Invasive aspergillosis in febrile neutropenia

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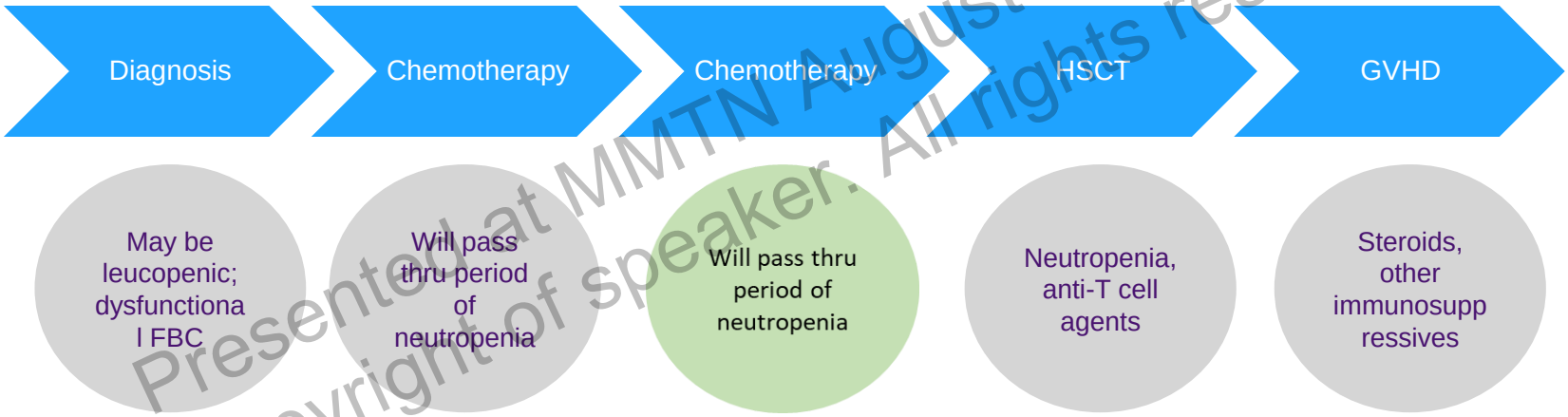
Disclosures

- In the past three years, Dr Tan has served on the advisory boards of Pfizer and MSD.

IA may occur at any time in course of patient's journey through leukemia/MDS



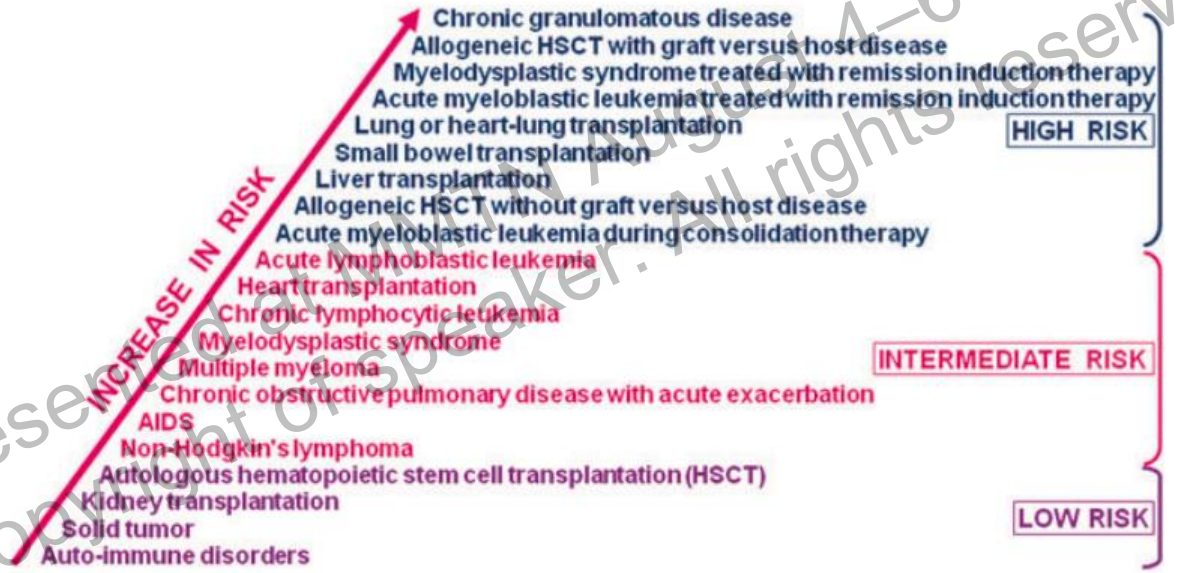
MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Invasive aspergillosis in hematologic malignancies

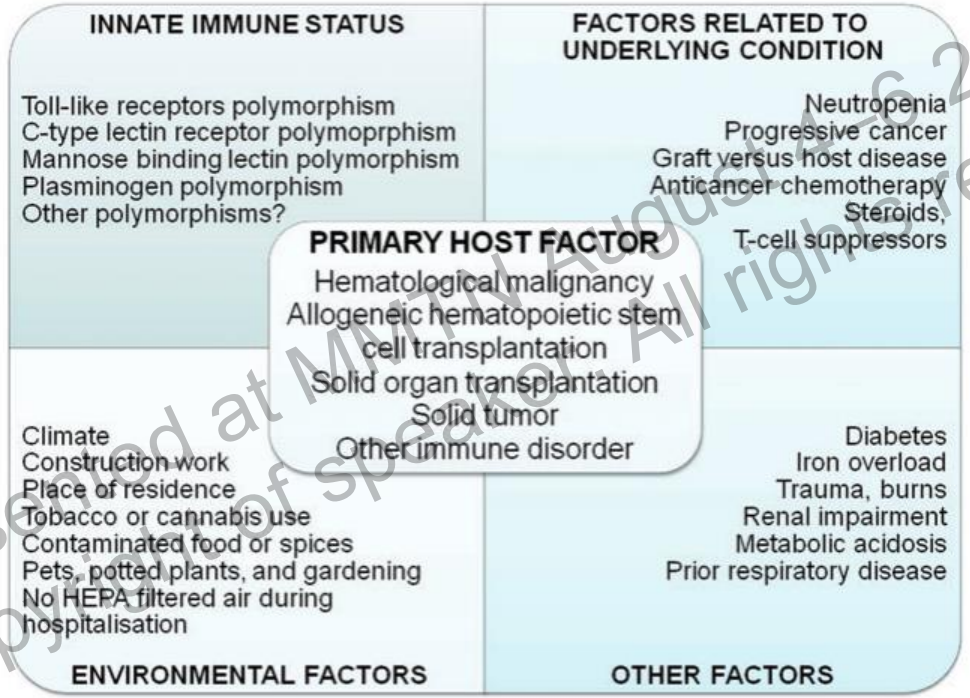
Lecture outline

- Epidemiology (risk groups)
- Diagnostic tools
- Treatment approaches

Risk of IA, by underlying disease



Herbrecht R et al. *Ann NY Acad Sc* 2012;1272:23



Herbrecht R et al. *Ann NY Acad Sc* 2012;1272:23

MYCOTIC INFECTIONS IN LEUKEMIC PATIENTS AT AUTOPSY

JOHN G. GRUHN, M.D., AND JOHN SANSON, M.D.

INCIDENCE OF LYMPHOMA AND LEUKEMIA WITH MYCOSES

Type ca.	Tot. autop. cases	With mycoses	
		No.	%
Lymphoma			
1941–1961	61	2	3
Leukemia			
1941–1961	103	25	24
1957–1961	54	21	39

Gruhn JG et al. *Cancer* 1963;16:61

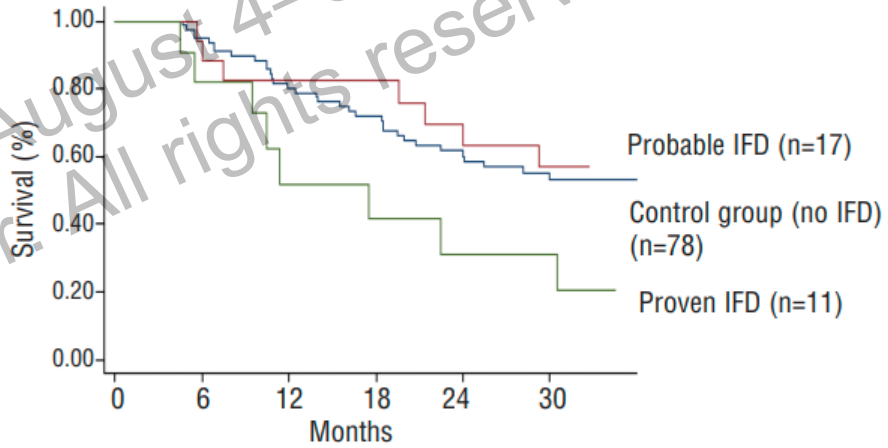
Impact of IA on leukemia survival

- 2000 – 2008
- 28 probable/proven cases of IA, vs 78 controls
- Next chemotherapy course delayed in 57% of IA pts, vs 20% of controls ($p<0.001$)
- Chemotherapy was changed in 29% of IA cases (vs 8%) of controls

Even C et al. *Haematologica* 2011;96:337

Impact of IA on leukemia survival

- On multi-variate analysis, determinants of event-free survival were:
  - Older age
  - WBC >100,000 X 10^9 at diagnosis
  - AML M6 or secondary AML
  - Proven IFD



