The Outcome of Invasive Fusariosis Has Improved in the Last Decade

M. Nucci[1], M. Vehreschild[2], E. Velasco[3], F. Queiroz-Telles[4], B. Simoes[5], C.A. Souza[6], S.Cesaro[7], N. Hamerschlak[8], O. Cornely[2], E. Anaissie[9]

1 Federal University of Rio de Janeiro, Rio de Janeiro, Brazil;

2 University Hospital Cologne, Cologne, Germany;

3 National Cancer Institute, Rio de Janeiro, Brazil;

4 Federal University of Paraná, Curitiba, Brazil;

5 University of São Paulo, Ribeirão Preto, Brazil;

6 State University of Campinas, Campinas, Brazil;

7 Azienda Ospedaliera Universitaria Integrata, Verona, Italy,

8 Hospital Albert Einstein, São Paulo, Brazil;

9 Univsersity of Cincinnati, Cincinnati, USA

Fusariosis: Introduction

- Plant pathogen, widely found in nature
- Normal host
  - Onychomycosis, intertrigo, keratitis
- Compromised host
  - Invasive disease, positive blood cultures, disseminated skin lesions
  - Neutropenic patients, T-cell immunodeficiency (acute leukemia, HCT)
- Emerging pathogen
  - 2nd agent of IFD in Brazil
    - 1-y incidence: 5.2% in allo HCT, 3.8% in AML

Nucci & Anaissie. Clin Microbiol Rev 2007;20:695-704
Nucci et al. Clin Microbiol Infect 2012 (in press)

Treatment of Fusariosis: Limited Options Based on In Vitro Data

MIC 50 of Antifungal Drugs Against *Fusarium*

	Ampho B	Vori	Posa
F. solani	1.0	>8.0	>8.0
F. oxysporum	0.5 – 2.0	4.0	1.0 - >8.0
F. verticillioides	2.0	>8.0	NR
F. moniliforme	1.0 – 2.0	NR	NR

NR = not reported

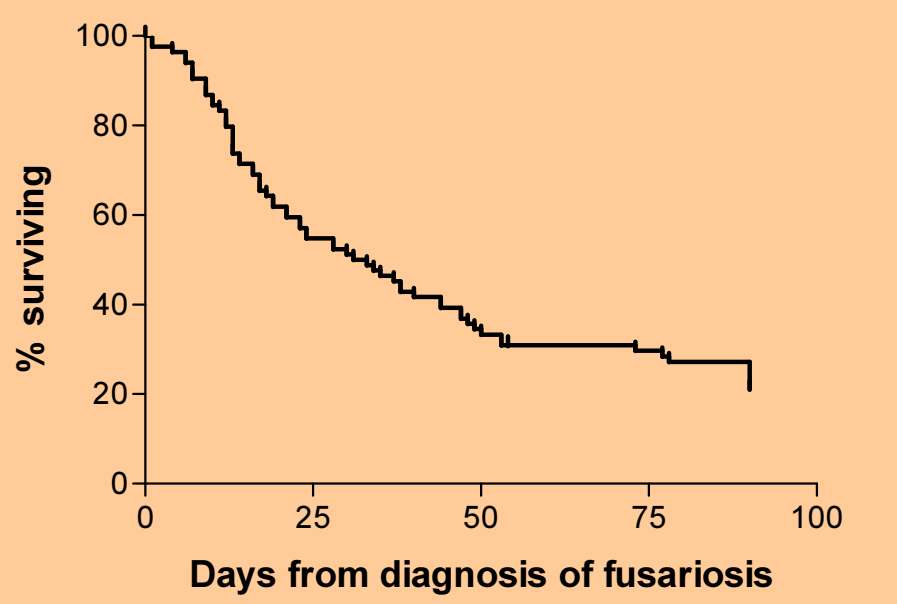
Nucci & Anaissie. Clin Microbiol Rev 2007;20:695-704

