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Persistent febrile neutropenia: diagnostic-driven *vs*. empirical antifungal therapy

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HOSPITALES UNIVERSITARIOS Virgen del Rocío

Disclosures

- Servicio Andaluz de Salud
- Astellas
- Pfizer
- MSD

Summary

- Persistent febrile neutropenia and **empirical antifungal therapy (EAT)** as the standard of care
  - Scientific basis of EAT
  - Considerations about EAT
- **Diagnostic-driven (DD-AT)** approaches
  - Definitions
  - Research in DD-AT: changing paradigm
  - Triggers for DD-AT
  - Cost-effectiveness of DD-AT
  - Requirements
- **Conclusions**

Persistent febrile neutropenia: background

- **Persistent fever** in neutropenic patients with hematological malignancies receiving chemotheray or undergoing stem cell transplant (SCT) represents a challenging issue
  - Unexplained febrile neutropenia despite 4-7 days of broad-spectrum antibacterial therapy
- Main presentation form of **Invasive Fungal Disease (IFD)**
- IFD remains a seriuos threat to these patients
  - Incidence is rising
  - Still a **major cause or morbidity and mortality** (attributable mortality 40-75%)

Pagano L, Haematologica 2006; Pagano L, CID 2007; Marr K, CID 2002; Freifeld A, IDSA. CID 2011; Kontoyiannis DP, CID 2010; Mezin J, Am J Health-System Pharmacy 2209;

Persistent febrile neutropenia: background

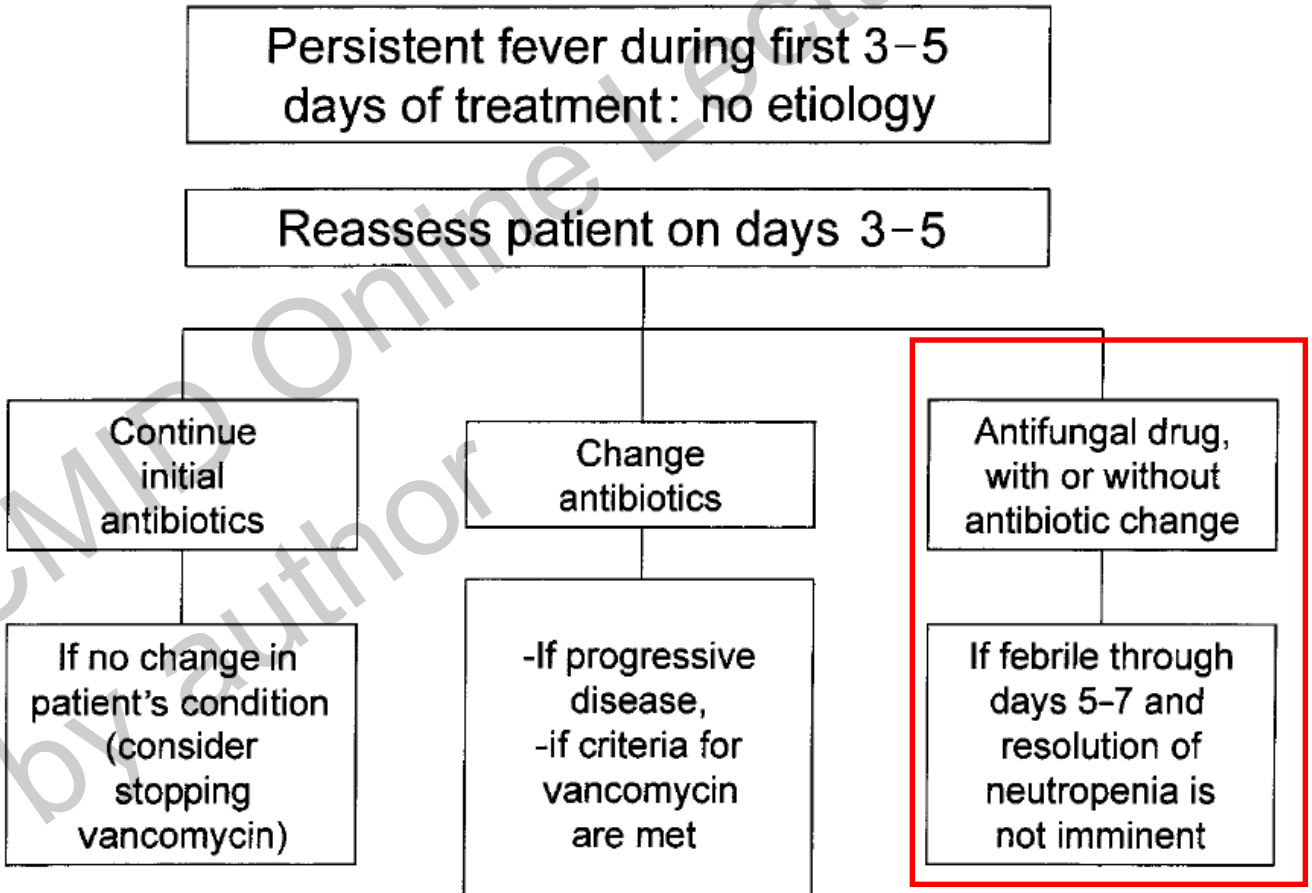
- **Lack of accurate diagnostic** tools for prompt diagnosis of IFD and limitations of invasive procedures
  - Dificulty in diagnosing IFD may **delay** an effective **antifungal therapy** resulting in **increased mortality**

- The standard of care for decades has been universal indication of **empirical antifungal therapy (EAT)**
  - Administration of amphotericin B (AmB) in neutropenic patients with persistent fever or relapsing fever
  - Goal: treating IFD before progression to overt disease

EAT: standard of care

2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer

Walter T. Hughes,[1] Donald Armstrong,[2] Gerald P. Bodey,[3] Eric J. Bow,[7] Arthur E. Brown,[2] Thierry Calandra,[9] Ronald Feld,[9] Philip A. Pizzo,[4,5] Kenneth V. I. Rolston,[3] Jerry L. Shenep,[1] and Lowell S. Young[6]



AI

Hughes W, IDSA Guidelines, CID 2002

How solid are scientific evidences supporting EAT?

How solid are scientific evidences supporting EAT?

- Empiric Antibiotic and Antifungal Therapy for Cancer Patients with Prolonged Fever and Granulocytopenia

PHILIP A. PIZZO, M.D.
K. J. ROBICHAUD, R.N.
FRED A. GILL, M.D.
FRANK G. WITEBSKY, M.D.
Bethesda, Maryland

