« Session : What's New on Diagnostic Modalities »

New Perspectives for Antigen Detection in the Diagnosis and Treatment of Invasive Fungal Infections

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UNIL | Université de Lausanne
Faculté de biologie et de médecine

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Candida   *Aspergillus*

**Inappropriate Initial Therapy of Candidemia
With Septic Shock :
Drop in Survival from 25 - 35% to < 5% !**

Kumar et al., Chest, 2009; 136: 1237-48

80-90%	**HOSPITAL / ICU**	10-20%
30-60%	**NEUTROPENIA / TRANSPLANTATION**	30-60%

The Next Step ?

Clinical Risk Profile
Cultures : Blood, BAL,
Colonization, ...

+

Detection of
Fungal Components

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Candida

MANNAN + ANTI-MANNAN

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Mannan / Anti-Mannan

- **Grading of evidence and recommendation, 3rd European Conference on Infections in Leukemia (ECIL-3) 2009**

  Mikulska et al., Crit Care, 2010; 14: R222

  ECIL, Bone Marrow Transplantation, 2012; 47: 846-54

  - **Combination Mannan and Anti-Mannan : BII**
  - **Candidemia : CII**
  - **Hepatosplenic Candidiasis : BIII**

- **Not included in 2008 EORTC-MSG diagnostic criteria**

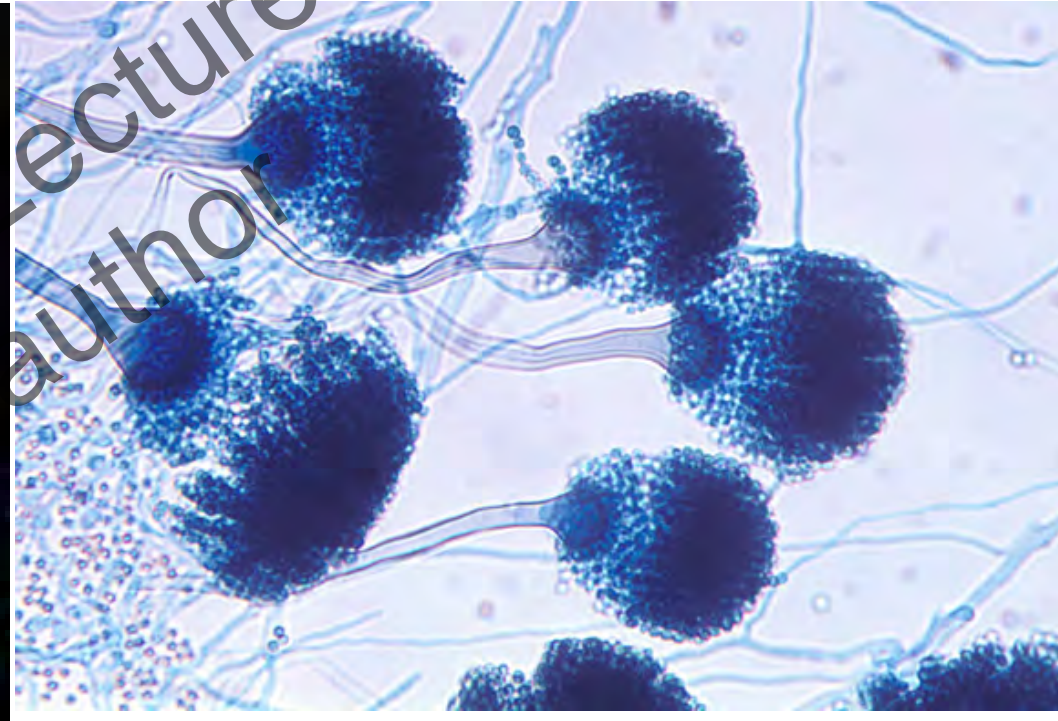- **… and in ICU PTS WITH NON-FUNGEMIC CANDIDIASIS ?**

