



UFCSPA

Universidade Federal de Ciências da Saúde
de Porto Alegre



6th ADVANCES AGAINST ASPERGILLOSIS

Madrid, Spain
27 Feb – 1 March 2014

Meliá Castilla Conference
and Convention Centre



Treatment of infections by cryptic *Aspergillus* species

Alessandro C. Pasqualotto

Porto Alegre, Brazil

Pre-Advances Against Aspergillosis Workshop:
Aspergillus Speciation in the 21st Century -
Implications for Laboratory and Clinical Practice

Disclosures

- Research grants
 - ✓ Pfizer, Gilead, MSD
- Speaker honoraria, advisory board
 - ✓ Pfizer, Gilead, MSD, Astellas

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 - ✓ Pfizer, Gilead, MSD, Astellas
- Intellectual conflict of interest
 - ✓ We should treat the patient, not the bug

The challenge



The challenge

cryptic aspergillus treatme x

www.ncbi.nlm.nih.gov/pubmed/?term=cryptic+aspergillus+treatment

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Results: 10

- [Population-based survey of filamentous fungi and antifungal resistance in Spain \(FILPOP Study\)](#)
 - Alastruey-Izquierdo A, Mellado E, Peláez T, Pemán J, Zapico S, Alvarez M, Rodríguez-Tudela JL, Cuenca-Estrella M; FILPOP Study Group. *Antimicrob Agents Chemother.* 2013 Jul;57(7):3380-7. doi: 10.1128/AAC.00383-13. Epub 2013 May 13. PMID: 23669377 [PubMed - indexed for MEDLINE] [Free PMC Article](#) [Related citations](#)
 - [Is azole resistance in *Aspergillus fumigatus* a problem in Spain?](#)
 - Escribano P, Peláez T, Muñoz P, Bouza E, Guinea J. *Antimicrob Agents Chemother.* 2013 Jun;57(6):2815-20. doi: 10.1128/AAC.02487-12. Epub 2013 Apr 29. PMID: 23629706 [PubMed - indexed for MEDLINE] [Free PMC Article](#) [Related citations](#)
 - [Azole resistance in *Aspergillus fumigatus* from bronchoalveolar lavage fluid samples of patients with chronic diseases](#)
 - Zhao Y, Stensvold CR, Perlin DS, Arendrup MC. *J Antimicrob Chemother.* 2013 Jul;68(7):1497-504. doi: 10.1093/jac/dkt071. Epub 2013 Mar 5. PMID: 23463213 [PubMed - indexed for MEDLINE] [Related citations](#)
 - [Current section and species complex concepts in *Aspergillus*: recommendations for routine daily practice](#)
 - Alastruey-Izquierdo A, Mellado E, Cuenca-Estrella M. *Ann N Y Acad Sci.* 2012 Dec;1273:18-24. doi: 10.1111/j.1749-6632.2012.06822.x. PMID: 23230833 [PubMed - indexed for MEDLINE] [Related citations](#)

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Try the new Display Settings option - Sort by Relevance

3 free full-text articles in PubMed Central
Population-based survey of filamentous fungi and antifungal r [Antimicrob Agents Chemother. 2013]
Is azole resistance in *Aspergillus fumigatus* a problem in [Antimicrob Agents Chemother. 2013]
Cryptic species and azole resistance in the *Aspergillus* [Antimicrob Agents Chemother. 2011]
[See all \(3\)...](#)

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Maybe unpublished data

The screenshot shows a web browser window with the URL www.aspergillus.org.uk/indexhome.htm?secure/conferences/confabstracts/inputform.php~main. The page features a blue header with navigation links: Site Updates, Home Page, Address Book, and Site Information. Logos for Pfizer (Site sponsor) and Fungal Infection Trust are present. A left sidebar contains menu items: Patient Information, Medical Information, Scientific Information, Educational Materials, Image Bank, Register Here, Library, Useful Links, and Search. The main content area is titled "Conference abstracts" and includes a "Searchable Conference Abstracts Database" section. This section has a Google Custom Search box and a "Simple Search" form with fields for Author(s), Keyword(s) (containing "cryptic"), and Choose conference (set to "Any (includes those not listed below)"). A "GO" button is at the bottom of the search form. A "Search tips" box on the left explains search syntax: % matches any string of characters (e.g., Frank% matches Frank, Franklin, Frankie); %ank matches Bank and plank; and _ matches any single character (e.g., c_t matches cat, cot, cut). An "ADD THIS" button is at the bottom of the tips box.

Nope ...

Aspergillus/Aspergillosis x

www.aspergillus.org.uk/indexhome.htm?secure/conferences/confabstracts/inputform.php~main

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Conference Abstract Search

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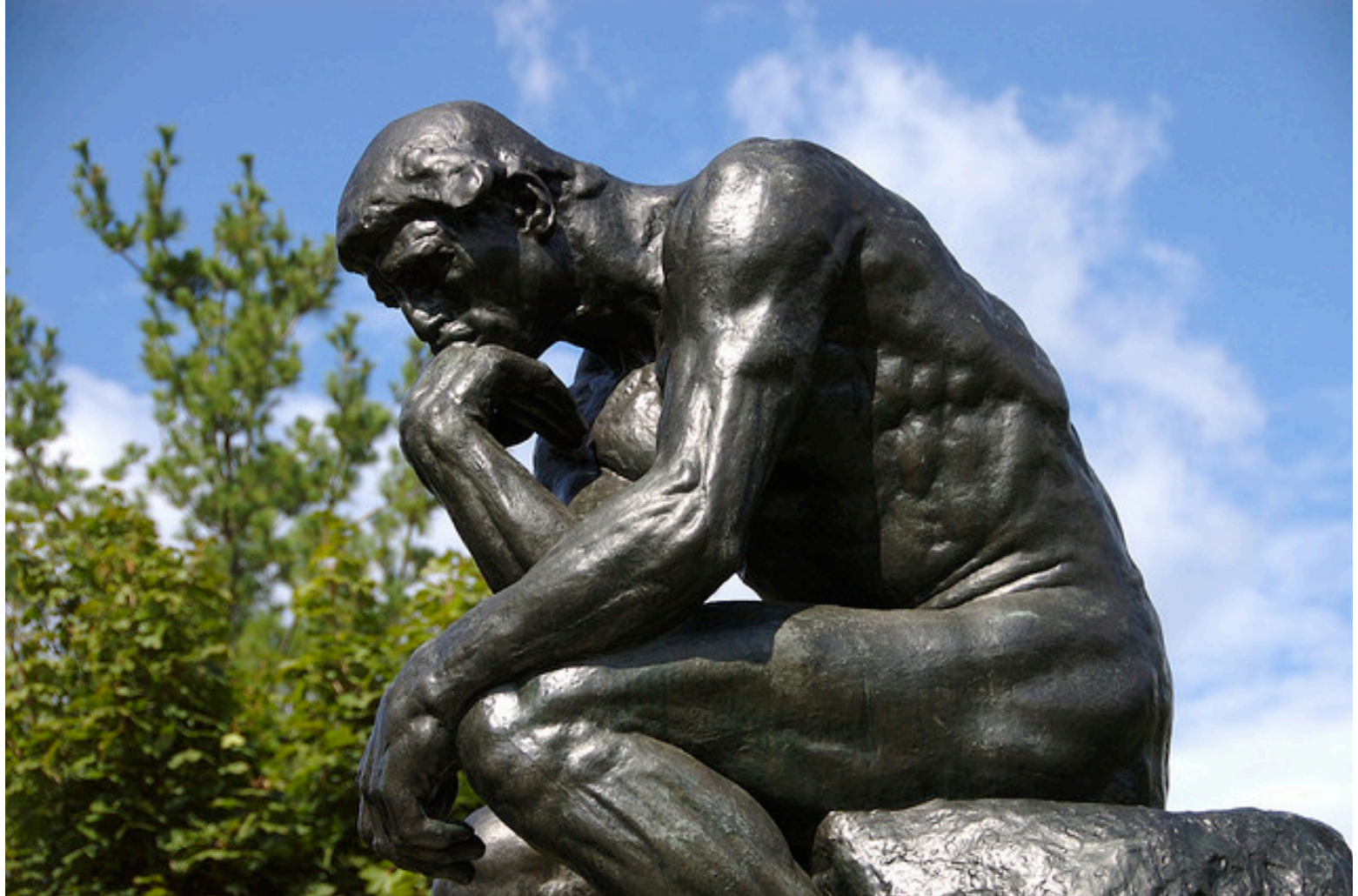
[Next](#) | [Last](#)