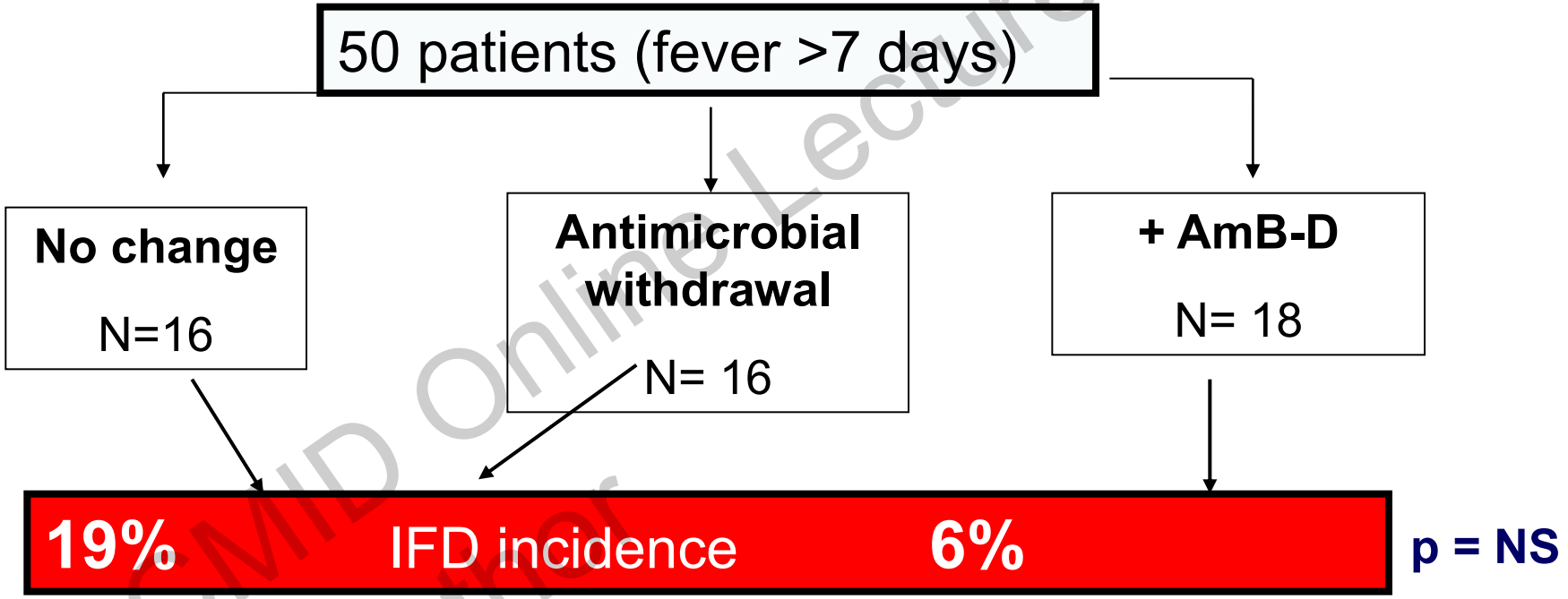
January 1982 The American Journal of Medicine Volume 72

- **Empiric Antifungal Therapy in Febrile Granulocytopenic Patients**

EORTC INTERNATIONAL ANTIMICROBIAL THERAPY COOPERATIVE GROUP*

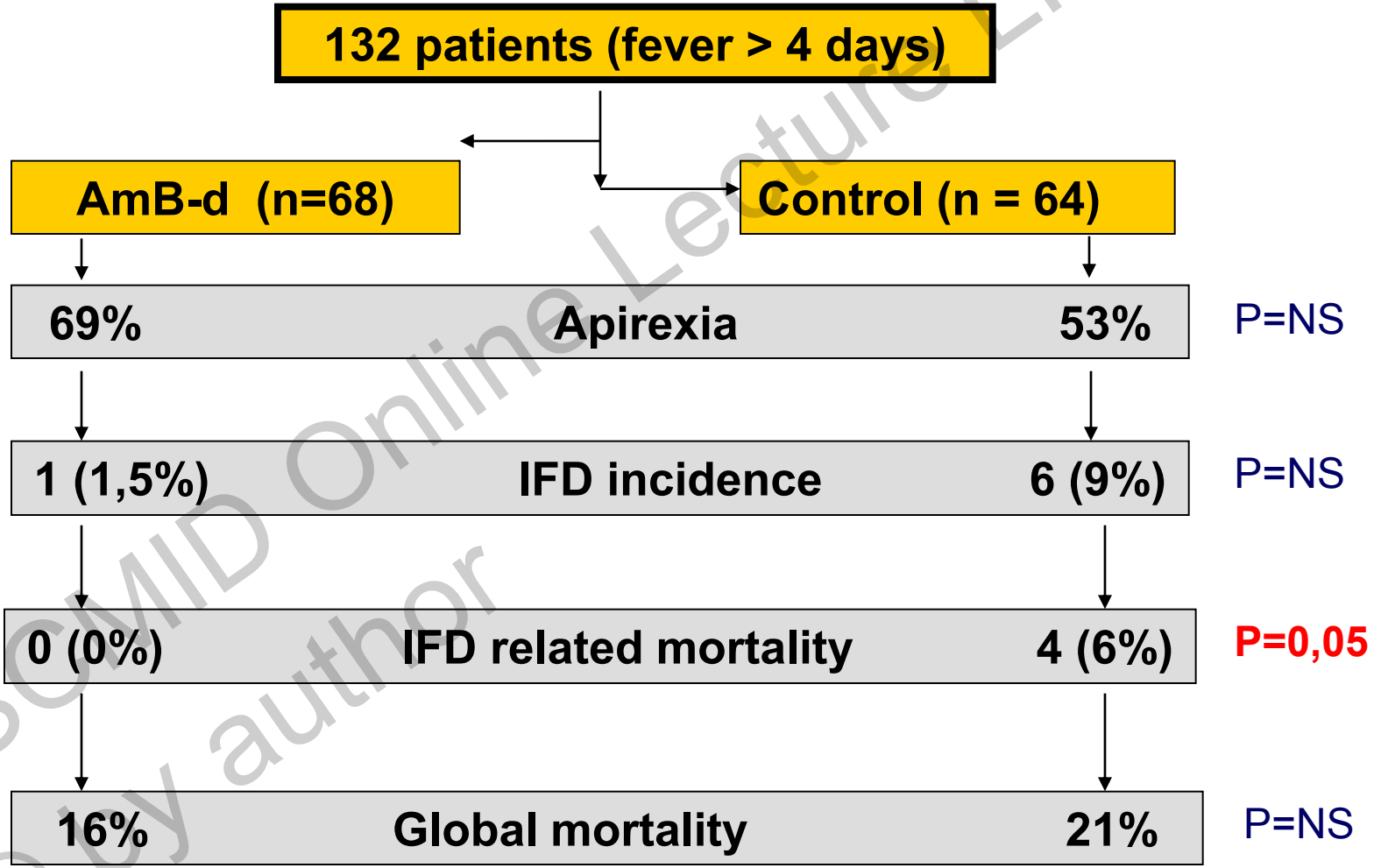
June 1989 The American Journal of Medicine Volume 86

Scientific basis of universal empirical antifungal therapy



Pizzo PA, NEJM 1986

Scientific basis of universal empirical antifungal therapy



EORTC, AJM 1989

EAT: comparative clinical trials

Year	Main author	Antifungal agent	n	Main variable	Main result
1998	White	AmB-D *vs* ADC	213	Composite	Equivalent
2000	Winston	AmB-D *vs* FLU	317	Composite	Equivalent
2000	Wingard	AmB-L *vs* AmB-LC	240	Seguridad	AmB-L
2001	Boogaerts	AmB-D *vs* ITC	384	Composite	Equivalent
1999	Walsh	AmB-D *vs* AL	702	Composite	Equivalent
2002	Walsh	AmB-L *vs* VRC	849	Composite	AmB-L
2004	Walsh	AmB-L *vs* CAS	1095	Composite	Equivalent

- Controversial composite end point
- EAT from 3-7 days from de onset of fever
- No common predefined diagnostic approach
- High NNT

EAT: comparative clinical trials

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2002	Walsh	AmB-L *vs* VRC	849	Composite	AmB-L
2004	Walsh	AmB-L *vs* CAS	1095	Composite	Equivalent

No answer to the question,
is EAT more effective than a placebo?

