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Can we start or stop antifungal therapy based on biomarkers detection?

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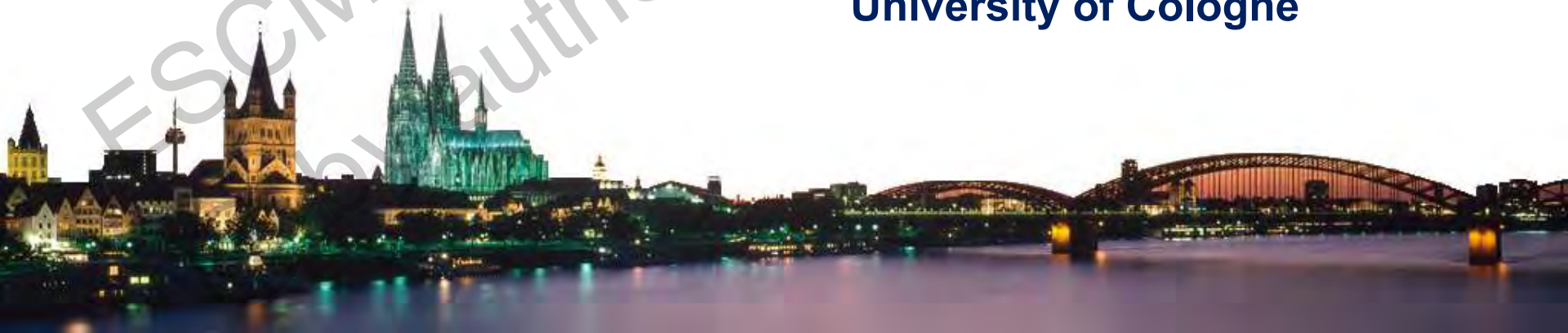


Transparency Declaration

- European Commission
  - FP7, IMI-JU 6 (COMBACTE), 8 (APC), 9 (CARE)
- European Organisation for Research and Treatment of Cancer (EORTC)
- European Society for Clinical Microbiology and Infectious Diseases (ESCMID)
- European Confederation of Medical Mycology (ECMM)
- German Federal Ministry of Research and Education
  - BMBF 01KN1106, 01KN0706, 01GH1001E, 01EZ0931, 01EK1422
- German Center for Infection Research (DZIF)
- German Research Foundation (DFG)
- German José Carreras Leukaemia Foundation (DJCLS)
- SME & Industry Research Grants, Trial Design, or Presenting for
  - 3M, Actelion, Astellas, AstraZeneca, Basilea, Bayer, Celgene, Cidara, Da Volterra, Daiichi Sankyo, F2G, Genentech, Genzyme, Gilead, GSK, Medpace, Merck Serono, MSD, Miltenyi, NanoMR, Novartis, Parexel, Pfizer, Quintiles, Rempex, Roche, Sanofi Pasteur, Shionogi, Summit, Vifor, Viropharma

Antifungal Strategies

Strategy	Definition
Prophylaxis	Administration of the antifungal agent is **initiated at a period of high risk** of infection to prevent fungal infections
Empirical Treatment	Initiation or modification of an existing antifungal re… **persistently febrile patients with neutropen…** 4–7 days in duration) that is without a known … is unresponsive to appropriate antibacterial agen…
Pre-Emptive Therapy	Similar to empirical antifungal therapy, preemptive therapy aims to treat a suspected early IFI but **uses radiologic studies, laboratory markers, or both** (rather th… alone) to stratify the likelihood of an IFI; m… criteria would trigger preemptive initiation … of antifungal therapy
Treatment of established IFI	Corresponds to patients who meet European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria **for proven and probable IFI**

Fever driven

Diagnosis driven

Segal BH et al. Clin Inf Dis 2007; 44: 402–9.

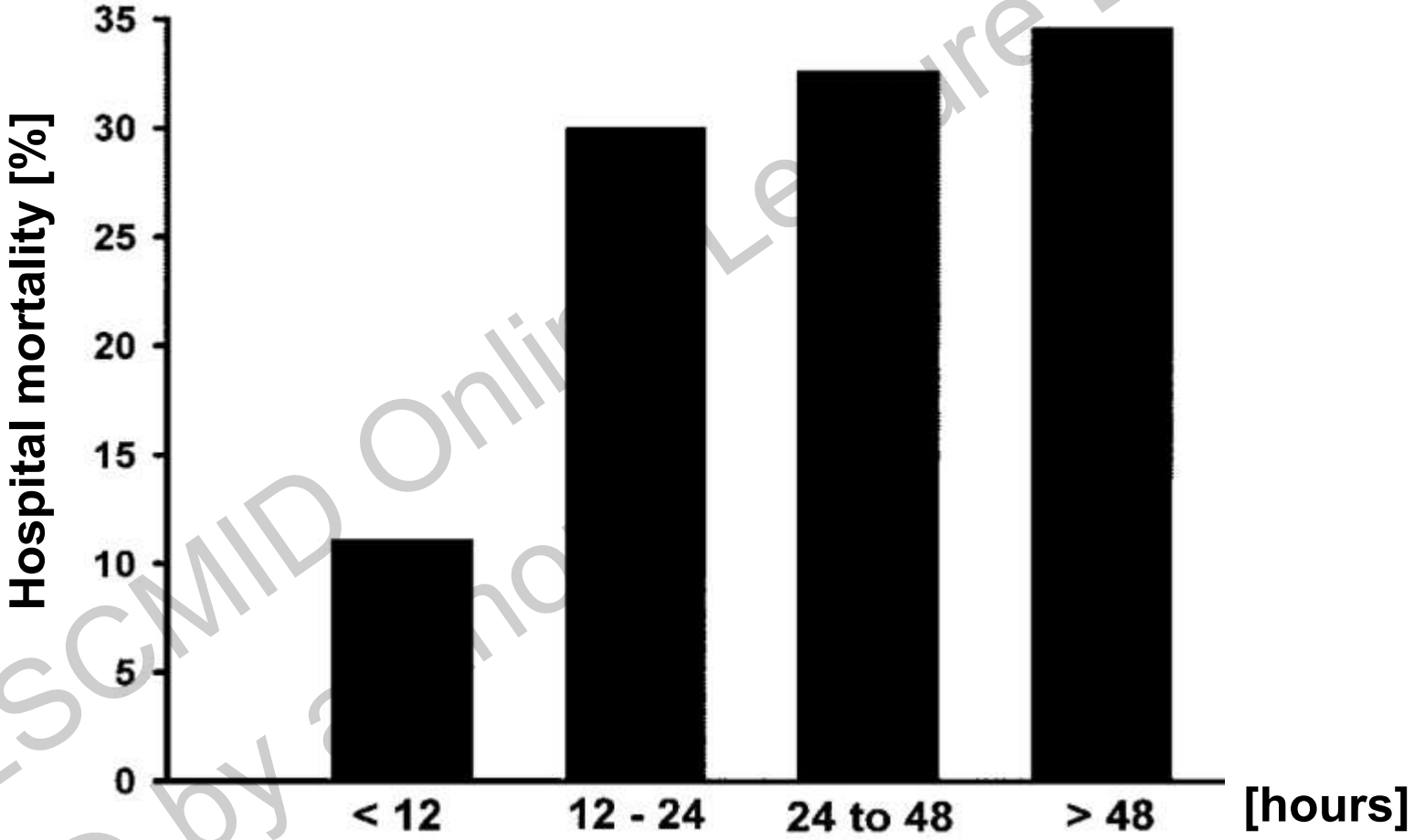
2 Biomarkers – 2 Fungi – 2 Decisions

	Start	Stop	Start	Stop
Candidiasis	N/A	N/A	BDG	BDG
Aspergillosis	GM	GM	BDG	BDG

You May Have Seen This Patient

- Patient ventilated, Pip/Tazo Day 6, persistent fever, otherwise stable, no pathogen isolated
- ICU rounds twice daily, continuous discussion pro/con empiric antifungal treatment
- The right decision: Depends …
- Did the patient undergo abdominal surgery ?
- Is the patient colonised ?