Conference Proceedings
27th Fungal Genetics Conference (FGC, 27th)
E. Kunitake, S. Tani, J. Sumitani, T. Kawaguchi
2013
Reference ID = 19126
424: ClbR and its paralog, ClbR2, regulate gene expression of cellulase genes in response to cellobiose in <i>Aspergillus aculeatus</i>.
The cellobiose- and cellulose-responsive induction of the cellobiohydrolase I (cbhI) and carboxymethylcellulase 2 (cmc2) genes is not regulated by XlnR, a Zn(II)2Cys6 transcriptional activator, in <i>Aspergillus aculeatus</i> . We have identified a novel activator containing a Zn(II)2Cys6 binuclear cluster motif designated as cellobiose-response regulator (ClbR), and which is not homologous to Clr-2/ClrB, a transcriptional activator controlling cellobiose-responsive induction in <i>Neurospora crassa</i> and <i>Aspergillus nidulans</i> . Interestingly ClbR regulates not only the expression of cbhI and cmc2 but also genes regulated by

So I felt in trouble



Worlds came to my mind



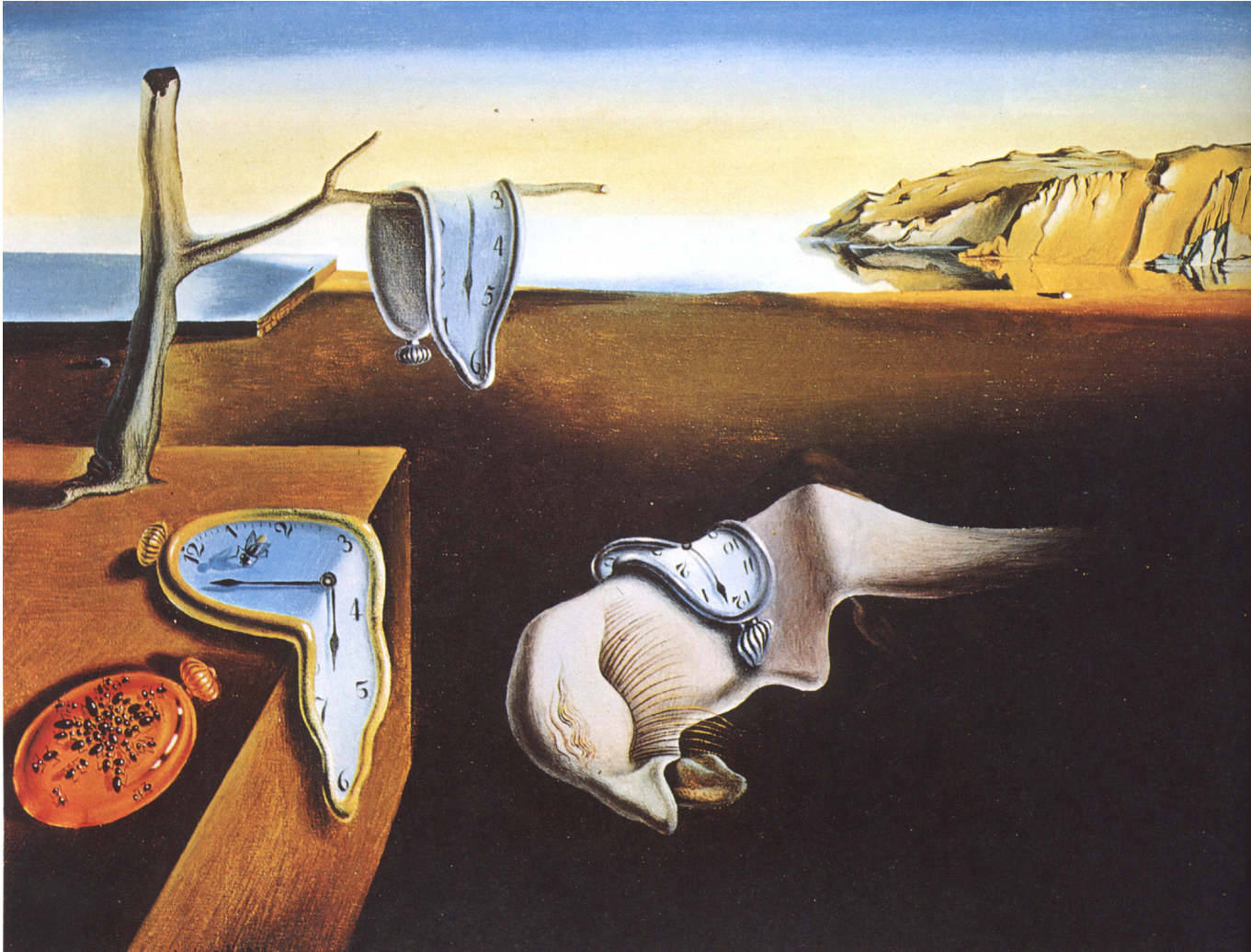
Like 'Nothing'



'Emptiness'



'Unreality'



'Desolation'



More and more confused

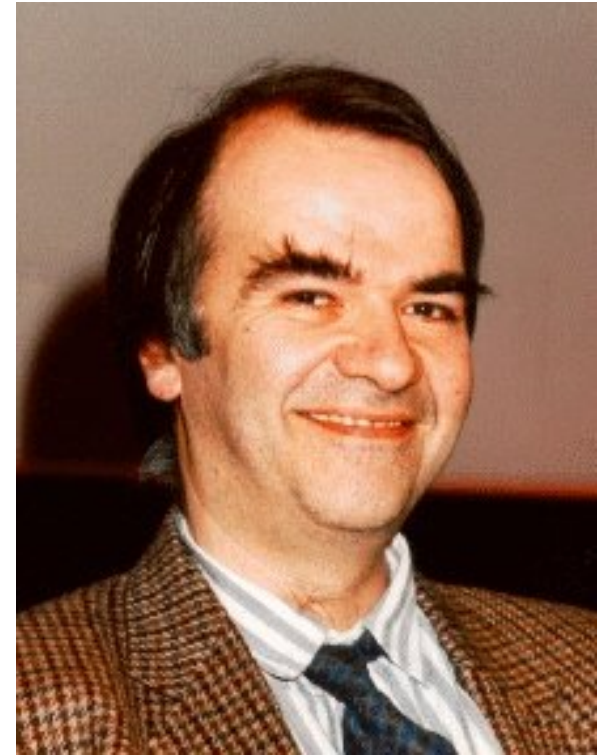
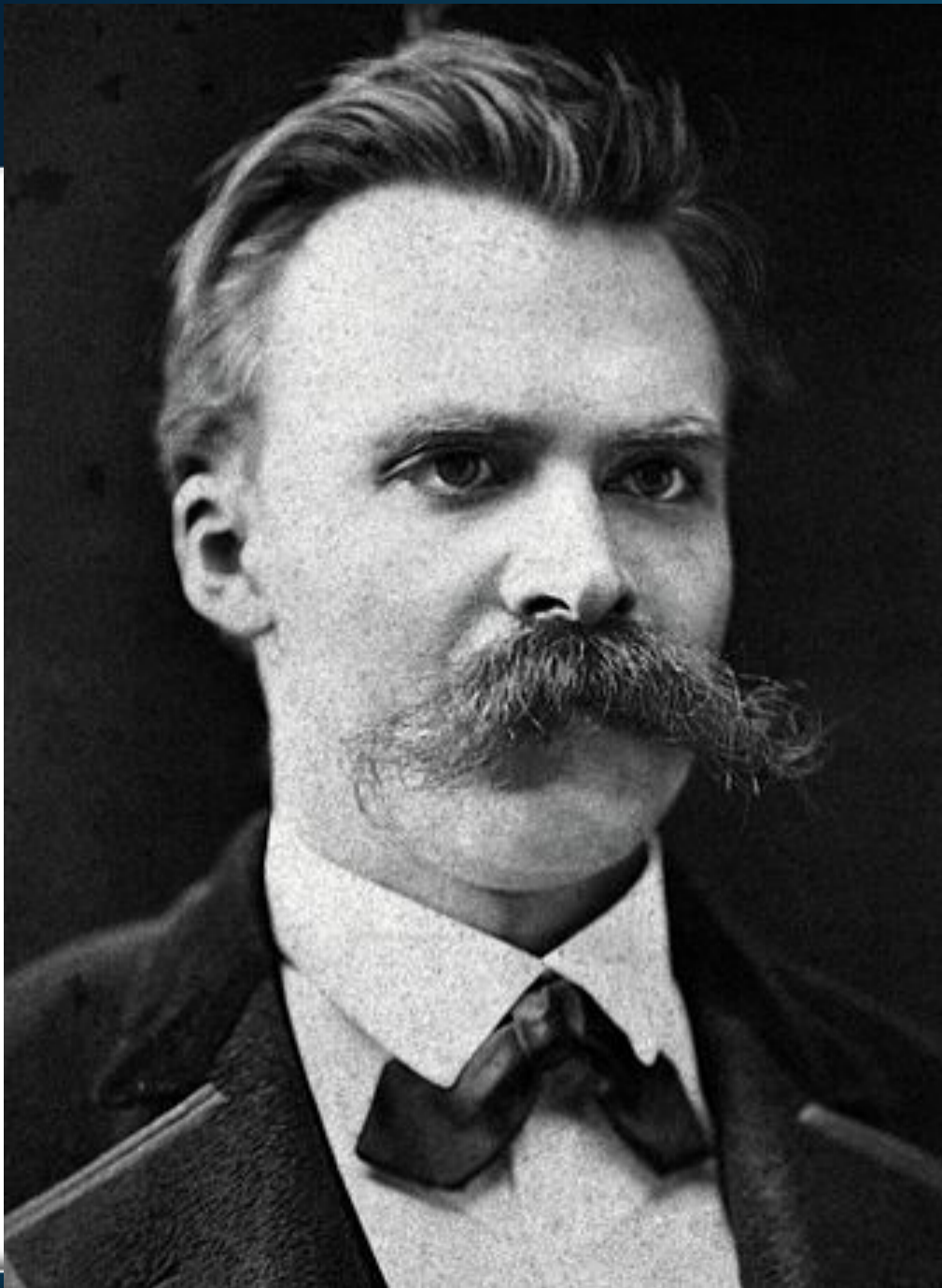


