusive in 65% (58/89) and resistance detected in 8/58 (14%)

**Table 2. Microbiology Results Including Bronchoalveolar Fluid Galactomannan, AsperGenius Polymerase Chain Reaction, and Culture**

| | BALf GM | | |
|---|---|---|---|
| | <0.5 | 0.5–0.99 | ≥1 |
| Number of patients (n)[a] | 215 | 32 | 74 |
| Aspergenius performed | 193 | 31 | 68 |
| PCR *Aspergillus* species–positive | 50 (26%) | 16 (52%) | 50 (74%) |
| PCR *Aspergillus* species–negative | 143 (74%) | 15 (48%) | 18 (26%) |
| PCR *Aspergillus fumigatus*–positive | 38 (20%) | 12 (39%) | 39 (57%) |
| PCR *Aspergillus fumigatus*–negative | 156 (80%) | 19 (61%) | 29 (43%) |
| PCR *Aspergillus terreus*–positive | 1 (0.5%) | 0 (0%) | 2 (3%) |

Huygens S et al. Clinical Infect Dis 2023

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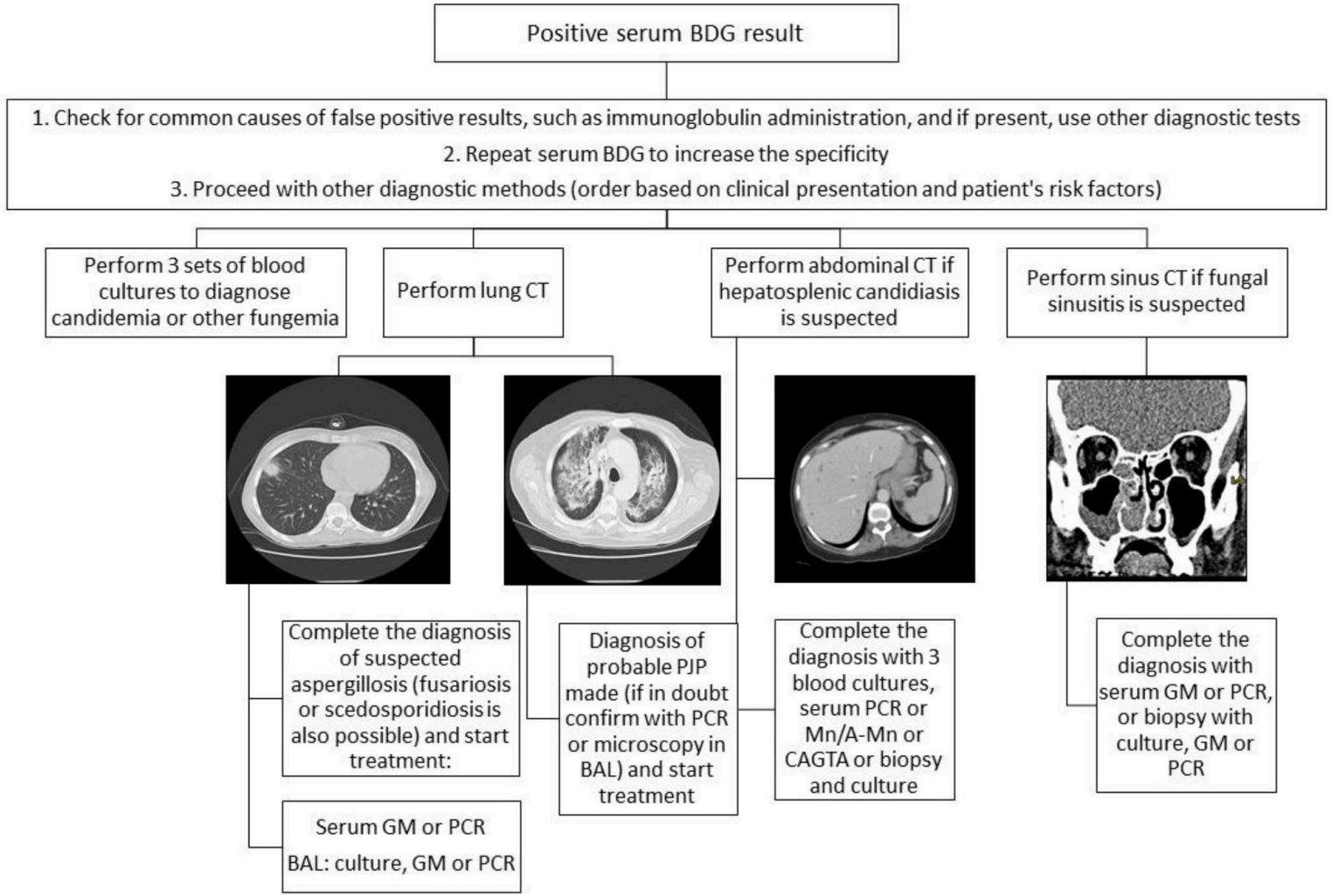
| | GM pos (N=77) | Culture pos (N=24) | PCR pos (N=119) | PCR pos in duplicate (N=67) | GM and culture neg but PCR pos (N=62) | **GM and culture neg but PCR pos in duplicate (N=28)** | GM, culture and PCR neg (N=154) |
|---|---|---|---|---|---|---|---|
| Antifungal therapy started at BAL (-5, +14 days) (n/N) | 72/77 (94%) | 23/24 (96%) | 105/119 (88%) | 62/67 (93%) | 52/62 (84%) | 24/28 (86%) | 105/154 (68%) |
| Median (IQR) days of antifungals | 27 (11 – 73) | 38 (17 – 88) | 32 (10 – 89) | 33 (12 – 89) | 34 (10 – 123) | 71 (15 – 135) | 18 (7 – 63) |
| **6-week mortality (n/N)** | **23/76 (30%)** | **8/24 (33%)** | **26/119 (22%)** | **16/67 (24%)** | **9/62 (15%)** | **4/28 (14%)** | **24/153 (16%)** |