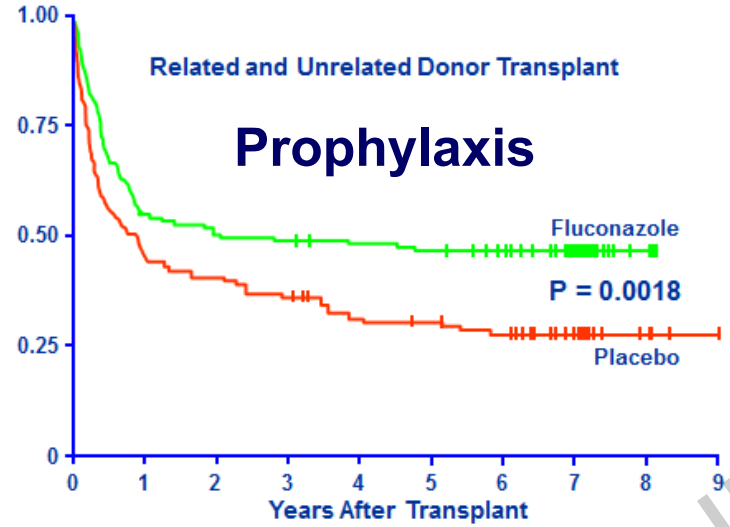
Treatment Delays Increase Mortality in IC



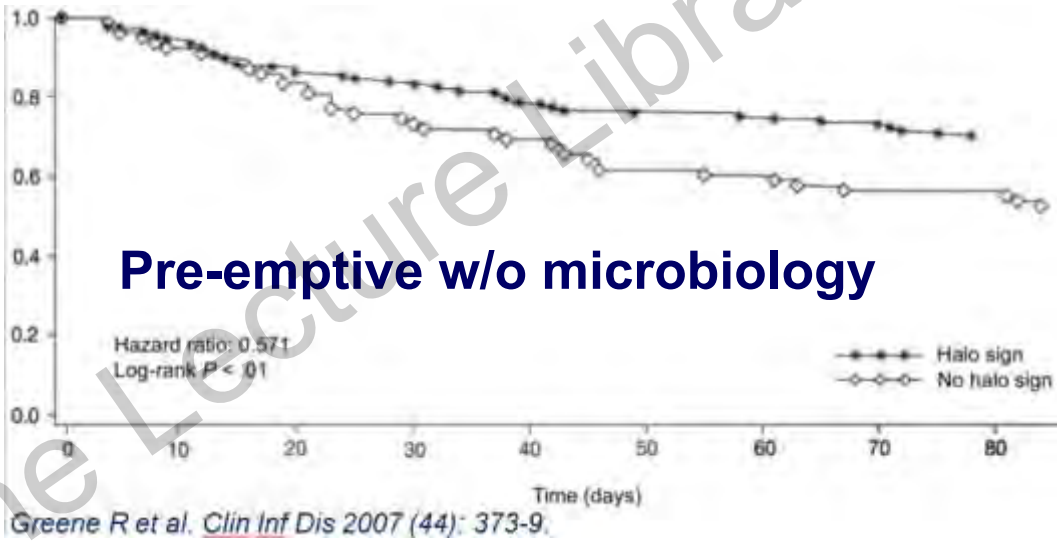
Morrell M et al. Antimicrob Agents Chemother 2005; 49:3640–3645.

Early Exposure to Antifungals is a Common Pattern of all Trials Improving Survival Rates

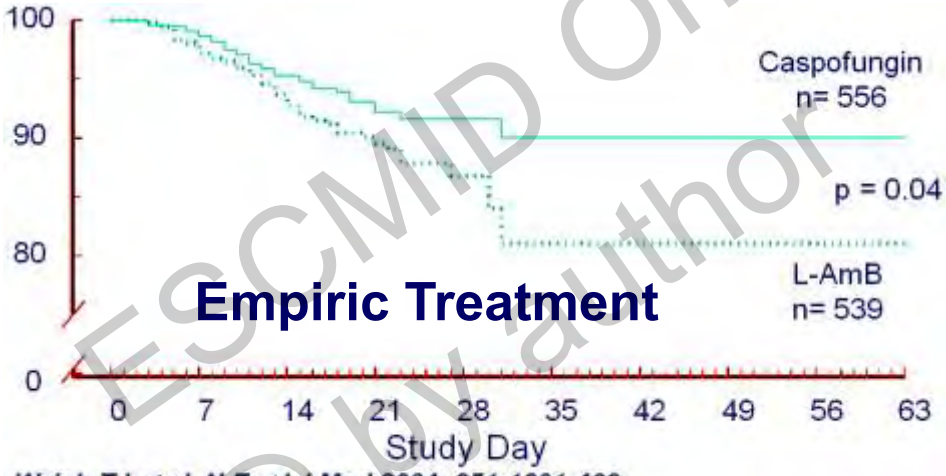
Trials That Yielded a Difference in Survival



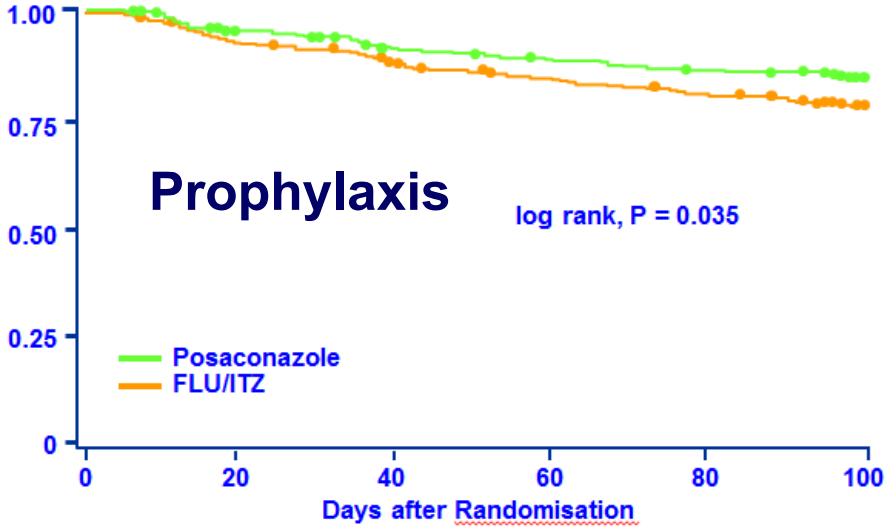
Slavin M et al. J Infect Dis 1995 / Marr K et al. Blood 2000.



Greene R et al. Clin Inf Dis 2007 (44): 373-9.



Walsh TJ et al. N Engl J Med 2004; 351:1391-402.



Cornely OA et al. N Engl J Med 2007.

Reliable Diagnostic Tests would Allow Early Treatment to be Targeted

Diagnostic Challenges

Diagnostic tools are too few and are unreliable

- „One fungus – one name“ we welcome
- „One fungus – one test“ is no ! solution
  - **Aspergillus – GM:** **10 years to a cut-off**
  - **Aspergillus – PCR:** **15 years to standardization**
  - **Mannan/Anti-Mannan:** **Any good at all?**
  - **ß-D-Glucan:** **Benefits not yet fully explored**

All rely on the same principle!