Even C et al. *Haematologica* 2011;96:337

MDACC autopsy study

Characteristics	1989-1993	1994-1998	1999-2003	2004-2008	p
Autopsies per 100 deaths	0.63	0.35	0.27	0.06	P<0.001
IFI prevalence	0.32	0.30	0.31	0.19	P<0.001
Severe neutropenia	90%	81%	70%	36%	P<0.001
Hi-dose steroids	19%	65%	50%	84%	P<0.001
IFI evident only at autopsy	84%	66%	68%	49%	P<0.001
IFI as cause of death	77%	81%	73%	49%	P<0.001
IFI b'thru on antifungals	10%	71%	64%	56%	P<0.001

Lewis RE et al. *Mycoses* 2013;56:638

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IFIs are less commonly found at autopsies

Lewis RE et al. *Mycoses* 2013;56:638

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Getting better at ante-mortem diagnosis

Lewis RE et al. *Mycoses* 2013;56:638

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Less frequent as COD

Lewis RE et al. *Mycoses* 2013;56:638

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Pt on antifungals still could be having IFI

Lewis RE et al. *Mycoses* 2013;56:638

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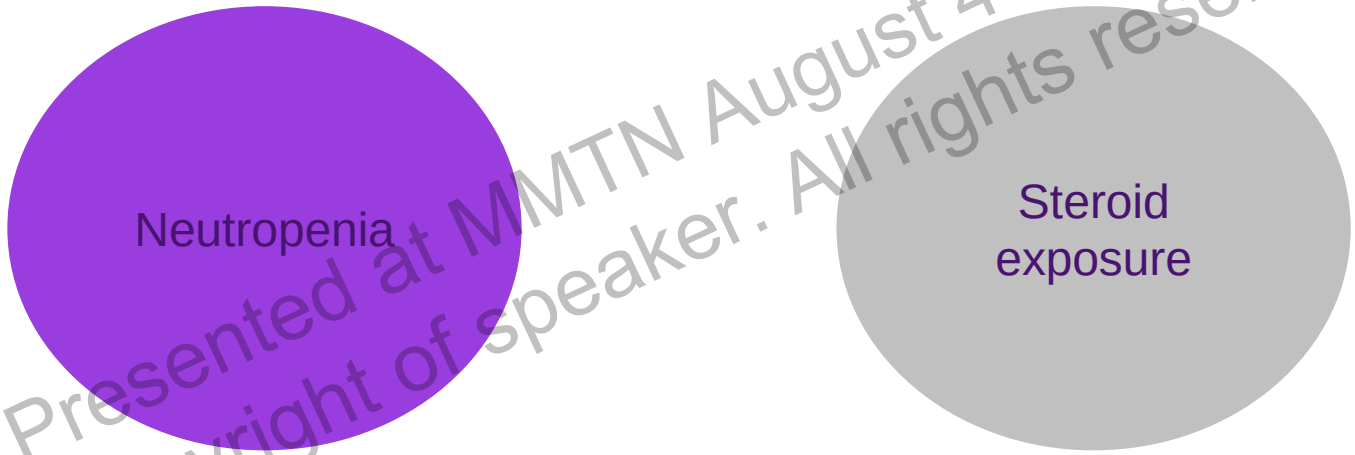
Primary host immune deficiencies predisposing to IA



Dagenais TRT et al. *Clin Microbiol Rev* 2009;22:447

Diagnostic modalities

Microbiology

- Microscopy
- Cultures
- Galactomannan (blood, csf)
- β-d-glucan (BDG)
- Aspergillus PCR

Radiology

- CXR
- CT scan
- MRI (sinuses/brain)
- PET-CT

Histopathology

Clinical Infectious Diseases

MAJOR ARTICLE

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

Probable

Proven

Possible

- Recent neutropenia (ANC <500)
- Recipient (allo-HSCT/SOTx)
- Haematologc malignancy
- Prolonged steroids*
- Received T-cell suppressants
- Received B-cell suppressants
- Inherited immunodef (eg, CGD, STAT 3 def)

Detailed definitions in article

*>0.3mg/kg/d for >3wk in prev 60d

Pulmonary - any of the 4 CT features below

Dense well-circumscribed nodule (± halo)
Cavity
Air crescent
Wedge-shaped consolidation (segmental/lobar)

Tracheobronchitis

Ulcer
Eschar
Plaque
Nodule
Pseudomembrane

Sinus, CNS disease – see article

Culture

Any growth of Aspergillus from BAL/sputum/trach aspirate

Galactomannan

Single serum GM ≥ 1
Single BAL GM ≥ 1
Single serum GM ≥ 0.7 with single BAL GM ≥ 0.8

Aspergillus PCR

2 consec bld specimens positive
BAL + in duplicate
1 bld and 1 BAL positive

Any of culture, GM or PCR

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Meta-analysis on serum GM for diagnosis of IA

Table 4. Pooled sensitivity and specificity of the galactomannan assay for diagnosis of invasive aspergillosis (IA).

	Cases of proven IA				Cases of proven or probable IA			
Studies	TP/(TP+FP)	Pooled sensitivity (95% CI)	TN/(TN+FP)	Pooled specificity (95% CI)	TP/(TP+FN)	Pooled sensitivity (95% CI)	TN/(TN+FP)	Pooled specificity (95% CI)
All	163/229	0.71 (0.68–0.74)	3601/4055	0.89 (0.88–0.90)	250/407	0.61 (0.59–0.63)	2839/3060	0.93 (0.92–0.94)
Studies limited to patients with hematological malignancy	106/152	0.70 (0.62–0.77)	2570/2808	0.92 (0.90–0.93)	177/304	0.58 (0.52–0.64)	2324/2457	0.95 (0.94–0.96)
Studies limited to patients undergoing BMT	49/60	0.82 (0.70–0.90)	722/843	0.86 (0.83–0.88)	32/49	0.65 (0.60–0.78)	17/26	0.65 (0.44–0.83)
Studies limited to solid-organ transplant recipients	2/9	0.22 (0.03–0.60)	180/215	0.84 (0.78–0.88)	9/22	0.41 (0.21–0.64)	210/247	0.85 (0.80–0.89)
Studies using EORTC/MSG criteria	74/116	0.64 (0.54–0.73)	2549/2869	0.89 (0.88–0.90)	211/354	0.60 (0.54–0.65)	2628/2823	0.93 (0.92–0.94)
Studies not using EORTC/MSG criteria	89/113	0.79 (0.70–0.86)	1052/1186	0.89 (0.87–0.90)	39/53	0.74 (0.60–0.85)	211/237	0.89 (0.84–0.93)

Pfeffer CD et al. *Clin Infect Dis* 2006;42:1417

Meta-analysis on serum GM for diagnosis of IA

Studies involving adult population only	58/93	0.62 (0.52–0.72)	1211/1398	0.87 (0.85–0.88)	102/140	0.73 (.46-.61)	802/889	0.90 (.88–0.92)
Studies of both pediatric and adult populations	70/93	0.75 (0.65–0.84)	1726/1875	0.92 (0.91–0.93)	92/196	0.47 (0.40–0.54)	1601/1701	0.94 (0.93–0.95)
Studies using a cutoff value of 0.5 for defining positivity	3/11	0.27 (0.06–0.61)	27/341	0.79 (0.74–0.83)	69/87	0.79 (0.69–0.87)	493/571	0.86 (0.83–0.89)
Studies using a cutoff value of 1.0 for defining positivity	85/107	0.79 (0.71–0.87)	1385/1598	0.87 (0.85–0.88)	103/159	0.65 (0.57–0.72)	1163/1242	0.94 (0.92–0.95)
Studies using a cutoff value of 1.5 for defining positivity	75/111	0.68 (0.58–0.76)	1946/2116	0.92 (0.91–0.93)	78/161	0.48 (0.41–0.56)	1183/1247	0.95 (0.93–0.96)

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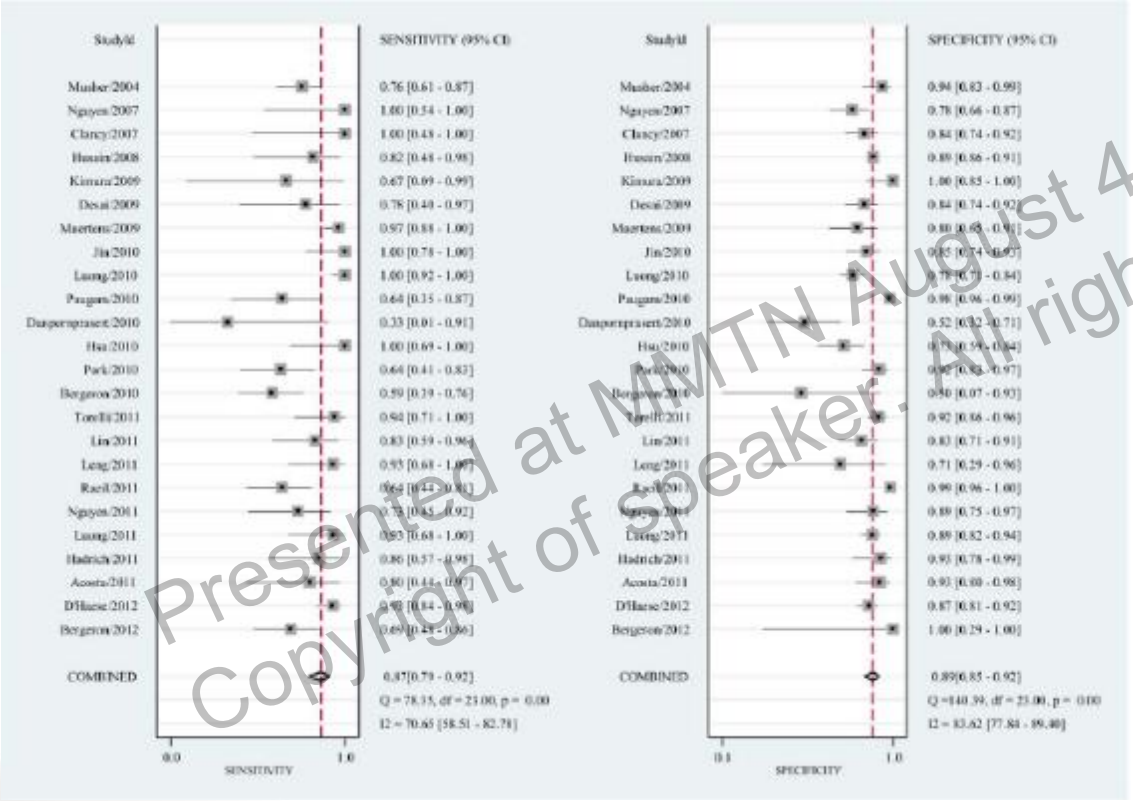
BAL GM – meta-analysis of 30 studies



