Designing new diagnostic-driven therapy concepts

Example: invasive aspergillosis in hematology patients

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Data supporting diagnostic-driven therapy

Reference	Type	Underlying condition	Fungal marker
Lin	feasibility	chemo	2 consecutive + nested PCR
Maertens	feasibility	Chemo or allo-SCT	2 consecutive + GM (0.5)
Oshima	feasibility	Allo-SCT	2 consecutive + GM (0.6) or β-D-glucan
Barnes	feasibility	Chemo or allo-SCT	2 (or 1 > 0.7) consecutive + GM (0.5) or PCR
Dignan	feasibility	Allo-SCT	No fungal marker
Girmenia	feasibility	Chemo or auto-SCT	2 consecutive + GM (0.5)
Aguilar-Guisado	feasibility	Chemo or allo-SCT	GM (0.5)
Schneider	feasibility	Chemo or allo-SCT	1 + GM (0.5)
Cordonnier	RCT	Chemo or auto-SCT	1 + GM (1.5)
Hebart	RCT	Allo-SCT	1 + PCR
Blennow	RCT	Allo-SCT	1 + PCR
Tan	RCT	Chemo or allo-SCT	2 consecutive +GM (0.5) or 1 + GM plus CT
Morrissey	RCT	Chemo or allo-SCT	1 + PCR or GM (0.5)
EORTC-IDG	RCT	Chemo or allo-SCT	1 + GM (0.5)

Modified from Girmenia C et al. Hematol Oncol 2012 Oct 5 [Epub ahead of print]

Patterns of Invasive Fungal Diseases

	Prophylaxis	Empirical	Diagnostics-driven (pre-emptive)				Directed
			I	II	III	IV	
Radiological signs & 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)	
Mycology results	Negative	Negative	Positive biomarker or culture	Negative	Positive biomarker or culture	Negative	Positive Biomarker or microscopy or culture
Evidence of IFD	No	No	No	No	No	Yes	Yes
Evidence of IFI	No	No	Yes	No	Yes	No	Yes
EORTC/MSG	-	-	-	-	-	Possible	Probable
Final diagnosis	no IMD		IMD cannot be excluded			IMD	

Maertens J, Nucci M, and Donnelly P. Haematologica 2012; 97:325-327

A selection of randomized clinical studies

Empirical versus pre-emptive antifungal strategy the "Prevert" study

Chemotherapy expected to cause neutropenia for at least 10 days and autologous HSCT

Enrolled at initiation of chemotherapy
Stratified by risk and antifungal prophylaxis
Antifungal strategy started on day 4 of persistent fever
Treatment of fever > 14 days: upon the investigator

Empirical

Persistent or recurrent fever

Pre-emptive

Clinically and imaging-documented pneumonia or acute sinusitis, septic shock, unexplained CNS symptoms, peri-orbital inflammation, skin lesions suggestive of IFI, HS abscesses, grade ≥3 mucositis, *Aspergillus* colonization, or one GM-ELISA (≥1.5)

In both groups: Ampho B (1mg/kg/d) or liposomal Ampho B (3mg/kg/d) according to the daily assessment of the creatinine clearance

Cordonnier C et al. Clin Infect Dis 2009; 48: 1042-1051

Galactomannan and PCR versus culture and histology

patients receiving induction-consolidation chemotherapy for acute myeloid or lymphoblastic leukemia or undergoing allogeneic HSCT

Enrolled within 48 h of start therapy
Stratified by center
GM and PCR testing twice a week (for 26 weeks)

Standard diagnostic

Upon clinical suspicion (fever..)

- **Cultures of blood, urine, (sputum), (faeces)**
- **High-resolution chest CT-scan**
- **Bronchoscopy and biopsy**
- **Empirical treatment recommended during work-up**

Biomarker-based Diagnostic

- **Single positive GM (> 0.5) or PCR**
- **Serially negative results for both test (in persistently neutropenic fever)**
- **High-resolution chest CT-scan**
- **Antifungal therapy for possible and probable cases (modified criteria, different from the current EORTC-MSG criteria)**

Morrissey CO et al. Lancet Infect Dis 2013; 13: 519-528

Ongoing EORTC 65091-06093 study

patients receiving remission-induction chemotherapy for acute myeloid leukemia or myelodysplastic syndrome or undergoing myeloablative allogeneic HSCT

Enrolled within 3 days of start therapy

Empirical

- unexplained persistent fever refractory to 4 full days of broad-spectrum antibacterial therapy or
- a new fever occurring >2 days after resolution of a first fever while continuing broad-spectrum antibiotics

Pre-emptive

- single blood galactomannan ELISA with index > 0.5
- new pulmonary infiltrate on chest-X ray and IFD cannot be readily excluded
- new dense well circumscribed lesion(s) with or without a halo sign, on a CT scan, consistent with IFD
- Aspergillus sp. recovered by culture from sputum

In both groups: Caspofungin standard dose

Selecting the primary end-point

Candidate primary endpoint	
Incidence of invasive aspergillosis	no
Reduction in invasive aspergillosis-related mortality	no
Length of stay in hospital	no
Antifungal therapy-related toxicity	no
Cost-effectiveness	no
Overall survival at day x	yes/?
Use of antifungal therapy	yes
Proportion of adequately treated patients	yes