That is Nihilism!

- Philosophical doctrine
- Negation of one or more putatively meaningful aspects of life

That is Nihilism!

- Philosophical doctrine
- Negation of one or more putatively meaningful aspects of life
- Sometimes used to explain the general mood of despair at a perceived pointlessness of existence



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What are we talking about?

- Cryptic species within main sections

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- It all started with *A. lentulus*
 - ✓ Poorly sporulating variant of *A. fumigatus*
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 - ✓ New species (n=4) – characterized by MLST
- Followed by reports in different geographical regions and from environmental samples

More on *A. lentulus*

A Case Report on *Aspergillus lentulus* Pneumonia

Şaban Gürcan¹, Melek Tikveşli¹, Sedat Üstündağ², Beyza Ener³

¹Department of Medical Microbiology, Trakya University Faculty of Medicine, Edirne, Turkey

²Department of Nephrology, Trakya University Faculty of Medicine, Edirne, Turkey

³Department of Medical Microbiology, Uludağ University Faculty of Medicine, Bursa, Turkey

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- 36 yr-old man, renal transplant patient
 - ✓ Pneumonia 4 months after transplant
 - ✓ *A. lentulus* on sputum

More on *A. lentulus*

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- 36 yr-old man, renal transplant patient
 - ✓ Pneumonia 4 months after transplant
 - ✓ *A. lentulus* on sputum
 - ✓ “Patient recovered on voriconazole” (MIC of 0.5 µg/ml)

More on *A. lentulus*

Table 1. Characteristics of some cases with colonisation or infection caused by *Aspergillus lentulus* in the literature

Underlying disease	Infection/ Colonisation	Immunosuppressive therapy history	Isolation sample	Reference
Chronic obstructive pulmonary disease (COPD)	Exacerbation of COPD	Yes	Bronchial aspirate	Alhambra et al. (3)
4 haematopoietic stem cell transplant recipients	Invasive aspergillosis	No data	Not data	Balajee et al. (9)
Arterial hypertension and end-stage chronic kidney disease	Pneumonia	Yes	Bronchoalveolar lavage fluid (BAL)	Montenegro et al. (8)
Cystic fibrosis	Colonisation of the airways	No	Sputum	Symoens et al. (13)
Heart transplantation for ischaemic cardiomyopathy	Pneumonia	Yes	1 BAL, 1 sputum, and 2 tracheal bronchial secretions	Zbinden et al. (14)
Renal transplant recipient	Pneumonia	Yes	Sputum	The present study

Neosartorya pseudofischeri

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2005, p. 5996–5999
0095-1137/05/\$08.00+0 doi:10.1128/JCM.43.12.5996–5999.2005
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Vol. 43, No. 12

Mistaken Identity: *Neosartorya pseudofischeri* and Its Anamorph Masquerading as *Aspergillus fumigatus*

S. Arunmozhi Balajee,¹ Jennifer Gribskov,¹ Mary Brandt,² James Ito,³
Annette Fothergill,⁴ and Kieren A. Marr^{1,5*}

*Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle, Washington*¹; *Centers for Disease Control and Prevention, Atlanta, Georgia*²; *City of Hope Medical Center, Duarte, California*³; *Fungus Testing Laboratory, University of Texas Health Science Center at San Antonio, San Antonio, Texas*⁴; and *Departments of Medicine and Microbiology, University of Washington, Seattle, Washington*⁵

Neosartorya pseudofischeri

- Authors were actually searching for *A. lentulus*
 - ✓ Three poorly sporulating isolates

Neosartorya pseudofischeri

- Authors were actually searching for *A. lentulus*
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- Very limited data for these 3 patients
 - ✓ HSCT → ABLC followed by vori plus caspo
 - ✓ Died due to progressive leukaemia

Neosartorya pseudofischeri

- Authors were actually searching for *A. lentulus*
 - ✓ Three poorly sporulating isolates
- Very limited data for these 3 patients
 - ✓ HSCT → ABLC followed by vorinostat plus caspofungin
 - ✓ Died due to progressive leukaemia
 - ✓ 2 patients with cystic fibrosis (sputum)

Neosartorya pseudofischeri

- Literature review

TABLE 1. *N. pseudofischeri* as a cause of invasive disease

Yr	Disease	Treatment	Outcome
1929	Sputum from patient with lung disease	NK ^a	NK
1971	Invasive aspergillosis	NK	NK
1990	Mycotic keratitis	Ketoconazole	Evisceration of the eye
1992	Graft-related endocarditis	Amphotericin B	Progression of disease, death
1994	Osteomyelitis	NK	NK
2002	Peritonitis	Liposomal amphotericin, itraconazole	Resolution
2004	Invasive aspergillosis	Amphotericin B	Resolution

^a NK, not known.

Neosartorya pseudofischeri

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^a NK, not known.

What can we learn from that?

Much more is known by now

A. lentulus

A. udagawae

A. viridinutans

A. fumigatiaffinis

A. novofumigatus

N. pseudofischeri

Fumigati section

Much more is known by now

A. alliaceus

Flavi

A. carneus
A. alabamensis

Terrei

A. tubingensis
A. awamori
A. acidus

Nigri

A. sydowii

Versicolores

A. westerdijkiae
A. persii

Circumdati

A. calidoustus
A. insuetus
A. keveii

Usti

How to identify them?

How to identify them?

- Fungal DNA sequencing!

Balajee SA, *et al.* J Clin Microbiol 2005; 43: 5996-9

Hong SB, *et al.* Mycologia 2005; 97: 1316-29

Balajee SA, *et al.* J Clin Microbiol 2009; 47: 877-84

Alastruey-Izquierdo A, *et al.* Antimicrob Agents Chemoter 2013; 57: 3380-7

How to identify them?

- Fungal DNA sequencing!
- ITS sequencing
 - ✓ Identification at the complex level

Balajee SA, *et al.* J Clin Microbiol 2005; 43: 5996-9

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How to identify them?

- Fungal DNA sequencing!
- ITS sequencing
 - ✓ Identification at the complex level
- Sequencing of other targets
 - ✓ Beta-tubulin / Calmodulin / Rodlet A genes

Balajee SA, *et al.* J Clin Microbiol 2005; 43: 5996-9

Hong SB, *et al.* Mycologia 2005; 97: 1316-29

Balajee SA, *et al.* J Clin Microbiol 2009; 47: 877-84

Alastruey-Izquierdo A, *et al.* Antimicrob Agents Chemoter 2013; 57: 3380-7

Are they frequent?

Are they frequent?

- Apparently not

Are they frequent?