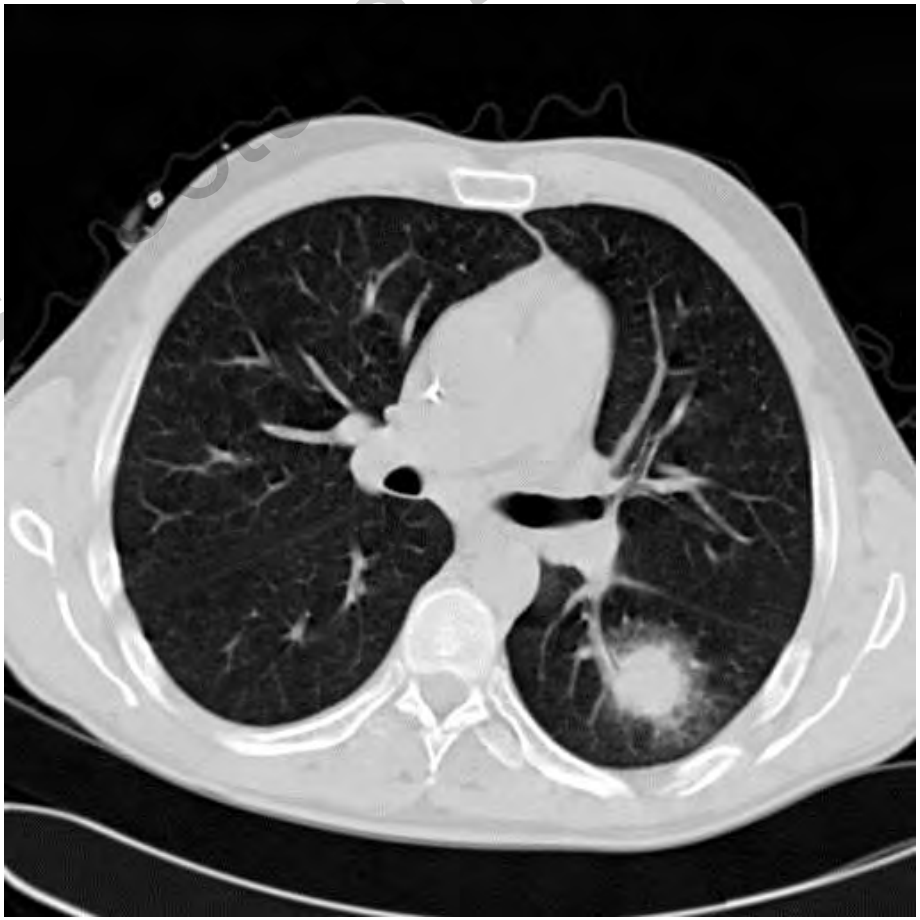
Give up the paradigm of proving the presence of the pathogen?

Galactomannan

Starting with Positive GM

- AML
- Neutropenia
- Fever >72h
- Cough
- Dyspnea
- Pleuritis

Galactomannan



A typical AmBiLoad Study Patient from Cologne.

Blood galactomannan

Population	Intention	Intervention	SoR	QoE	Comment
Prolonged neutropenic patients and allogeneic stem cell transplantation recipients not on mold-active prophylaxis	To diagnose invasive aspergillosis	Galactomannan in blood Draw samples every 3-4 days	A C	I III	Highest test accuracy requiring 2 consecutive samples with an OD index ≥0.5; prospective monitoring should be combined with HRCT and clinical evaluation
Patients with a hematological malignancy •Neutropenic •Non-Neutropenic	To diagnose invasive aspergillosis	Galactomannan in blood	 A B	 II II	Significant lower sensitivity in non-neutropenic patients

Morrissey 2013, Springer 2013, Leeflang 2008, Maertens 2007, Maertens 2002, Maertens 2001, Pfeiffer 2006, Cordonnier 2008, Maertens 2010

Diagnostic Tools - B-D-glucan Assay

Population	Intention	Intervention	SoR	QoE	Comment
Mixed population: Adult ICU, Hematological disorders, SOT	To diagnose IFD (not specific for aspergillosis)	Diagnostic assay	C	II	4 different assays; Fungitell FDA approved and available in US and Europe; others only available in Japan; overall sensitivity of 77% and specificity of 85% Specificity limits its value in this setting Two or more consecutive samples: sensitivity = 65%, specificity = 93%; studies included once to thrice weekly
		Screening assays	C	II	Varies with assay and cut-off: Wako assay sensitivity = 40-97%, specificity = 51-99%

Karageorgopoulos 2011, Lu 2011

Starting with Positive GM

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Review article

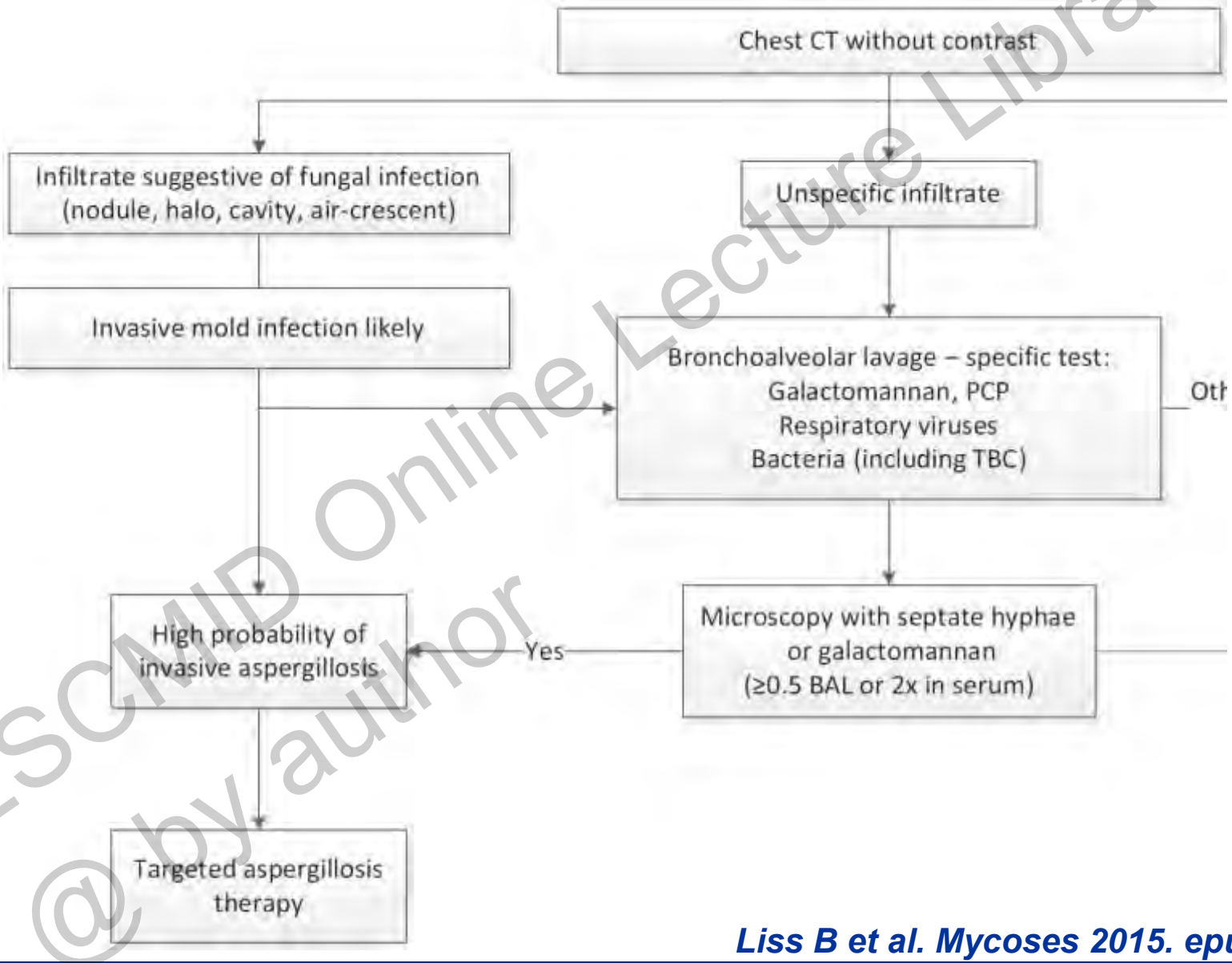
Our 2015 approach to invasive pulmonary aspergillosis

B. Liss,[1,2] J. J. Vehreschild,[1,2,3] C. Bangard,[4] D. Maintz,[4] K. Frank,[5] S. Grönke,[5] G. Michels,[5] A. Hamprecht,[6] H. Wisplinghoff,[6] B. Markiefka,[7] K. Hekmat,[8] M. J. G. T. Vehreschild[1,2,3] and O. A. Cornely[1,2,3,9,10]

[1]Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany, [2]Center for Integrated Oncology CIO KölnBonn, University of Cologne, Cologne, Germany, [3]German Centre for Infection Research (DZIF), partner site Bonn-Cologne, Cologne, Germany, [4]Department of Radiology, University Hospital of Cologne, Cologne, Germany, [5]Department III of Internal Medicine, Heart Centre of the University of Cologne, Cologne, Germany, [6]Institute for Medical Microbiology, Immunology and Hygiene, University Hospital of Cologne, Cologne, Germany, [7]Institute of Pathology, University Hospital of Cologne, Cologne, Germany, [8]Department of Cardiothoracic Surgery, University Hospital of Cologne, Cologne, Germany, [9]Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany and [10]Clinical Trials Centre Cologne, ZKS Köln, University of Cologne, Cologne, Germany

Liss B et al. Mycoses 2015: epub ahead.