Selecting the right population

- Include **high-risk** patients only
  - Positive predictive value of screening assays ~ prevalence of disease

Patient group	Prevalence of IA (%)	Positive predictive value (%)
Autologous HSCT recipients	2	16-25
Acute myeloid leukemia	13.7-14.6	73-80

  - Sensitivity and reliability of screening assays ~ fungal burden and extent of tissue invasion→ profound neutropenia
  - Risk of IA ~ sample size of the study (~ study end-point)
- Acute myeloid leukemia (remission-induction and re-induction) and myeloablative allogeneic HSCT

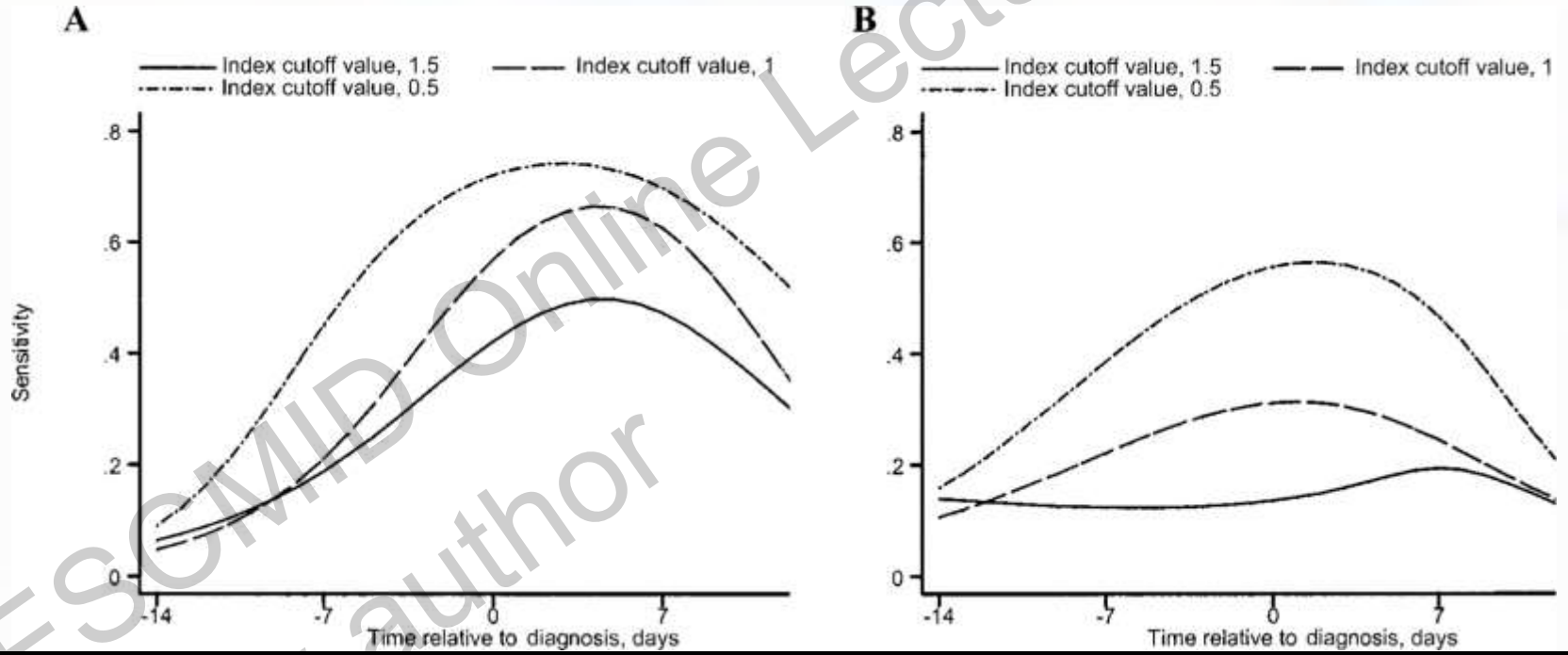
Comparing RCTs

	French (n=293) %	Australian (n=240) %	EORTC (ongoing) %
Allogeneic HSCT	0	79.5	?
Autologous HSCT	31	0	0
Acute myeloid leukemia	67.2	15.8	?
Acute lymphoblastic leukemia	3.7	4.7	0
Neutropenia	86	31.2	?