BAL galactomannan positivity was associated with higher mortality (p=0.004)

Mortality of patients with an isolated positive Aspergillus PCR in BAL was comparable to those with a negative PCR (p=0.83)

Huygens S et al. Clinical Infect Dis 2023

# BDG – to be used in combination only



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| Diagnosis | EORTC/MSG diagnostic criteria available for 20 years and updated, but not developed for daily clinical practice (e.g. bronchoinvasive aspergillosis – unclassified) |
| Prognosis | High mortality, particularly if ongoing severe immunosuppression > fear of rapid deterioration + **suboptimal diagnosis** > **leading to empirical therapy** |

Ascioglu S, *et al. Clin Infect Dis*. 2002;34(1):7–14; De Pauw B, *et al. Clin Infect Dis*. 2008;46(12):1813–21; Donnely JP, *et al. Clin Infect Dis.* 2020;71(6):367–76; Maertens JA et al J Antimicrob Chemother. 2018 Dec 1;73(12):3221-3230; Stemler et al. Ann Hematology 2020 Jul;99(7):1429-1440; Fleming et al. Intern Med J 2014 Dec; 44(12b):1283-97; Girmenia et al. Biol Blood Marrow Transplant. 2014 Aug;20(8):1080-8

# Empirical antifungal therapy

## 40 years ago

Definition: antifungal treatment in **neutropenic** patients with persistent fever despite 4-7 days of broad-spectrum antibiotics, or in patients with relapsing fever

Reason: IFD during neutropenia is impossible to diagnose:

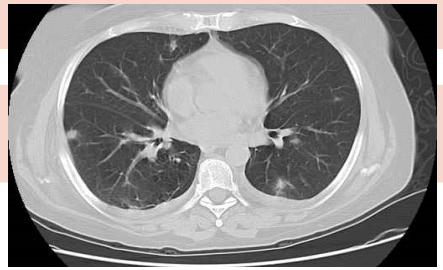
low yield of cultures,

late radiological signs on X-ray

and is associated with high mortality

## Today

- Widely available **galactomannan, with short turn-around time (use of point-of-care tests in selected cases)**
- **Rapidly available CT (same day)**
- Available **Aspergillus-PCR** in serum and BAL, serum glucan (IC, PjP) with short turn-around time
- Rapidly available **BAL** – to avoid false negative results due to antifungal treatment (Aspergillus PCR might be more helpful than GM)
- Rapidly available cerebral RM
- > Only as time-buying strategy
  Diagnostic availability is critical



**Pizzo et al. Am J Med 1982 (16 vs 18 patients)**
**EORTC Am J Med 1989 (64 vs 68 patients)**

*Clinical Infectious Diseases*

MAJOR ARTICLE

# Empiric vs Preemptive Antifungal Strategy in High-Risk Neutropenic Patients on Fluconazole Prophylaxis: A Randomized Trial of the European Organization for Research and Treatment of Cancer