MAJOR ARTICLE

Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Trial Comparing a High–Loading Dose Regimen with Standard Dosing (AmBiLoad Trial)

Oliver A. Cornely, Johan Maertens, Mark Bresnik, Ramin Ebrahimi, Andrew J. Ullmann, Emilio Bouza, Claus Peter Heussel, Olivier Lortholary, Christina Rieger, Angelika Boehme, Mickael Aoun, Heinz-August Horst, Anne Thiebaut, Markus Ruhnke, Dietmar Reichert, Nicola Vianelli, Stefan W. Krause, Eduardo Olavarria, and Raoul Herbrecht, for the AmBiLoad Trial Study Group^a

Cornely OA, *et al.* Clin Infect Dis 2007; 44: 1289-97

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We just can't say ...

Table 1. Characteristics of patients in a study of liposomal amphotericin B as initial therapy for invasive mold infection.

Characteristic	Liposomal amphotericin B dosage	
	3 mg/kg per day (n = 107)	10 mg/kg per day (n = 94)
Invasive aspergillosis		
Microbiologically confirmed	41 (38)	36 (38)
Halo sign on CT only ^{f,g}	62 (58)	56 (60)
Microbiologic criteria		
<i>Aspergillus</i> antigen only ^h	27 (25)	18 (19)
Culture and/or histologic findings only	14 (13)	16 (17)

In the more recent series

Medical Mycology February 2013, **51**, 128–135

informa
healthcare

Antifungal therapy and length of hospitalization in transplant patients with invasive aspergillosis

JOHN W. BADDLEY*, DAVID R. ANDES†, KIEREN A. MARR‡, CAROL A. KAUFFMAN§, DIMITRIOS P. KONTOYIANNIS#, JAMES I. ITO^, MINDY G. SCHUSTER\$, KYLE D. BRIZENDINE*, THOMAS F. PATTERSON@, G. MARSHALL LYON +, MICHAEL BOECKH&, ROBERT A. OSTER*, TOM CHILLER% & PETER G. PAPPAS*

**Department of Medicine, University of Alabama at Birmingham and Birmingham VA Medical Center, Birmingham, Alabama,*

†Department of Medicine, University of Wisconsin, Madison, Wisconsin, ‡Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, §Department of Medicine, University of Michigan and Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan, #Department of Medicine, MD Anderson Cancer Research Center, Houston, Texas,

^Department of Medicine, City of Hope National Medical Center, Los Angeles, California, \$Department of Medicine,

University of Pennsylvania, Philadelphia, Pennsylvania, @Department of Medicine, University of Texas Health Science Center and South Texas Veterans Healthcare System, San Antonio, Texas, + Department of Medicine, Emory University, Atlanta, Georgia,

&Department of Medicine, Fred Hutchinson Cancer Research Center, Seattle, Washington, and %Mycotic Diseases Branch, Centers for Disease Control, Atlanta, Georgia, USA

Baddley JW, *et al.* *Med Mycol* 2013; 51: 128-35

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In the more recent series

Table 1 Characteristics of 361 transplant patients with IA.

Characteristic	Total (%) N = 361	HSCT N = 228	SOT N = 133
Mean age ¹ (\pm SD)	49 \pm 14.7	46.1 \pm 14.9	54.1 \pm 12.7
Male sex	218/359 (60.7)	142 (62.3)	76/131 (58)
White race	297/332 (89.5)	185/205 (90.2)	112/127 (88.2)
Mortality at 6 weeks	114/358 (31.8)	82/225 (36.4)	32 (24.1)
Mortality at 12 weeks	173/358 (48.3)	129/225 (57.3)	44/133 (33.1)
Mean length-of-stay (days) ²	35.3 \pm 39.5	38.7 \pm 43.6	29.7 \pm 30.9
Mean length-of-stay in ICU (days) ³	7.6 \pm 15.4	5.1 \pm 11.6	11.8 \pm 19.6
Length of stay \geq 30 days	133/324 (41.0)	92/201 (45.8)	41/123 (33.3)
Time to IA (mean days \pm SD)	378.6 \pm 836.3	248.5 \pm 637.8	598.8 \pm 1060.0
Time to IA (median days)	101	88	152
Proven IA (vs. probable)	101 (28)	50 (21.9)	51 (38.4)
<i>Aspergillus fumigatus</i>	182 (50.4)	101 (44.3)	81 (60.9)

“etiologic Aspergillus species data were collected”

Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database

Dimitrios P. Kontoyiannis, Kieren A. Marr, Benjamin J. Park, Barbara D. Alexander, Elias J. Anaissie, Thomas J. Walsh, James Ito, David R. Andes, John W. Baddley, Janice M. Brown, Lisa M. Brumble, Alison G. Freifeld, Susan Hadley, Loreen A. Herwaldt, Carol A. Kauffman, Katherine Knapp, G. Marshall Lyon, Vicki A. Morrison, Genovefa Papanicolaou, Thomas F. Patterson, Trish M. Perl, Mindy G. Schuster, Randall Walker, Kathleen A. Wannemuehler, John R. Wingard, Tom M. Chiller, and Peter G. Pappas^a

TRANSNET data (1)

Table 1. Characteristics of Hematopoietic Stem Cell Transplant (HSCT) Recipients Who Developed ≥ 1 Invasive Fungal Infection (IFI) and a Description of All IFI Cases

Variable	Surveillance cohort	Incidence cohort
Invasive aspergillosis	425 (43)	301 (42)
<i>Aspergillus fumigatus</i>	187 (44)	134 (45)
<i>Aspergillus terreus</i>	22 (5)	17 (6)
<i>Aspergillus niger</i>	36 (9)	26 (9)
<i>Aspergillus flavus</i>	31 (7)	25 (8)
Multiple <i>Aspergillus</i> species	27 (6)	17 (6)
Other <i>Aspergillus</i> species	13 (3)	12 (4)
Unspecified <i>Aspergillus</i> species	109 (26)	70 (23)

“Species identification was performed using routine methods at the local laboratories ... species identification was confirmed at the CDC ...”

TRANSNET data (2)

MAJOR ARTICLE

Invasive Fungal Infections among Organ Transplant Recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET)

Peter G. Pappas, Barbara D. Alexander, David R. Andes, Susan Hadley, Carol A. Kauffman, Alison Freifeld, Elias J. Anaissie, Lisa M. Brumble, Loreen Herwaldt, James Ito, Dimitrios P. Kontoyiannis, G. Marshall Lyon, Kieren A. Marr, Vicki A. Morrison, Benjamin J. Park, Thomas F. Patterson, Trish M. Perl, Robert A. Oster, Mindy G. Schuster, Randall Walker, Thomas J. Walsh, Kathleen A. Wannemuehler, and Tom M. Chiller^a

TRANSNET data (2)

Table 1. Demographic Characteristics and Description of Invasive Fungal Infections (IFIs) Detected in the Transplant-Associated Infection Surveillance Network, 2001–2005

Variable	Surveillance cohort	Incidence cohort
Invasive aspergillosis	227 (18.8)	137 (18.8)
<i>Aspergillus fumigatus</i>	136/227 (59.9)	82/137 (59.9)
<i>Aspergillus terreus</i>	10/227 (4.4)	6/137 (4.4)
<i>Aspergillus niger</i>	13/227 (5.7)	8/137 (5.8)
<i>Aspergillus flavus</i>	16/227 (7.1)	8/137 (5.8)
Multiple <i>Aspergillus</i> species	28/227 (12.3)	19/137 (13.9)
Other <i>Aspergillus</i> species	8/227 (3.5)	5/137 (3.7)
Unspecified <i>Aspergillus</i> species	16/227 (7.1)	9/137 (6.6)

TRANSNET data (2)

Not a single mention to Aspergillus “section”, “complex”, “cryptic”, “sibling”, “weird” or “bizarre species” ...