Cordonnier C et al. Clin Infect Dis 2009; 48: 1042-1051
Morrissey CO et al. Lancet Infect Dis 2013; 13: 519-528

Antifungal prophylaxis

- Mold-active agents decrease the sensitivity of GM-ELISA and PCR assays
- Protocol-driven administration of effective anti-*Candida* prophylaxis



A. No prophylaxis

B. Mold-active prophylaxis

Marr K A et al. Clin Infect Dis. 2005;40:1762-1769

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No antifungal prophylaxis	55	0	0
Mold-active prophylaxis	5.4	65	0
Fluconazole	12.2	35	100

Cordonnier C et al. Clin Infect Dis 2009; 48: 1042-1051
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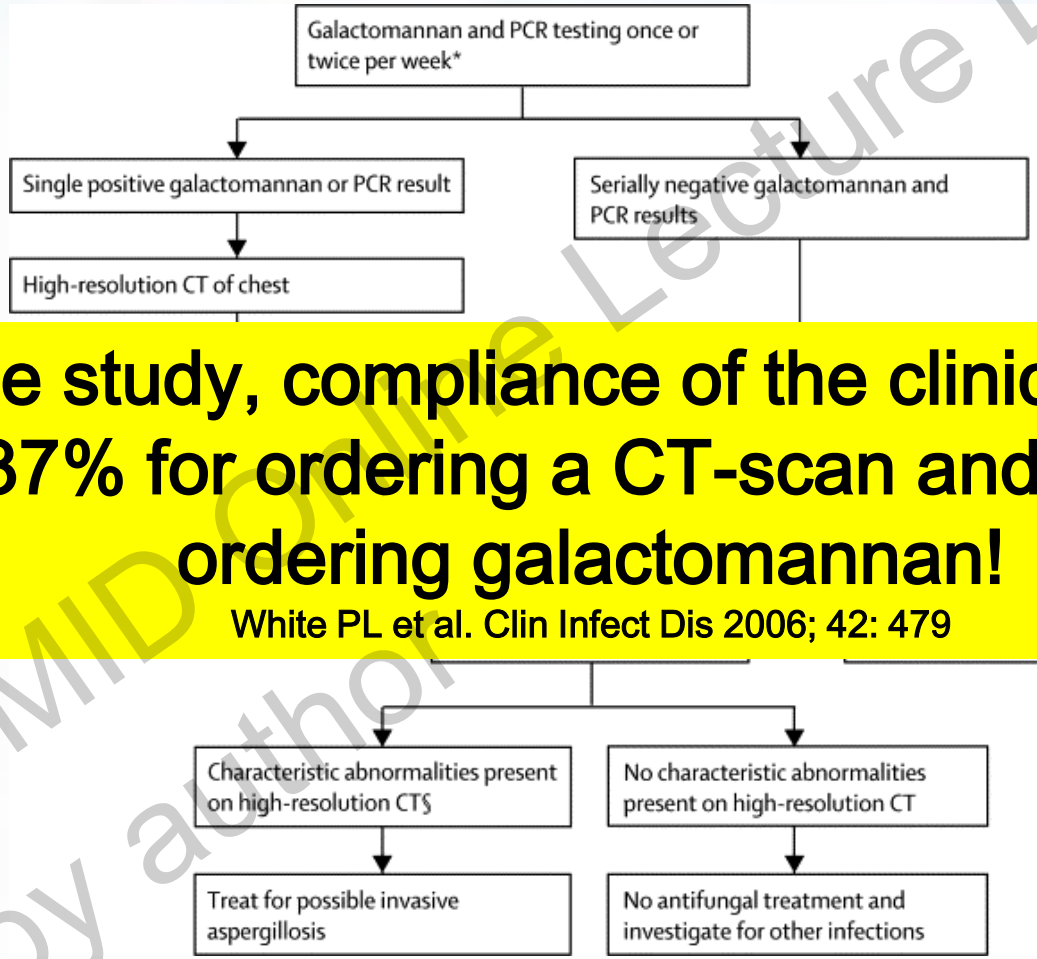
Design a clear and strict algorithm for then use (or not) of antifungal therapy