Aspergillus

GALACTOMANNAN

Galactomannan

- **BLOOD : solid data set for cut-off > 0.5 Index**
  - Different detection in neutropenic vs. non-neutropenic patients
  - Ongoing antifungal therapy : ↓ sensitivity, delayed positivity
  - False-positives : piperacillin/tazobactam, food, ….
  - Follow-up of therapy : galactomannan↓ if response / ↑ if failure
- **BAL : promising for cut-off > 0.5 Index, in both neutropenic and ICU patients**

- **3rd European Conference on Infections in Leukemia (ECIL) 2009 : <u>grading of evidence and recommendation AII</u>**

- **<u>Included in 2008 EORTC-MSG diagnostic criteria</u>**

Candida *Aspergillus*

1,3-BETA-D-GLUCAN

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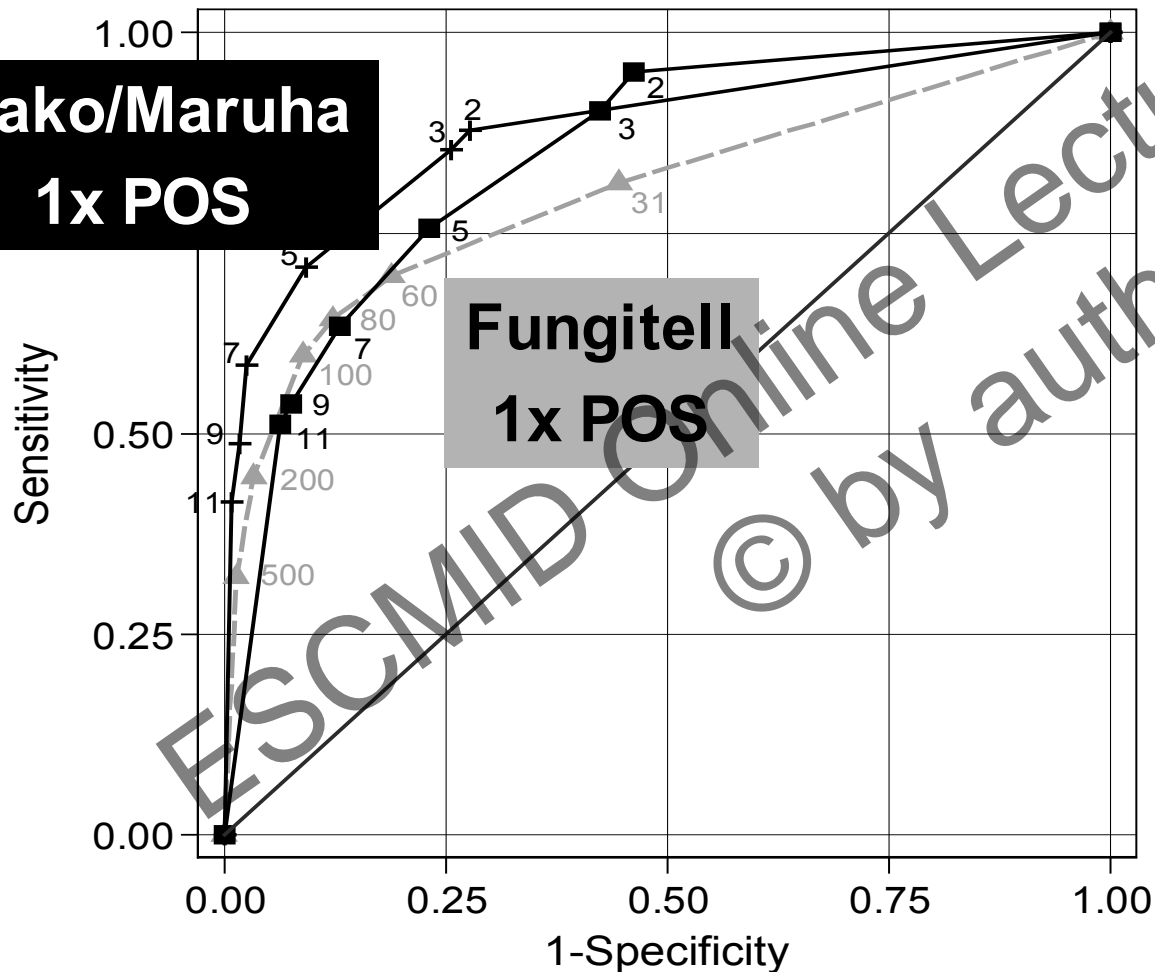# Slide withheld at request of author