Johan Maertens,[1] Tom Lodewyck,[2] J. Peter Donnelly,[3] Sylvain Chantepie,[4] Christine Robin,[5] Nicole Blijlevens,[3] Pascal Turlure,[6] Dominik Selleslag,[2] Frédéric Baron,[7] Mickael Aoun,[8] Werner J. Heinz,[9] Hartmut Bertz,[10] Zdeněk Ráčil,[11] Bernard Vandercam,[12] Lubos Drgona,[13] Valerie Coiteux,[14] Cristina Castilla Llorente,[15] Cornelia Schaefer-Prokop,[3] Marianne Paesmans,[8] Lieveke Ameye,[8] Liv Meert,[16] Kin Jip Cheung,[16] Deborah A. Hepler,[17] Jürgen Loeffler,[18] Rosemary Barnes,[19] Oscar Marchetti,[20,21] Paul Verweij,[3,©] Frederic Lamoth,[20] Pierre-Yves Bochud,[20] Michael Schwarzinger,[22] and Catherine Cordonnier[5]; for the Infectious Diseases Group and the Acute Leukemia Group of the European Organization for Research and Treatment of Cancer

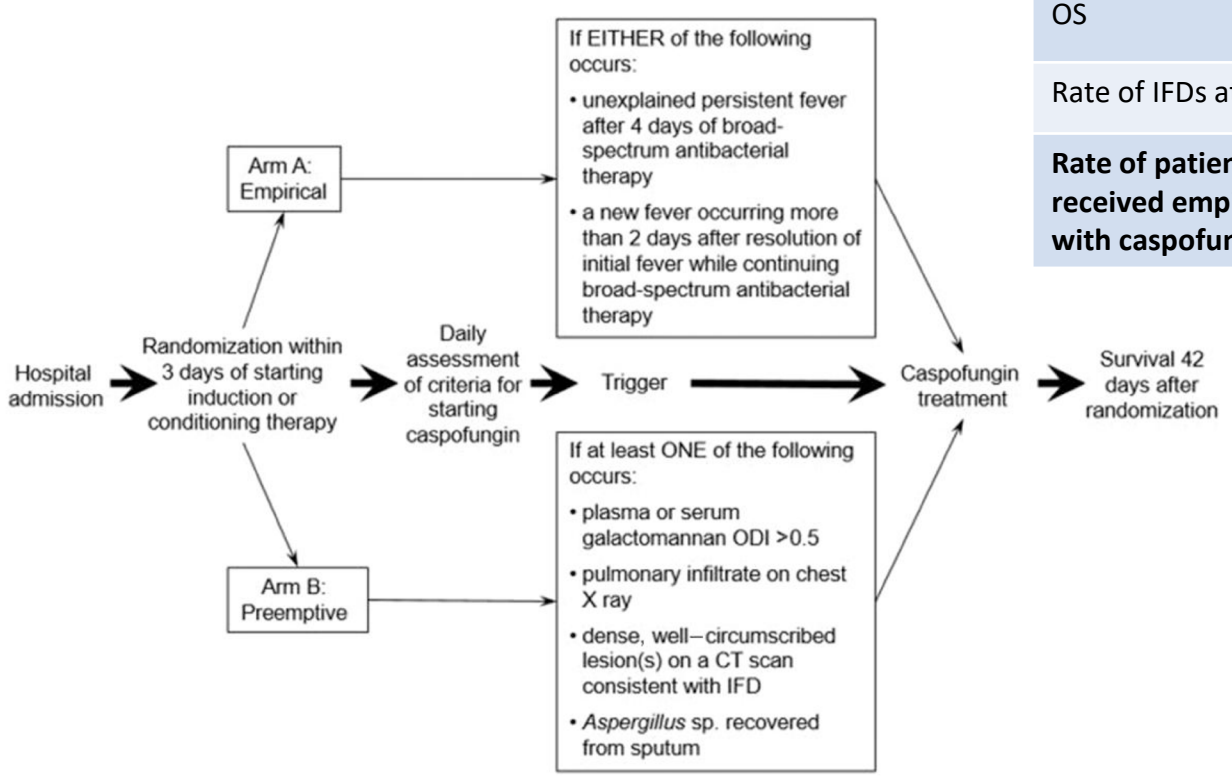



**Figure 1.** Study design. Abbreviations: CT, computed tomography; IFD, invasive fungal disease; ODI, optical density index