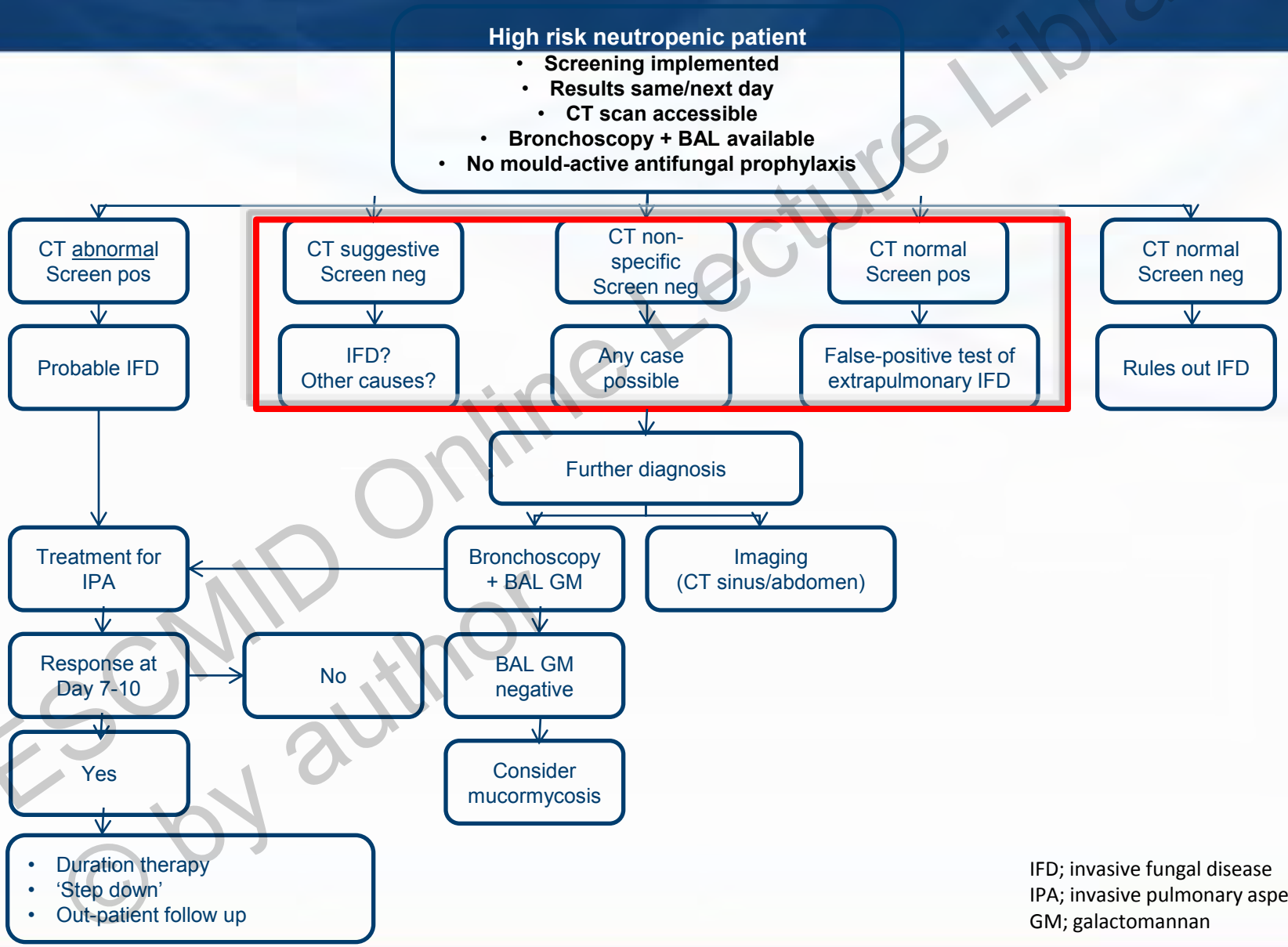


In one study, compliance of the clinicians was only 37% for ordering a CT-scan and ~50% for ordering galactomannan!

White PL et al. Clin Infect Dis 2006; 42: 479

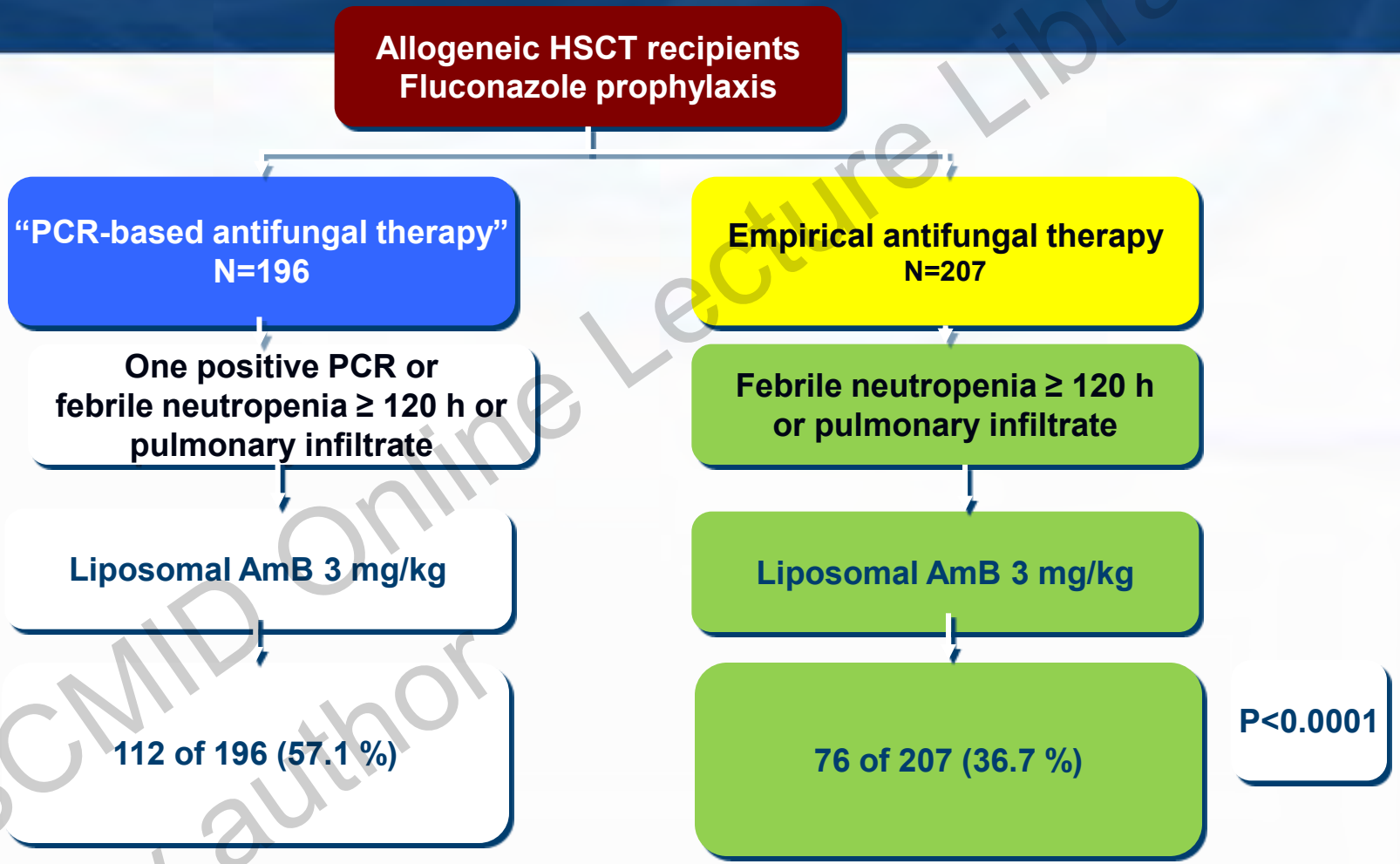
Morrissey CO et al. Lancet Infect Dis 2013; 13: 519-528