Taking 0.5 as cut-off (commonest in studies) sensi was 0.87, spec was 0.89, PLR was 8, NLR was 0.15

Zou M et al. *Plos One* 2012;7:e43347

Zou (PloS One 2012) meta-anal for BAL GM

Cut-off	DOR	SEN#	SPEC#	PLR	NLR
0.5	52.7	0.87	0.89	8.0	0.15
1.0	112.7	0.86	0.95	17.0	0.15

DOR – diagnostic odds ratio (single metric that incorp SEN, SPEC)
#Pooled

Likelihood ratio – metric that incorporates SEN, SPEC. PLR >10, NLR <0.1 provide convincing evidence for and against diagnosis

Zou M et al. *Plos One* 2012;7:e43347

BDG

Of 25 bacteremic patients, 14 were BDG positive (only one, with concomitant candidemia, was a true +)

Pickering JW et al. J Clin Microbiol 2005;43;5957

Can be falsely-positive in hemodialysis patients – depends on membrane

Kanda H et al. Kidney Int 2001;60:319

GM more specific than BDG for IA diagnosis
Bacteremic pts: false+ results much higher for BDG (37%) than GM (2%)
Overall benefit of BDG limited due to lack of specificity and high cost

Sulahian A et al. J Clin Microbiol 2014;52:328

BDG in BAL – similar sensitivity to GM for IA, but poor specificity, poor reproducibility

Rose SR et al. J Infect 2014;69:278

Many associations of false-positivity with blood products, likely because it elutes from cellulose membranes of filters

Nagasawa K et al. J Artif Organs 2003;6:49

- Recent neutropenia (ANC <500)
- Recipient (allo-HSCT/SOTx)
- Haematologc malignancy
- Prolonged steroids*
- Received T-cell suppressants
- Received B-cell suppressants
- Inherited immunodef (eg, CGD, STAT 3 def)

Detailed definitions in article

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Pulmonary - any of the 4 CT features below

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Cavity
Air crescent
Wedge-shaped consolidation (segmental/lobar)

Tracheobronchitis

Ulcer
Eschar
Plaque
Nodule
Pseudomembrane

Sinus, CNS disease – see article

Culture

Any growth of Aspergillus from BAL/sputum/trach aspirate

Galactomannan

Single serum GM ≥ 1
Single BAL GM ≥ 1
Single serum GM ≥ 0.7 with single BAL GM ≥ 0.8

Aspergillus PCR

2 consec bld specimens positive
BAL + in duplicate
1 bld and 1 BAL positive

Any of culture, GM or PCR

BDG not part of the criteria

Donnelly JP et al. *Clin Infect Dis* 2019

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Aspergillus PCR – early considerations

- How to interpret a positive result, since Aspergillus is ubiquitous in environment
  - Primer must be specific to aspergillus
  - + result in blood/serum or csf not a problem → most likely real (not 100% certainty coz small possibility of contamination of sampling tubes
- + result from BAL??
- Can be infection, colonization, bystander in inhaled air

Bretagne S et al. Abstract; 6th Trends in Medical Mycology conference 2013.

How useful is the blood* PCR for IA diagnosis?

Meta-analysis of 25 studies (2595 pts)

- For single PCR positivity as gold standard
  - pooled sensitivity was 84% (95%CI 75-91)
  - pooled specificity was 76% (95%CI 65-84)

*Whole blood or serum

Arvanitis M et al. *J Clin Microbiol* 2014;52:3731

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Meta-analysis of 25 studies (2595 pts)

- For single PCR positivity as gold standard
  - Pooled sensitivity was 84% (95%CI 75-91)
  - Pooled specificity was 76% (95%CI 65-84)
- If TWO positive PCR results needed to be considered positive,
  - Sensitivity was 64%
  - Specificity was 95%
  - **Diagnostic Odds Ratio 12.8**

For blood specimens, 2 positive PCRs can be considered highly indicative of invasive aspergillosis

*Whole blood or serum

Arvanitis M et al. *J Clin Microbiol* 2014;52:3731

Another meta-analysis supports 2 positives

	DOR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio	
				Positive	Negative
One PCR-positive sample	22·11 (7·77–62·92)	0·88 (0·75–0·94)	0·75 (0·63–0·84)	3·53	0·15
Two PCR-positive samples	21·33 (6·86–466·3)	0·75 (0·54–0·88)	0·87 (0·78–0·93)	6·04	0·28

DOR=diagnostic odds ratio.

One negative PCR likely sufficient to exclude proven/probable IA
TWO positive PCRs needed to rule the diagnosis in (improved specificity)

Mengoli C et al. *Lancet Infect Dis* 2009;9:89

PCR for screening – CDSR meta-analysis conclusions

- 19 cohorts published 2000 – 2013
- Majority had received chemotherapy for haematological malignancies or had undergone HSCT
- If single positive test used to define disease, out of 100 people with disease prevalence of 13%
    - 3 would be missed (sensitivity 80.5%, false-neg 19.5%) and 19 unnecessarily treated or sent for further tests (specificity 78.5%, false-positive 21.5%)

Cruciani M et al. *CDSR* 2015;Issue 10. Art no. CD009551

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- If 2 positive tests used to define disease, out of 100 people with disease prevalence of 13%,
  - 6 would be missed (sensitivity 58%, false-negative 42%) and 3 would be unnecessarily treated or sent for further tests (96.2% specificity, false-positive 3.8%)

Cruciani M et al. *CDSR* 2015;Issue 10. Art no. CD009551

Having access to both GM & PCR helps

Test (combination) and condition	Sensitivity (n = 16)	Specificity (n = 37)	PPV	NPV	Diagnostic odds ratio
PCR (BALF)	7/16 (43.8%)	37/37 (100%)	7/7 (100%)	37/46 (80.4%)	59.2[3.1–1,1132]
PCR (whole blood)	0/16 (0%)	37/37 (100%)	0/0 (0%)	37/37 (100%)	NA
GM 0.5 ODI (BALF)	6/16 (37.5%)	34/37 (91.9%)	6/9 (66.7%)	34/44 (77.3%)	6.8 [1.4–32.2]
GM 0.5 ODI (serum)	5/16 (31.3%)	37/37 (100%)	5/5 (100%)	37/48 (77.1%)	35.9 [1.8–699.3]
GM (BALF) 1.0 ODI	5/16 (31.3%)	35/37 (94.6%)	5/7 (71.4%)	35/46 (76.1%)	8.0 [1.3–46.9]
Culture (BALF)	3/16 (18.8%)	37/37 (100%)	3/3 (100%)	37/50 (74.0%)	19.44 [0.9–401.9]
GM 1.0 ODI (BALF) and/or GM 0.5 ODI (serum)	7/16 (43.8%)	35/37 (94.6%)	7/9 (77.8%)	35/46 (79.6%)	13.6 [2.4–77.1]
PCR (BALF) and/or GM 0.5 ODI (serum)	10/16 (62.5%)	37/37 (100%)	10/10 (100%)	37/43 (86.1%)	121.2 [6.3–2332]
PCR (BALF) and/or GM 1.0 ODI (BALF)	10/16 (62.5%)	35/37 (94.6%)	10/12 (83.3%)	35/41 (85.4%)	29.2 [5.1–167.5]
PCR (BALF) and/or GM 1.0 ODI (BALF) and/or GM 0.5 ODI (serum)	11/16 (68.8%)	35/37 (94.6%)	11/13 (84.6%)	35/40 (87.5%)	38.5 [6.5–227.1]
PCR (BALF) and/or GM 1.0 ODI (BALF) and/or culture (BALF) and/or GM 0.5 ODI (serum)	12/16 (75.0%)	35/37 (94.6%)	12/14 (85.7%)	35/39 (89.7%)	52.5 [8.5–324.0]

Eigl S et al. *Med Mycol* 2017;55:528

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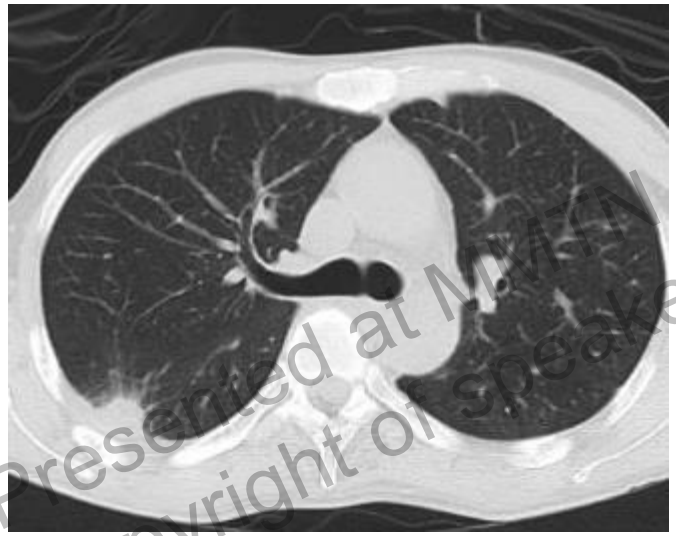
Why?

