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Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

Diagnosis of invasive fungal infections in hematological patients –
the IPA biomarker combination approach

Infektiologie Update 2016
25. Jahrestagung der PEG, Rostock

D. Buchheidt

Dept. of Internal Medicine, Mannheim University Hospital

Combination Antifungal Therapy for Invasive Aspergillosis

A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD

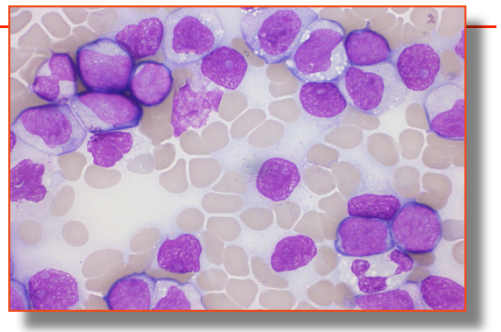
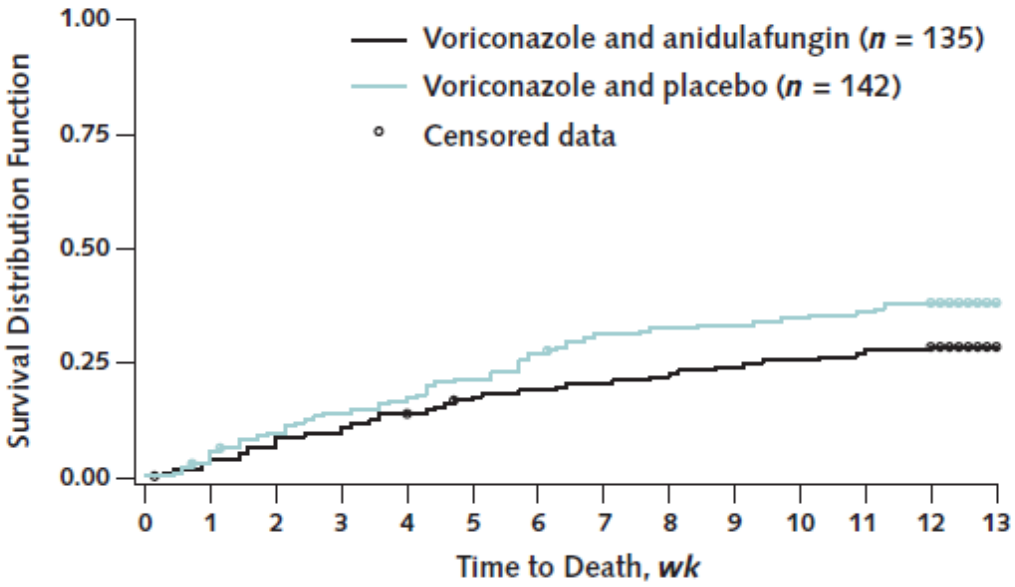


Figure 2. Cumulative incidence of death in the modified intention-to-treat population.



Log-rank, $P = 0.086$.

Conclusion: Compared with voriconazole monotherapy, combination therapy with anidulafungin led to higher survival in subgroups of patients with IA. Limitations in power preclude definitive conclusions about superiority.

IPA mortality rate ~ 30 % (12 weeks)

Ann Intern Med 162: 81-89 (2015)

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

Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P Kontoyiannis, Oliver A Cornely, Eric J Bow, Galia Rahav, Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Heinz, Raoul Herbrecht, William Hope, Meinolf Karthaus, Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag, Shmuel Shoham, George R Thompson III, Misun Lee, Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew J Ullmann

	Isavuconazole	Voriconazole
Certainty of diagnosis‡		
Proven invasive mould disease	29 (11%)	36 (14%)
Probable invasive mould disease	114 (44%)	93 (36%)
Possible invasive mould disease	88 (34%)	108 (42%)
No invasive mould disease	27 (10%)	21 (8%)
Mycological criteria		
No mycological evidence available§	92 (36%)	113 (44%)
Serum galactomannan positive	91 (35%)	94 (36%)
Non-sterile cytology, direct microscopy, or culture evidence of invasive mould disease	59 (23%)	39 (15%)

	Isavuconazole	Voriconazole
All-cause mortality		
ITT population	258	258
Day 42 all-cause mortality	48 (19%)	52 (20%)
Deaths	45 (17%)	50 (19%)
Unknown survival status†	3 (1%)	2 (1%)
Day 84 all-cause mortality	75 (29%)	80 (31%)
Deaths	72 (28%)	75 (29%)

Lancet 2016; 387: 760–69

Early diagnosis of invasive pulmonary aspergillosis in hematologic patients: an opportunity to improve the outcome

Marcio Nucci,[1] Simone A. Nouér,[1] Domenico Cappone,[1,2] and Elias Anaissie[3]