Diagnostic-driven management



IFD; invasive fungal disease
IPA; invasive pulmonary aspergillosis
GM; galactomannan

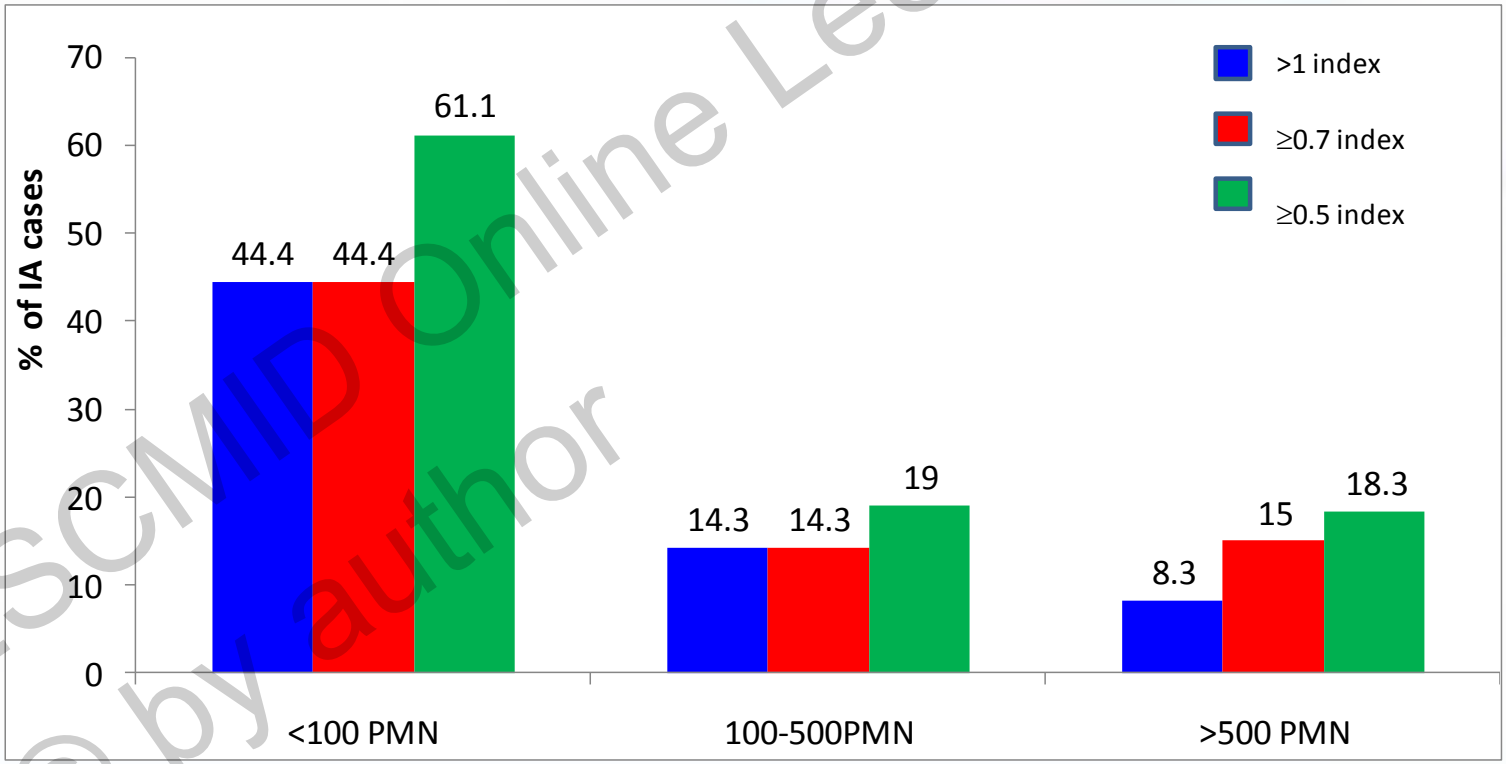
Avoid overlap



Hebart et al. Bone Marrow Transplant 2009; 43: 553-561.