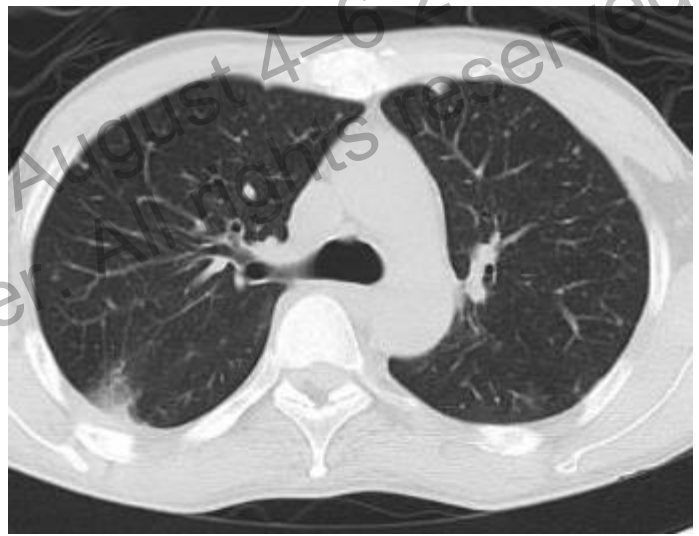
- Reason as pointed out:
- We have limited data on relationship between the release of fungal biomarkers and the stage(s) of disease
- Combination testing gives us opportunity to detect biomarkers that are differentially released at different stages of infection

White PL et al. *Clin Infect Dis* 2021;72(S2):S95

Radiology

The halo sign



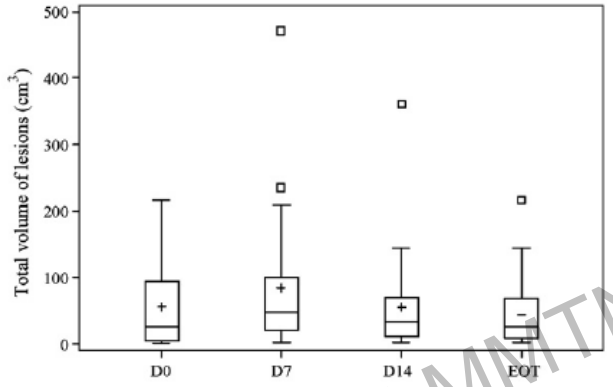


It is not static …

Nodules in IPA – how they change with time

- 30 pts with IPA from Combistrat study
- 26 probable, 4 proven
- Studied volume of CT lesions of IPA
- Assume – aspergillus lesions had ovoid shape, hence vol = length X width X height X π/6

Volume of nodule changes with time



Patients with reviewed CT scan, n	28	26	23	26
Number of lesions, median [range]	2 [1–12]	3 [1–10]	2 [1–10]	2 [0–7]
Median of total volume of lesions, [min; max], cm³	24.8 [1; 217]	48.2 [2; 472]	32.8 [2; 361]	25.8 [2; 217]
Relative volume change, median	1	1.60	1.36	0.76
Comparison with precedent visit*	NA	D7 vs D0 P = 0.003	D14 vs D7 P = 0.003	EOT vs D14 P < 0.001
Comparison with baseline*			D14 vs D0 P = 0.56	EOT vs D0 P = 0.11

* Wilcoxon's test on absolute changes (cm³).

Volume ↑ from D0 to D7 (1.6 fold, p = 0.003)

Volume ↓ from D7 to D14

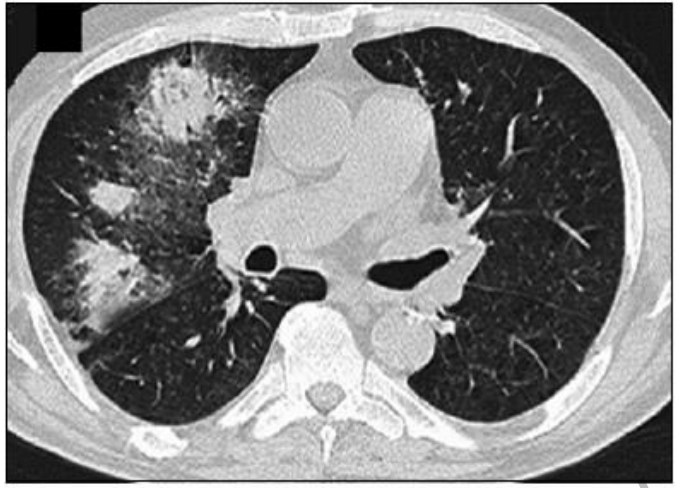
And ↓ again from D14 to EOT (med D17) (vol at EOT was 0.76 of vol at D14)

Caillot D et al. *Eur J Radiol* 2010;74:e172

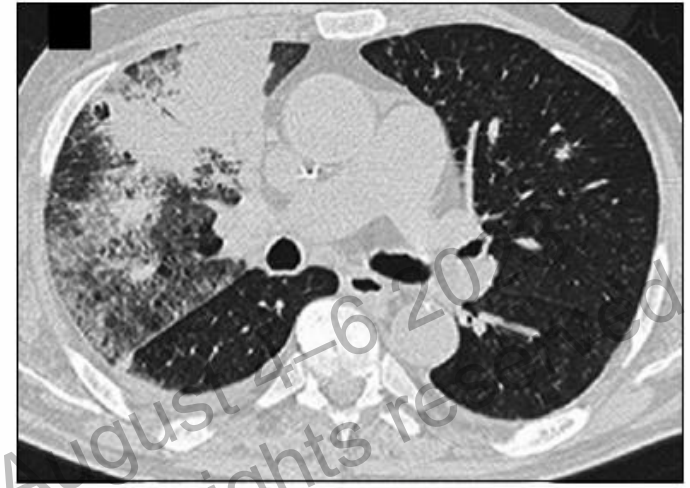
Increase in size with treatment augurs well

- Patients with favorable outcome had lesions of bigger total volume than those with an unfavorable outcome
- Why ↑ in size?
  - Defence mechanisms with infiltration of immune cells? (ie marker of early BM recovery)
  - Neutrophil recovery, improved ability to mount an immune response

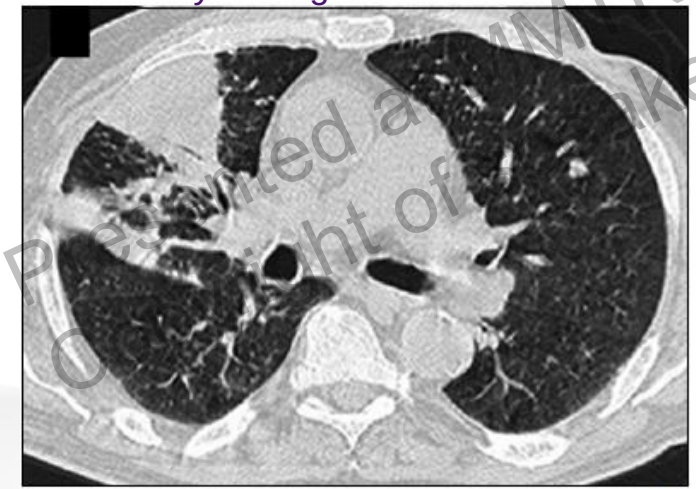
Caillot D et al. *Eur J Radiol* 2010;74:e172