2012-2015
pre-emptive: twice weekly galactomannan screening and CT scan on demand
549 included, 80% AML, 20% alloHSCT

| | Pre-emptive, % (95%CI) | Empirical, % (95%CI) | P |
|---|---|---|---|
| OS | 96.7% (93.8%–98.3%) | 93.1% (89.3%–95.5%) | NS |
| Rate of IFDs at day 84 | 7.7% (4.5%–10.8%) | 6.6% (3.6%–9.5%) | NS |
| **Rate of patients who received empirical treatment with caspofungin** | **27%** | **63%** | **<.001** |

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**Diagnosis**

EORTC/MSG diagnostic criteria available for 20 years and updated, but not developed for daily clinical practice (e.g. bronchoinvasive aspergillosis – unclassified)

**Prognosis**

High mortality, particularly if ongoing severe immunosuppression > fear of rapid deterioration + **suboptimal diagnosis** > **leading to empirical therapy**

**Prophylaxis**

High rate (>6-8%) of IMI in certain patient groups but not in others, thus anti-mould prophylaxis strongly recommended in certain groups

Breakthrough IFD present, also due to persistent immune deficit

**Treatment**

Drug-drug interactions between triazoles and numerous anti-neoplastic drugs – need for TDM

Frequent hepatic toxicity due to numerous causes (chemotherapy, hepatic Graft vs. Host Disease)

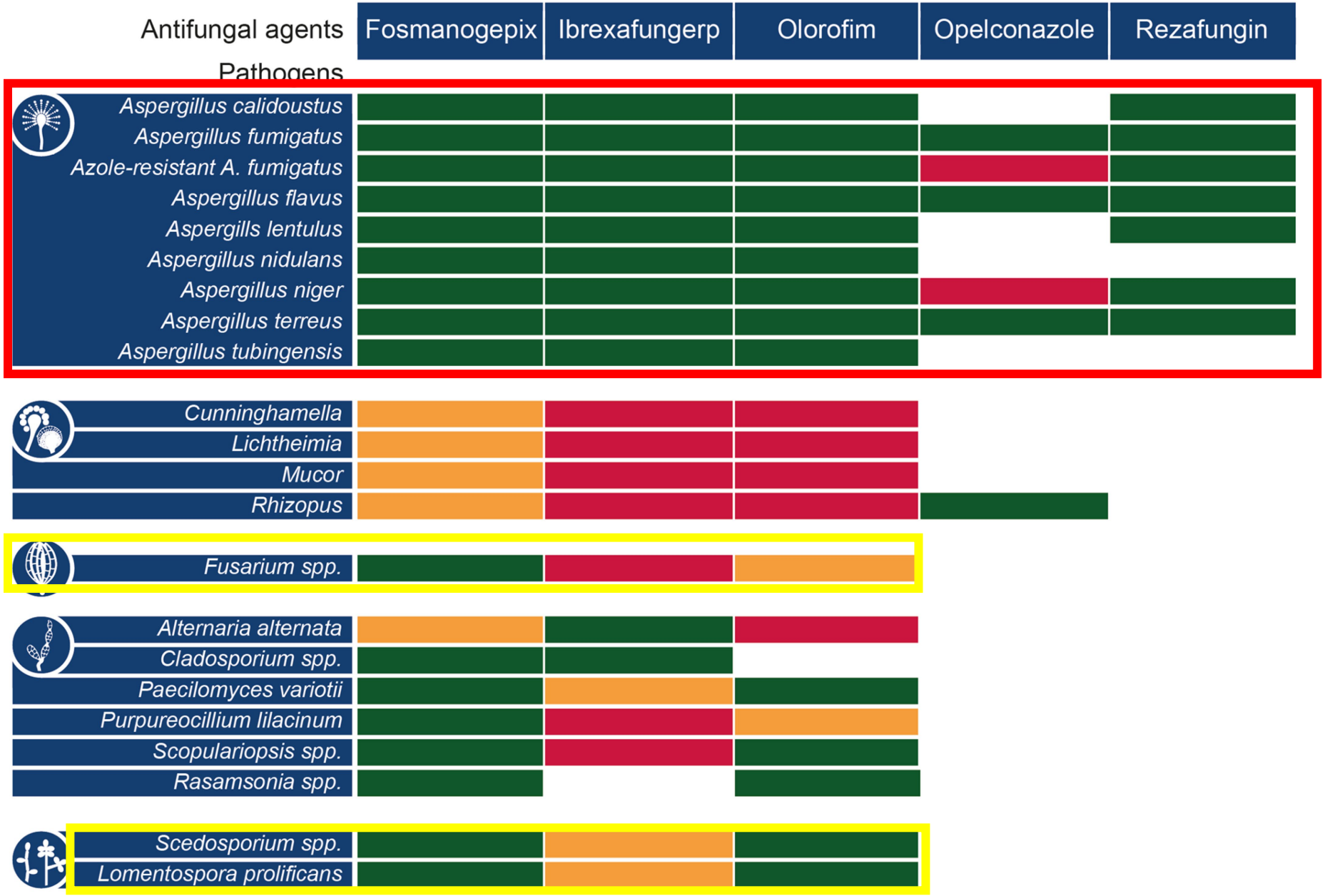
Optimal lenght of IMD treatment ? (until the resolution of immune deficit…)