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Outline

- **Beta-D-glucan assays**
- **Hematological patients : the ECIL meta-analysis**
- **Candidiasis in ICU patients**
- **Timing of diagnosis & assessment of response**
- **Different fungi : yeasts, molds, dimorphic fungi**
- **Beta-D-glucan in 2013**

ECIL Meta-Analysis of Beta-Glucan Antigenemia for Diagnosis of IFI in High-Quality Hemato-Oncological Cohort Studies

Lamoth, Cruciani, Mengoli, et al. for ECIL, Clin Infect Dis, 2012, 54 (5): 633-43

Wako/Maruha 1x POS

Fungitell 1x POS

Fungitell® (ACC, USA)

1x ≥ 80 pg/ml :

DOR 16.3, PPV 60%, NPV 90%

2x ≥ 80 pg/ml :

DOR 111.8, PPV 90%, NPV 90%

Legend:
- Fungitell 1 criterion A ROC area: 0.8002
- Wako/Maruha criterion A ROC area: 0.8448
- Wako/Maruha criterion B ROC area: 0.8782
- Reference

Comments

- Meta-analysis of <u>high-quality cohorts of HEM pts</u> from the 3rd European Conference on Infections in Leukemia, ECIL-3

  - <u>Prospective monitoring</u> in IFI cases and controls with <u>identical risk profiles : performance close to real life</u>

  - 2 positive values : higher diagnostic accuracy / PPV / NPV … BUT, SENSITIVITY 50-80% : <u>needs to be combined</u> with clinical, radiological, and microbiological assessment

- Similar performance of North-American and Japanese beta-D-glucan assays … so far, Japanese assays not available in Europe or North-America

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CRITICAL CARE

RESEARCH　　　　　　　　　　　　　　　**Open Access**

Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, Candida score, and colonization index

Brunella Posteraro[1], Gennaro De Pascale[2], Mario Tumbarello[3*], Riccardo Torelli[1], Mariano Alberto Pennisi[2], Giuseppe Bello[2], Riccardo Maviglia[2], Giovanni Fadda[1], Maurizio Sanguinetti[1] and Massimo Antonelli[2]