Considerations about EAT

- Persistent fever **not specific** for IFD
  - Chemotherapy, drug reactions, other infections…
  - Incidence of IFD range from 5-15%
- **Not demonstrating** to reduce the incidence and mortality of IFD and 2-10% of **breakthrogh IFD**
- **Earlier and more accurate diagnosis**
  - Revised published definitions for IFD
  - Indirect test for fungi available
  - Imaging test (thin-section CT-scan)
- More and safer **antifungal drugs** available

Maertens J CID 05, Cisneros JM EIMC 05; Jantunen, Eur J Haematol 2004; Kawazu J Clin Microbiol 2004; Maertens Br J Haematol 2004; Donelly J. P, Inter J Antimicrob Agents 2013.

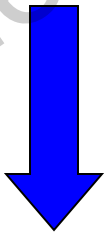
Considerations about EAT

Risk of over-treatment with toxic/expensive drugs

Potential resistance selection

Appearance of adverse reactions

Increased costs



Changes on the standard of care

Need for optimization of antifungal therapy approaches

Is EAT still the best option?

Donelly J. P, Inter J Antimicrob Agents 2013; Maertens, J. A et al. Haematologica 2012;97(3).

Diagnostic-driven antifungal therapy

- Definition and timing is clear for EAT
- Denomination of **pre-emptive antifungal (PAT)** therapy probably unfortunate
  - *"Antifungal treatment in neutropenic patients with clinical and/or microbiological findings suspected to be related to an IFD but insufficient to satisfy the criteria of proven/probable IFD"*
    - Different from traditional definition of "pre-emptive": treatment before disease, based on a predictive laboratory sign.

➢ Better "**diagnostic driven antifungal-therapy**" **(DD-AT)**:

➢ Treatment guided by clinical/radiological/microbiological results which may be suggestive of an established IFD.

Girmenia C et al. " A hematology consensus agreement on antifungal strategies for neutropenic patients with hematological malignancies and stem cell transplantation recipients" Hematological Oncology 2012

Patterns of IFD

Table 1. Patterns of invasive fungal disease in pratice, based on 2008 EORTC-MSG criteria.

	A	B	C				D	E
	-	-	I	II	III	IV	-	
Radiological signs and 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)		Not considered necessary
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Positive tissue or specimen from a sterile site
Clinical evidence of IFD	No	No	No	No	No	Yes	Yes	Yes
Mycological evidence of IFI	No	No	Yes	No	Yes	No	Yes	Yes
Final diagnosis	Unclassified					Possible IMD	Probable IMD	Proven IMD
Management	Prophylaxis	Empirical therapy	Diagnostic-driven (pre-emptive) therapy				Targeted therapy	

Maertens, J. A, Nucci M, Donnelly P.J. Haematologica 2012;97(3)

Research on DD-AT

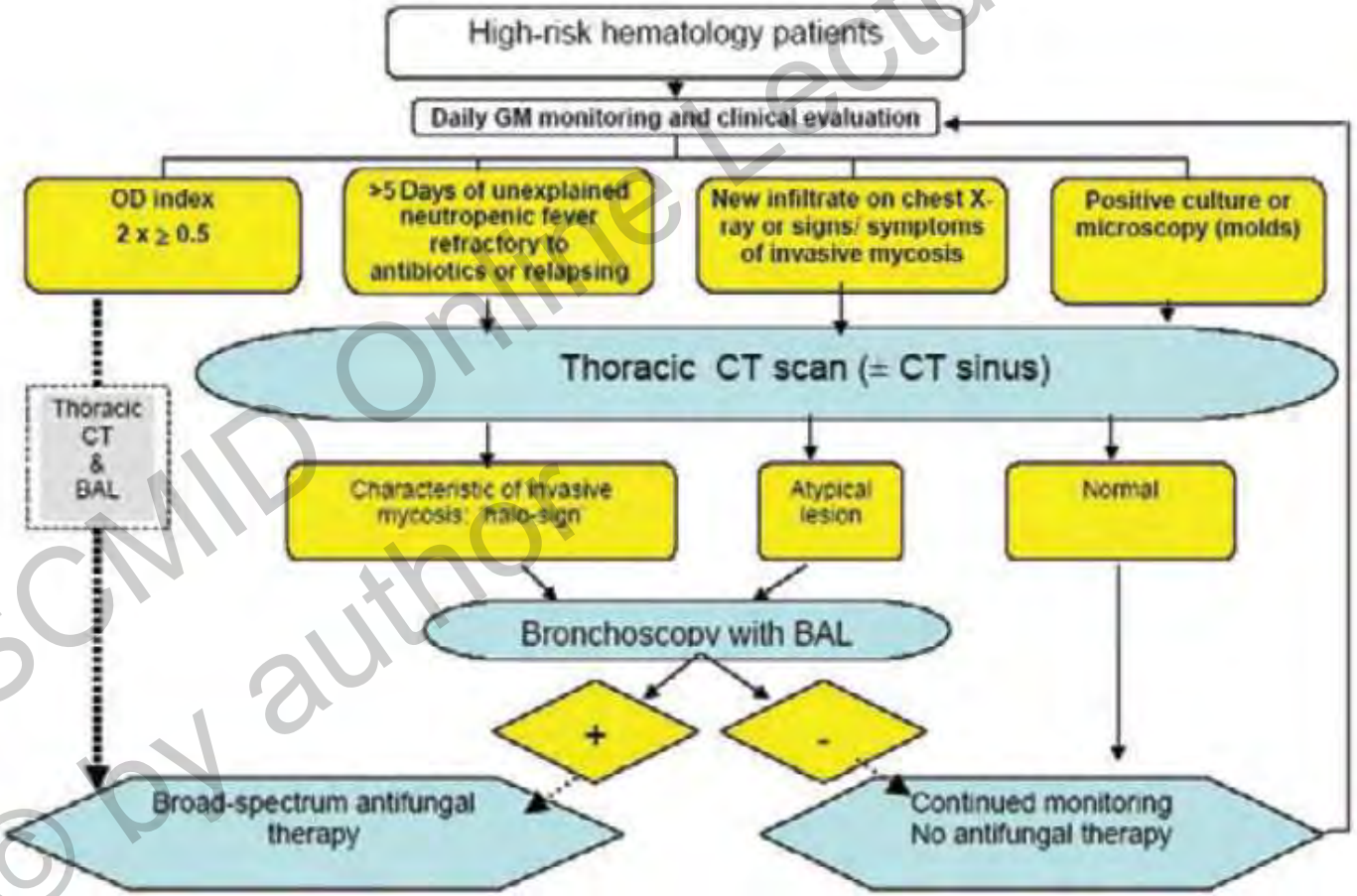
Year	N	Main author	Surveillance	Trigger in persistent fever	AT reduction	Non treated IFD
Randomised trials						
2009	293	Cordonnier C	-	Clinical signs + CT + GM	39%	1.2
2011	52	Tan BH	GM twice/week	GM (x2) or GM + CT	14%	-
2013	240	Morrissey C.O	GM + PCR twice/week	PCR or GM + CT or clinical signs + CT	52%	0
Feasibility studies						
2005	88	Maertens J	Thrice GM	Clinical signs + CT or GM	78%	2.4
2006	167	Cherif H	-	Clinical signs + CT and/or GM	76%	0
2009	53	Dignan FL	-	Clinical signs + CT	68%	0
2010	220	Girmenia C	-	Clinical signs + CT or GM	43%	1.2
2011	397	Pagano L	-	Clinical signs + CT or GM/culture	-	-
2012	85	Aguilar-Guisado	-	Clinical signs + CT or GM	38%	0

GM: galactomannan assay; CT: Computed tomography;

Galactomannan and Computed Tomography–Based Preemptive Antifungal Therapy in Neutropenic Patients at High Risk for Invasive Fungal Infection: A Prospective Feasibility Study

Clinical Infectious Diseases 2005; 41:1242–50

Johan Maertens,[1] Koen Theunissen,[1] Gregor Verhoef,[1] Johnny Verschakelen,[2] Katrien Lagrou,[3] Eric Verbeken,[4] Alexander Wilmer,[5] Jan Verhaegen,[3] Marc Boogaerts,[1] and Johan Van Eldere[3]



Empirical versus Preemptive Antifungal Therapy for High-Risk, Febrile, Neutropenic Patients: A Randomized, Controlled Trial

Clinical Infectious Diseases 2009; 48:1042–51

Catherine Cordonnier,[1] Cécile Pautas,[1] Sébastien Maury,[1] Anne Vekhoff,[4] Hassan Farhat,[11] Felipe Suarez,[5] Nathalie Dhédin,[6] Francoise Isnard,[7] Lionel Ades,[12] Frédérique Kuhnowski,[8] Françoise Foulet,[2] Mathieu Kuentz,[1] Patrick Maison,[3] Stéphane Bretagne,[2] and Michaël Schwarzinger[9,10]

Table 2. Efficacy end points in the intention-to-treat population (n = 293).