Design a clear and strict algorithm for the use (or not) of antifungal therapy

- **Define a study period**
  - **Incidence of disease varies over time**
  - **Performance of assays ~ change of host factors over time**

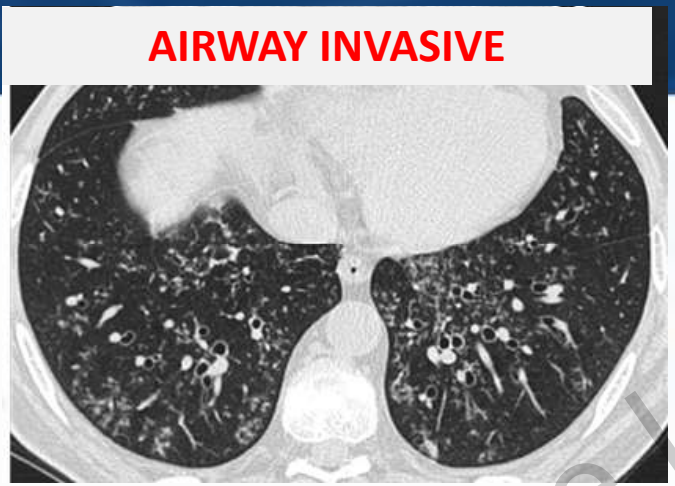


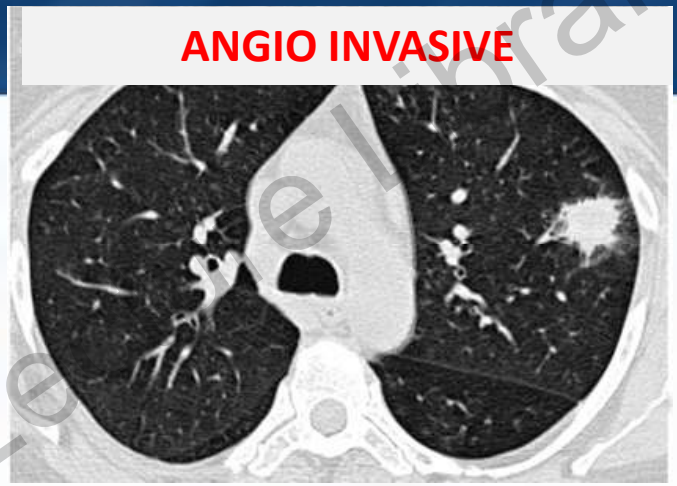
Cordonnier et al. Clin Microbiol Infect 2008, 15: 81-86

Design a clear and strict algorithm for the use (or not) of antifungal therapy

- **Define a study period**
- **Define triggers for ordering CT-scan**
  - A new cough, chest pain or hemoptysis
  - An abnormal chest radiograph
  - A positive culture for *Aspergillus* or other mold from any site
  - Microscopic evidence of hyphae in any invasive sample
  - Unresolved temperature after a number of days of antibiotics
  - Positive screening assay
- **Define 'characteristic' radiologic abnormalities**