The Outcome of Invasive Fusariosis in Immunocompromised Patients is Very Poor

84 cancer patients

90-day survival – 21%

Median survival – 32 days

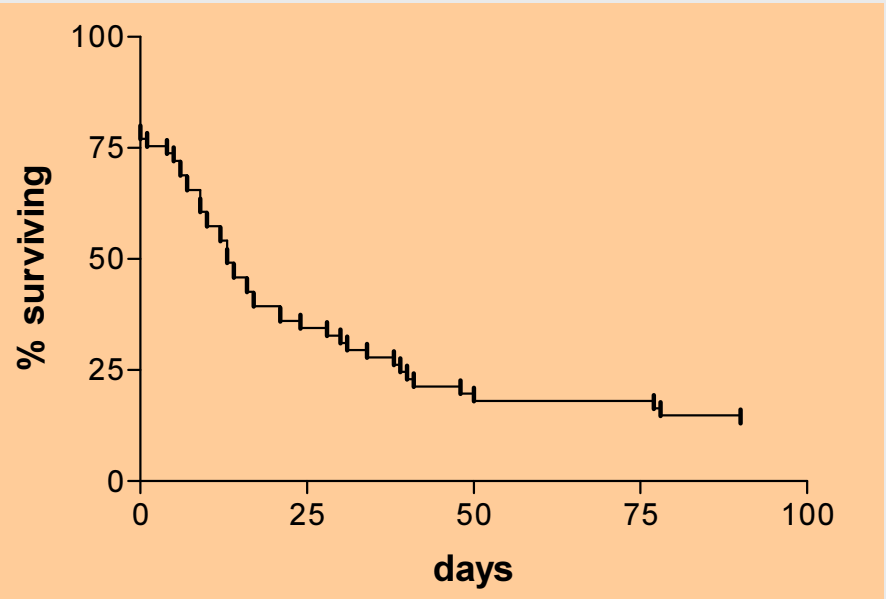


Nucci et al. Cancer 2003;98:315-9

61 HCT recipients

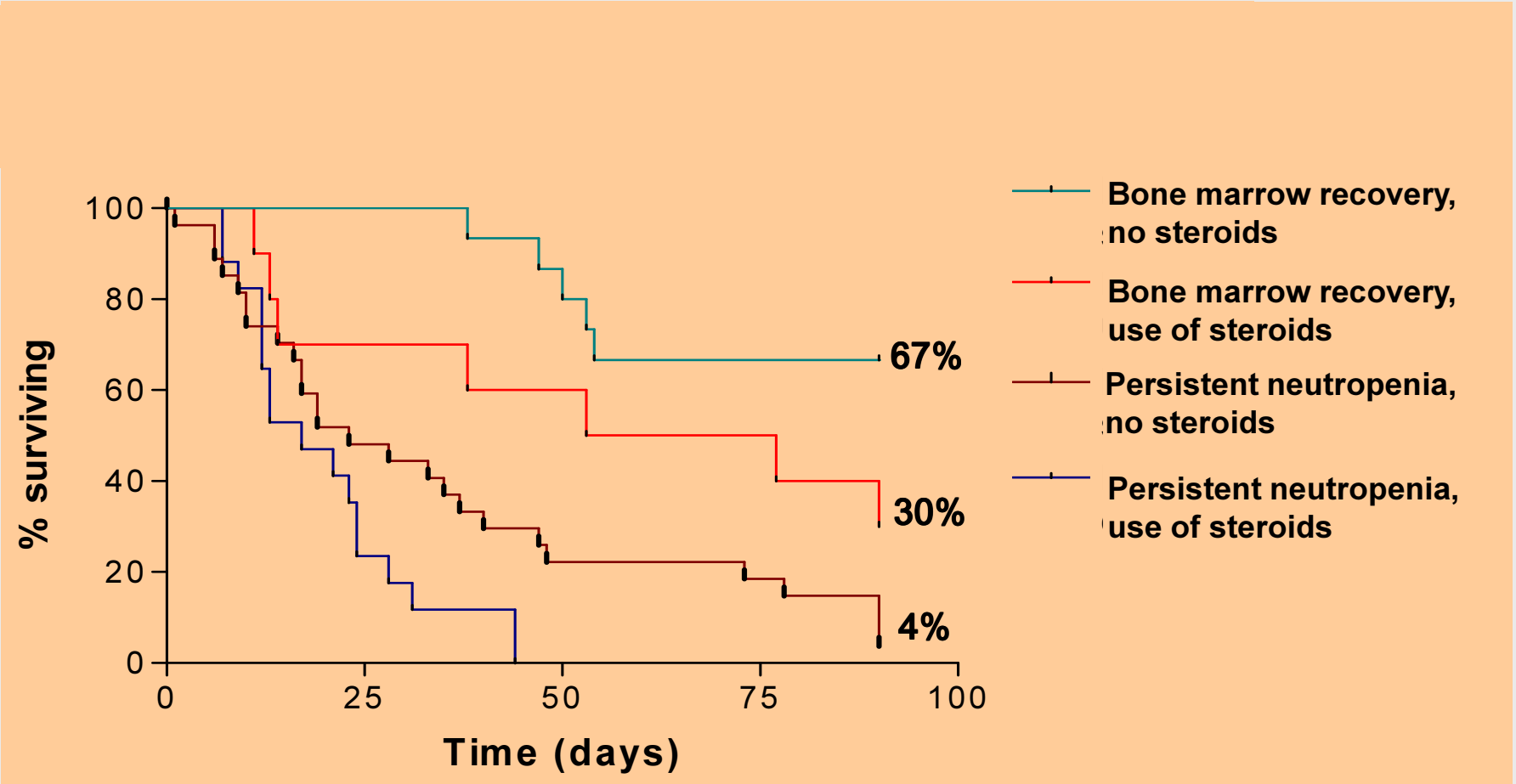
90-day survival – 13%

Median survival – 13 days



Nucci et al. Clin Infect Dis 2004;38:1237-42

Recovery of Host Defenses Strongly Impacts the Outcome



Nucci et al. Cancer 2003;98:315-9

New Data Suggest that the Outcome of Fusariosis has Improved

- 73 cases of invasive fusariosis treated with voriconazole
  - Hematologic malignancies (60%), HCT (18%)
  - Neutropenia (64%), disseminated disease (72%)
- Response rate: 38% in HCT, 45% in hematologic malignancy
- 90-day survival: 42%

Lortholary et al. AAC 2010;54:4446-50

Study Objectives

- To evaluate if the outcome of invasive fusariosis has improved in recent years
- To evaluate changes in underlying diseases, immunosuppression, clinical presentation and treatment strategies
- To evaluate if there is any correlation between MIC and outcome

Methods

- Retrospective review of cases of invasive fusariosis from two large databases
  - Invasive fusariosis network
  - Fungiscope