Efficacy end point	Empirical treatment arm (n = 150)	Preemptive treatment arm (n = 143)	Difference (95% CI)	P[a]
Primary				
Alive at study completion	146 (97.3)	136 (95.1)	−2.2 (−5.9 to 1.4)	.31
Secondary				
IFI	4 (2.7)	13 (9.1)	−6.4 (−10.9 to −1.9)	<.02
Baseline IFI due to				
Aspergillus species	2	6	…	
Candida species	0	3	…	
Breakthrough IFI due to				
Aspergillus species	2	2	…	
Candida species	0	2	…	
IFI-related mortality	0 (0)	3 (2.1)	−2.1 (−4.1 to 0.0)	.11
Duration of temperature ≥38°C,[b] days				
Median (IQR)	13 (5–21)	12 (5–20)	…	NS
Range	1–42	1–59	…	

NOTE. Data are no. (%) of patients, unless otherwise indicated. IFI, invasive fungal infection; IQR, interquartile range; NS, not significant.

[a] By Cochran-Mantel-Haenszel test for qualitative variables; by Wilcoxon sum-rank test for skewed quantitative variables.

[b] Excludes 14 patients without fever (8 in the empirical treatment group and 6 in the preemptive treatment group).

Empirical versus Preemptive Antifungal Therapy for High-Risk, Febrile, Neutropenic Patients: A Randomized, Controlled Trial

Clinical Infectious Diseases 2009; 48:1042–51

Catherine Cordonnier,[1] Cécile Pautas,[1] Sébastien Maury,[1] Anne Vekhoff,[4] Hassan Farhat,[11] Felipe Suarez,[5] Nathalie Dhédin,[6] Francoise Isnard,[7] Lionel Ades,[12] Frédérique Kuhnowski,[8] Françoise Foulet,[2] Mathieu Kuentz,[1] Patrick Maison,[3] Stéphane Bretagne,[2] and Michaël Schwarzinger[9,10]

Table 4. Subgroup analysis of patients receiving consolidation therapy or stem cell transplantation compared with patients receiving induction therapy, in the intention-to-treat population (n = 293).

	Consolidation therapy or transplantation			Induction therapy		
End point	Empirical treatment group (n = 72)	Preemptive treatment group (n = 70)	P[a] or difference (95% CI) in efficacy outcomes	Empirical treatment group (n = 78)	Preemptive treatment group (n = 73)	P[a] or difference (95% CI) in efficacy outcomes
Duration of neutrophil count <500 neutrophils/mm^3,[b] days						
Median (IQR)	11 (9–16)	12 (10–16)	NS	26 (21–31)	26 (18–32)	NS
Range	6–41	6–39		9–69	5–57	
Alive at study completion	72 (100)	68 (97.1)	−2.9 (−6.1 to 0.4)	74 (94.9)	68 (93.2)	−1.7 (−8.0 to 4.6)
Invasive fungal infection						
All	1 (1.4)	1 (1.4)	0 (−3.3 to 3.3)	3 (3.8)	12 (16.4)	−12.6 (−20.6 to −4.6)
Due to *Aspergillus* species	1 (1.4)	1 (1.4)	NS	3 (3.8)	7 (9.6)	NS
Due to *Candida* species	0 (0)	0 (0)	NS	0 (0)	5 (6.8)	<.05
Antifungal prophylaxis	40 (55.6)	40 (57.1)	NS	23 (29.5)	29 (39.7)	NS
Antifungal treatment	28 (38.9)	13 (18.6)	<.01	64 (82.1)	43 (58.9)	<.01
Duration of fever before antifungal treatment, median days (IQR)	6 (4–8)	6 (3–13)	NS	8 (6–14)	14 (8–18)	<.05
Change in creatinine clearance (at end of study minus at baseline), mean ± SD	−3.4 ± 15.5	−3.6 ± 15.3	NS	−13.7 ± 23.8[c]	−7.8 ± 35.0	<.05
Total costs of antifungal drugs, 2005 €						
Mean ± SD	1175 ± 2615	377 ± 1319	<.02	3246 ± 4832	2528 ± 4230	<.05
Range	0–11,122	0–7500		0–20,726	0–18,500	
Length of hospital stay, mean ± SD, days	25.4 ± 6.3	25.4 ± 7.4	NS	34.8 ± 11.5	35.0 ± 10.3	NS

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; NS, not significant.

[a] By χ^2 test or Fisher's exact test for qualitative variables; by Wilcoxon rank-sum test for skewed quantitative variables.

[b] Excludes 6 patients without neutropenia (4 in the empirical treatment group—including 1 in the autologous stem cell transplant subgroup, 1 in consolidation therapy subgroup, and 2 in the induction therapy subgroup—and 2 in the preemptive treatment group, both of whom were in the induction therapy subgroup).

[c] P < .001 by the paired t test comparing changes in creatinine clearance from baseline to study completion.

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 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

April 30, 2013

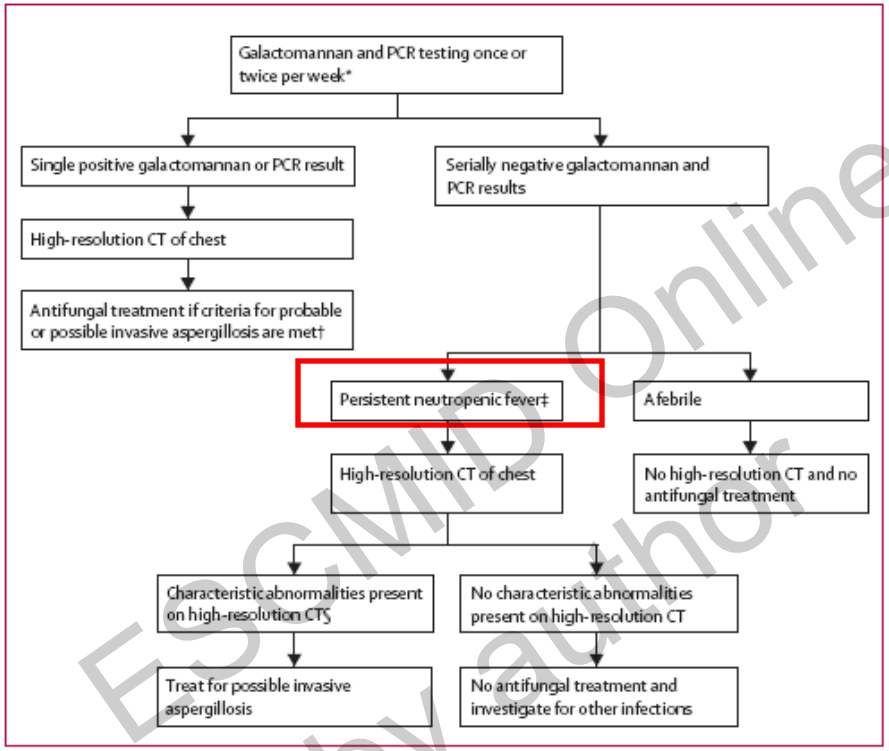


Figure 1: Diagnostic and treatment algorithm for the biomarker-based diagnostic strategy
*Frequency of testing depended on whether the patient was treated as an inpatient or an outpatient. †Irrespective of persistent neutropenic fever. ‡Despite use of broad-spectrum antibiotics and with no other cause identified. §Defined as dense, well-circumscribed lesion or lesions (larger than 1 cm diameter) with or without a halo sign, air-crescent sign, or cavity.[35]