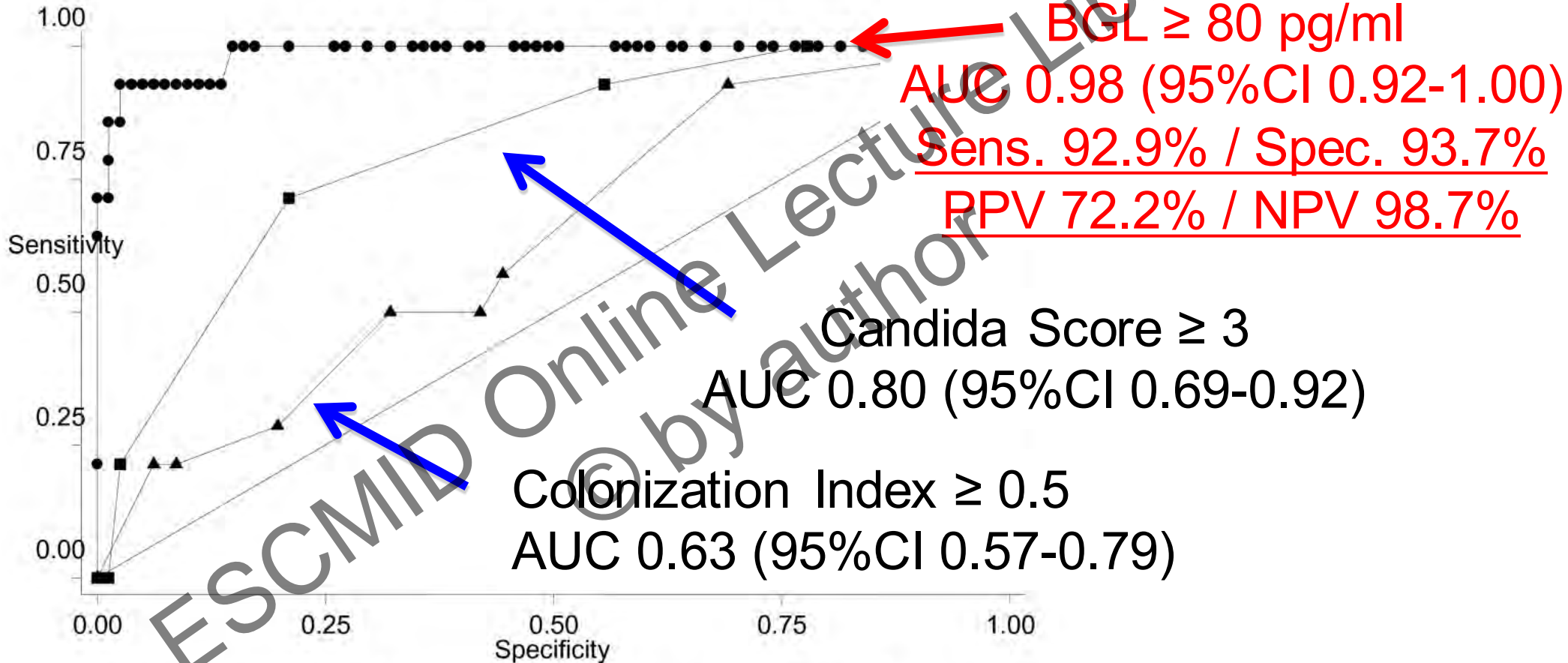Ospedale Gemelli, Università Cattolica, Roma, Italy

METHODS

- Inclusion criteria (ALL fullfilled) :
  - Medical ICU admission with sepsis
  - Not neutropenic / No IFI at baseline
  - ICU stay > 5 days

- Diagnostic assessment at inclusion :
  - Blood cultures
  - Beta-glucan ($\geq$ 80 pg/ml)
  - Candida score ($\geq$ 3)
  - Colonization index ($\geq$ 0.5)