- CRF: gender, age, underlying disease, treatment, HCT, steroids, GVHD, neutropenia, clinical manifestations, diagnosis, treatment and outcome
- Review of cases and classification as proven or probable according to EORTC/MSG criteria[1]

[1] de Pauw et al. Clin Infect Dis 2008;46:1813-21

Methods

- Cases from 1985 to 2011
  - Comparison between two periods:
    - 1985 – 2000 (PERIOD 1)
    - 2001 – 2011 (PERIOD 2)
- Outcome: survival 90 days from diagnosis
- Comparison between PERIOD 1 and PERIOD 2: Chi-square and Wilcoxon
  - Demographics, underlying disease and treatment, neutropenia, steroids, clinical presentation, diagnostics, treatment and outcome
- Prognostic factors: Uni and multivariate analysis (Cox regression)

Characteristics of 165 Patients with Invasive Fusariosis in the 2 Periods

Baseline Characteristics

Characteristic	Period 1 N=86	Period 2 N=79
Age, median (range)	31 (4 – 75)	48 (4 – 75)
Hematologic malignancy	99%	87%
Acute leukemia	63%	67%
Hematopoietic cell transplantation	40%	39%
Solid organ transplantation	1%	2%
Neutropenia	82%	85%
Receipt of corticosteroids	49%	56%

Text in red: $p<0.05$

Characteristics of 165 Patients with Invasive Fusariosis in the 2 Periods
Clinical manifestations