Starting with Positive GM



Liss B et al. Mycoses 2015. epub ahead.

AmBiGuard Monitoring

Patients routinely monitored for signs and symptoms of IFI throughout the study period

- Twice weekly galactomannan (GM) and β-D-glucan (BDG)
- Diagnostic workup if …. 1 positive GM/BDG antigen assay
- Algorithms followed for investigation and management of suspected IFI

Cornely OA et al. ASH 2014.

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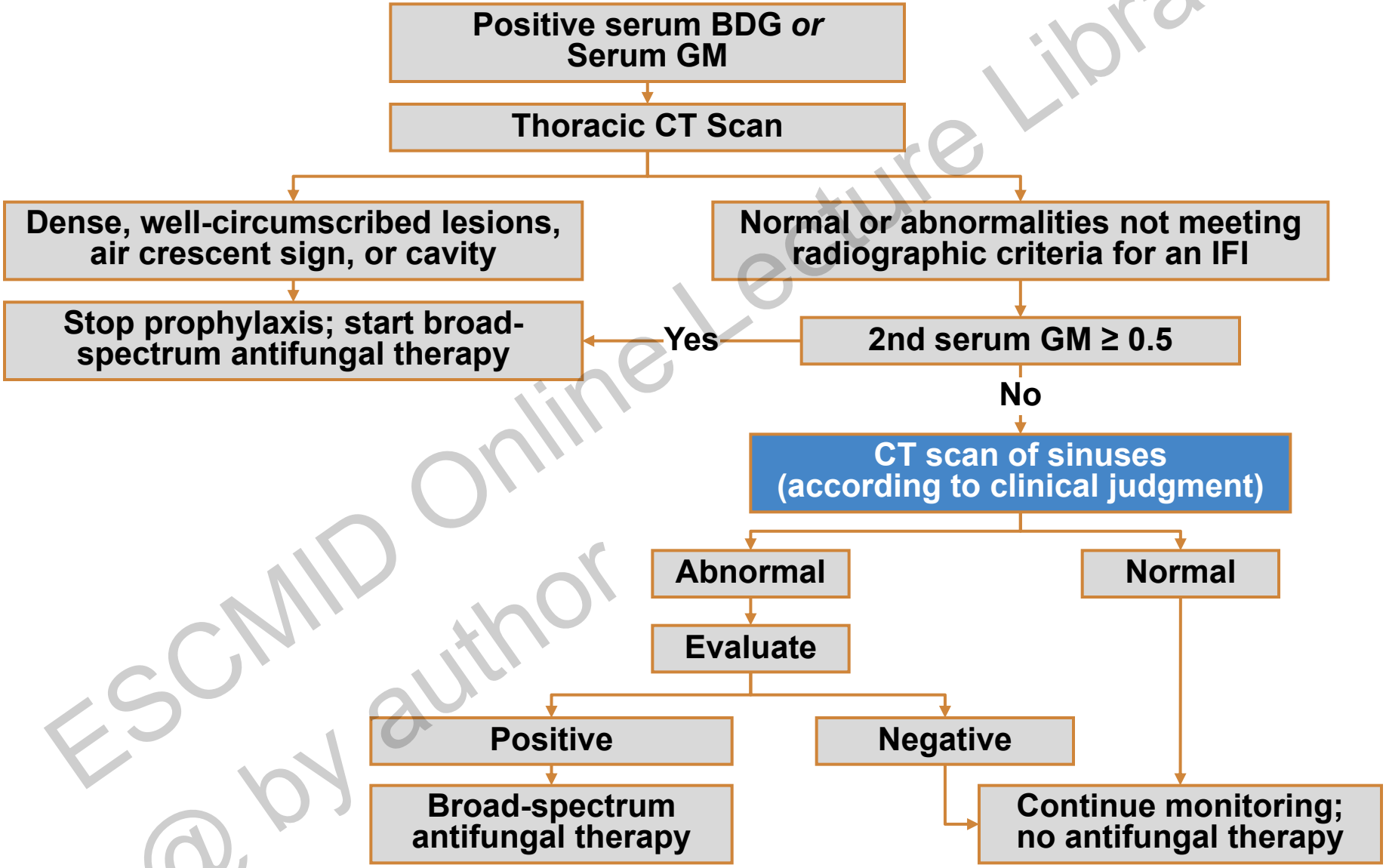
Algorithm for Suspected IFI



Cornely OA et al. ASH 2014.

SECURE Study – Baseline pathogens (mITT)

Pathogen Causing IFD[a, b]	Isavuconazole (N = 143)	Voriconazole (N = 129)
Proven/Probable IFD	29 (11.2%) / 114 (44.2%)	36 (14.0%) / 93 (36.0%)
Galactomannan only[c]	71 (49.7%)	68 (52.7%)
Aspergillus spp. only	49 (34.3%)	39 (30.2%)
Aspergillus spp. plus other filamentous fungi	3 (2.1%)	1 (0.8%)
Non-*Aspergillus* spp. only	5 (3.5%)	6 (4.7%)
Filamentous fungi NOS	14 (9.8%)	15 (11.6%)

[a]As assessed by the DRC

[b]*Note*, >90% of the mITT population had pulmonary involvement

[c]Serum: 1 value ≥0.7 or 2 serial values ≥0.5 – <0.7; Bronchoalveolar lavage: 1 value ≥1.0

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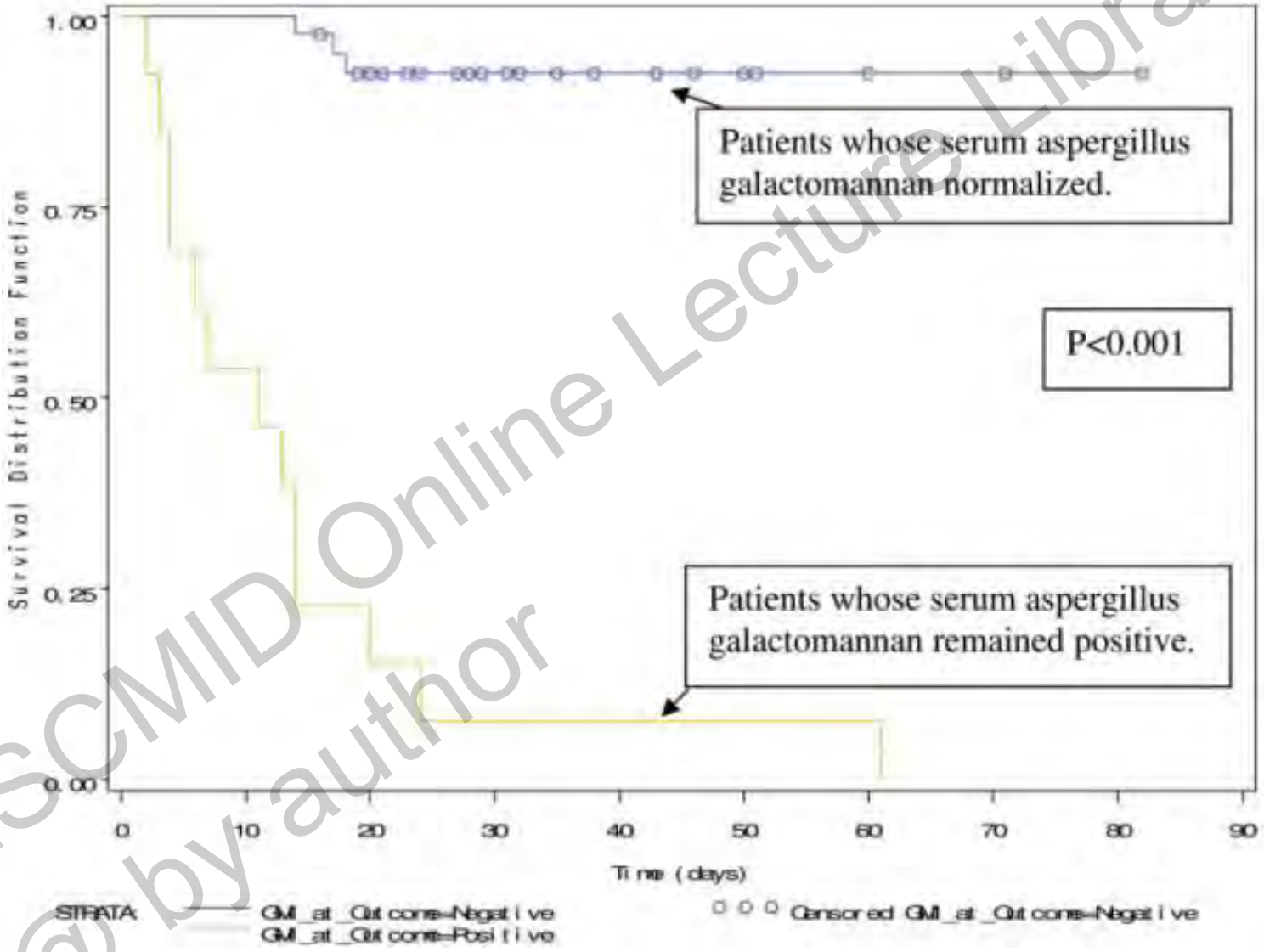
Stopping with Negative GM