95 patients included, 16 IFI :
<u>13 candidemias</u>, 1 *Candida* mediastinitis,
1 lung aspergillosis, 1 lung fusariosis
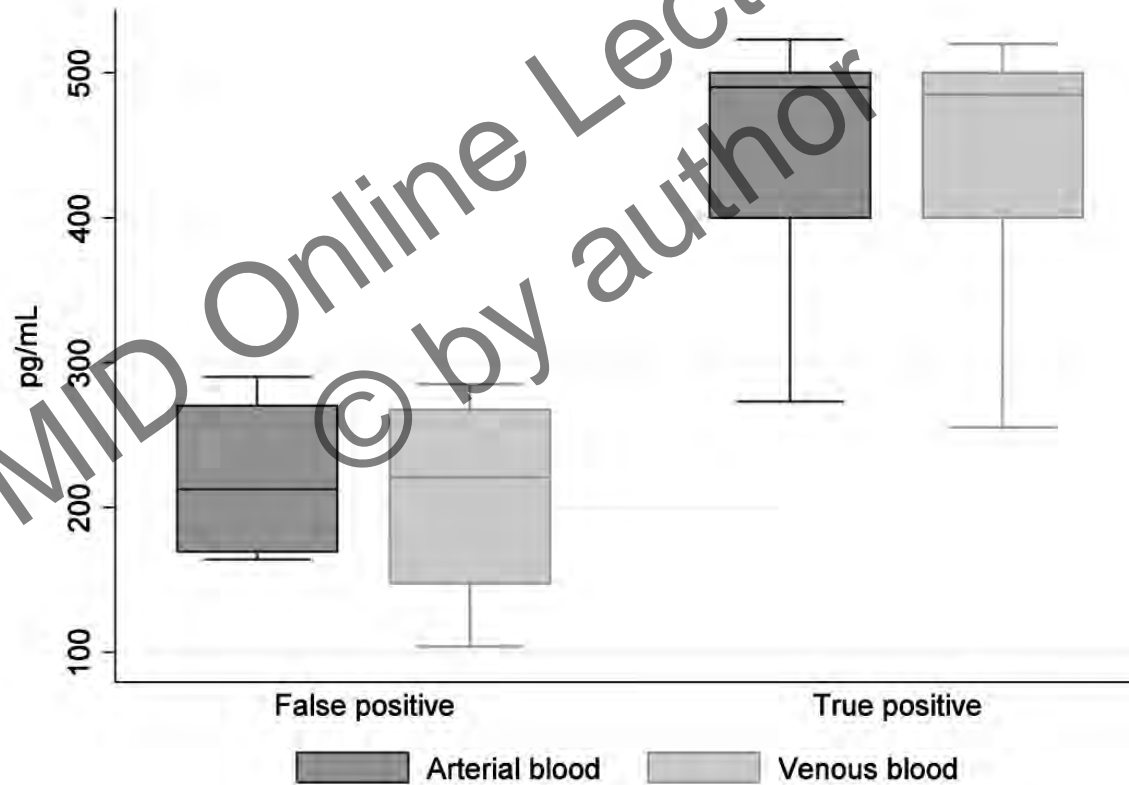
ROC CURVES

BGL ≥ 80 pg/ml
AUC 0.98 (95%CI 0.92-1.00)
Sens. 92.9% / Spec. 93.7%
PPV 72.2% / NPV 98.7%

Candida Score ≥ 3
AUC 0.80 (95%CI 0.69-0.92)

Colonization Index ≥ 0.5
AUC 0.63 (95%CI 0.57-0.79)

Positive BGL results
1-3 days before positive blood cultures

BGL IN BLOOD FROM ARTERIAL CATHETER VS. PERIPHERAL VENIPUNCTURE

Comments

- Single BGL ≥ 80 pg/ml at onset of sepsis in medical patients with ICU stay > 5 days

  - Accurate for EARLY diagnosis of candidemia

  - **Practical : simple patients' selection and one single blood sample (catheter = venipuncture) !**