CT scan features of invasive aspergillosis





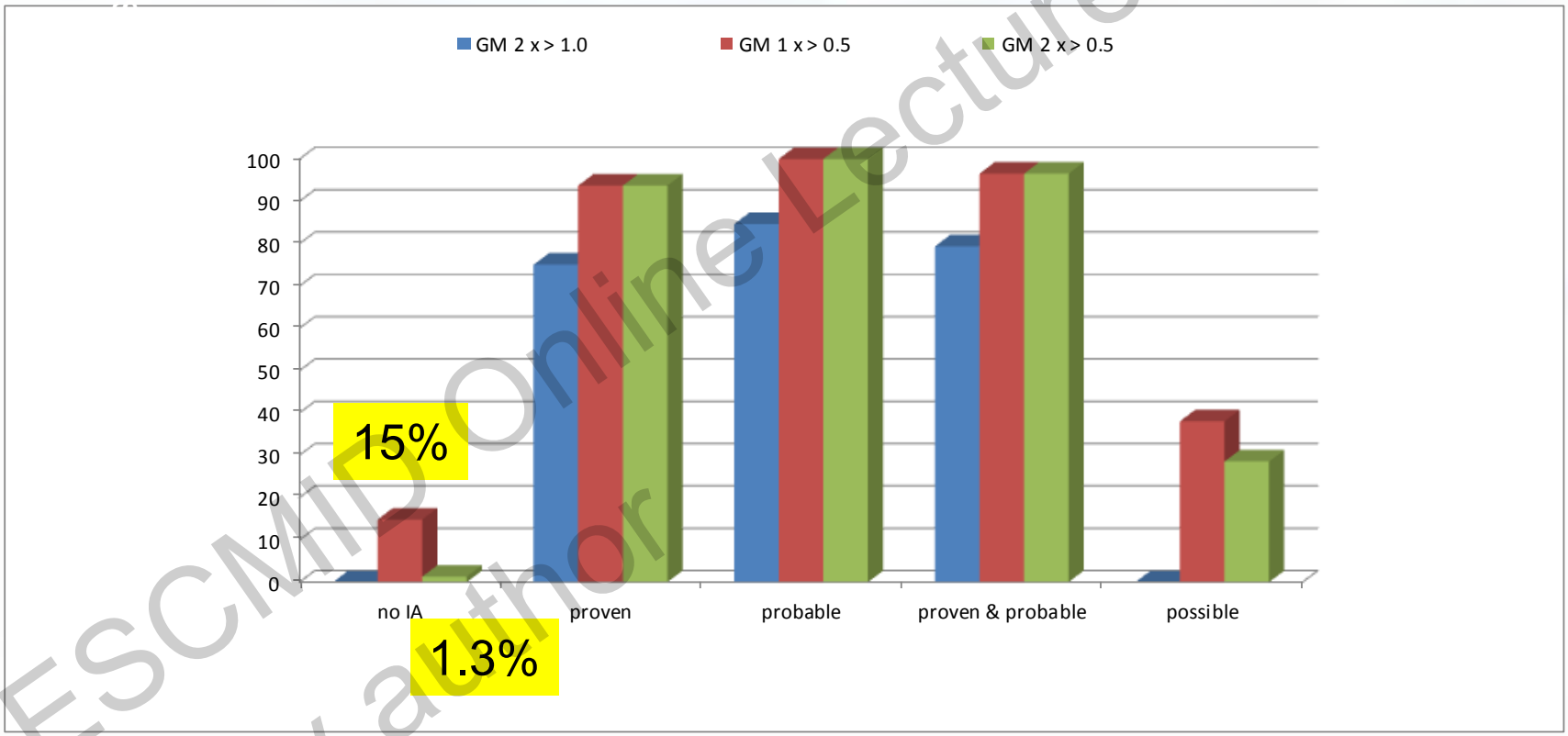
Signs	Allo HSCT (n=23)	Acute leukaemia (n=22)	Others (n=10)
Angio-invasive	3 (13%)	10 (45%)	1 (10%)
Airway-invasive	10 (44%)	3 (14%)	2 (20%)
Both angio- and airway-invasive	3 (13%)	2 (9%)	2 (20%)
Neither angio- nor airway-invasive	7 (30%)	7 (32%)	5 (50%)

Bergeron A. Blood 2012;119(8):1831-1837

Design a clear and strict algorithm for the use (or not) of antifungal therapy

- **Define a study period**
- **Define triggers for ordering CT-scan**
  - A new cough, chest pain or hemoptysis
  - An abnormal chest radiograph
  - A positive culture for *Aspergillus* or other mold from any site
  - Microscopic evidence of hyphae in any invasive sample
  - Unresolved temperature after a number of days of antibiotics
  - Positive screening assay
- **Define 'characteristic' radiologic abnormalities**
- **Triggers for starting antifungal therapy**
- **Drug of choice based on (institutional) guidelines**

Choice of test(s)
Significance of a single positive biomarker

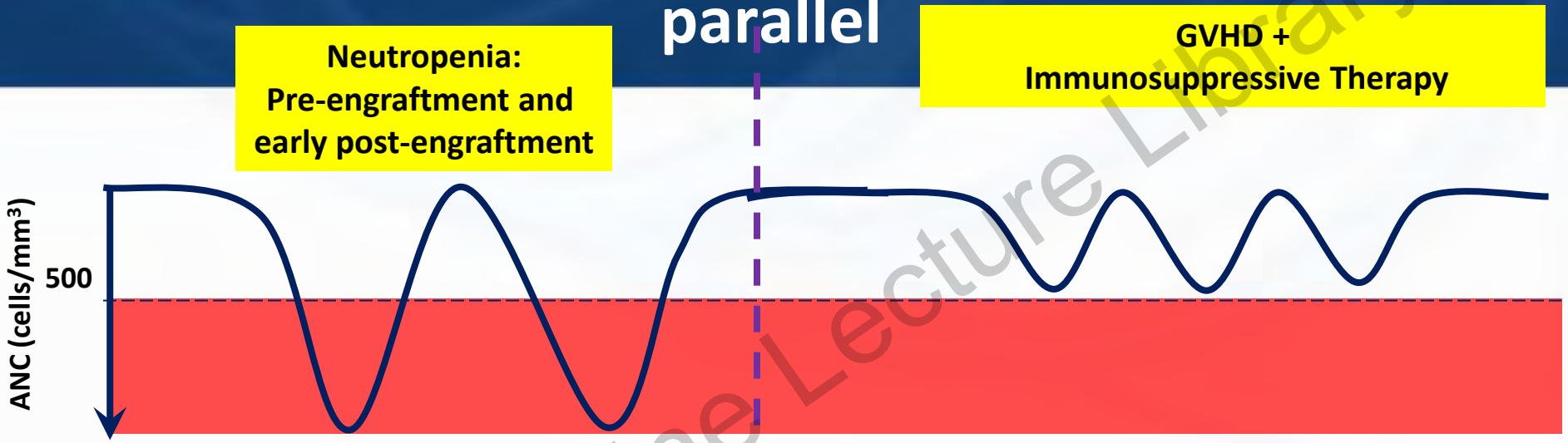


Maertens J et al. Br J Haematol 2004; 126: 852-860
See also results for PCR in Blennow et al. Bone Marrow Transpl 2010; 45: 1710