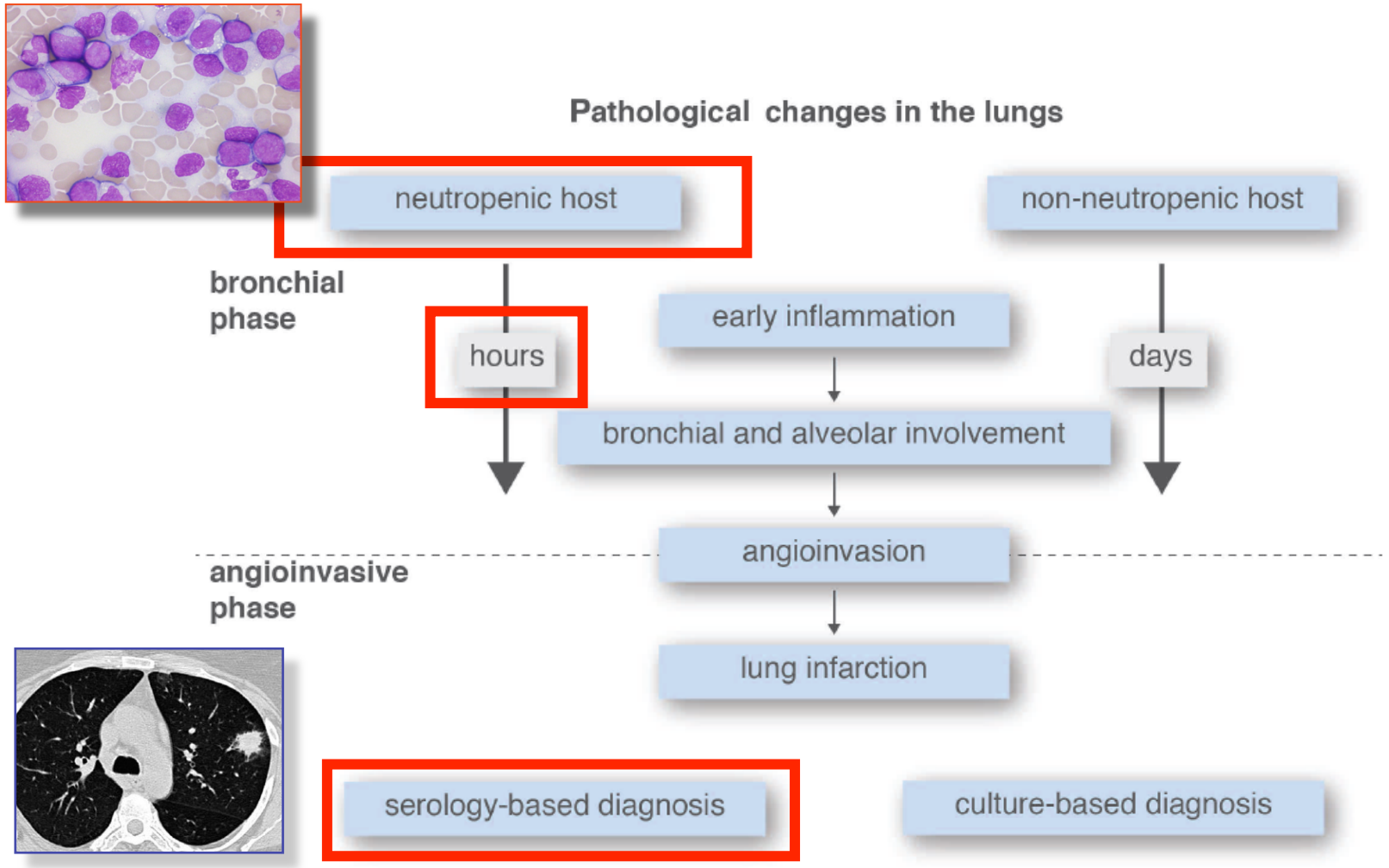
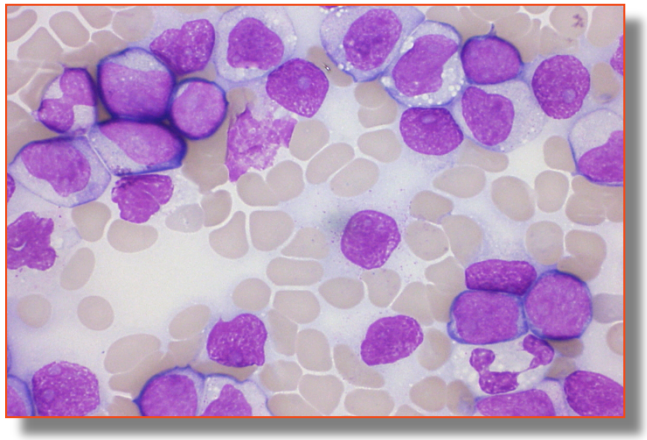


Figure 1. Evolution of invasive pulmonary aspergillosis in the bronchoalveolar and the angioinvasive phases in neutropenic and non-neutropenic patients.