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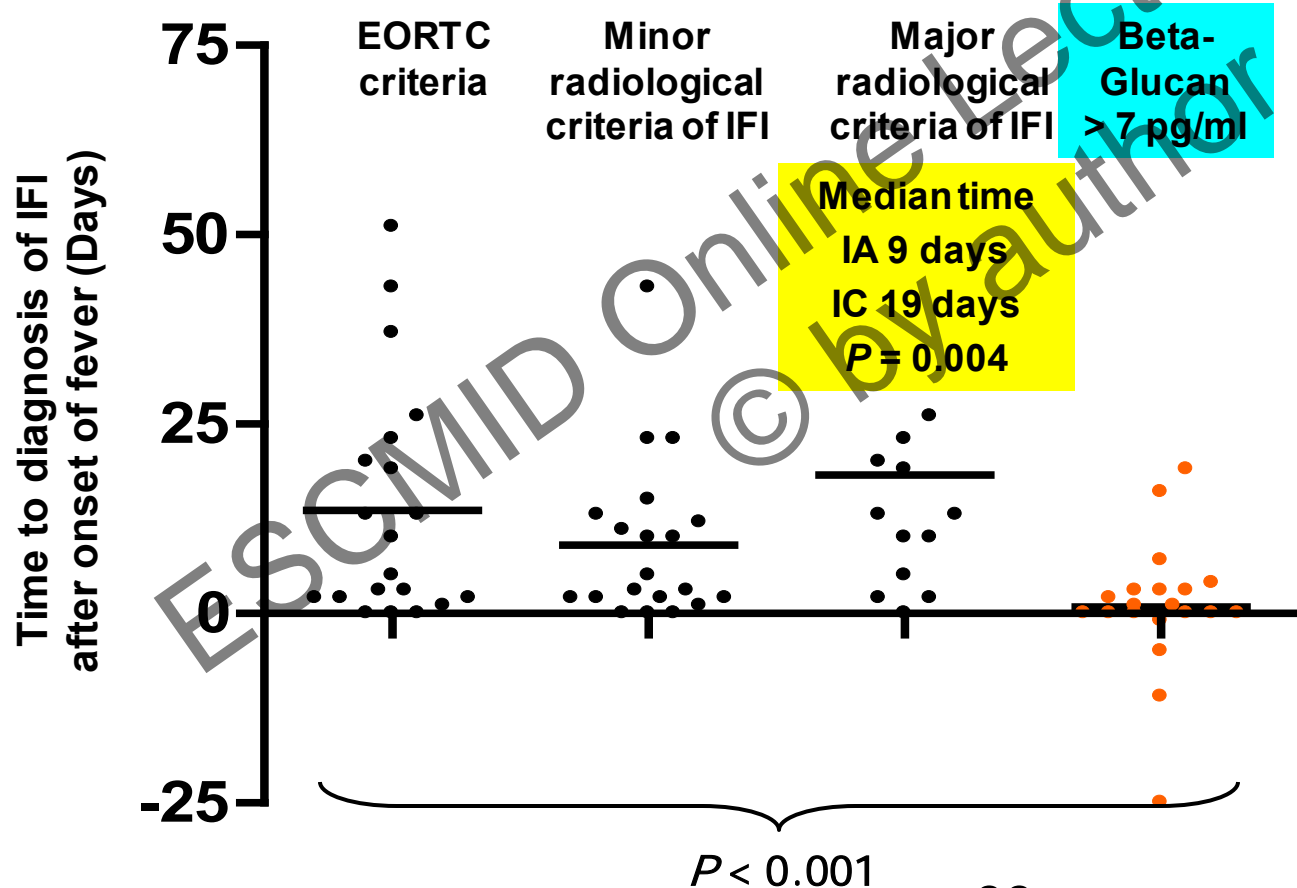
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Hematological Patients : Time Interval Between Onset of Neutropenic Fever as First Sign of IFI and Diagnosis
Senn et al., Clin Infect Dis, 2008; 46: 878-85

Scatter plot. Y-axis: Time to diagnosis of IFI after onset of fever (Days), from -25 to 75.

Categories:
- EORTC criteria
- Minor radiological criteria of IFI
- Major radiological criteria of IFI
- Beta-Glucan > 7 pg/ml

Median time
IA 9 days
IC 19 days
P = 0.004

Empirical antifungal therapy (before beta-glucan results) : median 1.5 days (range 0-10) after onset of fever

P < 0.001

Kinetics of Beta-Glucan in Hematological Patients Responding or not Responding to Antifungal Therapy