TRANSNET data (3)

JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 2009, p. 3138–3141
0095-1137/09/\$08.00+0 doi:10.1128/JCM.01070-09
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Vol. 47, No. 10

Molecular Identification of *Aspergillus* Species Collected for the Transplant-Associated Infection Surveillance Network[∇]

S. Arunmozhi Balajee,^{1*} Rui Kano,¹ John W. Baddley,^{2,11} Stephen A. Moser,³ Kieren A. Marr,^{4,5} Barbara D. Alexander,⁶ David Andes,⁷ Dimitrios P. Kontoyiannis,⁸ Giancarlo Perrone,⁹ Stephen Peterson,¹⁰ Mary E. Brandt,¹ Peter G. Pappas,² and Tom Chiller¹

*Mycotic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia*¹; *Department of Medicine*² and *Department of Pathology*,³ *University of Alabama at Birmingham, and Department of Medicine, Birmingham Veterans Affairs Medical Center*,¹¹ *Birmingham, Alabama*; *Fred Hutchinson Cancer Research Center, Seattle, Washington*⁴; *Johns Hopkins University, Baltimore, Maryland*⁵; *Duke University, Durham, North Carolina*⁶; *University of Wisconsin, Madison, Wisconsin*⁷; *M. D. Anderson Cancer Center, Houston, Texas*⁸; *Institute of Sciences of Food Production, National Research Council, Bari, Italy*⁹; and *National Center for Agricultural Utilization Research, U.S. Department of Agriculture, Peoria, Illinois*¹⁰

TRANSNET data (3)

JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 2009, p. 3138–3141
0095-1137/09/\$08.00+0 doi:10.1128/JCM.01070-09
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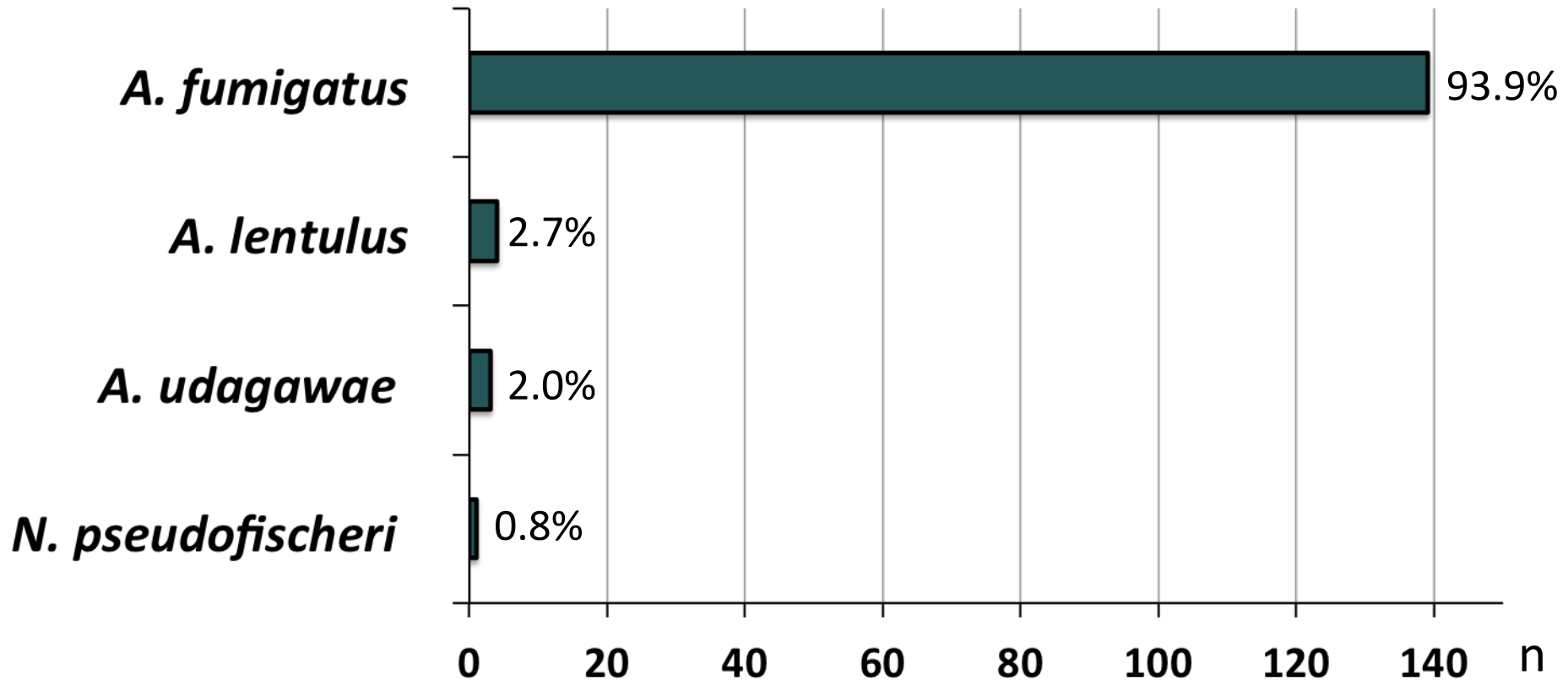
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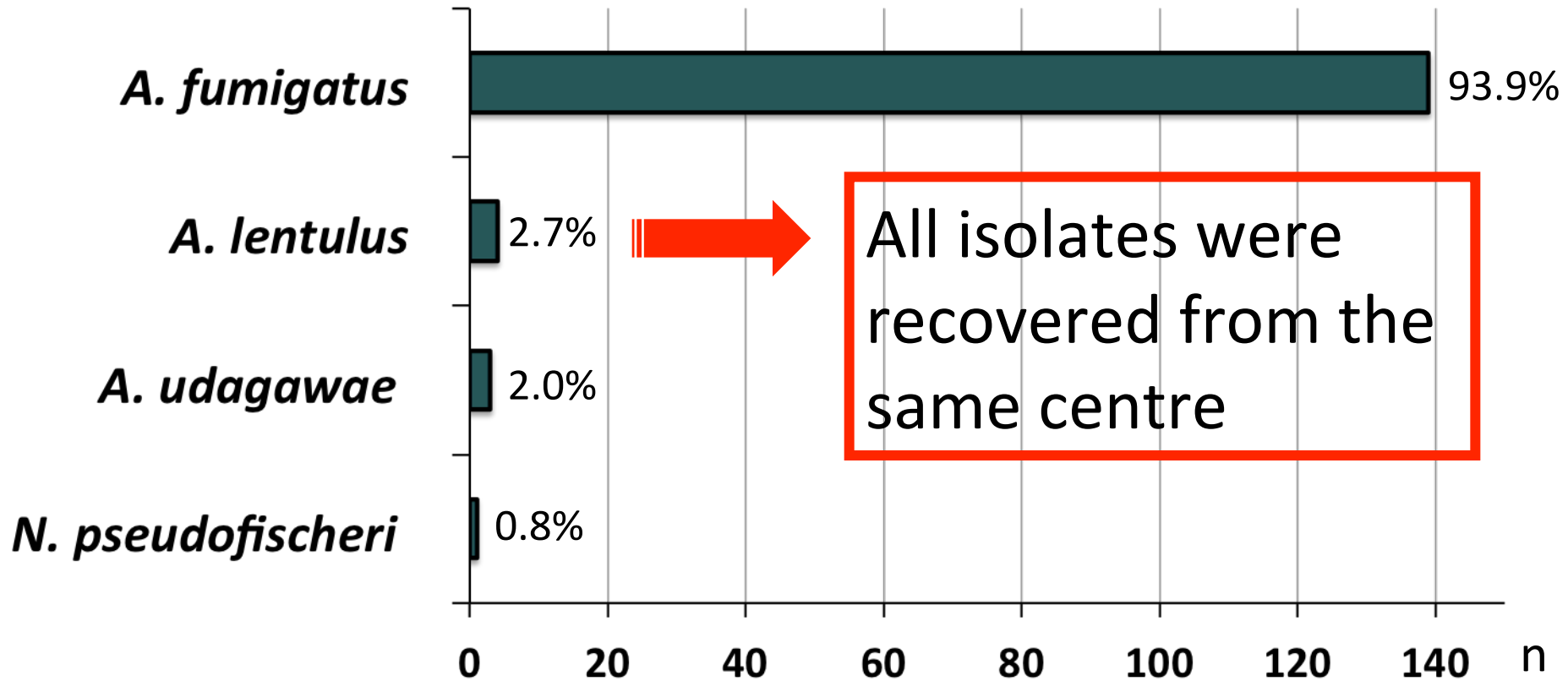
*Mycotic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia*¹; *Department of Medicine*² and *Department of Pathology*,³ *University of Alabama at Birmingham, and Department of Medicine, Birmingham Veterans Affairs Medical Center*,¹¹ *Birmingham, Alabama*; *Fred Hutchinson Cancer Research Center, Seattle, Washington*⁴; *Johns Hopkins University, Baltimore, Maryland*⁵; *Duke University, Durham, North Carolina*⁶; *University of Wisconsin, Madison, Wisconsin*⁷; *M. D. Anderson Cancer Center, Houston, Texas*⁸; *Institute of Sciences of Food Production, National Research Council, Bari, Italy*⁹; and *National Center for Agricultural Utilization Research, U.S. Department of Agriculture, Peoria, Illinois*¹⁰