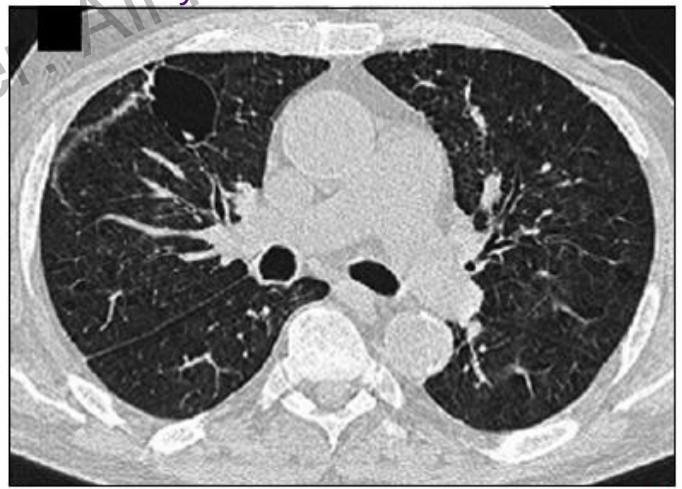
Day of diagnosis



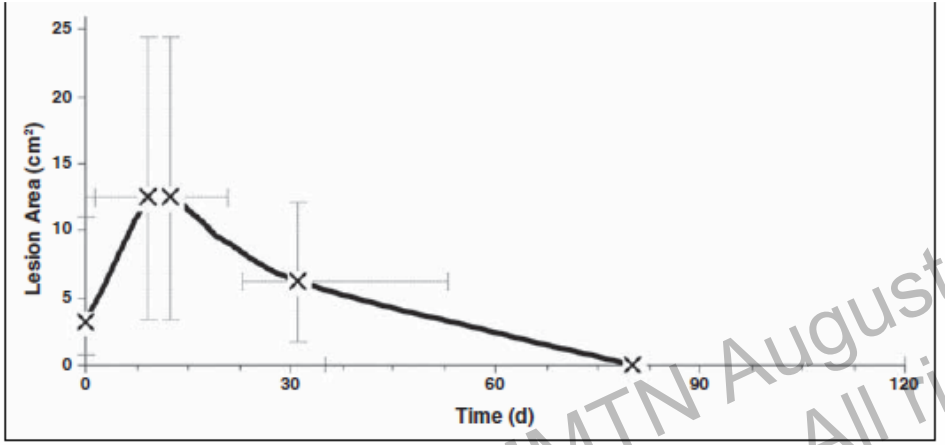
8 days later



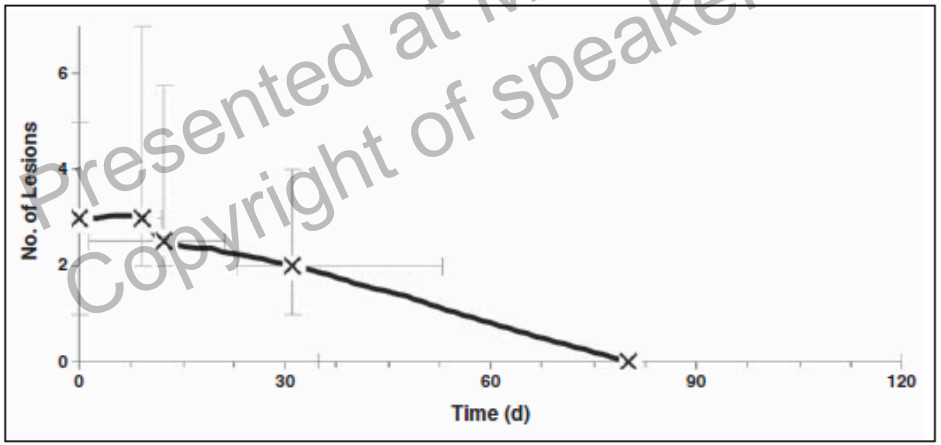
20 days later



Brodoefel H et al. *AJR* 2006;187:404



A



B

X:

Day of diag - D0

1st sight of max area - D9

Last sight of max area – D16

Time at ½ max area – D30

Time at compl CT resol – D86

Brodoefel H et al. *AJR* 2006;187:404

Halo sign – observed in 87.5% on Day 1

Median duration 5 days (mean 8, r 1 – 30)

Prevalence of halo

Day 4 – 62.5%

Day 8 - 37%

Day 16 – 17.5%

Crescent sign

Day 4 – 5%

Day 8 – 10%

Day 16 – 25%

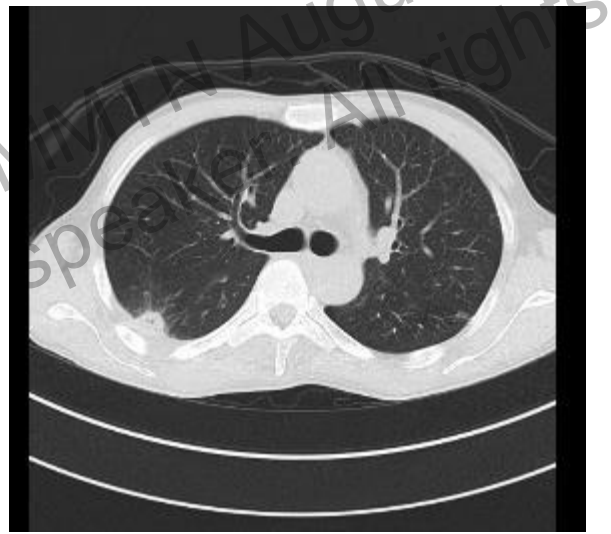
Day 32 – 45%

Cavities

Developed in 55%

Some have multiple cavitations

Median time to appearance of cavity – 21 (range 6-91)



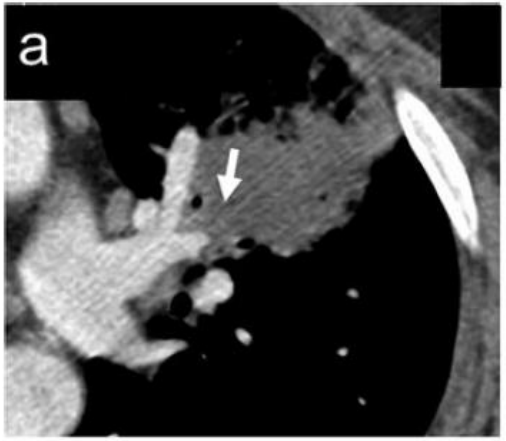
Brodoefel H et al. *AJR* 2006;187:404

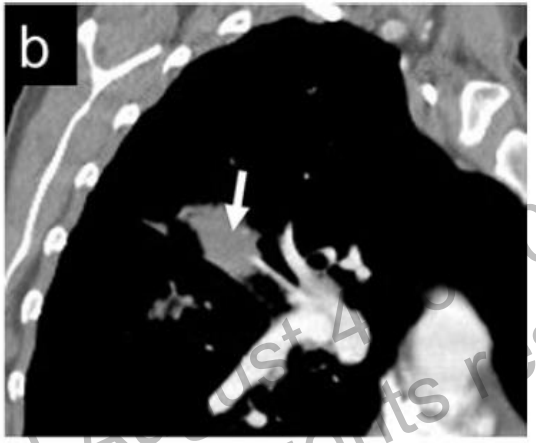
Computed Tomographic Pulmonary Angiography for Diagnosis of Invasive Mold Diseases in Patients With Hematological Malignancies

CT scans analyzed for “vascular occlusion” – interruption of a vessel at the border of a focal lesion, without depiction of the vessel inside or peripheral to the lesion

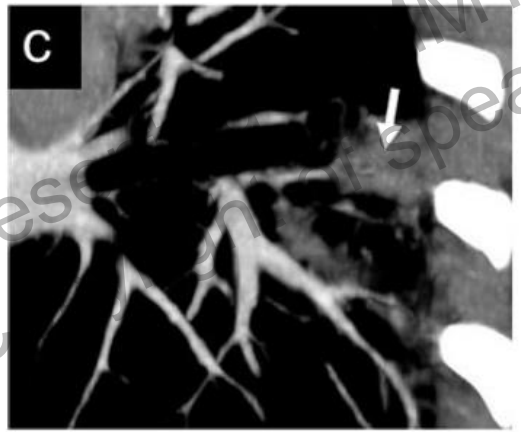
Needs to be present at least once in a patient

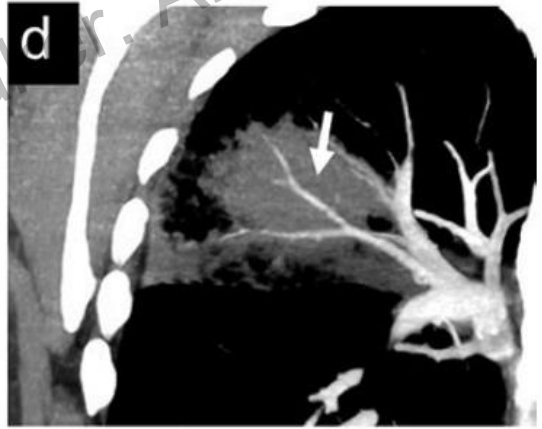
Stanzani M et al. *CID* 2012;54:610





a, b: true positives (IMI proven)





c: false+ (MSSA)

D: true neg (bacterial pneumonia)

Stanzani M et al. CID 2012;54:610

Treatment approaches

Given to prevent a disease

Given based on experience or observation (setting: febrile neutropenia)

Given based on early hint that infection is brewing (setting: febrile neutropenia)

"Diagnostic-driven"

Given when microbiology results are known

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Antifungal prophylaxis in haematological malignancies

Population	Intention	Intervention	SoR	QoE	Comment
Haematological malignancies, e.g. AML with prolonged and profound neutropenia	Lower incidence of IA	Posaconazole 200 mg tid suspension or 300 mg tablet qd	A	I	AML/MDS induction only. TDM especially with oral suspension. Tablets more bioavailable, bridging with posaconazole IV formulation possible
		L-AmB 12.5 mg 2 ×/weekly, nebulized, with undetermined dose of fluconazole	B	I	AML
		ABLC 3 mg/kg 3 ×/weekly	C	II_h	No difference to L-AmB regimen
		Micafungin 50 mg qd	C	II_t	
		L-AmB 10 mg/kg q7d	C	II_u	
		L-AmB 50 mg abs q2d	C	II_u	
		L-AmB 15 mg/kg q14 d	C	II_u	
		Voriconazole	C	II_t	Not better than fluconazole
		Itraconazole 400 mg/day, oral solution	D	II	No difference to fluconazole ($n = 195$) and more toxicity
Acute lymphoblastic leukaemia, remission induction chemotherapy	Lower incidence of IA	L-AmB 5 mg/kg biw	D	I	L-AmB more toxic than placebo, no significant reduction in IA rate
Autologous HSCT or treatment of haematological malignancies besides acute leukaemia	Lower incidence of IA	Any mould active agent	D	III	
Allogeneic HSCT (until neutrophil recovery)	Lower incidence of IA	Posaconazole 200 mg tid suspension or 300 mg tablet qd	B	II_t	Neutropenia duration approximately identical, TDM
		L-AmB 12.5 mg biw, nebulized, with fluconazole	B	II_t	
		Voriconazole 200 mg bid	C	I	Not better than fluconazole, TDM
		Micafungin 50 mg/day	C	I	But no difference in subgroup analysis for aspergillosis
		Itraconazole 400 mg/day oral solution	D	I	Toxicity issues; TDM
Allogeneic HSCT (after neutrophil recovery and no GvHD)		Any antifungal agent	D	III	No study demonstrated outcome advantage
Allogeneic HSCT (with moderate to severe GvHD and/or intensified immuno-suppression)		Posaconazole 200 mg tid suspension or 300 mg tablet qd	A	I	TDM
		Voriconazole 200 mg bid	C	II	Not better than fluconazole; TDM
		Itraconazole 400 mg/day, oral solution	C	II	Toxicity issues; TDM
		Micafungin 50 mg/day	C	III	Only few patients with GVHD