Surrogate- / biomarkers to “diagnose“ IPA



GM

BDG

LFD

PCR

+/- combination (s)

CT

(VOC ?, gliotoxin ?, CT angio ?, PET-CT ?, FunReacT ?, …)

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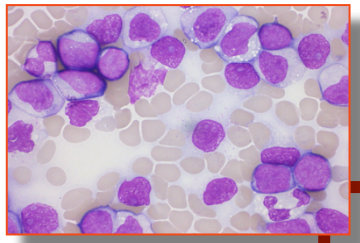
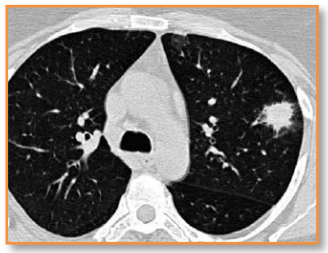
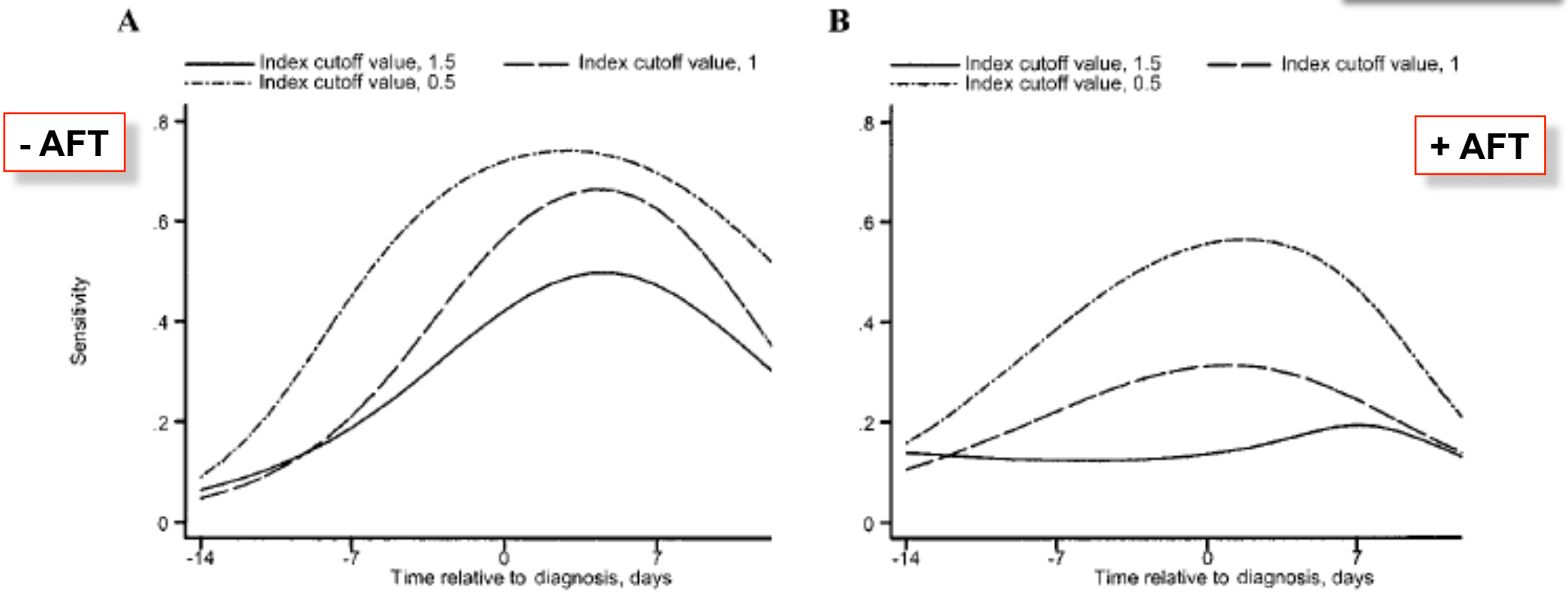




Antifungal Therapy Decreases Sensitivity of the *Aspergillus* Galactomannan Enzyme Immunoassay

Kieren A. Marr,[1,2] Michel Laverdiere,[3] Anja Gugel,[1] and Wendy Leisenring[1,2]



Clinical Infectious Diseases 2005; 40:1762–9

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Diagnosis and Antimicrobial Therapy of Lung Infiltrates in Febrile Neutropenic Patients (allogeneic SCT excluded) Updated Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO)

G. Maschmeyer[1], J. Carratalà[2], D. Buchheidt[3], A. Hamprecht[4], C.P. Heussel[5], C. Kahl[6], J. Lorenz[7], S. Neumann[8], C. Rieger[9], M. Ruhnke[10], H. Salwender[11], M. Schmidt-Hieber[12], E. Azoulay[13]