	Standard diagnosis group (n=122)	Biomarker diagnosis group (n=118)	% difference between groups (95% CI)	p value
Received empirical treatment with antifungal drugs	39 (32%)	18 (15%)	17% (4 to 26)	0·002
Mortality				
All-cause	18 (15%)	12 (10%)	5% (−4 to 14)	0·31
Invasive aspergillosis-related	6 (5%)	3 (3%)	2% (−2·5 to 7·3)	0·5
Other invasive fungal disease-related*	0	2 (2%)	..	0·24
Incidence of invasive aspergillosis				
Proven	1 (1%)	1 (1%)	..	1·0
Probable	0	16 (14%)	−14% (−20 to −7)	<0·0001
Possible	0	6 (5%)	−5% (−9 to −1)	0·013
Incidence of other invasive fungal disease†				
Proven	4 (3%)	5 (4%)	..	0·75
Probable	0	1 (1%)	..	0·49

Data are n (%). Results for possible other invasive fungal disease are not shown because cases were not individually identified by microscopic or culture methods. * *Scedosporium prolificans* fungaemia (n=1), disseminated mucormycosis (*Rhizopus* sp; n=1). † *Candida guilliermondii* (n=1), *Candida glabrata* (n=3), *Candida krusei* (n=1), *Candida parapsilosis* (n=1), *Rhizopus* sp (n=1), *Rhizopus microsporus* (n=1), *S prolificans* (n=1), *Exserohilum* sp (n=1).

Table 2: Empirical treatment with antifungal drugs, mortality, and incidence of invasive fungal infections through 26 weeks of follow-up

Bone Marrow Transplantation (2010) 45, 159–164

www.nature.com/bmt

ORIGINAL ARTICLE

Empirical antifungal therapy in selected patients with persistent febrile neutropenia

M Aguilar-Guisado[1], I Espigado[2], E Cordero[1], M Noguer[3], R Parody[2], J Pachón[1] and JM Cisneros[1]

[1]Infectious Disease Service, Virgen del Rocio University Hospital, Seville, Spain; [2]Hematology Service, Virgen del Rocio University Hospital, Seville, Spain and [3]Oncology Service, Virgen del Rocio University Hospital, Seville, Spain

Universal antifungal therapy is not needed in persistent febrile neutropenia: a tailored diagnostic and therapeutic approach

Manuela Aguilar-Guisado,[1,2] Almudena Martín-Peña,[1,2] Ildefonso Espigado,[1,3] Maite Ruiz Pérez de Pipaon,[2] José Falantes,[3] Fátima de la Cruz,[3] and José M. Cisneros[1,2]

[1]Spanish Network for Research in Infectious Diseases, [2]Service of Infectious Diseases, Clinical Microbiology and Preventive Medicine, University Hospital Virgen del Rocío, Sevilla, Spain; [3]Hematology Service, [4]University Hospital Virgen del Rocío, Sevilla, Spain; University Hospital Virgen del Rocío/Instituto de Biomedicina de Sevilla (IBIS), Sevilla, Spain

haematologica | 2012; 97(3)

- N=85 episodes of persistent febrile neutropenia (2007-2009)
  - N=35 (41%) high risk patients
  - Antifungal prophylaxis with fluconazole (allo-SCT) or posaconazole (alo-TPH and GVHD)

Persistent febrile neutropenia (>4 days)

Step one: clinical evaluation of severity

NO ← Step one: clinical evaluation of severity → SÍ

Step two: evaluation of the focus of fever

NO ← Step two: evaluation of the focus of fever → SÍ

No antifungal therapy
Diagnostic work-up

Repeated blood cultures
GM twice a week
Thin section thorax CT
Abdominal US

No IFD/alternative diagnosis

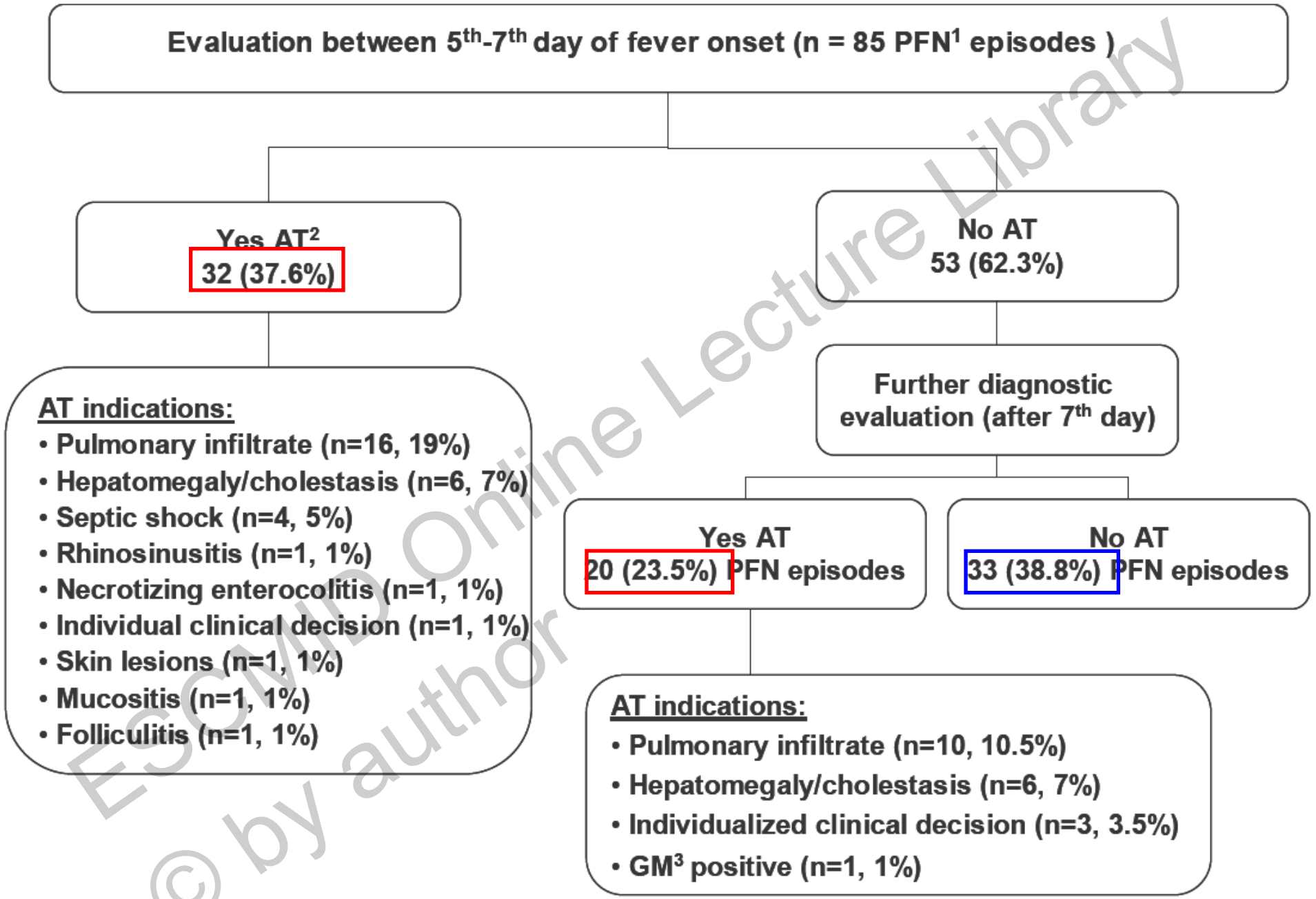
No antifungal therapy

Diagnostic-driven antifungal therapy:

