Changing epidemiology and management of fungal infections in the compromised host

Claudio Viscoli; ESCMID Fellow
Infectious Disease
University of Genova
Ospedale Policlinico San Martino
Thank you for this award

To my pupils for nominating me for this award

• Valerio Del Bono
• Elio Castagnola
• Matteo Bassetti
• Malgorzata Mikulska
• Daniele Giacobbe
• Alessio Mesini

The ESCMID Executive Committee for recognizing my long work in the field of Infectious Diseases
Potential conflicts of interest

• Received grants as speaker/moderator in national or international meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott, BMS, Novartis

• Received grants for participation in national or international advisory boards by Gilead, Astellas, MSD, Pfizer, Novartis

• Obtained research grants for my institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, Novartis

• Expert for the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA

• Member of several local boards (Genoa, Liguria, Italy and my hospital) (Hospital Infection Control and Antibiotic Stewardship, HIV, vaccination, Hospital Formulary)
What I would like to discuss with you today

- Emerging (or rare) pathogens
- Antifungal stewardship
  - Antifungal prophylaxis in hematology
  - Therapy of Candida infections: the role of combining PCT and beta-d-glucan for driving antifungal therapy
MUCOR
FUSARIUM
CANDIDA AURIS
Mucormycosis

- Second more common IFD in hematology
- Next most important risk group is diabetes (usually poorly controlled)
- Distinctive angioinvasive disease (fungal vasculitis)
- Three forms
  - Rhinocerebral diseases
  - Pulmonary infiltrates with nodules (reverse halo sign)
  - Wound infections
- Diagnosis
  - Typical hyphal invasion at biopsy
  - Culture rarely positive
  - No serological marker (fucomannan, ECCMID 2018)
  - Tissue biomolecular diagnosis
- High morbidity and mortality
Lewis R, Mycoses 2013

Prevalence per 100 autopsy examinations

Years of examination

- Aspergillus
- Candida
- Mucorales
- Fusarium
- Mixed Aspergillus-Candida
RESEARCH ARTICLE

Increasing incidence of mucormycosis in a large Spanish hospital from 2007 to 2015: Epidemiology and microbiological characterization of the isolates

Jesús Guinea¹,²,³,⁴*, Pilar Escribano¹,²*, Antonio Vena¹,², Patricia Muñoz¹,²,³,⁴, María del Carmen Martínez-Jiménez¹,², Belén Padilla¹,²,³, Emilio Bouza¹,²,³,⁴

The incidence of mucormycosis in cases/100,000 hospital admissions during 2007–2015 increased significantly with respect to that reported in 1988–2006 (3.3 vs. 1.2; P<0.05).
Epidemiology and Outcome of Zygomycosis: A Review of 929 Reported Cases

Maureen M. Roden,1 Theoklis E. Zaoutis,2,4 Wendy L. Buchanan,1 Tena A. Knudsen,1 Tatyana A. Sarkisova,1 Robert L. Schaufele,1 Michael Sein,1 Tin Sein,1 Christine C. Chiou,6 Jaclyn H. Chu,2 Dimitrios P. Kontoyiannis,5 and Thomas J. Walsh1

1Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland; 2Division of Infectious Diseases, The Children’s Hospital of Philadelphia, and 3Department of Pediatrics and 4Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; 5M. D. Anderson Cancer Center, University of Texas, Houston; and 6National Yang Ming University, Taipei, Taiwan

Diabetes

- Pulmonary 16%
- Sino-orbital 15%
- Sinus 8%
- Other 8%
- Cutaneous 10%
- Rhinocerebral 43%

Malignancy

- Pulmonary 60%
- Sino-orbital 5%
- Sinus 10%
- Rhinocerebral 4%
- Other 6%
- GI 3%

n = 337

n = 154
Skin and then disseminated *Lichtheimia* infection in a liver transplant recipient.
Skin and then disseminated *Lichtheimia* infection in a liver transplant recipient
ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

Frederic Tissot, Samir Agrawal, Livio Pagano, Georgios Petrikkos, Andreas H. Groll, Anna Skiada, Cornelia Lass-Flörl, Thierry Calandra, Claudio Viscoli and Raoul Herbrecht