Ann Oncol 26(1): 21-33 (2015). Epub 2014 May 15

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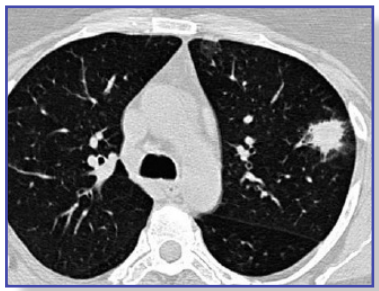
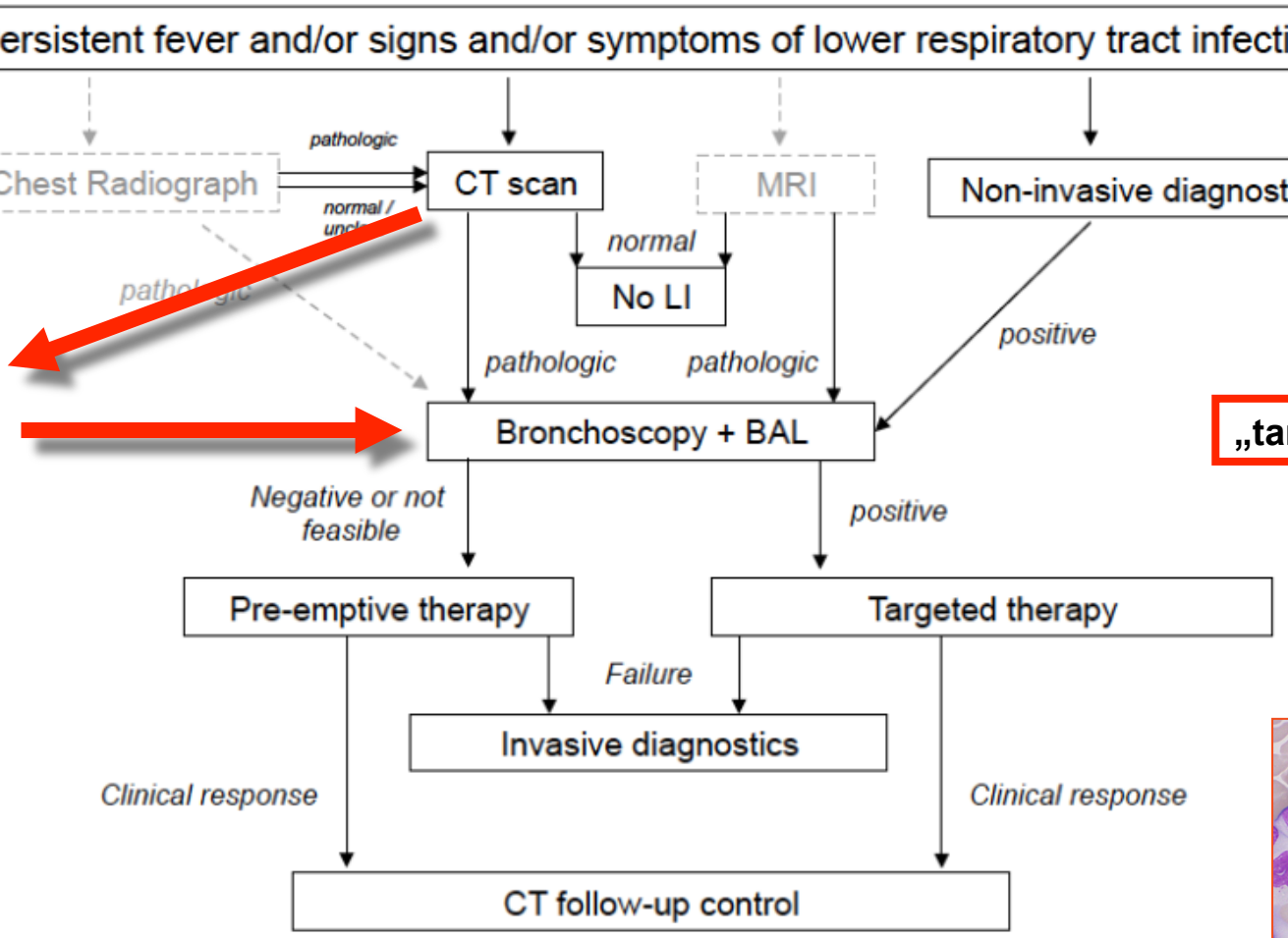
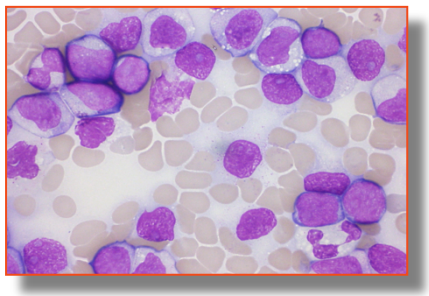




„targeted diagnostic“



Galactomannan in Bronchoalveolar Lavage for Diagnosing Invasive Fungal Disease

Kristina Affolter[1], Michael Tamm[1], Kathleen Jahn[1], Jörg Halter[2], Jakob Passweg[2], Hans H. Hirsch[3], and Daiana Stolz[1]

Methods: A total of 568 hematologic cases undergoing diagnostic bronchoscopy because of respiratory symptoms and/or suspected IFD between 2009 and 2013 at a tertiary care center in Switzerland were included in this prospective, observational cohort study.

