Top papers in Mycology

Clinical mycology

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Disclosures

Travel support from Gilead, Astellas, Pfizer and MSD.
Epidemiology
Review
Global and Multi-National Prevalence of Fungal Diseases—Estimate Precision

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An analysis of 43 published reports (>2000 million people)
Leading International Fungal Education (LIFE)

- Since 2013, the LIFE portal has facilitated the estimation of the burden of serious fungal infections country by country for over 5.7 billion people (>80% of the world’s population)

- The term “burden” encompasses annual incidence, period or total prevalence and, in the case of recurrent vulvovaginal candidiasis, annual prevalence

- The estimates are not a substitute for high quality epidemiological study or comprehensive surveillance

- Rough approximation and a means of comparing countries
A map showing completed country estimates of fungal diseases by August 2017
<table>
<thead>
<tr>
<th>Fungal Disease</th>
<th>Annual Incidence</th>
<th>Global Burden</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin, hair, nail</td>
<td></td>
<td>~1,000,000,000</td>
<td></td>
</tr>
<tr>
<td>Fungal keratitis</td>
<td></td>
<td>~1,000,000</td>
<td></td>
</tr>
<tr>
<td>Mucosal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>~2,000,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophageal candidiasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septicemia</td>
<td></td>
<td>~6,500,000</td>
<td>Adults only, starts from age 4</td>
</tr>
<tr>
<td>Fungal rhinosinusitis</td>
<td></td>
<td>~12,000,000</td>
<td>Adults only, probably uncommon in children</td>
</tr>
<tr>
<td>Acute invasive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive candidiasis</td>
<td>~750,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>&gt;300,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em> pneumonia in AIDS and non-AIDS</td>
<td>~500,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcosis in AIDS</td>
<td>~223,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>&gt;10,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated histoplasmosis</td>
<td>~100,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talaromycosis *</td>
<td>~8000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Here, we have reviewed the incidence and prevalence of invasive aspergillosis in 40 countries accounting for a global population higher than 2000 million people (29% of the world population).
- Fungal diseases kill more than 1.5 million and affect over a billion people
- Still a neglected topic by public health authorities
- The aim of these papers (facilitated by LIFE) is that they may stimulate much better national (and international) epidemiological studies, supported by improved diagnostics in each country
Candida auris: the current situation in Europe
Bloodstream or other type of infection was reported in 150 cases (24.2%).

Number of reported *Candida auris* cases by year and infection or colonisation, European Union and European Economic Area countries, 2013–2017 (n = 620)
Geographic distribution of *Candida auris* cases reported in European Union / European Economic Area countries, 2013–2017 (n = 620)

*Euro Surveill.* 2018;23(13)

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Laboratory capability

- Laboratory capability to detect and identify *C. auris* was available in 21 of the 29 responding countries, either by formally designated mycology reference laboratories (n = 12 countries) or by laboratories with a reference function (n = 9 countries)

- MALDI-TOF (17 labs), sequencing of genetic loci (9 labs), sequencing of ITS domains of rRNA (6 labs)

*Euro Surveill.* 2018;23(13)
Conclusions

- *C. auris* is detected with increasing frequency and large outbreaks have occurred in Europe since 2013.

- To mitigate the risk from the introduction of *C. auris* and to prevent and control its further spread, adequate laboratory capacity, surveillance, and infection control preparedness is required in all EU/EEA countries.
An ongoing outbreak in Spain
April 2016 - January 2017
Colonized patients: 140
Candidemia: 41 patients
87.8% in SICU
All isolates resistant to fluconazole and voriconazole and susceptible to amphotericin B.
Thirty-day mortality: 41.4%
Severe septic metastasis (spondylodiscitis, endocarditis): 12%
Epidemic curve of candidemia episodes (n=41) and new colonized patients (n=140) by *C. auris* from April 2016 to January 2017.
2016

Colonizations (n=335)

Candidemias (n=80)

2017

2018

Courtesy of Javier Pemán
Risk factors
Beyond neutropenia and other traditional risk factors for IFIs...
Emergence of ibrutinib-related IFIs

- Ibrutinib: inhibitor of Bruton tyrosine kinase (BTK)
- B-cell cancers (mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstrom macroglobulinemia, diffuse large B-cell lymphoma, primary CNS lymphoma)