Ascioglu S, *et al. Clin Infect Dis*. 2002;34(1):7–14; De Pauw B, *et al. Clin Infect Dis*. 2008;46(12):1813–21; Donnely JP, *et al. Clin Infect Dis.* 2020;71(6):367–76; Maertens JA et al J Antimicrob Chemother. 2018 Dec 1;73(12):3221-3230; Stemler et al. Ann Hematology 2020 Jul;99(7):1429-1440; Fleming et al. Intern Med J 2014 Dec; 44(12b):1283-97; Girmenia et al. Biol Blood Marrow Transplant. 2014 Aug;20(8):1080-8

# Invasive aspergillosis. First line treatment

| | ECIL-6 2016 | IDSA 2016 (Strength of recommendation and evidence) | ESCMID – ECMM – ERS 2018 | Australia 2021 |
|---|---|---|---|---|
| **Voriconazole** | **A I (oral CIII) TDM indicated** | **Strong. High quality** | **A I** | **A I** |
| **Isavuconazole** | **A I** | **Alternative to voriconazole *A II*** | **A I** | **A I** |
| **Posaconazole** | - | - | - | **A I*** |
| **L-AMB 3mg/kg** | **B I** | **Strong. Moderate quality** | **B II** | **B II** |
| **ABLC 5mg/kg** | **B II** | **Weak. Low quality** | **C III** | - |
| **ABCD** | **C I** | **Weak. Low quality** | **D I** | - |
| **D-AMB** | **A I against use** | - | **D I** | - |
| **Caspofungin** | **C II** | **Not recommended** | **C II** | **C II** |
| **Micafungin** | - | **Weak. Moderate quality** | **C III** | **C II** |
| **Anidulafungin** | - | - | - | - |
| **Itraconazole** | **C III** | - | **C III** | - |
| **Voriconazole + anidulafungin** | **C I** | **Weak. Moderate quality** | **C I** | **C I** |
| **Other combinations** | **C III** | - | **D III** | - |

Tissot et al. Haematologica 2017; Patterson et al. CID 2016; Ullmann et al. CMI 2018; Douglas et al. Internal Medicine Journal 2021; *Posaconazole not inferior to voriconazole - Maertens et al. Lancet. 2021




Hoenigl M, et al. The Antifungal Pipeline: Fosmanogepix, Ibrexafungerp, Olorofim, Opelconazole, and Rezafungin. Drugs. 2021 Oct;81(15):1703-1729. doi: 10.1007/s40265-021-01611-0.

# When Primary Antifungal Therapy Fails

**Table 1. Causes of antifungal therapy failure.**

| Causes of antifungal therapy failure |
|---|
| Host factor |
| Severity of illness |
| Persistence of immunodeficiency (e.g., neutropenia or use of corticosteroids) |
| Primary (intrinsic) drug resistance |
| Wrong diagnosis |
| Mixed infection |
| Low concentration of the drug at the site of infection |
| Pharmacokinetic and pharmacodynamic |
| Drug interactions |
| Biofilms |
| Poor vascular supply (e.g., abscess and necrotic tissue) |
| Drug toxicities (direct and with drug interactions) |
| Development of resistance (secondary) |
| Misdiagnosis of failure—immune reconstitution inflammatory syndrome |

Nucci M and Perfect JR. Clinical Infectious Diseases 2008


Best abstracts will be granted travel awards!