Haematologica 2017
Volume 102(3):433-444
<table>
<thead>
<tr>
<th>Table 9. ECIL-6 recommendations for first-line therapy of mucormycosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
</tr>
<tr>
<td>Management includes antifungal therapy, surgery and control of underlying conditions</td>
</tr>
<tr>
<td>Antifungal therapy</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
</tr>
<tr>
<td>Posaconazole</td>
</tr>
<tr>
<td>Combination therapy</td>
</tr>
<tr>
<td>Control of underlying condition</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Rhino-orbito-cerebral infection</td>
</tr>
<tr>
<td>Soft tissue infection</td>
</tr>
<tr>
<td>Localized pulmonary lesion</td>
</tr>
<tr>
<td>Disseminated infection</td>
</tr>
<tr>
<td>Hyperbaric oxygen</td>
</tr>
<tr>
<td>Recommendation against use</td>
</tr>
<tr>
<td>Combination with deferasirox</td>
</tr>
</tbody>
</table>
**Management** | **Recommandation**
---|---
Surgical debridment + Lip AmB ≥5mg/Kg/day | A II
Posaconazole 200 mg q6 (solution) | A II
Control of the underlying condition | Recommended
G-CSF in neutropenic | A II
Isavuconazole

4.1 Therapeutic indications

CRESEMBA is indicated in adults for the treatment of
- invasive aspergillosis
- mucormycosis in patients for whom amphotericin B is inappropriate
Difficult diagnosis

Difficult treatment

Difficult to understand when to stop therapy
Altini C, et al


**18F-FDG PET/CT contribution to diagnosis and treatment response of rhino-orbital-cerebral mucormycosis**

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**ImmunopET/MR imaging allows specific detection of Aspergillus fumigatus lung infection in vivo**

Anna-Maria Rolle\(^a,1\), Mike Hasenberg\(^b,1\), Christopher R. Thornton\(^c\), Djamshid Solouk-Saran\(^b\), Linda Männ\(^b\), Jüliane Weski\(^b\), Andreas Maurer\(^a\), Eliane Fischer\(^d\), Philipp R. Spycher\(^d\), Roger Schibli\(^d\), Frederic Boschetti\(^e\), Sabine Stegemann-Koniszewski\(^f,g\), Dunja Bruder\(^f,g\), Gregory W. Severin\(^h,i\), Stella E. Autenrieth\(^j\), Sven Krappmann\(^k\), Genna Davies\(^c\), Bernd J. Pichler\(^a\), Matthias Gunzer\(^b,2\), and Stefan Wiehr\(^a,2\)

**PNAS**
Fusariosis

- Spores ubiquitous in air, soil. Plant pathogen
- Venous catheter contamination without dissemination possible

- **75% disseminated disease in neutropenic pts**
  - Fever
  - multiple skin lesions: black eschar w/gray halo
  - myalgias, painful subcutaneous lesions
  - lung, liver, kidney, spleen, brain

- Grows easily in blood culture
- Mortality high (50%), but reduced with the advent of voriconazole
ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>SoR</th>
<th>QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised patients</td>
<td>First-line treatment</td>
<td>A</td>
<td>Ilt,r</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td></td>
<td>B</td>
<td>Ilt,r</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td></td>
<td>C</td>
<td>III</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td></td>
<td>D</td>
<td>Ilt,u</td>
</tr>
<tr>
<td>Any echinocandin</td>
<td></td>
<td>D</td>
<td>III</td>
</tr>
<tr>
<td>Any combination therapy</td>
<td></td>
<td>C</td>
<td>III</td>
</tr>
<tr>
<td>Salvage treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td></td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td>A</td>
<td>III</td>
</tr>
</tbody>
</table>
Candida auris
Investigation of the First Seven Reported Cases of *Candida auris*, a Globally Emerging Invasive, Multidrug-Resistant Fungus — United States, May 2013–August 2016

*Early Release / November 4, 2016 / 65*

Simultaneous emergence of multidrug resistant *Candida auris* on three continents confirmed by whole genome sequencing and epidemiological analyses