Ullmann AJ et al. *Clin Microbiol Infect* 2018;24:e1

Antifungal prophylaxis in haematological malignancies

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		ABLC 3 mg/kg 3 ×/weekly	C	II_h	No difference to L-AmB regimen
		Micafungin 50 mg qd	C	II_t	
		L-AmB 10 mg/kg q7d	C	II_u	
		L-AmB 50 mg abs q2d	C	II_u	
		L-AmB 15 mg/kg q14 d	C	II_u	
		Voriconazole	C	II_t	Not better than fluconazole
		Itraconazole 400 mg/day, oral solution	D	II	No difference to fluconazole ($n = 195$) and more toxicity
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Allogeneic HSCT (after neutrophil recovery and no GVHD)		Any antifungal agent	D	III	No study demonstrated outcome advantage
Allogeneic HSCT (with moderate to severe GVHD and/or intensified immuno-suppression)		Posaconazole 200 mg tid suspension or 300 mg tablet qd	A	I	TDM
		Voriconazole 200 mg bid	C	II	Not better than fluconazole; TDM
		Itraconazole 400 mg/day, oral solution	C	II	Toxicity issues; TDM
		Micafungin 50 mg/day	C	III	Only few patients with GVHD

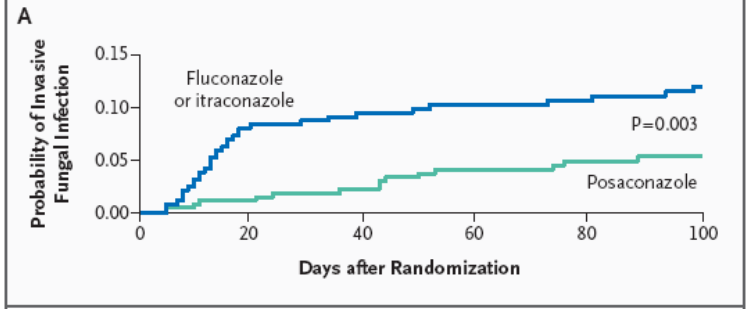
Ullmann AJ et al. *Clin Microbiol Infect* 2018;24:e1

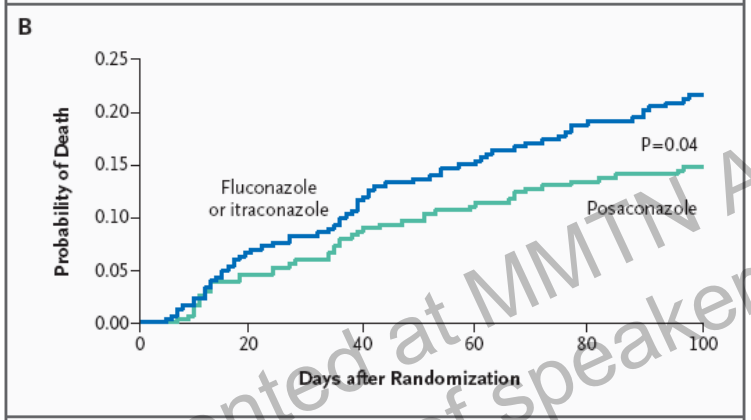
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

Oliver A. Cornely, M.D., Johan Maertens, M.D., Drew J. Winston, M.D., John Perfect, M.D., Andrew J. Ullmann, M.D., Thomas J. Walsh, M.D., David Helfgott, M.D., Jerzy Holowiecki, M.D., Dick Stockelberg, M.D., Yeow-Tee Goh, M.D., Mario Petrini, M.D., Cathy Hardalo, M.D., Ramachandran Suresh, Ph.D., and David Angulo-Gonzalez, M.D.*





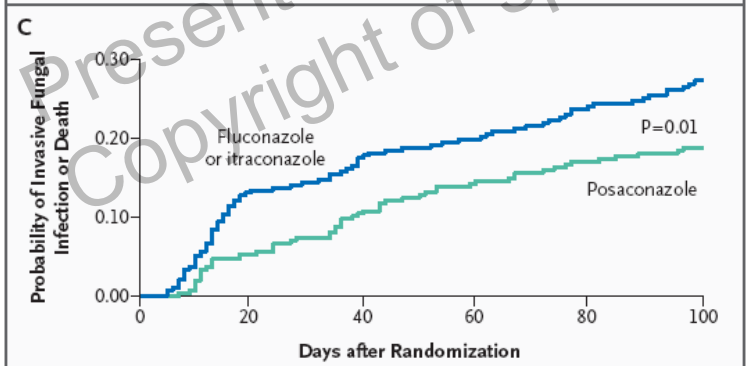
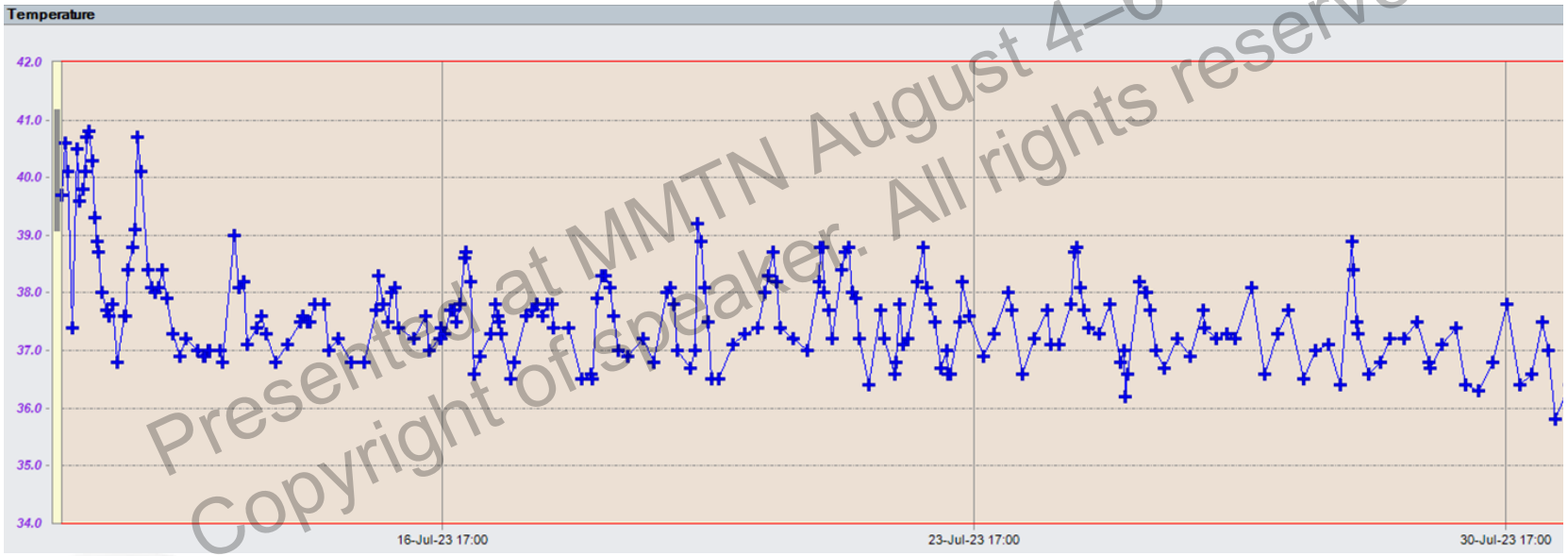


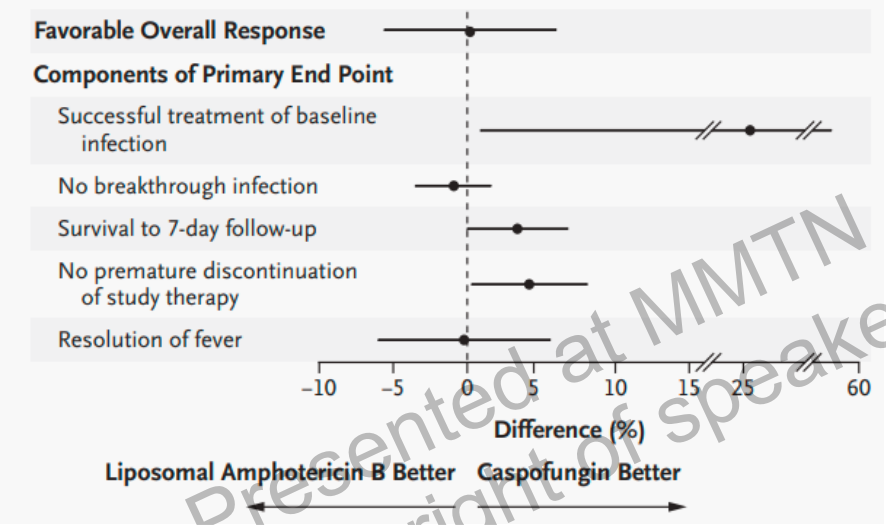
Figure 1. Kaplan–Meier Curves for Time to Invasive Fungal Infection (Panel A), Death from Any Cause (Panel B), and Invasive Fungal Infection or Death (Panel C) over the 100-Day Period after Randomization.