Woods G et al. Cancer 2007.

EFISG ESCMID FUNGAL INFECTION STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

Consensus statement: Discontinuation of targeted therapy (SoR: C)

- The range of the duration of treatment is huge and the evidence base to support any particular recommendation is weak
- Need to separate between targeted and salvage or secondary prophylaxis (and long-term toxicity)
- Need to consider iv oral switch in stable and PK-reliable patients
  - Duration depending upon reconstitution of the immune system, continuing GvHD, etc. (i.e. secondary prophylaxis)
  - Need CR (radiographic imaging, scaring allowed) which includes no clinical or microbiological evidence of disease prior to discontinuation
- Close monitoring (e.g radiographical imaging) once discontinued.

1,3-ß-D-Glucan

Starting with Positive BDG

Table 5 Possible confounding factors of BG reactivity

Variable at the time of BG sampling[a]	Variable present		Variable absent		*p*-Value[f]
	Frequency (no. of sampling episodes)	Mean BG level, pg/ml (95 % CI)	Frequency (no. of sampling episodes)	Mean BG level, pg/ml (95 % CI)	
Fungal mucosal colonization[b]	63	86.1 (63.8–108)	400	76.2 (69.0–83.4)	ns
Bacteremia[c]	15	70.6 (31.3–110)	662	72.3 (67.3–77.4)	ns
Admitted to ICU	9	196 (86.1–306)	668	70.6 (65.8–75.4)	0.0007
Dialysis[d]	9	78.3 (20.4–136)	668	72.2 (67.1–77.2)	ns
Intravenous immunoglobulins[e]	9	177 (61.1–293)	668	70.9 (66.0–75.7)	ns
Plasma, coagulation factors, or albumin[f]	16	159 (85.7–232)	661	70.1 (65.4–74.9)	0.0145
Total parenteral nutrition[g]	119	79.8 (66.2–93.4)	558	70.7 (65.3–76.0)	ns
Intravenous antibiotics of any kind[h]	184	75.7 (64.9–86.4)	493	71.0 (65.4–76.6)	ns
Piperacillin–tazobactam[h]	22	65.5 (44.9–86.2)	655	72.5 (67.4–77.6)	ns
Meropenem[h]	107	70.1 (57.1–83.2)	570	72.7 (67.3–78.1)	ns
Ceftazidime[h]	20	106 (52.7–160)	657	71.2 (66.3–76.1)	ns
Vancomycin[h]	45	68.4 (52.9–83.9)	632	72.5 (67.3–77.8)	ns
Pegylated asparaginase[i]	85	118 (93.0–142)	592	65.7 (61.5–70.0)	<0.0001

Starting with Positive BDG – Raising the Cut-off may Improve Assay Performance

Table 4 Positive and negative predictive values at different hypothetical IFI prevalence rates and with different strategies for BG testing, based on the previously suggested optimal cut-off level of 158 pg/ml

Hypothetical prevalence of IFI	Strategy for BG testing to define IFI (pg/ml)					
	Mean BG >158[a]		One BG >158[b]		Two consecutive BG >158[c]	
	PPV	NPV	PPV	NPV	PPV	NPV
5 %	0.54	1.0	0.16	0.99	0.49	0.99
8 %	0.66	0.99	0.24	0.99	0.62	0.99
12%[d]	0.75	0.99	0.33	0.99	0.71	0.98
15 %	0.80	0.99	0.39	0.98	0.77	0.97
20 %	0.85	0.98	0.48	0.98	0.82	0.96

Hammerström et al. EJCMID 2015.

Pre-emptive Therapy: ß-D-Glucan

Popu-lation	Intention	Inter-vention	SoR	QoE	Reference	Comments
ICU	Early treatment of invasive candidiasis / candidaemia	To treat when ß-D-glucan test is positive	C	II_u	Desmet JCM 2009 Digby Clin Diagn Lab Immunol 2003 Koo CID 2009 Mohr JCM 2011 Presterl Int JID 2009 Takesue WJSurg 2004 Pickering JCM 2005	•Low specificity •Low sensitivity •High NPV •False positives with •Haemodialysis •Other fungal or •Bacterial infection •Wound gauze •Maybe useful in PCP

Cornely OA et al. Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37.

Stopping with Negative BDG

Descriptive analysis of biomarkers at EOT assessment (FAS)*

	Placebo		Micafungin 100 mg	
Biomarker	n		n	
Mean change (SD) from baseline at EOT				
Beta-D-glucan†, pg/mL	54	53.0 (355.7)	44	-34.9 (206.6)
***Candida* antibody, AU/mL**	103	13.1 (21.4)	87	12.7 (20.9)
Mannan antigen, pg/mL	103	24.2 (281.3)	87	18.0 (236.8)
EOT assessment				
PCR detection of *Candida* in patients (%)	105	7.6%	89	5.6%

***Biomarker data were not available for all patients in the FAS; †Positive results ≥62.5 pg/mL) provided, negative results recorded and imputed as <62.5 pg/mL**