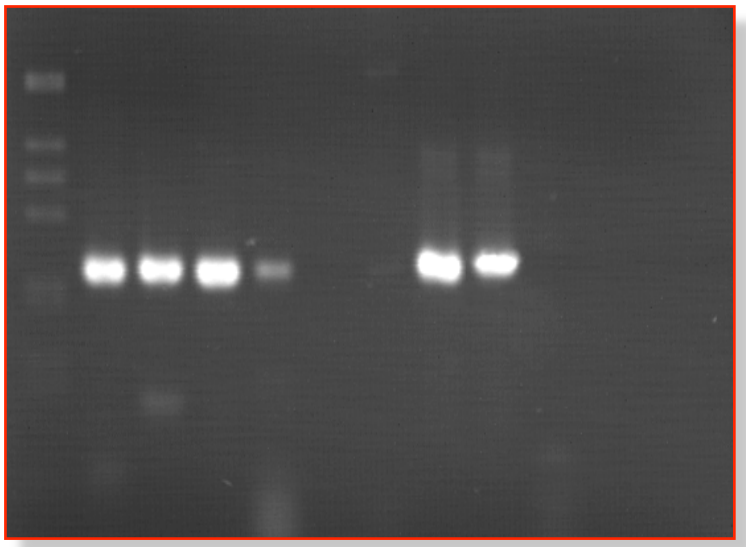
Table 3. Diagnostic Performance of Galactomannan Determination in the Bronchoalveolar Lavage in 530 Cases of Immunocompromised Patients with Hematologic Malignancies

	Sensitivity	Specificity	PPV	NPV	PLR	NLR
As compared with EORTC/MSG						
Proven	0.50 (0.12–0.88)	0.71 (0.67–0.75)	0.02 (0.04–0.06)	0.99 (0.98–1.0)	1.72 (0.77–3.88)	0.70 (0.32–1.57)
Proven and probable	0.49 (0.35–0.63)	0.73 (0.69–0.77)	0.16 (0.11–0.23)	0.93 (0.90–2.48)	1.81 (1.32–2.48)	0.70 (0.53–0.92)
Proven and probable*	0.73 (0.55–0.87)	0.74 (0.70–0.78)	0.16 (0.10–0.22)	0.98 (0.96–0.99)	2.76 (2.14–3.56)	0.37 (0.21–0.65)
Proven and probable and possible	0.35 (0.29–0.41)	0.75 (0.70–0.80)	0.52 (0.44–0.60)	0.60 (0.54–0.65)	1.40 (1.07–1.82)	0.87 (0.77–0.97)
As compared with clinical judgment						
Receiving empirical antifungal treatment	0.42 (0.34–0.50)	0.75 (0.71–0.80)	0.39 (0.31–0.47)	0.78 (0.73–0.82)	1.69 (1.30–2.20)	0.77 (0.67–0.90)
Suspicion of IFD on radiologic studies	0.34 (0.27–0.42)	0.73 (0.68–0.78)	0.37 (0.30–0.46)	0.70 (0.65–0.75)	1.27 (0.97–1.67)	0.90 (0.79–1.02)

Am J Respir Crit Care Med Vol 190, Iss 3, pp 309–317, Aug 1, 2014

PCR applications

etecting pathogens difficult to cultivate:



1988 ***HIV***

1989 ***CMV***

1989 ***Toxoplasma gondii***

1993 ***Borrelia burgdorferi***

1993 ***Aspergillus fumigatus***

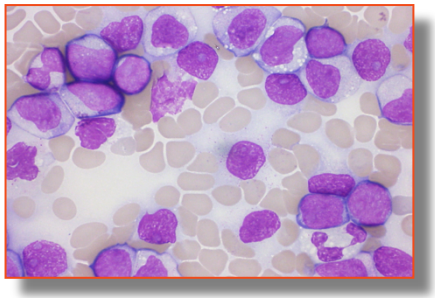
…

…

... and diagnosing infectious diseases

Prospective multicentre PCR-based *Aspergillus* DNA screening in high-risk patients with and without primary antifungal mould prophylaxis

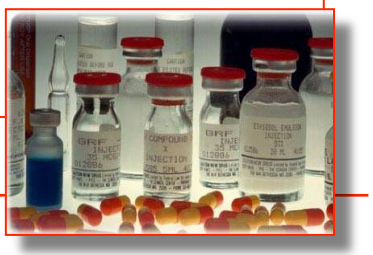
J. Springer[1], M. Lackner[2], D. Nachbaur[3], M. Girschikofsky[4], B. Risslegger[2], W. Mutschlechner[2], J. Fritz[5], W. J. Heinz[1], H. Einsele[1], A. J. Ullmann[1], J. Löffler[1] and C. Lass-Flörl[2]



18% and 38%, respectively. The sensitivity, specificity and positive predictive value (PPV) of PCR were superior in antifungal drug-naive patients, being 71.4%, 92.3%, and 62.5%, respectively. The last of these key performance indicators (PPV) was moderate in patients receiving primary prophylaxis, at 5.4%. Negative predictive values for both strategies applied were 100% with and 98.3% without antifungal mould prophylaxis. PCR has the potential to play a decisive role in the diagnosis and management of *Aspergillus* infections in centres not applying primary antifungal mould prophylaxis.