Shawn R. Lockhart¹, Kizee A. Etienne¹, Snigdha Vallabhaneni¹, Joveria Farooqi², Anuradha Chowdhary³, Nelesh P. Govender⁴, Arnaldo Lopes Colombo⁵, Belinda Calvo⁶, Christina A. Cuomo⁷, Christopher A. Desjardins⁷, Elizabeth L. Berkow¹, Mariana Castanheira⁸, Rindizani E. Magobo⁴, Kauser Jabeen², Rana J. Asghar⁹, Jacques F. Meis¹⁰,¹¹, Brendan Jackson¹, Tom Chiller¹, Anastasia P. Litvintseva¹
<table>
<thead>
<tr>
<th>Resistance patterns</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>100%</td>
</tr>
<tr>
<td>Other triazoles</td>
<td>3-73%</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>13-35%</td>
</tr>
</tbody>
</table>

Almost all susceptible to echinocandins

**About 40% resistant to ≥2 drugs**

Few of them R to all families
Why a worrisome phenomenon

- Potential to cause outbreaks
- High mortality, apparently higher than other *Candida* strains
- Resistance profile
- Apparent interhuman transmission
- Spreading pattern similar to MDR bacteria
- Biofilm formation and ability to survive on inanimate surfaces
- Need for screening and isolation

Lamoth and Kontoyiannis, JID 2017,
C. parapsilosis and fluconazole resistance 2009 – 2015
What I would like to discuss with you today

- Emerging (or rare) pathogens
- Antifungal stewardship
  - Antifungal prophylaxis in hematology
  - Therapy of *Candida* infections: the role of combining PCT and beta-d-glucan for driving antifungal therapy
Why mold-active prophylaxis is attractive in malignancies

- High mortality in Aspergillus
- If surviving, need for long term therapy/secondary prophylaxis
- Impact on the outcome of the underlying disease
The activity of mold-active prophylaxis has been shown effective.

Effectiveness is another issue.
<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological malignancies, e.g. AML with prolonged and profound neutropenia</td>
<td>Lower incidence of IA</td>
<td>Posaconazole 200 mg TID suspension or 300mg tablet QD</td>
<td>A</td>
<td>I</td>
<td>AML/MDS induction only. TDM especially with oral suspension. Tablets more bioavailable, bridging with posaconazole IV formulation possible</td>
</tr>
<tr>
<td>Condition</td>
<td>Treatment</td>
<td>Quality</td>
<td>Evidence</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------------</td>
<td>---------</td>
<td>----------</td>
<td>--------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Allogeneic HSCT (with moderate to severe GvHD)</td>
<td>Posaconazole 200mg TID suspension</td>
<td>A</td>
<td>I</td>
<td>TDM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole 200mg BID</td>
<td>C</td>
<td>II</td>
<td>Not better than fluconazole; TDM</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Invasive fungal diseases in patients with AML during front-line chemotherapy: comparison of patients who received oral amphotericin B primary antifungal prophylaxis (control group) with patients who received oral posaconazole primary antifungal prophylaxis (posaconazole group).

<table>
<thead>
<tr>
<th>Invasive fungal disease (IFD)</th>
<th>Control group (58 pts)</th>
<th>Posaconazole group (99 pts)</th>
<th>P value</th>
<th>Absolute Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with proven/probable IFD</td>
<td>30 (51.7)</td>
<td>23 (23.2)</td>
<td>0.0004</td>
<td>-28.5% (-12.9 to -42.8)</td>
</tr>
<tr>
<td><strong>Mould</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>25 (43.1)*</td>
<td>15 (15.1)*</td>
<td>0.0002</td>
<td>-27.9% (-13.4 to -42.0)</td>
</tr>
<tr>
<td>Aspergillus flavus</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. fumigatus</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus species*</td>
<td>21</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zygomycosis</td>
<td>3 (5.2)*</td>
<td>1 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhizopus orizae</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rizomucor pusillus</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucor species</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cunninghamella species</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yeast</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive candidiasis</td>
<td>3 (5.2)*</td>
<td>5 (5.0)*</td>
<td>1</td>
<td>+0.12% (-9.5 to 7.0)</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. guilliermondii</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geotrichum capitatum</td>
<td>1 (1.7)</td>
<td>2 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumocystis jirovecii</td>
<td>1*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with possible IFD</td>
<td>6 (10.3)</td>
<td>7 (7.1)</td>
<td>0.55</td>
<td>+1.9% (+9.3 to -8.6)</td>
</tr>
<tr>
<td>Total patients with IFD</td>
<td>36 (62.1)</td>
<td>30 (30.3)</td>
<td>&lt;.0001</td>
<td>-31.7% (-15.7 to -45.8)</td>
</tr>
<tr>
<td>Pre-emptive or empiric antifungal therapy</td>
<td>9 (15.5)</td>
<td>5 (2.0)</td>
<td>0.04</td>
<td>-10.5% (-0.1 to -22.2)</td>
</tr>
</tbody>
</table>