“Over 10% of the isolates associated with IA in transplant recipients were found to be cryptic species”

Fumigati section (67.4%)



Fumigati section (67.4%)



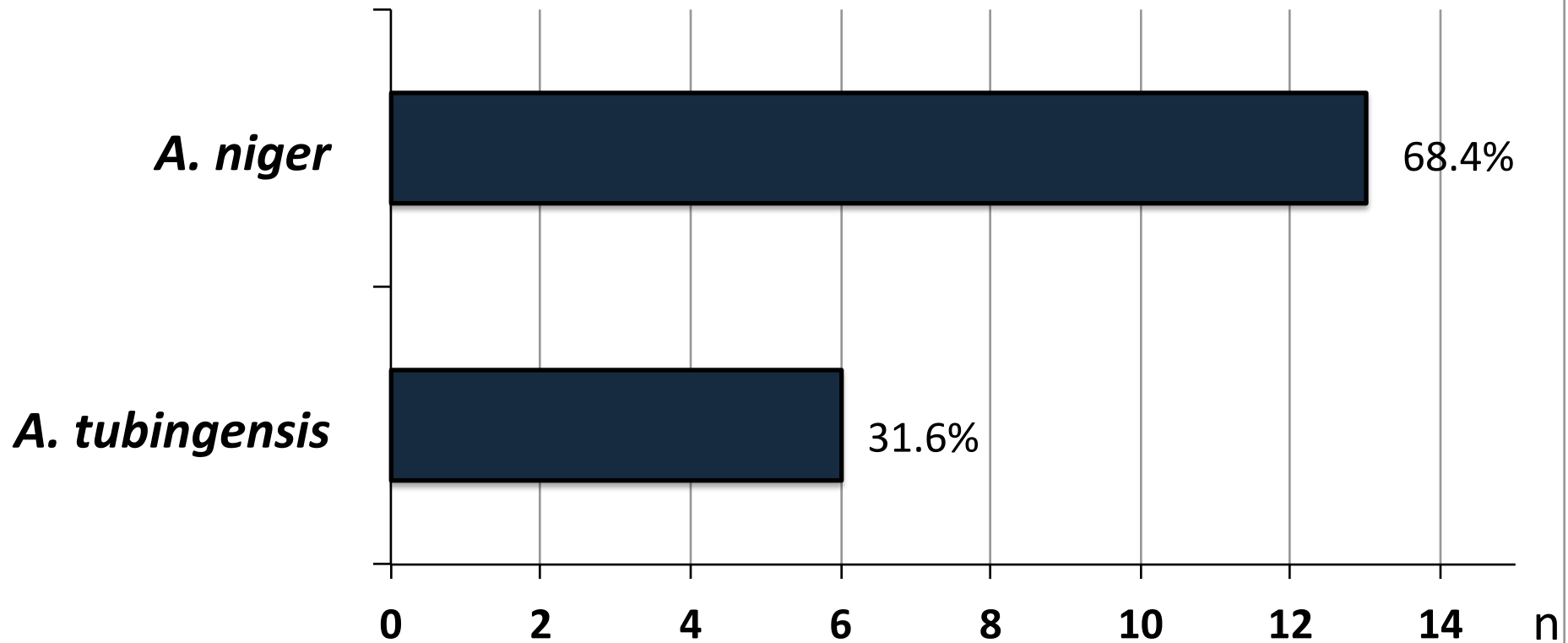
Flavi and Terrei sections

- 100% homology with sequenced ATCC strains

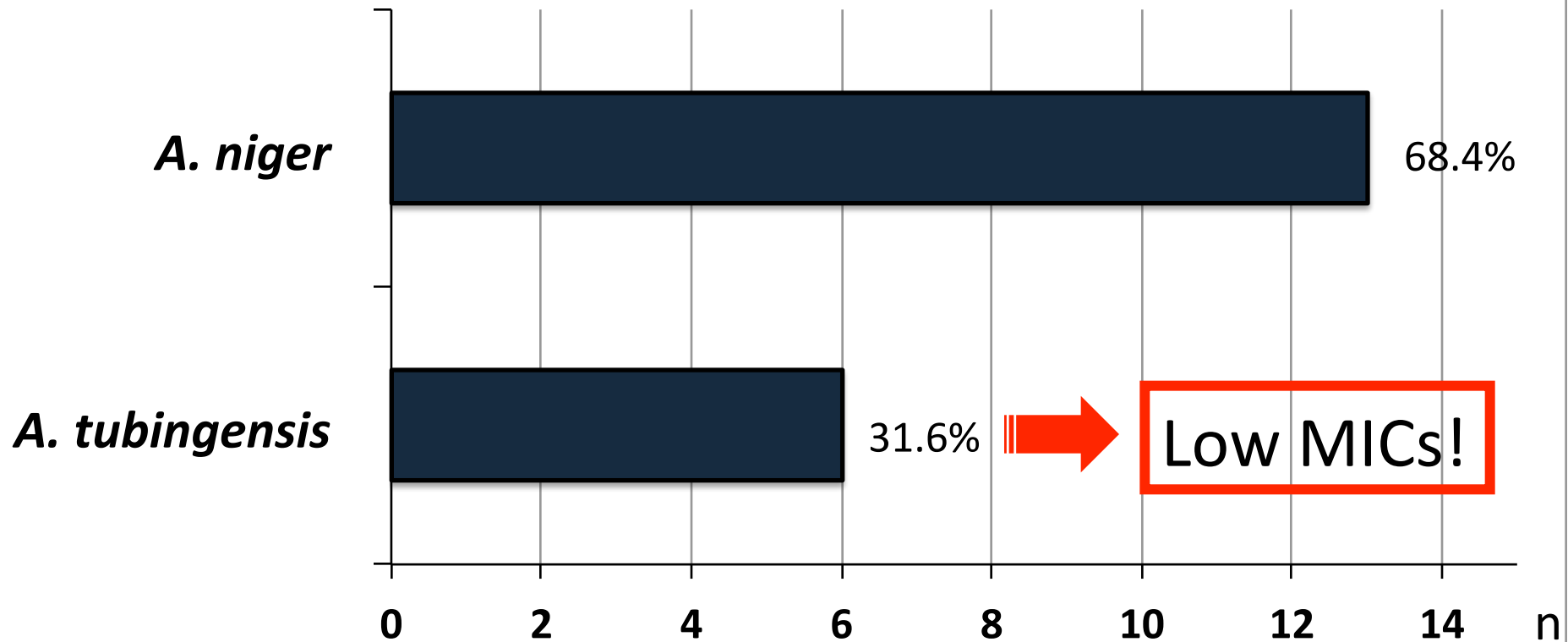
Flavi and *Terrei* sections

- 100% homology with sequenced ATCC strains
 - ✓ Which means no cryptic species

Nigri section (8.7%)

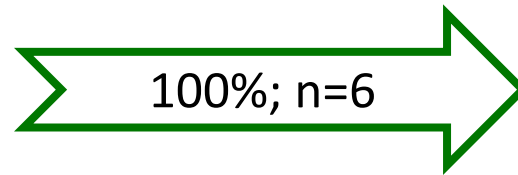


Nigri section (8.7%)



Other groups

A. ustus



A. calidoustus

Other groups

A. ustus

100%; n=6

A. calidoustus

A. versicolor

40%; n=2

A. sydowii

Other groups

A. ustus

100%; n=6

A. calidoustus

A. versicolor

40%; n=2

A. sydowii

A. nidulans

100%; n=1

Emericella quadrilineata

In the latest RCT

A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis

Kieren A. Marr,¹ Haran Schlamm,² Scott T. Rottinghaus,² Shyla Jagannatha,² Eric J. Bow,³ John R. Wingard,⁴ Peter Pappas,⁵ Raoul Herbrecht,⁶ Thomas J. Walsh,⁷ Johan Maertens⁸ and the Mycoses Study Group

¹Johns Hopkins University School of Medicine, Baltimore, MD, USA; ²Pfizer Inc, New York, NY, USA; ³CancerCare Manitoba, University of Manitoba, Winnipeg, Canada; ⁴University of Florida Shands Cancer Center, Gainesville, FL, USA; ⁵University of Alabama, Birmingham, AL, USA; ⁶Department of Oncology & Hematology, Hôpital de Hautepierre, Strasbourg, France; ⁷Weill Cornell Medical College, New York, NY, USA; ⁸Department of Hematology, University Hospital Gasthuisberg, Leuven, Belgium

LB 2812

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- 227 patients with proven/probable IA

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LB 2812

- 227 patients with proven/probable IA
 - ✓ 218 were diagnosed based on GM only
 - ✓ No sequencing results were reported

Solo España lo tiene!