Severe sepsis/ septic shock Blood cultures	Caspofungin L-Amb
Pneumonia Thoracic TSCT, BAL, GM	Voriconazole L-Amb*
Rhinosinusitis Sinus CT, rhinoscopy	Voriconazole L-Amb*
CNS Abscess Abscess biopsy	Voriconazole L-Amb*
Abdominal focus Abdominal US/ CT	Caspofungin L-Amb

Probable or proven IFD → **Targeted antifungal therapy**

Aguilar-Guisado M, Haematologica 2012



Aguilar-Guisado M, Haematologica 2012

Sensitivity and specifity of a diagnostic-driven antifungal therapy approach

Table 4. Sensitivity and specificity of the diagnostic and therapeutic approach for selecting hematology patients with persistent febrile neutropenia for antifungal therapy.

	Invasive fungal infection N.	Not invasive fungal infection N.	Total N.
Antifungal therapy	22	30	52
No antifungal therapy	0	33	33
Total	22	63	85

	Value	95% C. I. Lower limit	Upper limit
Sensitivity	100%	85.1	100
Specificity	52.4 %	40.3	64.2
Positive predictive value	42.3%	29.9	55.8
Negative predictive value	100%	89.6	100

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Aguilar-Guisado M, Haematologica 2012

Comparison of efficacy (overall succes response) of a empirical vs. a diagnostic-driven antifungal therapy approach

Table 5. Comparison of the overall success rate obtained by the diagnostic and therapeutic approach and in the clinical trial reported by Walsh *et al.*[9] in which universal empirical antifungal therapy was used.

End point	Diagnostic and therapeutic approach (Cisneros *et al.*[12]) (N. = 85)	Caspofungin (Walsh *et al.*[9]) (N. = 556)	Liposomal amphotericin B (Walsh *et al.*[9]) (N.=539)
Overall successful response, N. (%)	31 (36.5)	190 (33.9)	181 (33.7)
Components of the primary end-point			
Successful treatment of baseline proven or probable IFI[1]	9/11 (81.8)	14/27 (51.9)	7/27 (25.9)
Absence of proven or probable breakthrough IFI	84/85 (98.8)	527 (94.8)	515 (95.5)
Survival for ≥ 7 days after completion of study therapy	74/85 (87)	515 (92.6)	481 (89.2)
Resolution of fever for at least 48 h during neutropenia	36/85 (42.3)	229 (41.2)	223 (41.4)
No therapy discontinuation prematurely because of toxicity or lack of efficacy	80/85 (94.1)	449 (89.7)	461 (85.5)

Proven and probable [1]IFI: invasive fungal infections were considered.

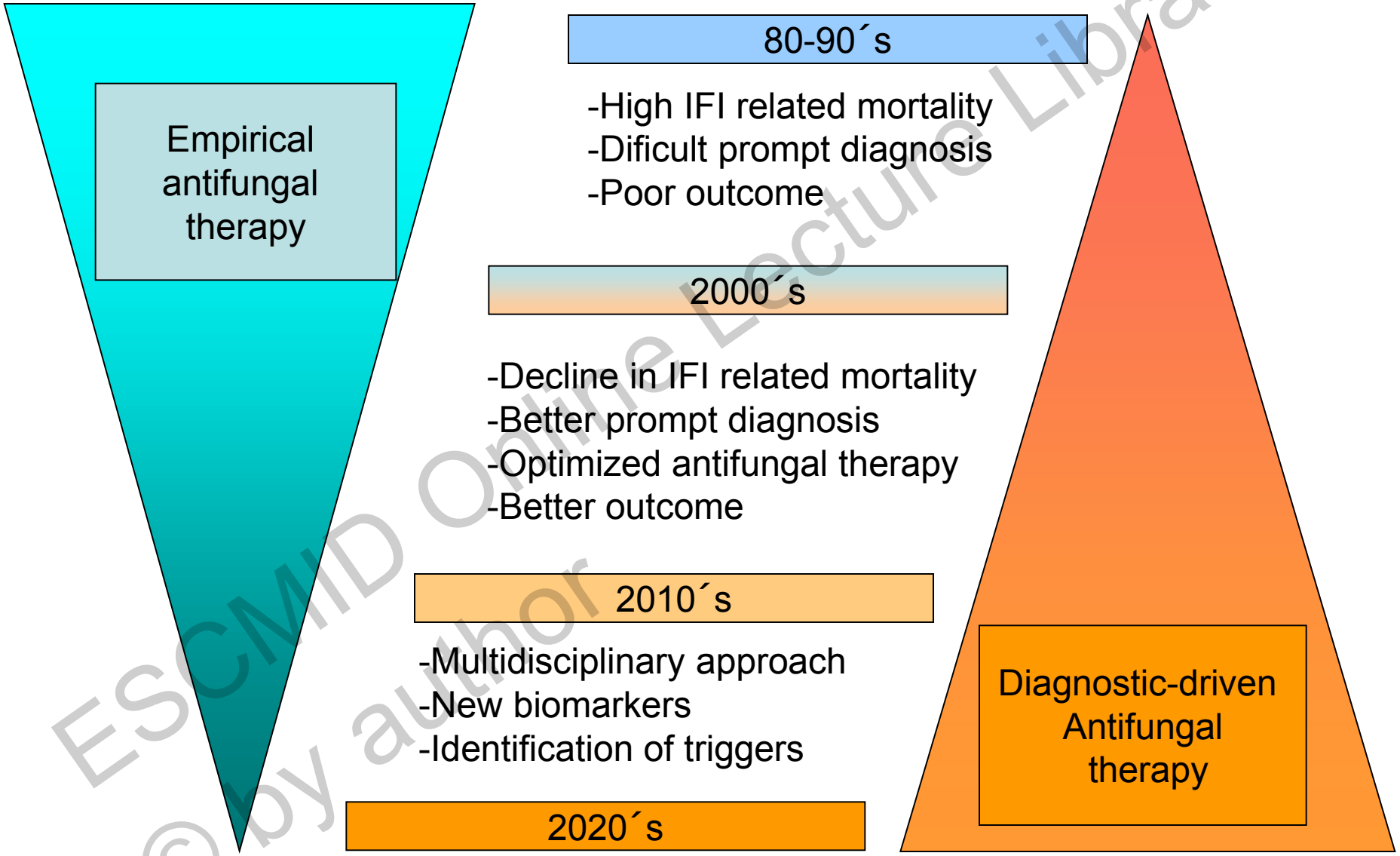
- Global mortality:
  - 15.3% (11/72)
- IFD attributable mortality
  - 2.8% (2/72)