Senn et al., Clin Infect Dis, 2008; 46: 878-85

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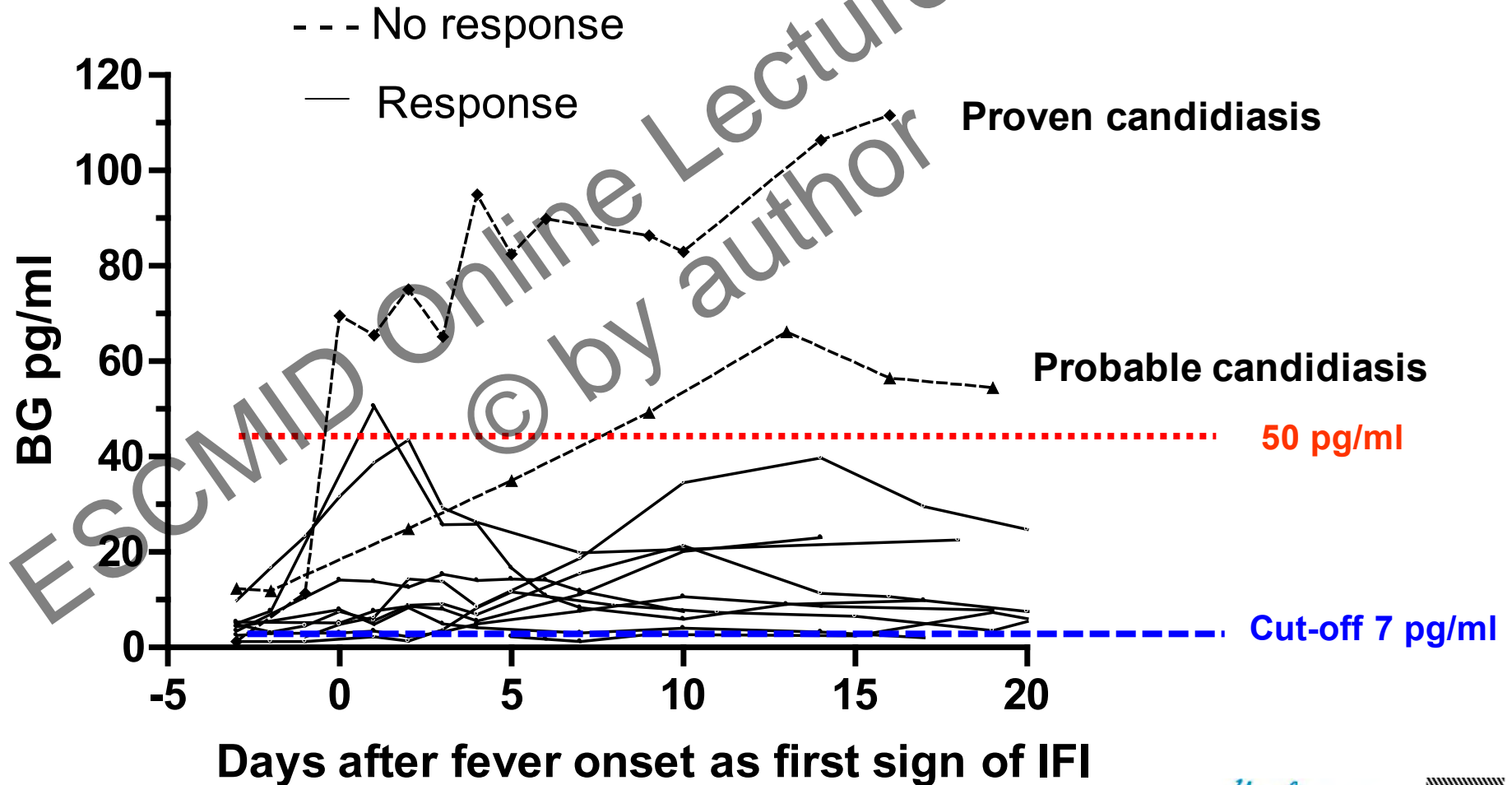
Comments

- Beta-D-glucan
  - Early diagnosis of IFI in HEM pts
  - Value may reflect both severity of infection and clinical outcome
  - In follow-up it remains positive at low levels despite response to antifungal therapy ....
  - Similar observations in the FUNGINOS cohort of high-risk surgical ICU patients with non-fungemic intra-abdominal candidiasis

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Proven + probable invasive candidiasis (IC) /
Proven + probable invasive aspergillosis (IA)