Population-Based Survey of Filamentous Fungi and Antifungal Resistance in Spain (FILPOP Study)

A. Alastruey-Izquierdo,^a E. Mellado,^a T. Peláez,^b J. Pemán,^c S. Zapico,^d M. Alvarez,^e J. L. Rodríguez-Tudela,^a M. Cuenca-Estrella,^a
FILPOP Study Group

National Center for Microbiology, Madrid, Spain^a; Hospital General Universitario Gregorio Marañón, Madrid, Spain^b; Hospital Universitario La Fe, Valencia, Spain^c; Hospital Universitario Donostia, Guipuzcoa, Spain^d; Hospital Universitario Central de Asturias, Oviedo, Spain^e

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***First study to evaluate the frequency of cryptic
Aspergillus species in Europe***

Alastruey-Izquierdo A, *et al.* Antimicrob Agents Chemoter 2013; 57: 3380-7

UFCSPA

Cryptic species 14.4%

TABLE 2 Species isolated and number of strains by study period (October versus May)

Species	No. (%) of strains		
	October 2010	May 2011	Total
<i>Aspergillus fumigatus</i>	98 (47.6)	58 (50.0)	156 (48.5)
<i>Aspergillus flavus</i>	18 (8.74)	9 (7.76)	27 (8.39)
<i>Aspergillus terreus</i>	18 (8.74)	8 (6.90)	26 (8.07)
<i>Aspergillus tubingensis</i>	21 (10.2)	1 (0.86)	22 (6.83)
<i>Aspergillus niger</i>	17 (8.25)	4 (3.45)	21 (6.52)
<i>Aspergillus nidulans</i>	5 (2.43)	3 (2.59)	8 (2.48)
<i>Rhizopus arrhizus</i>	6 (2.91)	1 (0.86)	7 (2.17)
<i>Scedosporium boydii</i>	1 (0.49)	5 (4.31)	6 (1.86)
<i>Aspergillus</i> species ^a	9 (4.37)	9 (7.76)	17 (5.28)
<i>Scedosporium</i> species ^b	4 (1.94)	5 (4.31)	9 (2.80)
<i>Penicillium</i> species ^c	1 (0.49)	5 (4.31)	6 (1.86)
<i>Fusarium</i> species ^d	1 (0.49)	3 (2.59)	4 (1.24)
Mucorales species ^e	4 (1.94)	1 (0.86)	5 (1.55)
Other ^f	3 (1.46)	4 (3.45)	7 (2.17)
Total	206 (100.00)	116 (100.00)	322 (100.00)

^a The *Aspergillus* species isolated included *A. alliaceus*, *A. calidoustus*, *A. carneus*, *A. fumigatiaffinis*, *A. insuetus*, *A. keveii*, *A. lentulus*, *A. sygowii*, *A. viridinutans*, *A. weterdijkiae*, and *N. pseudofischeri*.

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Down to 7.7% by excluding section *Nigri*

“*Candida non-albicans*”?

Are they more resistant?



Are they more resistant?

- Hell yeah

FILPOP study data

TABLE 4 *Aspergillus* species strains resistant to amphotericin B, itraconazole, voriconazole, and posaconazole *in vitro*

Species (no. of isolates)	No. (%) ^a with:			
	AMB MIC > 2 mg/liter	ITC MIC > 2 mg/liter	VRC MIC > 2 mg/liter	PSC MIC > 0.25 mg/liter
<i>A. fumigatus</i> (156)	0	0	0	1 (0.6)
<i>A. flavus</i> (27)	4 (14.8)	0	0	0
<i>A. terreus</i> (26)	7 (27)	0	0	0
<i>A. tubingensis</i> (22)	0	1 (4.5)	0	0
<i>A. niger</i> (21)	0	0	0	0
<i>A. nidulans</i> (8)	1 (12.5)	0	0	0
<i>A. calidoustus</i> (4)	0	2 (50)	4 (100)	4 (100)
<i>A. alliaceus</i> (3)	3 (100)	0	0	0
<i>A. lentulus</i> (3)	1 (33.7)	3 (100)	0	0
<i>A. sydowii</i> (1)	0	0	0	1 (100)
<i>A. carneus</i> (1)	0	0	0	0
<i>N. pseudofischeri</i> (1)	0	0	0	0
<i>A. viridinutans</i> (1)	0	0	0	0
<i>A. fumigatiaffinis</i> (1)	1 (100)	1 (100)	0	0
<i>A. insuetus</i> (1)	1 (100)	1 (100)	1 (100)	1 (100)
<i>A. westerdijkiae</i> (1)	1 (100)	0	0	0
<i>A. keveii</i> (1)	0	1 (100)	1 (100)	1 (100)
Total (277)	19 (6.8)	10 (3.6)	6 (2.2)	8 (2.9)

^a AMB, amphotericin B; ITC, itraconazole; VRC, voriconazole; PSC, posaconazole.

Less responders?



Less responders?

- Not sure!
 - ✓ Limited pathogenicity?
 - ✓ Colonization in many (if not most) cases

Should we search for them?

Should we search for them?

- Possibly

Should we search for them?

- Possibly
 - ✓ But is it cost-effective?

Should we search for them?

JOURNAL OF CLINICAL MICROBIOLOGY, Apr. 2009, p. 877–884
0095-1137/09/\$08.00+0 doi:10.1128/JCM.01685-08
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Vol. 47, No. 4

GUEST COMMENTARY

Sequence-Based Identification of *Aspergillus*, *Fusarium*, and *Mucorales* Species in the Clinical Mycology Laboratory: Where Are We and Where Should We Go from Here?[∇]

S. A. Balajee,^{1*} A. M. Borman,² M. E. Brandt,¹ J. Cano,³ M. Cuenca-Estrella,⁴ E. Dannaoui,⁵
J. Guarro,³ G. Haase,⁶ C. C. Kibbler,⁷ W. Meyer,⁸ K. O'Donnell,⁹ C. A. Petti,¹⁰
J. L. Rodriguez-Tudela,⁴ D. Sutton,¹¹ A. Velegraki,¹² and B. L. Wickes¹³

Should we search for them?

“Taken together, data regarding differences in pathogenicity and in vivo drug susceptibilities of the various species within Aspergillus and Fusarium complex do not categorically suggest that identification within these taxa will impact clinical and therapeutic decision making, at least at the present time.”

Should we search for them?

“Taken together, data regarding differences in pathogenicity and in vivo drug susceptibilities of the various species within Aspergillus and Fusarium complex do not categorically suggest that identification within these taxa will impact clinical and therapeutic decision making, at least at the present time.”

“ However, identification to species/strain level could inform the epidemiology of fungal infections and can be critical in outbreak investigations”

So how to treat them?

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- There is virtually no clinical data!

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 - ✓ Low frequency / not likely to influence choice of empirical or primary antifungal use

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 - ✓ Combination antifungal therapy? No data
- We must therefore rely on *in vitro* information
 - ✓ MICs to azoles usually high
 - ✓ Ampho B usually remains active
 - ✓ Varies largely among isolates / species

So how to treat them?

- A basic question remains ...
 - ✓ Should we sequence all moulds in clinical practice?

So how to treat them?

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 - ✓ Should we sequence all moulds in clinical practice?
- Yes, that gives us additional information

So how to treat them?