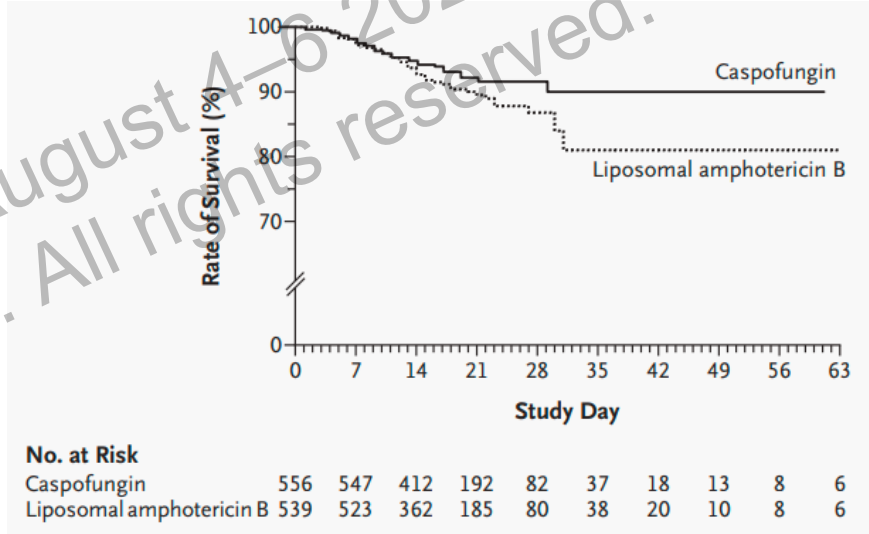
P values were estimated with the log-rank test. Data were censored on the last date of contact or on day 100 after randomization, whichever was sooner.

The persistently febrile neutropenic



Caspofungin versus Liposomal Amphotericin B for Empirical Antifungal Therapy in Patients with Persistent Fever and Neutropenia



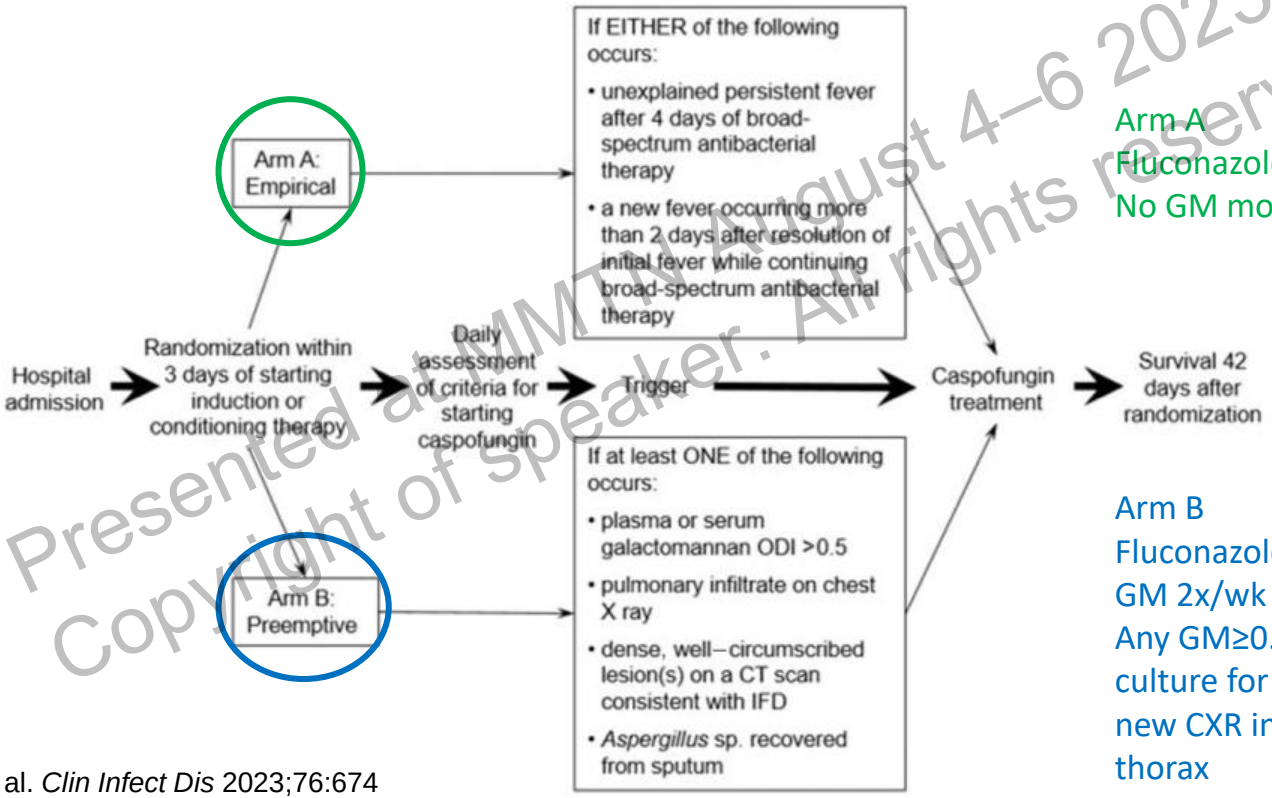


Success (composite end-point): 33.9% (CSP) vs 33.7% (LamB)

Pre-specified 7-d survival end-point: better in CSP arm (p=0.04)

Walsh TJ et al. *N Engl J Med* 2004;351:1391

Head-to-head comparison – empiric vs pre-emptive approach



Arm A
Fluconazole prophylaxis
No GM monitoring

Arm B
Fluconazole prophylaxis
GM 2x/wk
Any GM≥0.5, a + sputum culture for Aspergillus, or a new CXR infiltrate → CT thorax

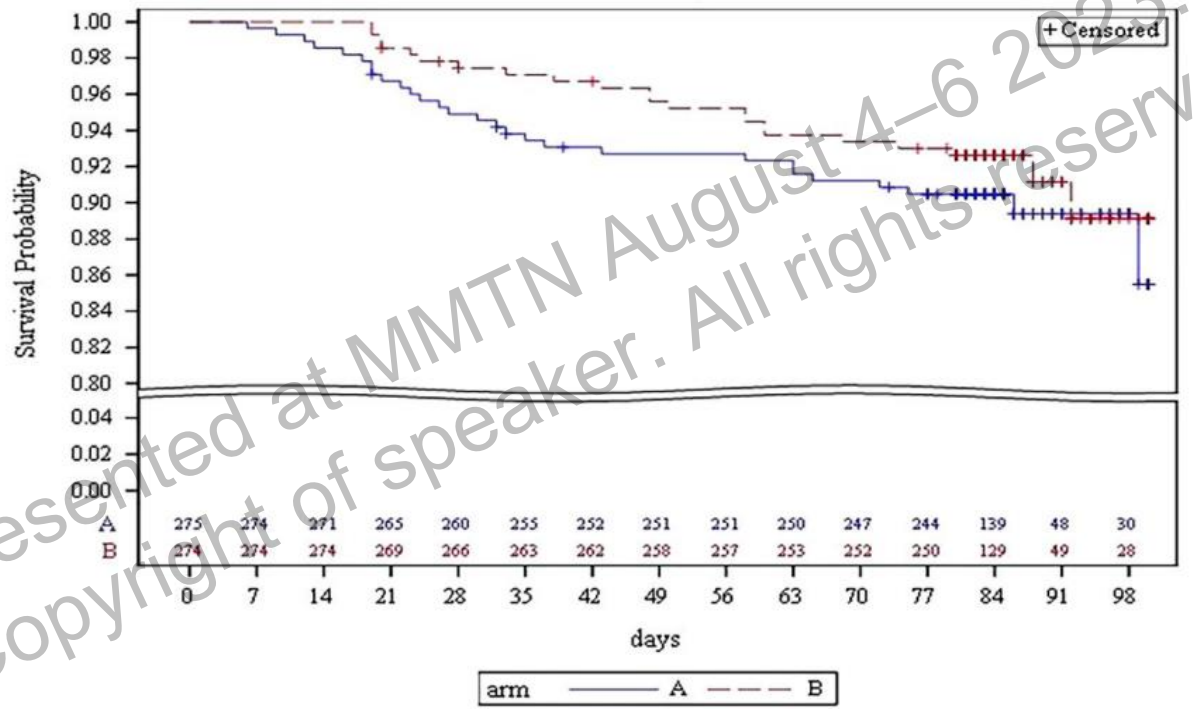
Maertens J et al. *Clin Infect Dis* 2023;76:674

Pre-emptive arm received caspofungin less often

	Arm A – Empiric (N = 275)	Arm B – Pre-emptive (N = 274)	p
No. of subjects given caspofungin per protocol	173 (63%)	73 (27%)	<0.001
Proven/probable aspergillosis (all participants)	18 (6.6%)	21 (7.7%)	0.61

Maertens J et al. *Clin Infect Dis* 2023;76:674

Empirical or pre-emptive – no survival difference



Overall survival at day 42: Arm A: 93.1% (95% CI, 89.3-95.5%) and Arm B: 96.7% (95% CI, 93.8-98.3%)

Maertens J et al. *Clin Infect Dis* 2023;76:674

There is not one approach that suits all patients, and different strategies are required for different patient groups depending on risk of disease, use of prophylaxis and availability of tests.