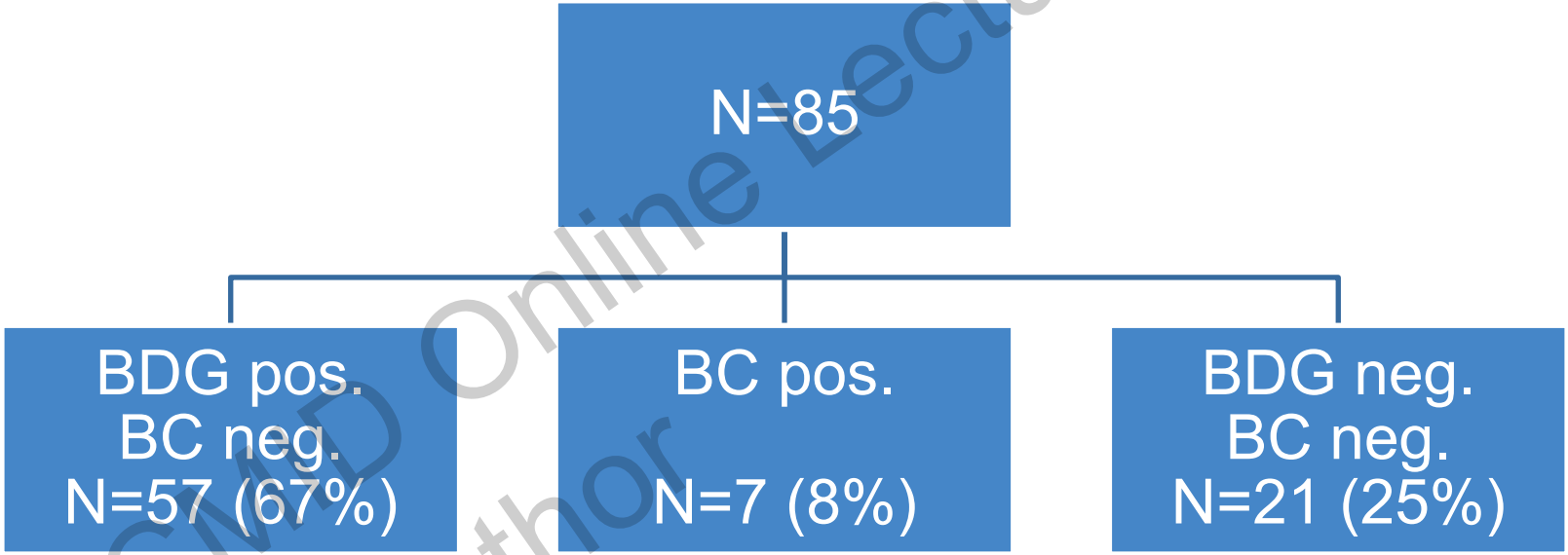
Stopping with Negative BDG

- 85 of 2148 ICU patients had all of the below:
  1. CVC
  2. Antibiotic treatment
  3. 2 of: dialysis, surgery, pancreatitis, steroids/immunosuppression, parenteral nutrition
  4. 1 of: fever, hypothermia, hypotension, leukocytosis, acidosis, or CRP↑

- Received echinocandin treatment and
  - ➢ Diagnostic screening
    - – Day 1 and 2: Blood culture
    - – Day 1, 2, and 3: β-D-Glucan

Nucci M et al. ICAAC 2014; M-1754.

Stopping with Negative BDG



Nucci M et al. ICAAC 2014; M-1754.

LFD
PCR
T2
T-cells

Biomarker/LFD

Population	Intention	Intervention	SoR	QoE	Comment
Hematological malignancy and solid organ transplant	Diagnose IA	Evaluation of LFD using BAL samples (retrospective study)	B	III	Sensitivity and specificity of BAL LFD tests for probable IPA were 100% and 81% (PPV 71%, NPV 100%); 5 pts with possible IPA had positive LFD ; no proven patients
Hematopoietic stem cell transplantation (HSCT)	Diagnose IA LFD using serum samples	Prospective screening in 101 patients undergoing allo-HSCT Comparison to Asp-GM to serum	B	III	IA: 1 proven, 9 probable, 20 pos. 1 serum vs 2 serum samples positive: sensitivity 40%/20%; specificity 86.8%/97.8%; diagnostic odds ratio 3.03/11.13
Immunocom-promised pts (hematological malignancies 64%)	Diagnose IA	Evaluation of LFD using BAL samples (retrospective study)	B	II	Sensitivities for LFD, GM, BDG, PCR were between 70 and 88%; combined GM (cut-off >1.0 ODI) with LFD increased the sensitivity to 94%, while combined GM (>1.0) with PCR resulted in 100% sensitivity (specificity for probable/proven IPA 95-98%).

Hönigl et al. 2012, Held et al. 2013, Hönigl et al. 2014

BAL *Aspergillus* PCR

EFISG ESCMID FUNGAL INFECTION STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Patients undergoing allogeneic stem cell transplantation recipients not on mold-active prophylaxis	To predict IA	BAL PCR	B	II	Einsele, Lancet, 1998	In house assay
Patients with hematological malignancies and prolonged neutropenia ICU pts (mixed pts populations) Lung Tx pts	To diagnose IA	BAL PCR	B	II	Tang, Am Rev Respir Dis, 1993 Bretagne, JCM, 1995 Jones, J Clin Pathol, 1998 Skladny, JCM, 1999 Buchheidt, CID, 2001 Hayette, JCM, 2001 Buchheidt, Brit J Haem, 2002 Raad, Chest, 2002 Spiess, JCM, 2003 Meletiadis, Med Mycol, 2003 Sanguinetti, JCM, 2003 Rantakokko, JCM, 2003 Lass-Flörl, JCM, 2004 Musher, JCM, 2004 Khot, BMC Inf Dis, 2008 Frealle, EJClinMicrobInfDis,2009 Bergeron, JCM, 2011 Luong, Transpl 2011 Buess, BMC Inf Dis, 2012 Reinwald, Eur J Hematol, 2012 Reinwald, JAC, 2012 Hönigl et al, JCM 2014	Methodically different in-house assays; better performance in pts without AFT; PCR+GM: increases specificity

Antifungal Stewardship – Rapid Diagnostics

Clinical Practice Patterns in Hospitalized Patients at Risk for Invasive Candidiasis: Role of Antifungal Stewardship Programs in an Era of Rapid Diagnostics

Setting

- Prospective cohort study
- Patients with candidemia or receiving systemic antifungals
- University-affiliated tertiary care hospital

Endpoints

- Time to initiation of therapy
- *Candida* species and time to identification
- Indications for antifungal use

Aitken SL et al. *Ann Pharmacother* 2014; 48 (6): 683-690.

Antifungal Stewardship – Rapid Diagnostics

Clinical Practice Patterns in Hospitalized Patients at Risk for Invasive Candidiasis: Role of Antifungal Stewardship Programs in an Era of Rapid Diagnostics

Table 1. Sensitivity and Specificity of Rapid Diagnostic Tests.

Rapid Diagnostic	*Candida* Species Detected	*Candida* Detected in Current Study (%)	Date Test is Performed	Sensitivity	Specificity	Positive Predictive Value
T2Candida assay	*C albicans*, *C parapsilosis*, *C krusei*, *C glabrata*, *C tropicalis*	98%	Day of blood culture	98%	98%	91%[a]
MALDI-TOF MS	All[b]	100%	Day of yeast identification	94%	100%	94%[c]
PNA-FISH	*C albicans*/*C parapsilosis* (probe 1), *C glabrata*/*C krusei* (probe 2), *C tropicalis* (probe 3)	98%	Day of yeast identification	98%	98%	99%[c]

Abbreviations: MALDI-TOF, matrix-assisted laser desorption/ionization time of flight; PNA-FISH, fluorescence in situ hybridization using peptide nucleic acid probes.

[a]Assume an 18% rate of occurrence of candidemia multiplied by percentage of *Candida* detected.

[b]MALDI-TOF was assumed to identify all clinically relevant *Candida* species.

[c]Assume a 100% rate of occurrence of candidemia multiplied by percentage of *Candida* detected.

Aitken SL et al. *Ann Pharmacother* 2014; 48 (6): 683-690.

Antifungal Stewardship – Rapid Diagnostics

Clinical Practice Patterns in Hospitalized Patients at Risk for Invasive Candidiasis: Role of Antifungal Stewardship Programs in an Era of Rapid Diagnostics

Results

- N=162 patients with candidemia
- Average time to yeast identification: 2.2 ± 1.3 days
- Average time to start of antifungal therapy: 3.5 ± 2.1 days
  - 0.6 ± 0.2 days for T2Candida
  - 2.6 ± 1.3 days for PNA-FISH (peptide nucleic acid probes)
  - 2.5 ± 1.4 days for MALDI-TOF
- T2Candida in simulation resulted in fewer doses of echinocandins