PPV without antifungal (*Aspergillus*-active) prophylaxis 62,5 %,

PPV during AFP 5,4%



Clin Microbiol Infect 22(1): 80-86 (2016)

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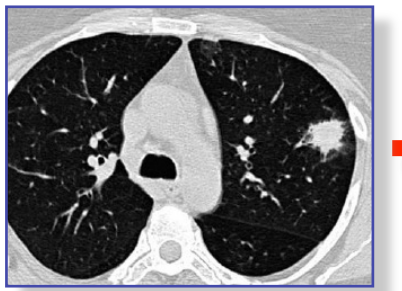
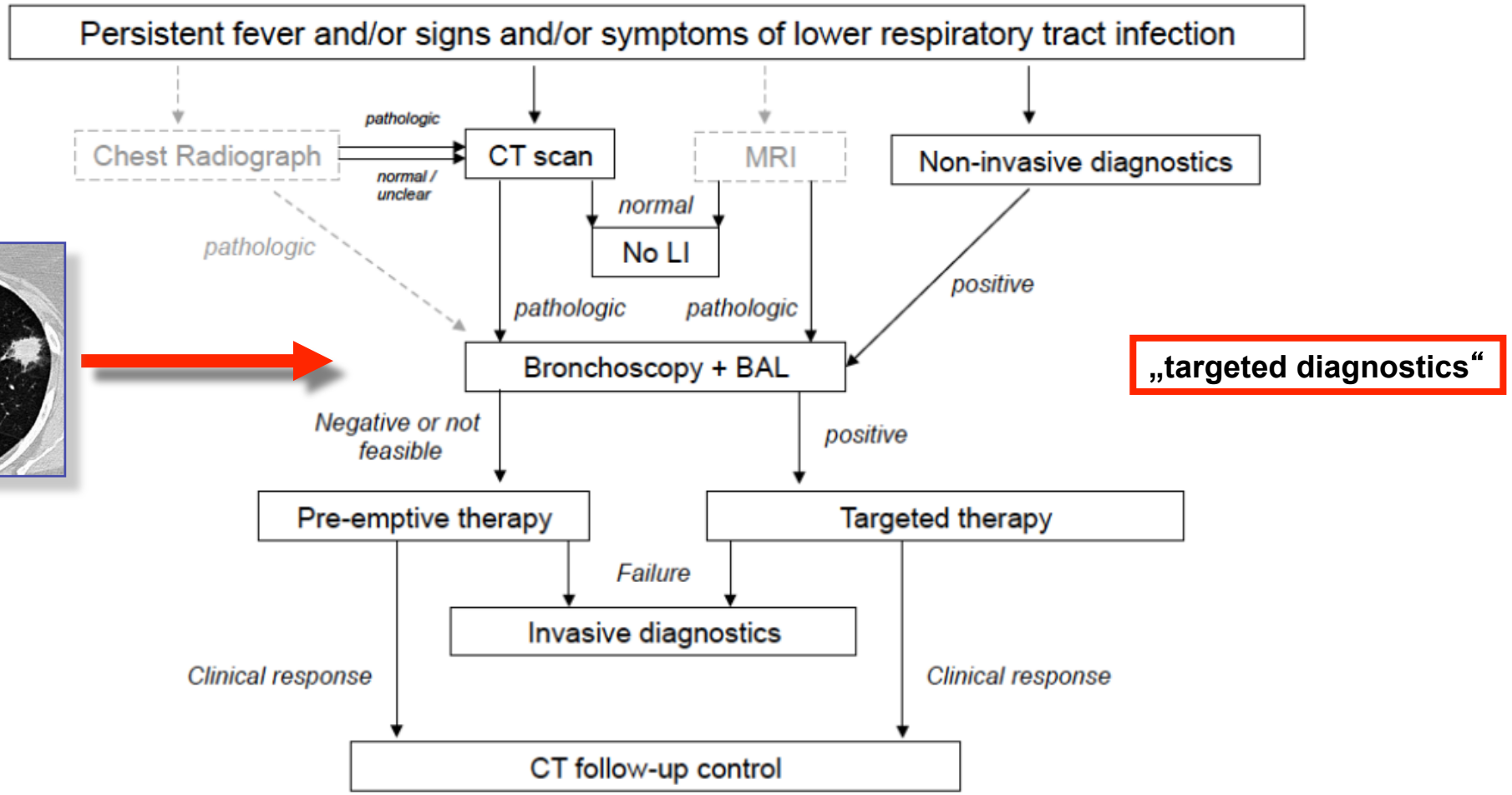




„targeted diagnostics“

EUROPEAN JOURNAL OF Haematology

European Journal of Haematology 89 (120–127)

ORIGINAL ARTICLE

Diagnosing pulmonary aspergillosis in patients with hematological malignancies: a multicenter prospective evaluation of an *Aspergillus* PCR assay and a galactomannan ELISA in bronchoalveolar lavage samples

Mark Reinwald[1], Birgit Spiess[1], Werner J. Heinz[2], Jörg J. Vehreschild[3], Cornelia Lass-Flörl[4], Michael Kiehl[5], Beate Schultheis[6], Stefan W. Krause[7], Hans-Heinrich Wolf[8], Hartmut Bertz[9], Georg Maschmeyer[10], Wolf-Karsten Hofmann[1], Dieter Buchheidt[1]

AGIHO INFEKTIONEN IN DER HÄMATOLOGIE UND ONKOLOGIE
FACHGRUPPE DER DGHO

Utility of bronchoalveolar lavage fluid galactomannan alone or in combination with PCR for the diagnosis of invasive aspergillosis in adult hematology patients: a systematic review and meta-analysis.

Heng SC, Morrissey O, Chen SC, Thursky K, Manser RL, Nation RL, Kong DC, Slavin M.