Manifestation	Period 1 N=86	Period 2 N=79
Fever	92%	87%
Skin lesions	77%	70%
Pneumonia	54%	51%
Sinusitis	34%	28%
Disseminated disease	77%	71%

$p>0.05$ for all comparisons

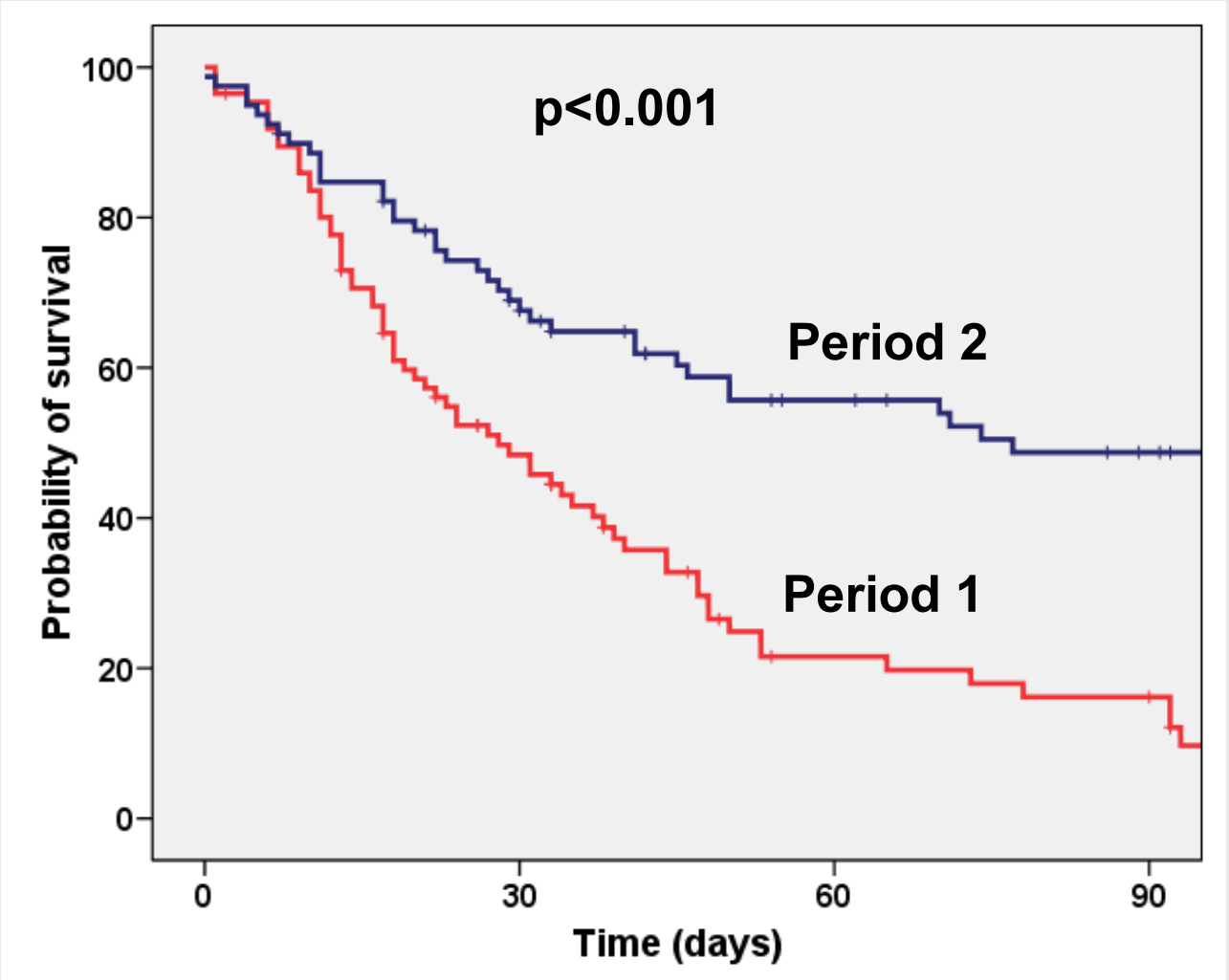
Species ID available in 33 cases only, *F. solani* (72%), *F. oxysporum* (15%)