Choice of test(s)

- Standardized methods for collecting, processing, and transport of samples!
- Frequency of testing
- GM-ELISA and PCR: good negative predictive value
- Combined use may optimize sensitivity and positive predictive value
  - Minimize uncertainty surrounding interpretation of single + and intermittently +
  - Maximize adherence to the protocol
- GM release and DNA release may not occur in parallel:
  - GM: neutropenic phase during angio-invasion
  - PCR: following neutrophil recovery and corticosteroids due to hyphal damage of neutrophils

GM release and DNA release may not occur in parallel



Cellular trafficking BAL fluid	No influx of PMN	Rapid and extensive increase in PNM
Pathology	Diffuse pneumonia Few bronchiolitis No neutrophil infiltration	Foci of pneumonia Exsudative bronchiolitis Neutrophil infiltration
Fungal development	Invasion by large numbers of hyphae	Small numbers of conidia
Chitin	High in all organs	Low in all organs
Galactomannan	High	Very low

Balloy et al. Infect Immun 2005; 73: 494 & Chamilos et al. Haematologica 2006; 91: 986

The Cardiff experience:
Anti-mould prophylaxis plus a neutropenic care pathway

549 adult patients undergoing SCT, remission-induction for AML/MDS, or intensive chemotherapy for relapsed/refractory disease

Oral itraconazole solution 5 mg/kg/day with serum levels measured weekly (target >0.5 mg/L)
(alternatives: fluconazole 400 mg/d or liposomal amphotericin B @7 mg/kg once a week)

GM EIA and PCR twice weekly in SCT recipients and during fever in all others (same day reporting for GM and next day reporting for PCR)

High resolution CT scan in line with published standards of care
(Denning et al. Lancet Infect Dis 2003;3:230–240)

No empirical antifungal therapy in patients receiving adequate (>0.5 mg/L) prophylaxis

AML, acute myeloblastic leukaemia; MDS, myelodysplastic syndromes; EIA, enzyme-linked immunoassay

Barnes R A et al. J Infect 2013;67:206–214

Diagnostic accuracy for the detection of invasive aspergillosis

- As individual assays, both PCR and GM EIA provide excellent sensitivity (>92.5%) and NPV (>98.5%) for proven/probable disease, confirming the ability of these markers to rule out disease and enabling empirical therapy to be withheld with confidence
  - When used together, these biomarkers show optimal performance as a screening test with 98.1% sensitivity, NPV of 99.6% and a negative likelihood ratio (LR) of 0.04 for proven and probable disease!
- Neither PCR nor GM EIA can be used to diagnose invasive aspergillosis on the basis of a single test: PPV <31.7% and positive LR <4.1
- Using a combined strategy with multiple positive results for both assays provides optimal specificity (94.9%), PPV (55.6%) and positive LR (11.2), suggesting that a combination of biomarkers is the most accurate method of ruling in disease

NPV, negative predictive value; LR, likelihood ratio

Barnes R A et al. J Infect 2013;67:206–214

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No antifungal prophylaxis	55	0	0
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Fluconazole	12.2	35	100
Test	GM	GM + PCR	GM

Cordonnier C et al. Clin Infect Dis 2009; 48: 1042-1051
Morrissey CO et al. Lancet Infect Dis 2013; 13: 519-528

Randomization

400 mg fluconazole

On admission and each Monday and Thursday thereafter
Obtain blood for PCR & beta-D-glucan

400 mg fluconazole

On admission and each Monday and Thursday thereafter
Obtain blood for GM, PCR, beta-D-glucan

5 ml Serum
Baseline, then 2x weekly

Neutropenia and fever

Order blood cultures, chest X-ray, appropriate specimens

Trigger for caspofungin treatment

a) 4 days persistent fever
OR
b) New fever occurring > 2 days after resolution of a first fever under broad spectrum antibacterial therapy

a) Single plasma or serum GM ELISA with index >0.5
OR
b) Aspergillus sp. recovered by culture from sputum
OR
c) New pulmonary infiltrate on chest-X-ray and an IFD cannot be readily excluded
OR
d) Newly dense well circumscribed lesions (s) with or without a halo sign, on a CT scan consistent with an IFD

Diagnostic work up once trigger is met

Obtain blood for GM, PCR, beta-D-glucan.
DO NOT USE for patient management
Order chest X-ray

5 ml Serum

Obtain blood for GM, PCR, beta-D-glucan
Order CT scan to be done as soon as possible and at least within the next 3 days

Start caspofungin once daily

Every Monday and Thursday
Obtain blood for GM, PCR, beta-D-glucan.
DO NOT USE for patient management

5 ml Serum
2x weekly

Every Monday and Thursday
Obtain blood for GM, PCR, beta-D-glucan

5 ml Serum
EOT + Hospital Discharge

Survival status

Survival status

Conclusion
A coordinated approach across different specialties