Promises of New Diagnostic Tools – Example

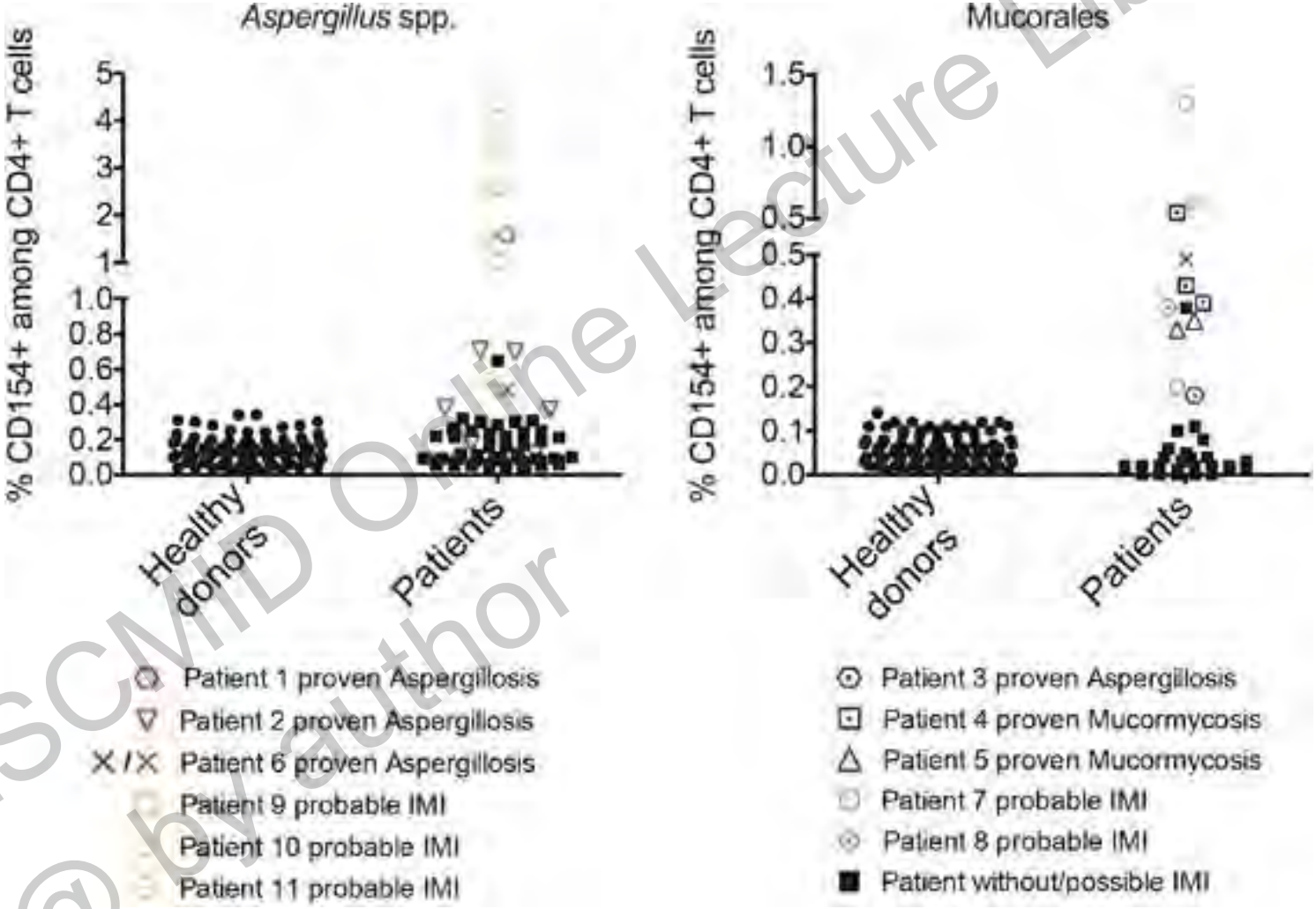
Turning to host response instead of fungal molecules

- T cells as specific diagnostic sensors for invasive fungal infections
- Monitor mold-reactive CD154+ peripheral blood T cells
- Pilot study completed

Bacher P, Steinbach A et al. Am J Resp Crit Care Med 2015.

Promises of New Diagnostic Tools – Example

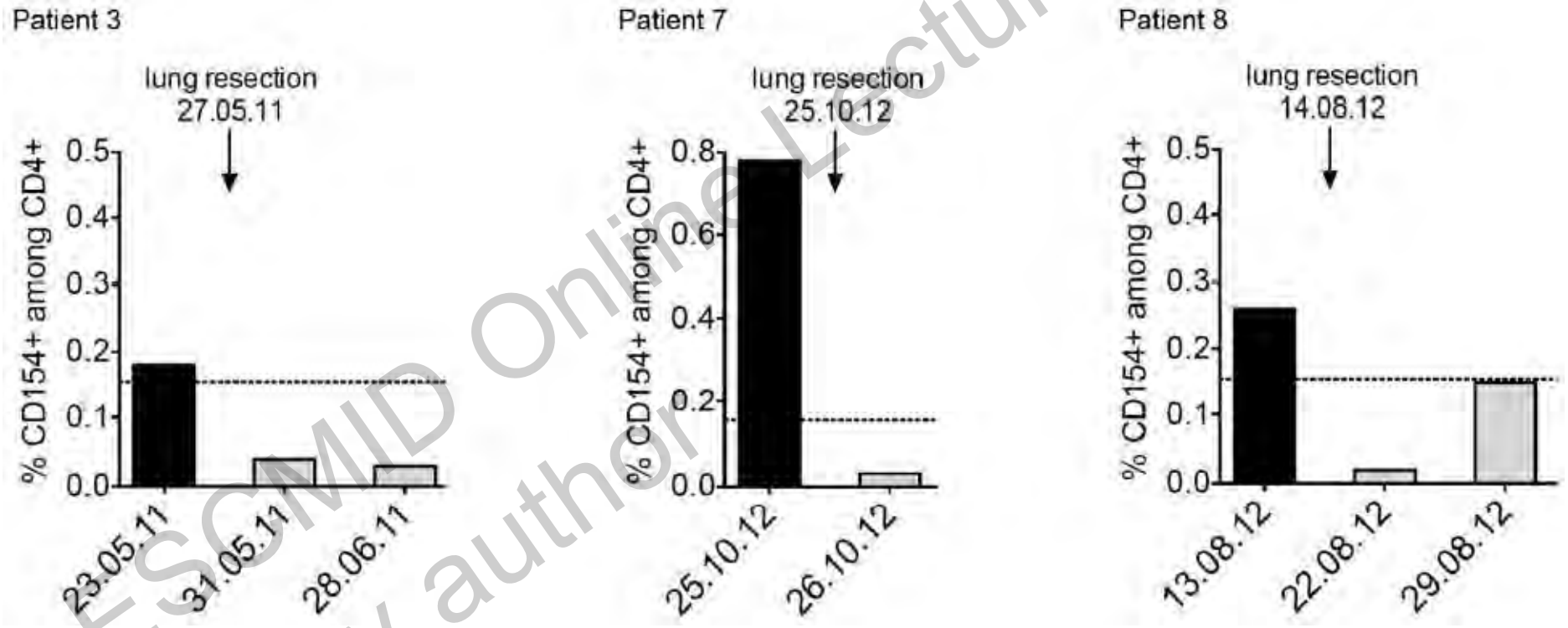
Frequencies of fungus-reactive T cells



Bacher P, Steinbach A et al. Am J Resp Crit Care Med 2015.

Promises of New Diagnostic Tools – Example

Mold-reactive T cell frequencies and fungal burden in 3 patients with invasive mold infection



Bacher P, Steinbach A et al. Am J Resp Crit Care Med 2015.

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Making Use of GM, BDG, Baseline CT, and Biopsy in Hematology Patients

A comprehensive diagnostic approach using galactomannan, targeted β-D-glucan, baseline computerized tomography and biopsy yields a significant burden of invasive fungal disease in at risk haematology patients

- N=203
- Intensive therapy
- Expected neutropenia ≥10 d
- Prospective, F/U median (range) of 556 (12–730) d
- Baseline CT, GM biw, targeted BDG in possible IFD or when GM positive

Ceesay MM et al. Br J Haematol 2014.