Characteristics of 165 Patients with Invasive Fusariosis in the 2 Periods
Treatment

Treatment	Period 1 N=86	Period 2 N=79
Deoxycholate amphotericin B	81%	23%
Lipid amphotericin B	15%	11%
Voriconazole	0	42%
Combination therapy	0	20%
G or GM-CSF	46%	54%
Granulocyte transfusions	21%	8%

Text in red: $p<0.05$

Outcome of Invasive Fusariosis in the 2 Periods



Non-significant Variables by Univariate Anaysis

- Demographics: age, gender
- Underlying disease, HCT
- Clinical manifestations: fever, skin lesions (presence and pattern), lung involvement, sinusitis, fungemia
- Treatment: treatment with liposomal amphotericin B, combination therapy, receipt of G-CSF or GM-CSF, granulocyte transfusions

Univariate and Multivariate Predictors of 90-day Death

Variable	Univariate	Multivariate
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Period (2 vs. 1)	0.39 (0.26 – 0.60)	0.87 (0.50 – 1.51)
Hematopoietic cell transplantation	1.52 (10.4 – 2.23)	1.18 (0.66 – 1.67)
Treatment with d- AMB	2.59 (1.24 – 3.49)	1.52 (0.91 – 2.54)
Disseminated disease	2.10 (1.24 – 3.49)	1.54 (0.82 – 2.87)

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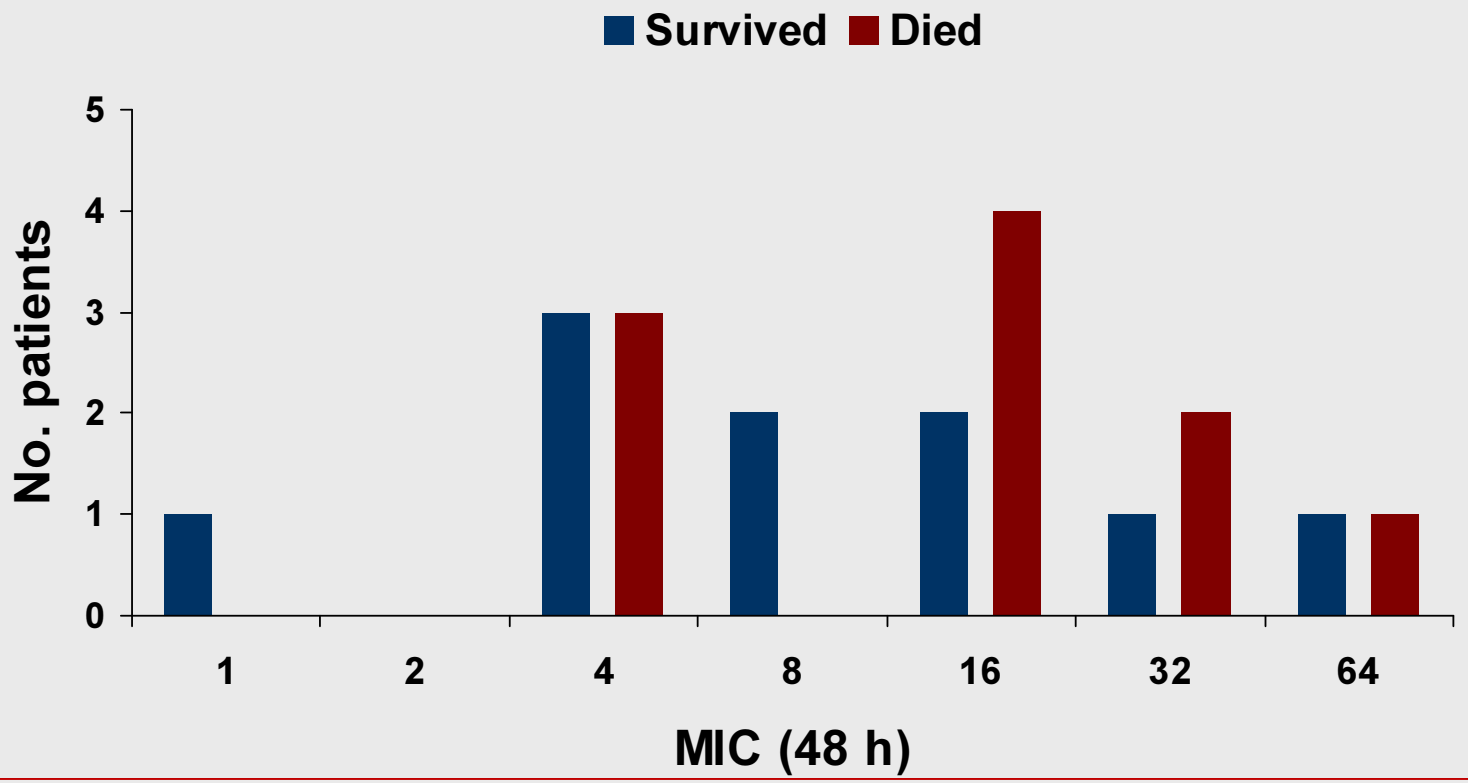
Disseminated disease	2.10 (1.24 – 3.49)	1.54 (0.82 – 2.87)
Receipt of corticosteroids	1.69 (1.15 – 2.48)	1.77 (1.17 – 2.68)
Persistent neutropenia	3.62 (2.33 – 5.65)	3.17 (2.02 – 4.97)
Treatment with voriconazole	0.31 (0.17 – 0.57)	0.44 (0.21 – 0.90)