We conducted a systematic review and meta-analysis of **16 studies involving 783 adults** with hematological malignancies to derive summary estimates of the overall accuracy of BAL-GM for diagnosing IA.
Summary estimates of BAL-GM using an optical density (OD) index cutoff value of 1.5 for proven and probable IA were: sensitivity 0.92 (95% CI = 0.48-0.99), specificity 0.98 (95% CI = 0.78-1.00), … .

Comparing serum GM and Aspergillus PCR testing on BAL fluid, BAL-GM conferred greater sensitivity, but lower specificity than the serum GM test, and similar specificity as the PCR assay. **The use of BAL-GM with serum GM or BAL-PCR tests increased the sensitivity moderately when a positive result was defined by either assay.**

GM quantification in BAL fluid at an OD index cutoff value of 1.5 has excellent sensitivity and specificity to assist clinical decision-making in confirming or excluding a diagnosis of IA when results are interpreted with clinical findings.

Crit Review Microbiol, 41(1):124-34 (2015)

Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial

C Orla Morrissey, Sharon C-A Chen, Tania C Sorrell, Samuel Milliken, Peter G Bardy, Kenneth F Bradstock, Jeffrey Szer, Catriona L Halliday, Nicole M Gilroy, John Moore, Anthony P Schwarer, Stephen Guy, Ashish Bajel, Adrian R Tramontana, Timothy Spelman, Monica A Slavin, for the Australasian Leukaemia Lymphoma Group and the Australia and New Zealand Mycology Interest Group

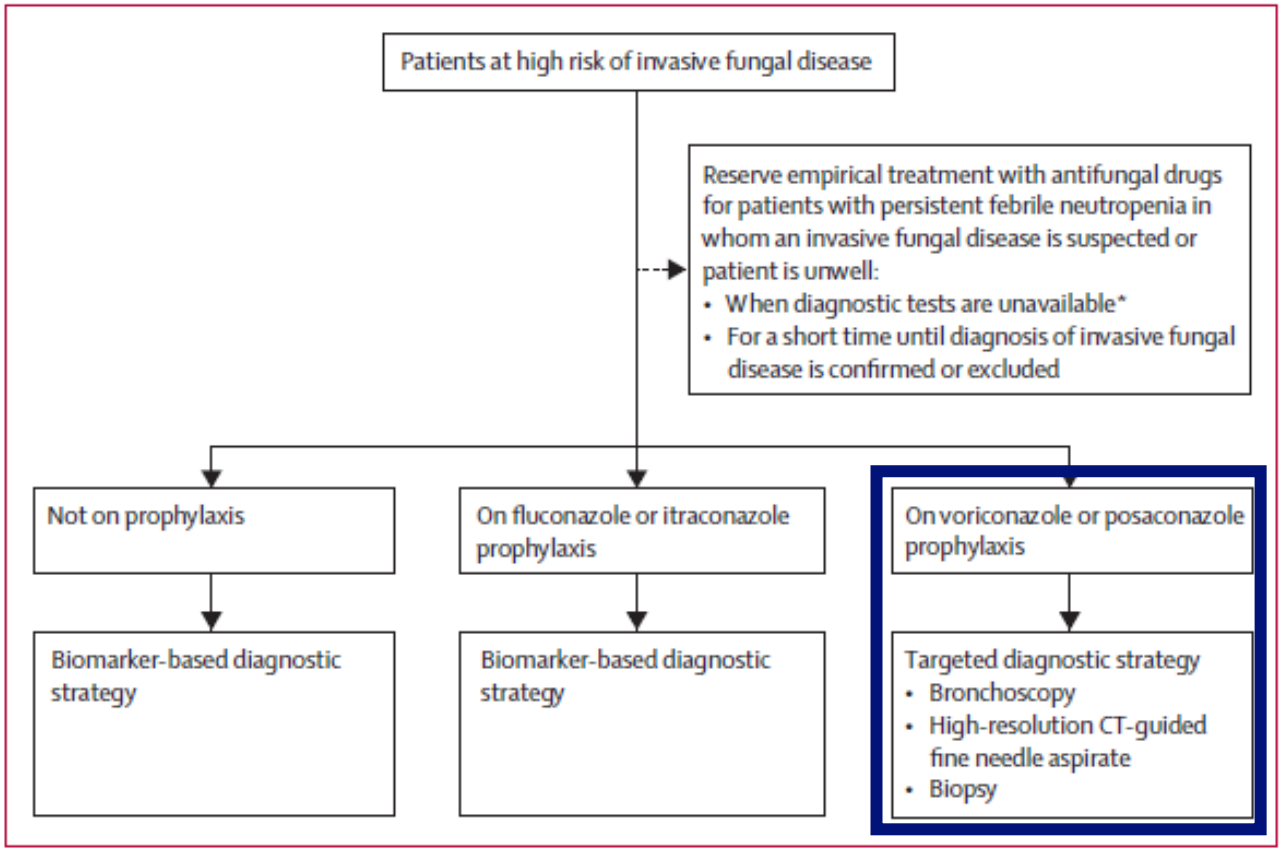


Figure 3: **Integrated antifungal strategies for patients at risk of invasive fungal disease**