NNT =6

NNT = 78

Aguilar-Guisado M, Haematologica 2012

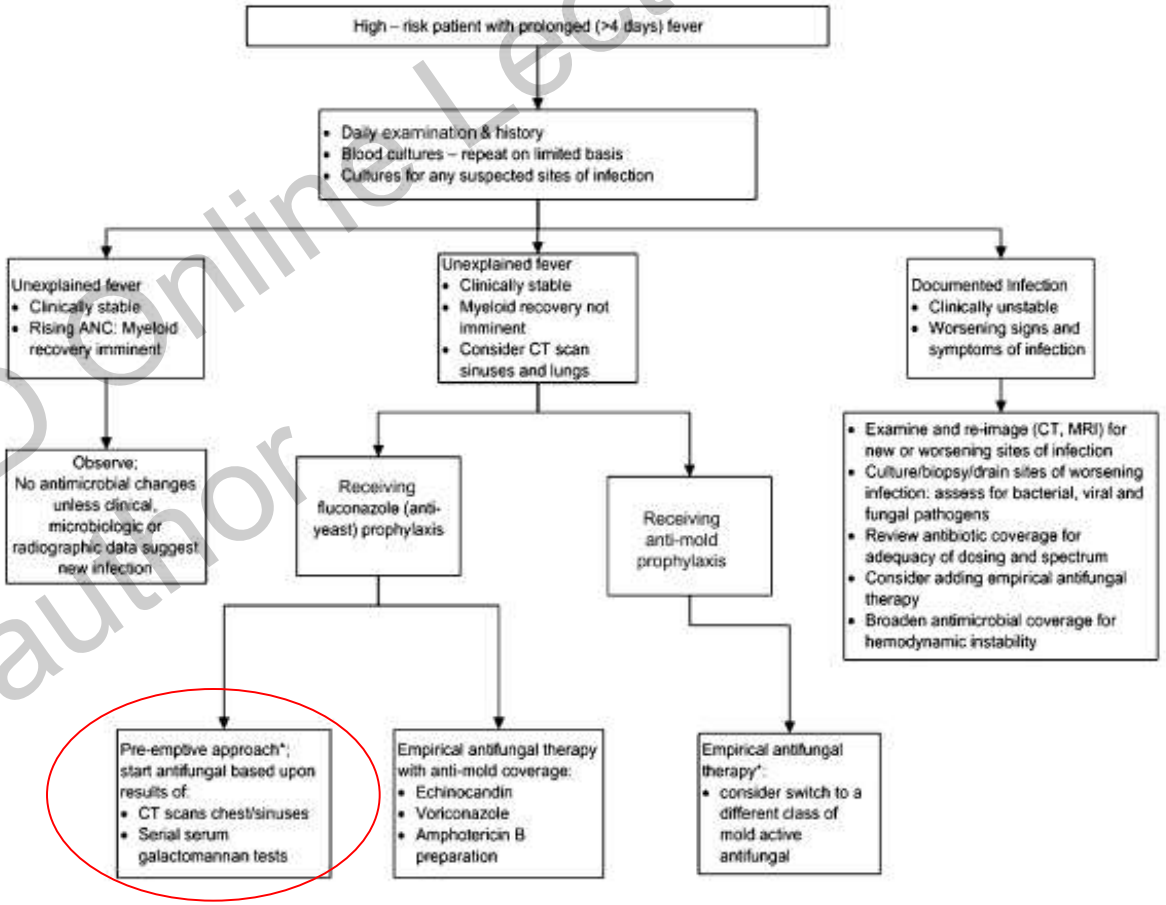
Historic scenario



Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

CID 2011:52 (15 F



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29. Preemptive antifungal management is acceptable as an alternative to empirical antifungal therapy in a subset of high-risk neutropenic patients. Those who remain febrile after 4–7 days of broad-spectrum antibiotics but are clinically stable, have no clinical or chest and sinus computed tomography (CT) signs of fungal infection, have negative serologic assay results for evidence of invasive fungal infection, and have no recovery of fungi (such as *Candida* or *Aspergillus* species) from any body site may have antifungal agents withheld (**B-II**). Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified.

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

VII. What Is the Role of Empirical or Pre-emptive Antifungal Therapy and Which Antifungal Should be Used?

Recommendations

High risk

28. Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be >7 days (A-I). Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving anti-mold prophylaxis, but switching to a different class of anti-mold antifungal that is given intravenously should be considered (**B-III**).

Triggers for DD-AT

Table 3. Entry into the empirical and diagnostic-driven pathways

Approach	Criteria
Empirical	persistent or refractory fever despite broad-spectrum antibiotics for 3–7 days and no alternative microbiological aetiology found
Diagnostic-driven	
Clinical evidence	respiratory—non-specific pulmonary infiltrates on chest X-ray, cough, chest pain, haemoptysis, dyspnoea, pleural rub or effusion
	sinonasal infection—rhinorrhoea, epistaxis, ulceration or eschar of nasal septum or hard palate, maxillary pain, periorbital swelling
	focal neurological signs or symptoms
	nodular or vesicular skin lesions
Mycological evidence	detection of galactomannan[39] or *Aspergillus* by PCR,[11] in a screening strategy (see text)

Agrawal S et al. Optimizing management of IMD. JAC 2011.

Triggers for DD-AT: clinical findings

- Clinical/radiological findings suggesting IFD (without EORCT criteria)
  - New pulmonary infiltrate not responding to antibacterial therapy
  - Rhinosinusistis, cutaneous, cerebral, hepatosplenic or gastrointestinal lesions.
- Clinical signs of “posible” IFD (EORTC criteria)
- Severe sepsis/septic shock
  - In patients not receiving antifungal profilaxis (candidemia)
- Mucositis or diarrhoea: not usually indications for AT

Girmenia C et al. “ A hematology consensus agreement on antifungal strategies for neutropenic patients with hematological malignancies and stem cell transplantation recipients” Hematological Oncology 2012

Triggers for DD-AT

Table 2. Recommended actions for triggers suggestive of IFD

Trigger	Action	Comments
Radiological signs (non-specific lung infiltrate)	diagnostic investigations [bronchoscopy, BAL, PCR[a], GM (serum/BAL fluid), culture/microscopy from tissue, tissue biopsy]	rule out bacterial, viral and non-infectious causes
Clinical symptoms (cough, chest pain, shortness of breath)	diagnostic investigations [bronchoscopy, BAL, PCR[a], GM (serum/BAL fluid), culture/microscopy, tissue biopsy]	rule out bacterial, viral and non-infectious causes
Any new lung infiltrate plus haemoptysis/chest pain/sudden respiratory deterioration/sinusitis	start antifungal therapy (continue with diagnostic investigations)	rule out bacterial, viral and non-infectious causes
New suggestive clinical symptom and radiological sign[b]	start antifungal therapy (continue with diagnostic investigations)	rule out bacterial, viral and non-infectious causes

BAL, bronchoalveolar lavage; GM, galactomannan.
[a]Where available.
[b]Other than pulmonary.

Drgona L et al, AAC 2013;68 Suppl 3:iii17-iii24.

Triggers for DD-AT: microbiological tools

- **Galactomanann** from serum or BAL
  - Two consecutive serum samples ≥0.5 or one sample >0.7, or LBA sample >1.
  - High NPV (>85%), higher sensitivity and specificity in en LBA
  - Not equivalent to antifungal therapy
- **PCR and beta-D-glucan**
  - Uncertain role until standarized and validated
- **Isolation of fungi in non-sterile site**
  - *C. tropicalis, Trichosporum, G. capitatum*
  - *Aspergillus* sp., *Scedosporium* sp., or *Fusarium* sp.