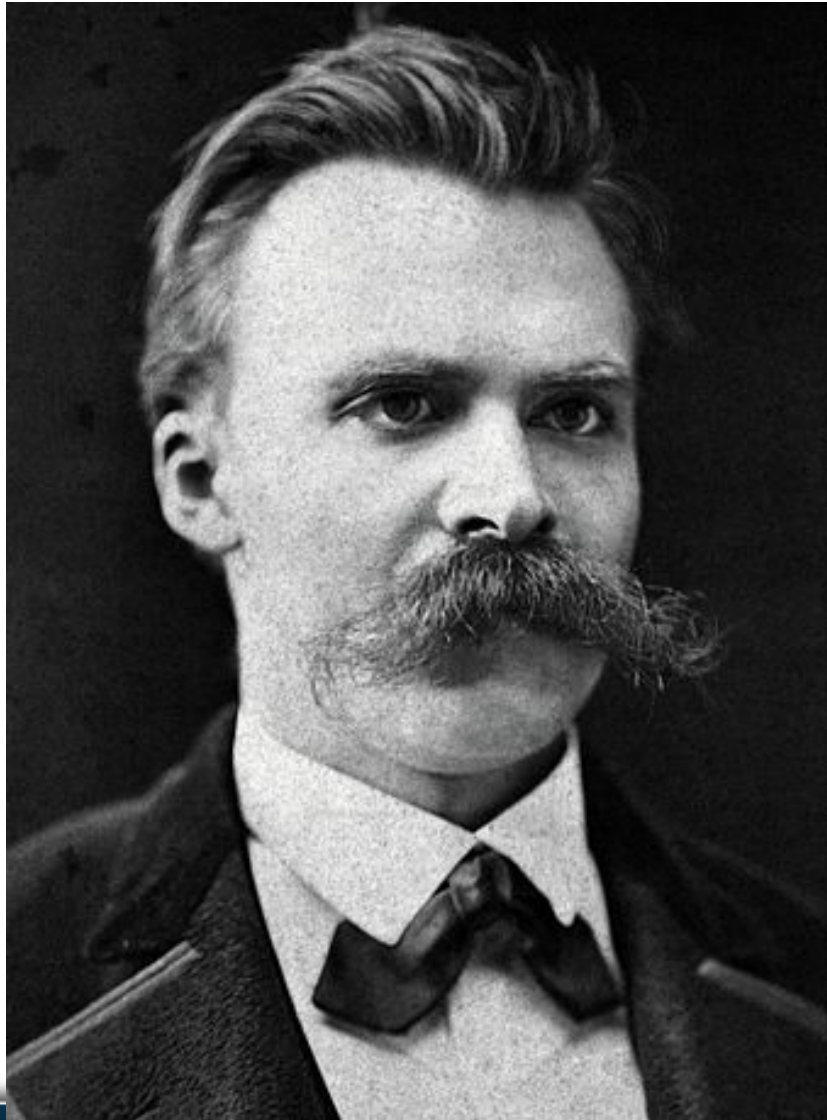
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- Yes, that gives us additional information
- **But**
 - ✓ Increments on costs / complexity of diagnosis
 - ✓ Limited knowledge on the meaning of the results

So how to treat them?

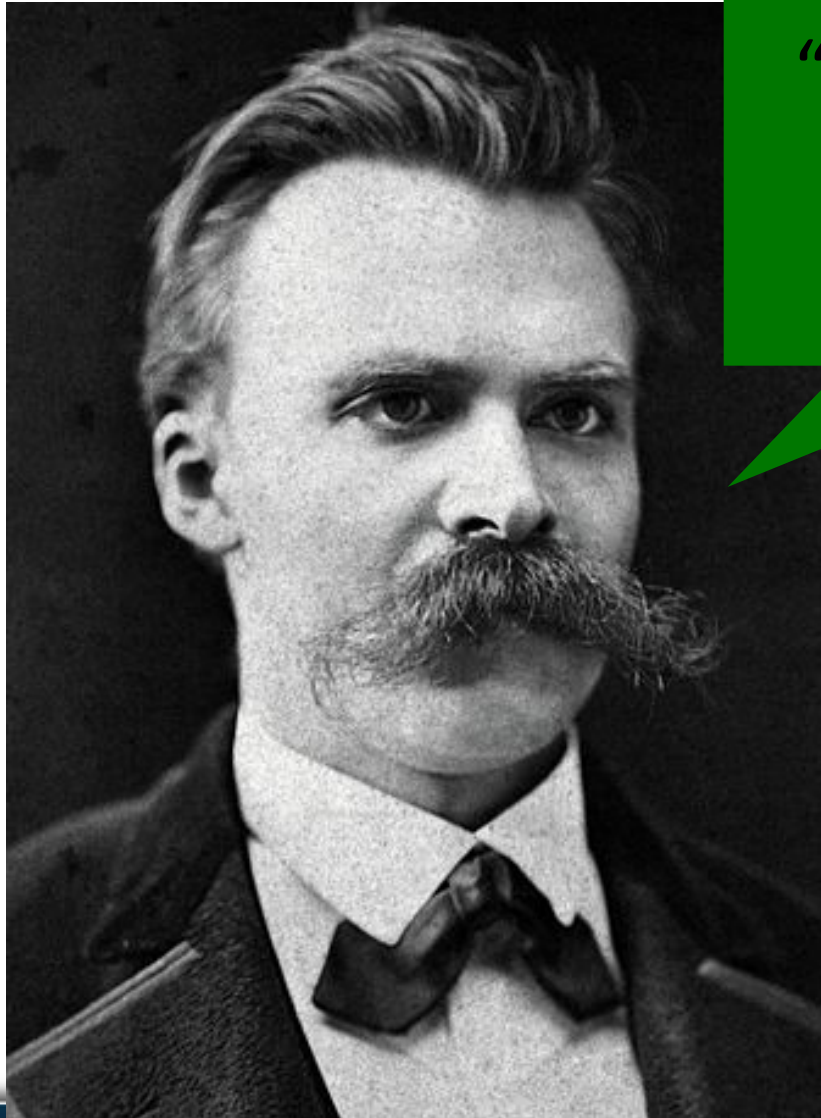
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 - ✓ Should we sequence all moulds in clinical practice?
- Yes, that gives us additional information
- But
 - ✓ Increments on costs / complexity of diagnosis
 - ✓ Limited knowledge on the meaning of the results
- Is the label 'for research use only' applicable in these cases?



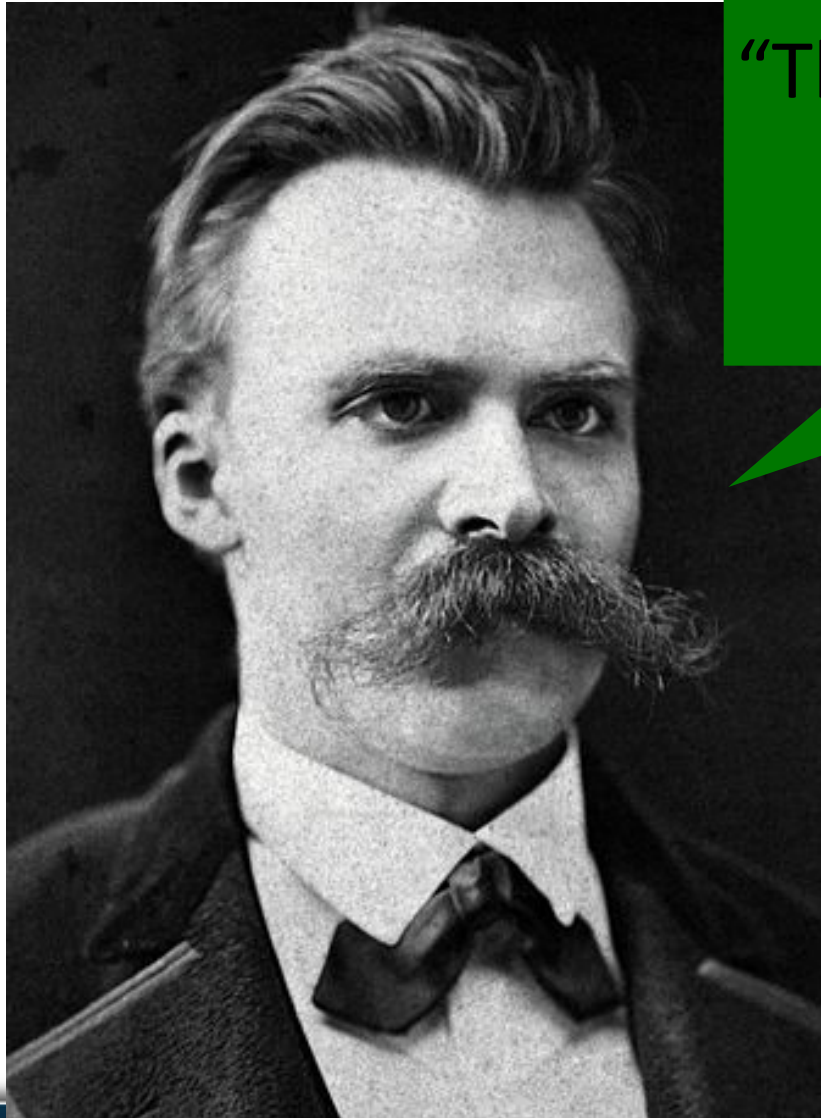
**The beauty of
the little devil**



UFCSPA



“Only sick music
makes money
today”



“There are no beautiful surfaces without a terrible depth.”

Muchas gracias!

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