Text in red: $p<0.05$

Correlation Between Voriconazole in vitro Susceptibility of *Fusarium* Isolates and 90-day Survival in 20 Cases



	Survived	Died	
MIC 50 (range)	8 (1 – 64)	16 (4 – 64)	p=0.39
MIC 90	64	64	

Limitations of the Study

- Retrospective data collection, with limited information on
  - Changes in characteristics of underlying diseases, treatments, supportive care practices
  - Duration of corticosteroid exposure
  - Cumulative dose of corticosteroids
  - Time from first clinical manifestation to diagnosis
  - Time from diagnosis to treatment
  - Dose of antifungals

Conclusions

- No significant changes in patients characteristics over time
- Changes in treatment practices
  - ↓ deoxycholate amphotericin B
  - ↑ voriconazole and combination therapy
- Improved outcome
  - 16% 90-day probability of survival in period 1 vs. 49% in period 2
- Poor prognostic factors: receipt of corticosteroids and persistent neutropenia
- Receipt of voriconazole associated with better outcome despite no correlation with MIC

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Contributor	Site	Contributor	Site
Sevtap Arikan	Ankara, Turkey	Cornelia Lass-Flörl	Innsbruck, Austria
Hartmut Bertz	Freiburg, Germany	Maria Teresa Montagna	Bari, Italy
Angelo Atala	Juiz de Fora, Brazil	Claudio G. Castro Jr	Porto Alegre, Brazil
Simone Cesaro	Padova, Italy	Sherif B. Mossad	Cleveland, Ohio, USA
Georg Härter	Ulm, Germany	Dilara Ogunc	Antalya, Turkey
Mauro Salles	São Paulo, Brazil	Marco Rotolo	Florianópolis, Brazil
Werner Heinz	Würzburg, Germany	Livio Pagano	Rome, Italy
Raoul Herbrecht	Strasbourg, France	Alessandro Pasqualotto	Porto Alegre, Brazil
Emil Hermansen	Copenhagen, Denmark	Zdenek Racil	Brno, Czech Republic
Arnaldo L. Colombo	São Paulo, Brazil	Adriana Seber	São Paulo, Brazil
Martin Hönigl	Graz, Austria	Martin Schaller	Tübingen, Germany
Andreas Josting	Lippstadt, Germany	Don Sheppard	Montreal, Canada
Anupma Kindo	Porur, Chennai, India	Isabel Spriet	Leuven, Belgium

Fungi scope
Global Rare Fungal Infection Registry

Maria Vehreschild, Oliver Cornely