*Three patients with a diagnosis of invasive aspergillosis were diagnosed with P. jiroveci infection (1 case), zygomycosis (1 case) and candidemia (1 case) during the same chemotherapy-induced neutropenia period. *One patient with a diagnosis of invasive aspergillosis was diagnosed with a concomitant invasive candidiasis. * In these cases a diagnosis of invasive aspergillosis was obtained by a positive test for aspergillus galactomannan antigen (see text for details) or by compatible histopathological findings.
Factors to consider in prophylaxis

Number Needed To Treat

Prevalence of disease

Safety

Cost

Microbiota impact

Resistance induction

ESCMID eLibrary © by author
Proposed changes to the ECIL 3 recommendations

- Set a threshold for the incidence of invasive mould disease to 8% (as documented by the PIMDA audit\(^1\))
- BII recommendation for voriconazole: no specific study in AML/MDS but results inferred from data during neutropenic pre-engraftment phase in allo-BMT recipients
- Change the way doses are reported from the Latin to the “q” system; for example q6h, q8h, q12h, q24h

\(^1\) A European period-prevalence study to estimate the rate of invasive pulmonary mould disease (PIMDA study)
Donnelly et al Poster P0028a ECCMID 2014, Barcelona, Spain
Australian Guidelines

Antifungal prophylaxis in adult stem cell transplantation and haematological malignancy

M. A. Slavin,1,2,3 C. H. Heath,4 K. A. Thursky,1,2 C. O. Morrissey,3,5 J. Szer,6 L. M. Ling,7 S. T. Milliken8 and A. P. Grigg6

studies specific to these clinical settings. The use of a mould-active agent, such as itraconazole or posaconazole, may be justified in this group, particularly if an institution’s incidence of IFI in this population is over 10% or there are additional patient risk factors such as pre-existing neutropenia or severe mucositis (grade D recommendation). Otherwise, fluconazole 400 mg daily is recommended.
What I would like to discuss with you today

- Epidemiology of IFD and emerging (or rare) pathogens
- Antifungal stewardship
  - Antifungal prophylaxis in hematology
  - Combination of PCT and beta-d-glucan for driving antifungal therapy in ICU
Procalcitonin levels in surgical patients at risk of candidemia

Alvise Martini a, Leonardo Gottin a, Nicola Menestrina a, Vittorio Schweiger a, Davide Simion a, Jean-Louis Vincent b,*

Cortegiani et al. BMC Anesthesiology 2014; 14:9
http://www.biomedcentral.com/1471-2253/14/9

RESEARCH ARTICLE
Open Access

Procalcitonin as a marker of Candida species detection by blood culture and polymerase chain reaction in septic patients

Andrea Cortegiani*, Vincenzo Russotto, Francesca Montalto, Grazia Foresta, Giuseppe Accurso, Cesira Palmeri, Santi Maurizio, Raineri and Antonino Giarratano

DOI 10.1007/s00134-006-0306-3

Serum procalcitonin measurement contribution to the early diagnosis of candidemia in critically ill patients

Pierre Emmanuel Charles
Frédéric Dalle
Serge Aho
Jean-Pierre Quenot
Jean-Marc Doise
Hervé Aube
Nils-Olivier Olsson
Bernard Blettery