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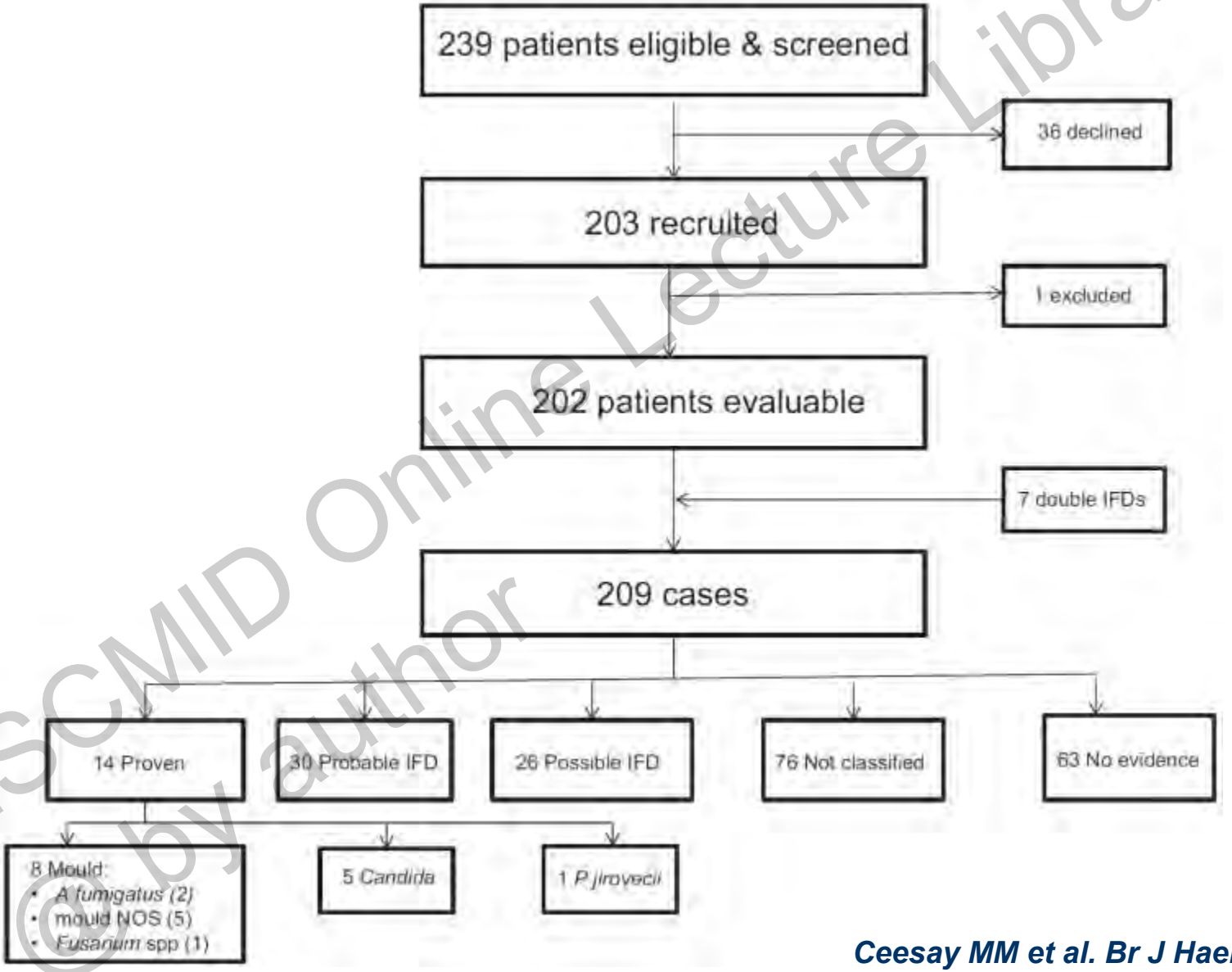
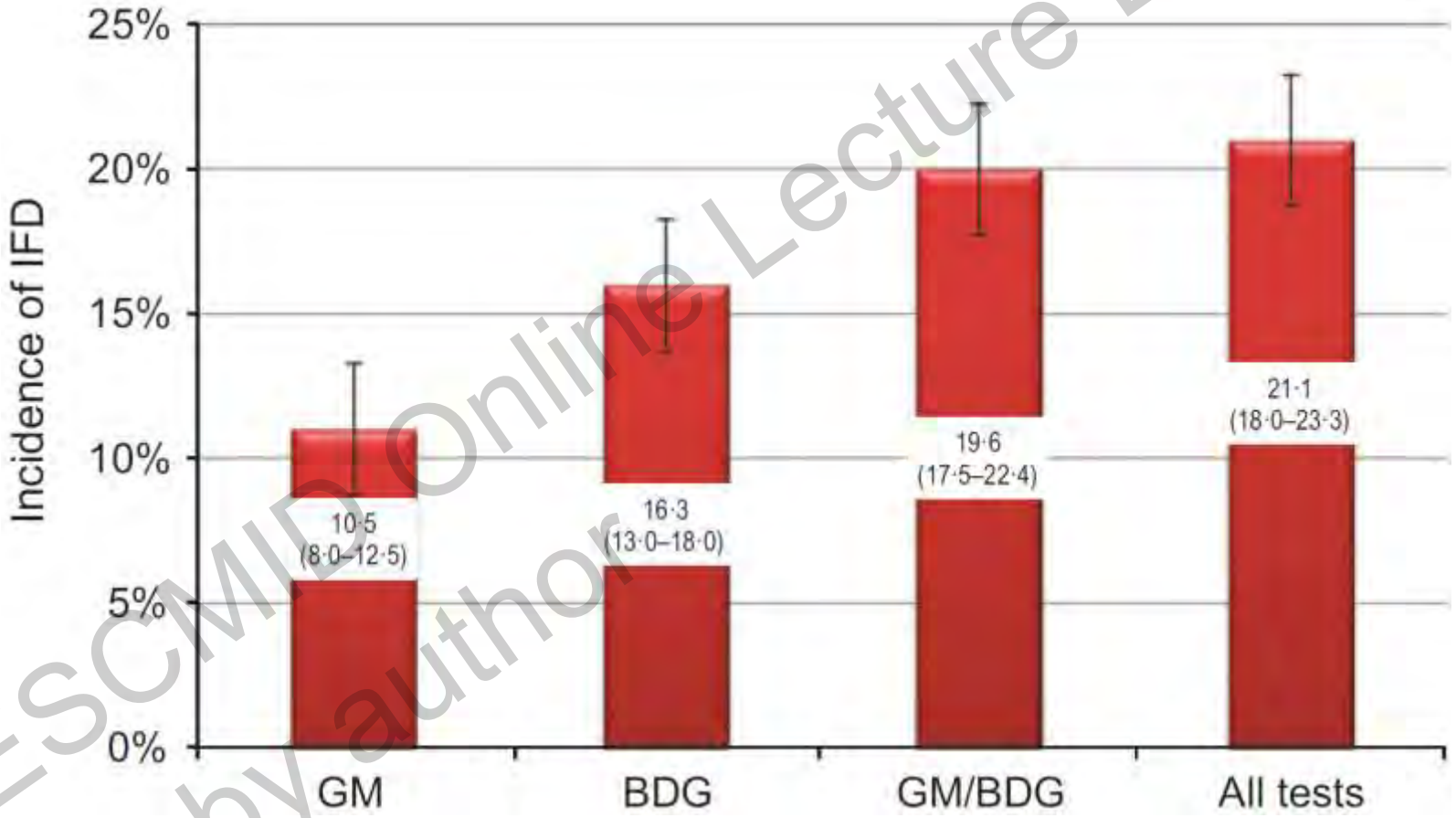
Making Use of GM, BDG, Baseline CT, and Biopsy in Hematology Patients



Ceesay MM et al. Br J Haematol 2014.

Making Use of GM, BDG, Baseline CT, and Biopsy in Hematology Patients

Incidence (95% CI) of proven/probable IFD by tools used



= GM, BDG, CT, biopsy, blood cultures, BAL, autopsy

Ceesay MM et al. Br J Haematol 2014.

Summary of Current Use of GM & BDG

- Positive GM should trigger immediate diagnostic work-up
- Negative GM is a pre-requisite, but not sufficient for stopping treatment
- Positive BDG should not trigger treatment
- Negative BDG should be used for stopping empiric Candida-directed treatment

Both tests should ideally be used in the context of clinical judgement, other IVD assays, and imaging studies

Institutional algorithms should be informed by ESCMID-ECMM guidance.

TIMM
Trends in Medical Mycology

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