J Antimicrob Chemother. 67 (9), 2260-2270 (2012)

J Antimicrob Chemother
doi:10.1093/jac/dks208

Journal of Antimicrobial Chemotherapy

Therapy with antifungals decreases the diagnostic performance of PCR for diagnosing invasive aspergillosis in bronchoalveolar lavage samples of patients with haematological malignancies

Mark Reinwald[1]*†, Margit Hummel[1]†, Elena Kovalevskaya[1], Birgit Spiess[1], Werner J. Heinz[2], Jörg Janne Vehreschild[3], Beate Schultheis[4], Stefan W. Krause[5], Bernd Claus[6], Thomas Suedhoff[7], Rainer Schwerdtfeger[8], Stefan Reuter[9], Michael G. Kiehl[10], Wolf-Karsten Hofmann[1] and Dieter Buchheidt[1]

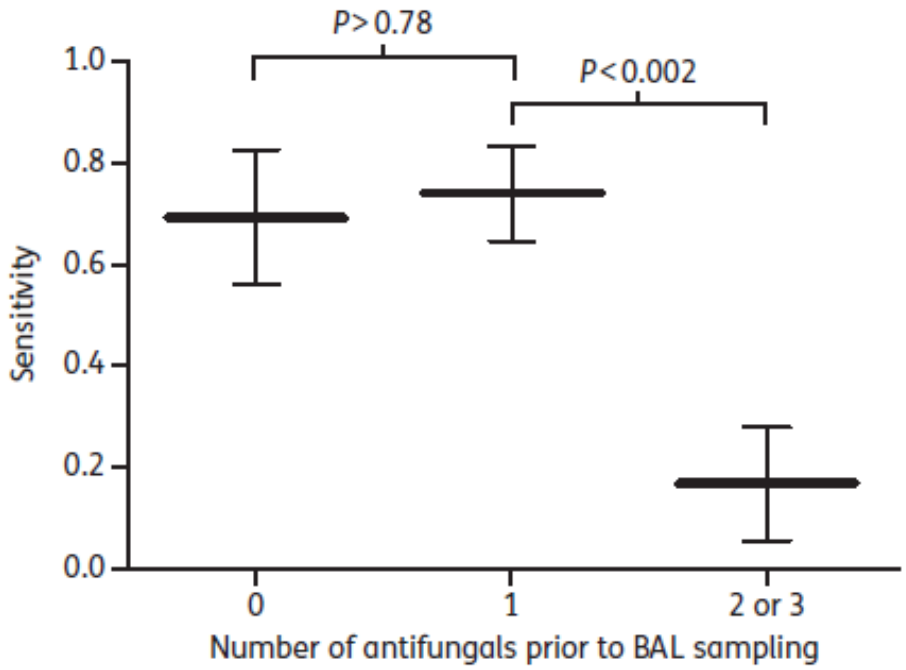
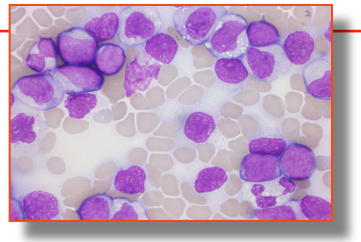


Figure 1. Sensitivity values relative to the number of antifungals given prior to BAL sampling. Mean and standard error of the mean; *P* values calculated using the Mann–Whitney *U*-test.

- 226 BAL samples
- nested *Aspergillus* PCR assay
- sensitivity of : 0.69
  specificity: 0.87
  (for pts without antifungal treatment prior to BAL sampling)

Diagnosis of invasive fungal infections in hematological patients by combined use of galactomannan, 1,3-beta-D-glucan, *Aspergillus* PCR, multifungal DNA-microarray and *Aspergillus* azole resistance PCRs in blood and bronchoalveolar lavage samples – results of a prospective multicenter study

T. Boch, B. Spiess, O.A. Cornely, J.J. Vehreschild, P.M. Rath, J. Steinmann, W.J. Heinz, J. Hahn, S.W. Krause, M.G. Kiehl, G. Egerer, T. Liebregts, M. Koldehoff, M. Klein, F. Nolte, M.C. Mueller, N. Merker, S. Will, M. Mossner, H. Popp, W.-K. Hofmann, M. Reinwald, D. Buchheidt



OBJECTIVES:

… defining the optimal use of biomarkers and clinical samples.

METHODS:

Concurrent bronchoalveolar lavage (BAL) and peripheral blood samples of 99 hematological patients with suspected IFD were investigated within a multicenter prospective study.

…

RESULTS:

IFD were classified as proven (n=3), probable (n=34), possible (n=33), and no IFD (n=29).

…

The combination of GM (BAL) with BDG (blood) showed sensitivity/specificity of 92%/93%.

Combining GM (BAL) with PCR (BAL) showed sensitivity/specificity of 85%/97%.

…

Available online 5 July 2016

CLINICAL MICROBIOLOGY AND INFECTION

OFFICIAL PUBLICATION OF ESCMID

Combination of biomarkers is superior to their sole use in diagnosing IFD, particularly IPA, in hematological high risk pts.

Integrating blood and BAL samples into a diagnostic algorithm is an advantageous approach.