Girmenia C et al. " A hematology consensus agreement on antifungal strategies for neutropenic patients with hematological malignancies and stem cell transplantation recipients" Hematological Oncology 2012

Choice of antifungal drug

- No specific indication: according to clinical presentation
  - Pulmonary infiltrate, rhinosinusitis or CNS involvement with negative microbiological exams:
    - *Aspergillus* sp. or mucorales: AmB-L
  - Pulmonary infiltrate or rhinosinusitis with positive galactomanann:
    - *Aspergillus* sp.: voriconazole (alternative: AmB-L)
  - Enterocolitis:
    - Mostly yeast: echinocandin (alternative fluconazole or AmB-L)
  - Non-focused fever and positive galactomanann:
    - *Aspergillus* sp.: voriconazole (alternative: AmB-L)
    - While continuing diagnostic efforts

Girmenia C et al. " A hematology consensus agreement on antifungal strategies for neutropenic patients with hematological malignancies and stem cell transplantation recipients" Hematological Oncology 2012

DD-AT: cost-effectiveness

- The selection of antifungal therapy approaches should consider also **economic consequences**
- Several **pharmacoeconomic analyses** comparing diverse **antifungal drugs in EAT indication**
  - Most comparing either caspofungin or voriconazole with L-Amb
  - Methodological limitations not allowing generalization
  - Drug adquisition costs: not best guide to choose the most cost-effective antifungal therapy

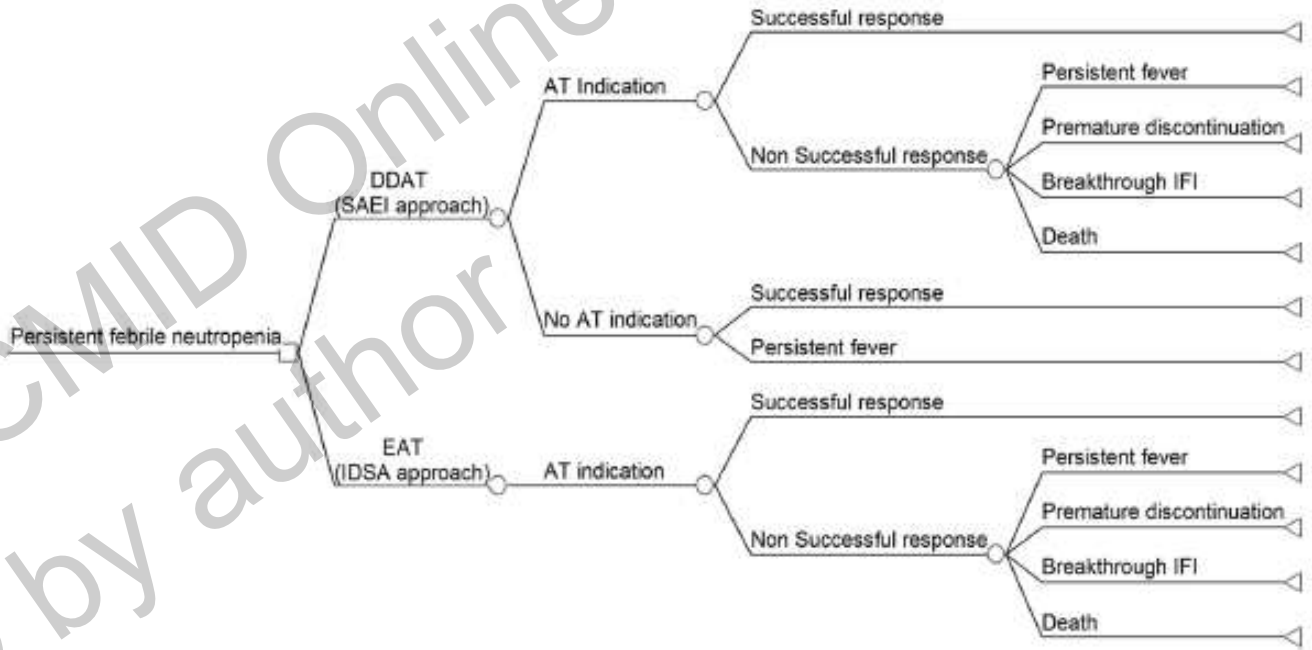
– Scarce information about cost-effectiveness assessment **comparing** DD-AT with standard approach

Turner S.J, Expert Rev Pharmacoecon Outconmes Res, 2013

DD-AT: cost-effectiveness

Cost-Effectiveness Analysis Comparing Two Approaches for Empirical Antifungal Therapy in Hematological Patients with Persistent Febrile Neutropenia

Almudena Martín-Peña,[a,b] M. Victoria Gil-Navarro,[c] Manuela Aguilar-Guisado,[a,b] Ildefonso Espigado,[b,d] Maite Ruiz Pérez de Pipaón,[a,b] José Falantes,[d] Jerónimo Pachón,[e] José M. Cisneros[a,b]



Martín-Peña et al. AAC 2013

DD-AT: cost-effectiveness

TABLE 5 Proportional costs of both approaches to manage persistent febrile neutropenia in a hematological patient

	DDAT approach[b]			Standard approach[c]		
Therapy outcome[a]	Proportion (%)	Cost (€)/patient	Weighted cost (€)	Proportion (%)	Cost (€)/patient	Weighted cost (€)
Overall successful response	36.5	8,309	3,033	33.9	11,692	3,964
Successful response with EAT	17. 2	10,845	1,911	33.9	11,692	3,964
Successful response without EAT	18.81	5,964	1,122			
Overall failure response	63.5	13,976	8,875	66.1	20,915	13,825
Failure response with EAT	43.57	17,635	7,683	66.1	20,915	13,825
Death	12.9	10,288	1,327	9.04	11,726	1,060
Breakthrough IFI	1.17	17,575	207	4.84	22,390	1,084
Premature discontinuation	8.23	20,669	1,701	19.91	22,339	4,448
Persistent fever	21.18	20,963	4,440	32.33	22,394	7,240
Failure response without AT	19.98	5,964	1,191			
Total cost per patient			11,910			17,789

Table 7. Cost/effectiveness analysis.

	DD-AT approach	Standard approach
Cost, €	11,910	17,789
Δ Cost, €	-	5880
Effectiveness	36.5	33.9
Δ effectiveness	-	-2.6
Cost/ effectiveness	32,750	52,555
Δ C/ E	dominant	dominated

Martín-Peña et al. AAC 2013

DD-AT: requirements

- **Availability** of diagnostic test and minimun expectations in radiology, histopathology and microbiology.
- **Written local clinical pathways** (guidelines translation into standarized local clinical practice) specifying timelines
- **Strict adherence** to predefined and consensual diagnostic and therapeutic algortihms.
- Full **cooperation of nursing and medical team** looking after the patient: **hematologists, infectiuos diseases specialists, microbiologists, radiologists, nurses and pharmacists**
- Appropiated **equipment and expertise**

Agrawal S et al. Optimizing management of IMD. JAC 2011.

DD-AT: requirements

Figure 1. Diagram of the key members of the IFD-MDT.

Ben-Ami R et al. MDT approach to IMD management. JAC 2011.

Conclusions

1. Current evidence support an individualized, multidisciplinary, **diagnostic-driven approach: efficacy, safety and cost-effectiveness**
   - Design an approach taking into account center features and epidemiology, to be applicable locally
   - Start antifungal therapy following the triggers of this approach while awaiting the results of a comprehensive diagnostic work-up
   - Decide whether to stop, change or continue that treatment depending upon the results

2. **Empirical therapy** should be continued in centers in which appropiate **diagnostic procedures are not available** or not well organized.

For the future

- Prospective, randomised comparative multicenter study is ongoing (by the ID group of the EORTC)
  - Diagnostic driven *vs*. empirical approach
  - Predefined antifungal therapy and endpoint (overall survival).
- Better identification of individual risk factors for IFD including genetic profile
- Improve early diagnosis of occult IFD (laboratory and imaging studies)
- Increase the specificity of DD-AT approaches

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