BG Assay	Cut-off	Sensitivity	Specificity	PPV	NPV	Efficiency
Fungitell	60-120 pg/ml (1-3 values)	67 – 83 / 25 – 88	90 – 100 / 90 – 100	63 – 100 / 70 – 100	96 – 98 / 96 – 99	89 – 98 / 89 – 99
Fungitec-G	20-40 pg/ml (1 value)	50 / 63 – 100	83 / 76 – 83	21 / 16 – 19	95 / 96 – 100	81 / 75 – 84
Wako / Maruha	7-11 pg/ml (2 values)	59 / 45 – 60	96 / 96 – 99	67 / 64 – 83	94 / 95	91 / 91 – 95
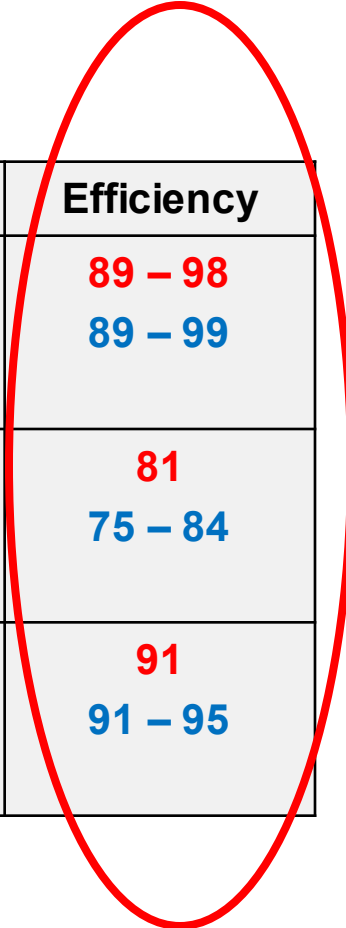
Beta-Glucan Antigenemia (Fungitell® - U.S.A.) for Diagnosis of Candidemia / Invasive Candidiasis Due to Different *Candida* Species
Ostrosky-Zeichner et al., Clin Infect Dis, 2005; 41: 654-9

6 Hospitals, United States
1 SINGLE SAMPLE/patient within 72h after documentation of candidiasis

	Beta-Glucan > 60 pg/ml
C. albicans	30/36 (83%)
C. glabrata	21/26 (81%)
C. tropicalis	10/11 (91%)
C. parapsilosis	13/18 (72%)
C. krusei	3/3 (100%)

Beta-D-Glucan in Other IFI

Pneumocystis jirovecii

- **HIV pts. : sensitivity 87-100%, specificity 65-100%**
- Useful if BAL not feasible (or neg. BAL & high clinical suspicion)
- Hematological patients and SOT ?

Other fungi : FEW – NO data

- *Histoplasma* : sensitivity ~ 90%, specificity 70%
- *Cryptococcus* : LOWER levels than in other fungi …
- **Zygomycetes :** LOWER levels than in other fungi …
- **Other molds** : ?

Comments

- Beta-D-glucan as MULTIPLEX fungal biomarker
  - Equivalent in aspergillosis and candidiasis
  - Useful in *Pneumocystis jirovecii*
  - In other fungi LOW levels or lacking data

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Beta-Glucan in 2013

- HEMATOLOGICAL PATIENTS : Aspergillus + *Candida*
  - ECIL (*BMT, 2012; 47: 846-54*) :
    Monitoring in acute leukemia / allo-HSCT (NNT 5-20) : BII
  - Microbiological criterion in 2008 EORTC-MSG classification
  - For preemptive therapy ?
- ICU PATIENTS : *Candida* >> Aspergillus
  - Sepsis : may anticipate detection of candidemia
  - Recurrent perforation/leakage : early detection of non-fungemic intra-abdominal candidiasis (NNT 3)
- *Pneumocystis jirovecii* in HIV pts … and in non-HIV ?
- BAL ? Children ?

- BUT ... costs + complex (real time results ?), contaminations (Ig, dialysis, gauzes, …) : looking for automated assays + central labs

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