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Combined use of serum (1,3)-β-D-glucan and procalcitonin for the early differential diagnosis between candidaemia and bacteraemia in intensive care units

Daniele Roberto Giacobbe\textsuperscript{1}*, Małgorzata Mikulska\textsuperscript{1}, Mario Tumbarello\textsuperscript{2}, Elisa Furfaro\textsuperscript{1}, Marzia Spadaro\textsuperscript{1}, Angela Raffaella Losito\textsuperscript{2}, Alessio Mesini\textsuperscript{1}, Gennaro De Pascale\textsuperscript{3}, Anna Marchese\textsuperscript{4}, Marco Bruzzone\textsuperscript{5}, Paolo Pelosi\textsuperscript{6,7}, Michele Mussap\textsuperscript{8}, Alexandre Molin\textsuperscript{6}, Massimo Antonelli\textsuperscript{3}, Brunella Posteraro\textsuperscript{9}, Maurizio Sanguinetti\textsuperscript{10}, Claudio Viscoli\textsuperscript{1}, Valerio Del Bono\textsuperscript{1} and on behalf of ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva)

Inclusion criteria

- Adult patients with candidaemia and bacteraemia
- With a beta-D-glucan test performed within 48 hours before or after the index culture
- With a PCT measured within 24 hours before or after the index culture
Total of patients with candidaemia (n = 93)

Excluded (n = 17)
- Unmeasured BDG and/or PCT, or markers measured not close to the positive culture

Patients with candidaemia (n = 76)

Patients with candidaemia* (n = 73)
Patients with bacteraemia** (n = 93)
Patients with mixed infections (n = 3)

Excluded (n = 3)
- Mixed infections

Included patients with candidaemia (n = 73)

Included patients with bacteraemia (n = 93)
BDG values (pg/ml) vs Type of infection (Bacteraemia vs Candidaemia)
ROC

BDG
113 pg/ml

PCT
1.93 ng/ml
Fig. 4 Positive predictive value (PPV) and negative predictive value (NPV) for candidaemia of (1,3)-β-D-glucan (BDG) and procalcitonin (PCT) considered both separately and in combination. Cut-offs for...
In conclusion

- From the early years when only deoxy-Ampho B was available and diagnosis was extremely difficult we have made enormous progresses in diagnosis, prevention and therapy.
- Clinical mycology has become a complicated exercise, since we have more drugs, more diagnostic tools.
- More drugs, more patients at risk, more diagnostic tools mean more responsibility.
New indications?

Everything is changing with the expanding number of biological drugs used in hematology.

Some of them might change the spectrum of infectious complications, changing the risk of IFD.
In conclusion

- A devastating disease, resembling a tumor
- Much more frequent than commonly believed, especially in South-East Asia
- Often difficult to understand whether or not the disease is still progressing and difficult to assess duration of treatment (no markers) (active or scar?)
- Comparison of subsequent MR imaging maybe the only tool
- PET CT may be useful in making this distinction
“An once of prevention is worth a pound of cure” is true only when you know the true weight of prevention

Galactomannan testing might be useful for early diagnosis of fusariosis

Małgorzata Mikulska\textsuperscript{a,}\textsuperscript{*}, Elisa Furfaro\textsuperscript{a}, Valerio Del Bono\textsuperscript{a}, Francesca Gualandi\textsuperscript{b}, Anna Maria Raiola\textsuperscript{b}, Maria Pia Molinari\textsuperscript{c}, Paola Gritti\textsuperscript{d}, Maurizio Sanguinetti\textsuperscript{d}, Brunella Posteraro\textsuperscript{d}, Andrea Bacigalupo\textsuperscript{b}, Claudio Viscoli\textsuperscript{a}
Galactomannan not only Aspergillus
There are several unmet needs

Mucor

- We need earlier diagnosis and reliable prognostic tools (PET?)
- We need serological markers
- We need more active antibiotics

Candida auris

- We need to understand better the extent of its diffusion worldwide
- Outbreaks should be blocked
- Carriers should be identified