Barnes R, Rogers T and Maertens J. J Antimicrob Chemother 2019;74: sup 2: ii21

Targeted therapy

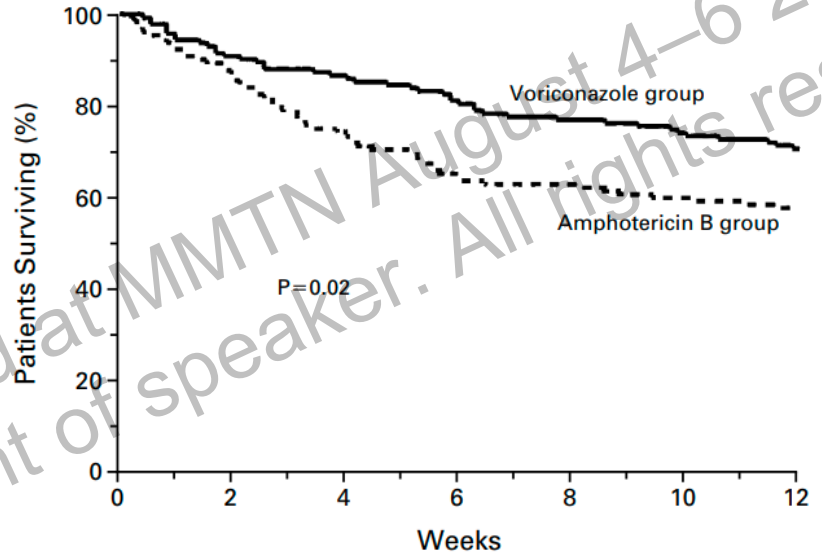
ESCMID guide (aspergillosis)

Targeted therapy of pulmonary disease—first line

Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Comment
1] Neutropenia (non-allo HSCT recipients) 2] Allo-HSCT (during neutropenia) 3] Allo-HSCT (w/o neutropenia) or other non-neutropenic patients	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
		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
		L-AmB 3 mg/kg	B	II	II_t	II_t	
		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

Ullmann AJ et al. *Clin Microbiol Infect* 2018;24:e1

VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS



No. at Risk							
Voriconazole	144	131	125	117	111	107	102
Amphotericin B	133	117	99	87	84	80	77

Herbrecht R et al. *N Engl J Med* 2002;347:408

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

	ISV	VRC	95% CI
All-cause mortality			
ITT 42d ACM	19%	20%	-1 (-7.8 to 5.7)
ITT 84d ACM	29%	31%	-1.4 (-9.2 to 6.3)
mITT 42d ACM	20%	23%	-2.6 (-12.2 to 6.9)
mITT 84d ACM	30%	37%	-5.5 (-16.1 to 5.1)
myITT 42d ACM	19%	22%	-2.7 (-12.9 to 7.5)
myITT 84d ACM	28%	36%	-5.7 (-17.1 to 5.6)

ITT: all who were enrolled, randomly assigned & received at least 1 dose of study drug
mITT: all ITT patients with proven or probable IMD
myITT: subset of mITT patients with proven or probable IA
ACM: all-cause mortality

Lancet 2016; 387: 760–69

ISV *vs* VRC – safety data

	ISV	VRC	p
Skin	**33%**	**42%**	**0.037**
Rash	7%	11%	
Erythema	4%	6%	
Eye	**15%**	**27%**	**0.002**
Impairment	2%	7%	
Photophobia	1%	2%	
Psy	**27%**	**33%**	**0.1515**
Hallucinations	2%	4%	
Hepatobiliary	**9%**	**16%**	**0.016**
↑ bilirubin	2%	4%	

Lancet 2016; 387: 760–69

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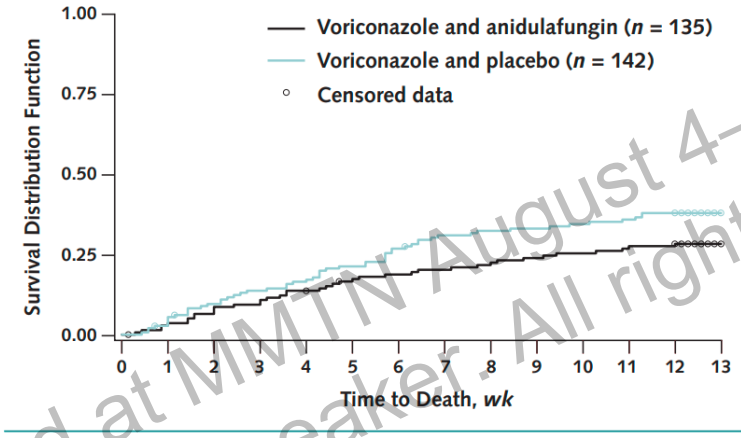
Why VRC + ANF got a C



Log-rank, $P = 0.086$.

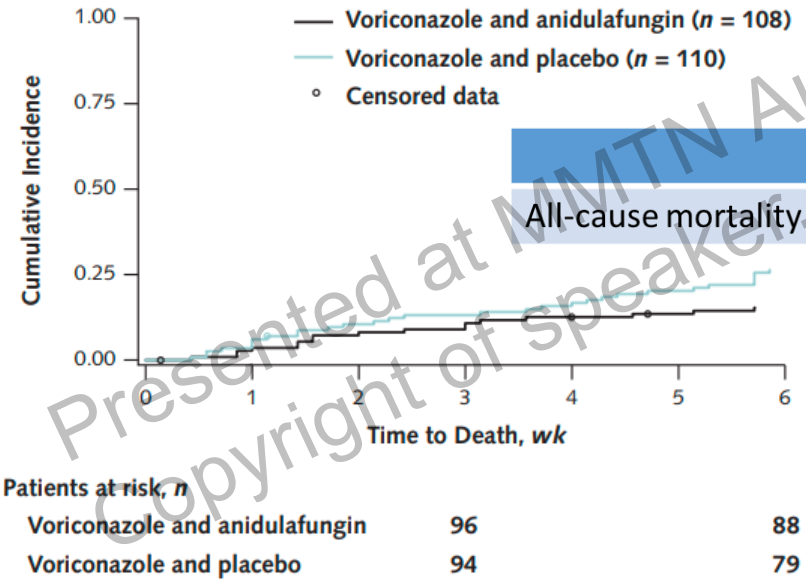
Table 2. Mortality Outcomes in the Modified Intention-to-Treat Population, by Regimen

Variable	Deaths, *n/N (%)**		Treatment Difference (95% CI), *percentage points*†
	Monotherapy	Combination Therapy	
Overall	39/142 (27.8)	26/135 (19.5)	−8.3 (−19.0 to 1.5)
Overall 12-wk mortality	55/142 (39.4)	39/135 (29.3)	−10.1 (−21.4 to 1.1)

Marr KA et al. *Ann Intern Med* 2015;162:81

VRC + ANF cut death in GM+ sub-group

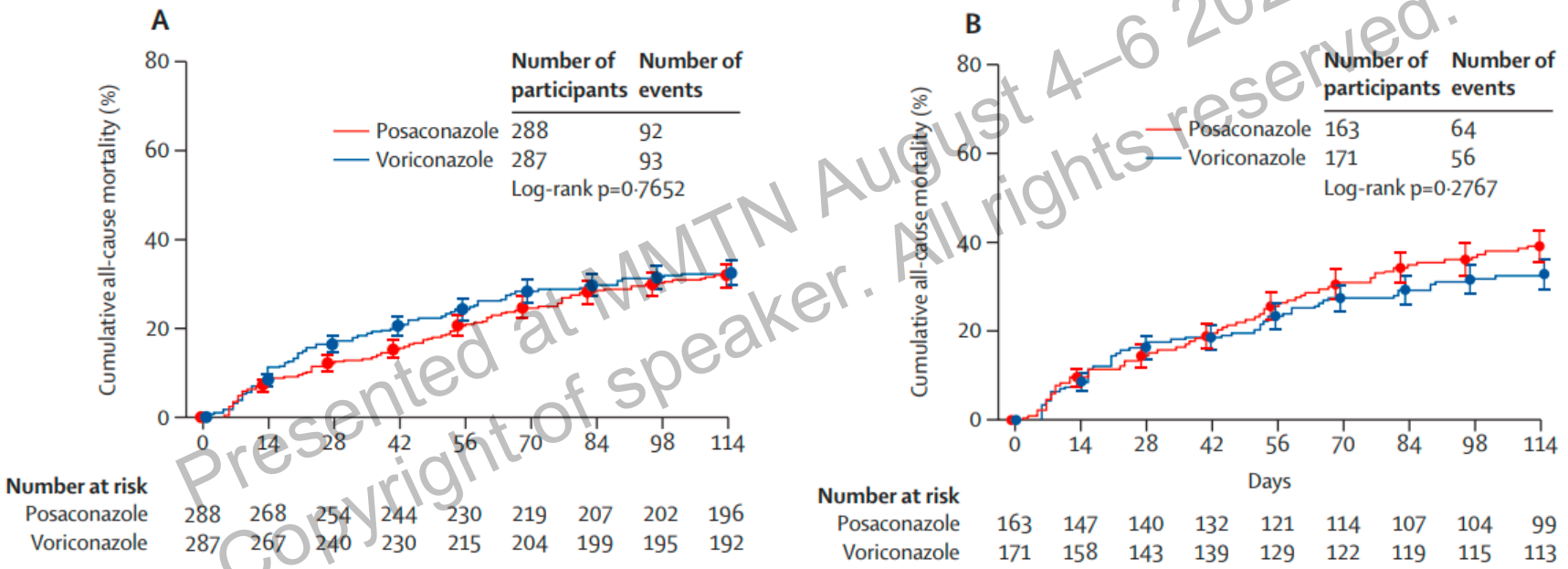
Figure 3. Outcomes in the positive galactomannan subgroup.



	Combination	Voriconazole alone	P (95%CI)
All-cause mortality	15.7%	27.3%	0.037 (-22 to -0.4)

Marr KA et al. *Ann Intern Med* 2015;162:81

Posaconazole vs voriconazole for IA



A: ITT population; B: Full analysis set (ie, ITT with proven/probable IA)
Marttens JA et al. *Lancet* 2021;397:499

Summary

- Great strides have been made against aspergillosis
- Neutropenia and steroids are biggest risk factors
- With diagnostic tools and drugs, one can develop different approaches to the prevention, diagnosis and treatment of aspergillosis
- Prophylaxis is an option in the highest-risk haematological patients
- The approach to prolonged fever in neutropenia is an approach to possible invasive fungal diseases

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Thank you