<table>
<thead>
<tr>
<th>Type and Status of Cancer</th>
<th>Type of IFI (No. of Cases)</th>
<th>Frequency of IFI, %</th>
<th>Patients, No.</th>
<th>Median Follow-up, mo</th>
<th>Study Timing, Month/Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed CLL/SLL</td>
<td>IA (2)</td>
<td>0.5</td>
<td>391</td>
<td>9.4</td>
<td>6/2012–11/2013</td>
<td>Byrd et al [10]</td>
</tr>
<tr>
<td>Relapsed WM</td>
<td>IA (1)</td>
<td>3.2</td>
<td>31</td>
<td>18.1</td>
<td>8/2014–2/2015</td>
<td>Dimopoulos et al [9]</td>
</tr>
<tr>
<td>Relapsed MCL</td>
<td>Cryptococcosis (1), PJP (1), histoplasmosis (1)</td>
<td>2.7</td>
<td>111</td>
<td>26.7</td>
<td>2/2011–1/2014</td>
<td>Wang et al [7]</td>
</tr>
<tr>
<td>Relapsed/refractory DLBCL</td>
<td>None</td>
<td>0</td>
<td>80</td>
<td>11.5</td>
<td>5/2012–5/2013</td>
<td>Wilson et al [8]</td>
</tr>
<tr>
<td>Refractory CLL/SLL</td>
<td>PJP (1)</td>
<td>0.7</td>
<td>145</td>
<td>27.6</td>
<td>1/2013–6/2013</td>
<td>O’Brien et al [21]</td>
</tr>
<tr>
<td>Refractory PCNSL³</td>
<td>IA (7), PJP (1)</td>
<td>44</td>
<td>18</td>
<td>15.5</td>
<td>8/2014–3/2016</td>
<td>Lionakis et al [12]</td>
</tr>
<tr>
<td>Refractory PCNSL</td>
<td>IA (2)</td>
<td>1</td>
<td>18</td>
<td>NA</td>
<td>9/2015–8/2016</td>
<td>Choquet et al [24]</td>
</tr>
<tr>
<td>Refractory PCNSL</td>
<td>IA (1)</td>
<td>5</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
<td>Grommes et al [25]</td>
</tr>
</tbody>
</table>

ESCMID eLibrary © by author
Promising therapeutic effects of ibrutinib in PCNSL, but also

Increased aspergillosis, linked to BTK-dependent fungal immunity
Murine model of *Aspergillus* infection in *Btk* knockout (*Btk*-/-) and wild-type (*Btk*+/+) mice. At 14 days of observation after pharyngeal aspiration of *A. fumigatus*, 7/26 *Btk*-/- mice exhibited mortality compared with 0/20 *Btk*+/+ mice (p = 0.013; logrank test).
2013-2017: 33 cases of IFI from 16 French centers

Invasive aspergillosis in 27/33, 11 cases (40.7%) CNS

Cryptococcosis (4), mucormycosis (1), pneumocystis (1)

Median time between ibrutinib initiation and IFI diagnosis was 3 months.
Diagnostics
A proposed algorithm for the diagnosis of mucormycosis in patients with diabetes
Literature review in Mexico: 250 cases

Overall mortality: 52%
An algorithm for diagnosis and treatment of rhino-orbito-cerebral mucormycosis in patients with diabetes mellitus

“Red flags”/warning signs

- Cranial nerve palsy
- Diplopia, sinus pain
- Proptosis, periorbital swelling
- Orbital apex syndrome, palatine ulcer
- If these signs are not found in the first visit, consider re-evaluation if standard management of sinusitis fails
Treatment
Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa


Treatment options in resource – limited settings
More than 100,000 deaths each year from cryptococcal meningitis

- Case fatality rate in sub-Saharan Africa: 70% at 3 months
- The international standard induction treatment of 2 weeks of amphotericin B deoxycholate plus flucytosine is not available in most African clinical centers
- Most countries: monotherapy with fluconazole
- Mortality associated with this treatment is 50 to 60% at 10 weeks and 70% at 1 year.

Design of the study

- Open-label, phase 3, randomized, noninferiority, multicenter trial
- Nine centers in Malawi, Zambia, Tanzania and Cameroon
- Five regimens:
  1. Oral fluconazole (1200mg) plus flucytosine for 2 weeks
  2. Amphotericin B (1mg/kg) plus fluconazole for 1 week, followed by fluconazole for one week
  3. Amphotericin B (1mg/kg) plus flucytosine for 1 week, followed by fluconazole for one week
  4. Amphotericin B (1mg/kg) plus fluconazole for 2 weeks
  5. Amphotericin B (1mg/kg) plus flucytosine for 2 weeks

- After induction, fluconazole: 800mg for 2 weeks, 400mg for 6 weeks and 200mg thereafter.
678 randomized patients in the intention-to-treat analysis

<table>
<thead>
<tr>
<th></th>
<th>Mortality at 2 weeks</th>
<th>Mortality at 10 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral regimen</td>
<td>18.2%</td>
<td>35.1%</td>
</tr>
<tr>
<td>1 week amphotericin B</td>
<td>21.9%</td>
<td>36.2%</td>
</tr>
<tr>
<td>2 weeks amphotericin B</td>
<td>21.4%</td>
<td>39.7%</td>
</tr>
</tbody>
</table>
Difference in mortality between the 1-week amphotericin B-flucytosine group and amphotericin B-fluconazole group

P = 0.002 by log-rank test

- Amphotericin B plus fluconazole
- Amphotericin B plus flucytosine

Weeks since Randomization
Conclusions

In resource-limited settings:

- One week of amphotericin B plus flucytosine was the most effective option for induction therapy

- In the absence of availability of amphotericin B or in conditions in which amphotericin B cannot be administered safely, the oral combination of fluconazole plus flucytosine provides an effective and sustainable alternative.
Report of the largest series to date focusing on PVE-C
Prosthetic valve endocarditis caused by *Candida* spp. (PVE-C)

- **Mortality:** 57-62.5%

- **ESCMID and IDSA Guidelines:** based on expert opinions or small case series → combination of surgery and subsequent azole treatment

- No convincing data about the clinical benefit of early surgery for all patients

- **ESCAPE study:** retrospective analysis of PVE-C cases collected in Spain and France between 2001 and 2015
Prosthetic valve endocarditis caused by *Candida* spp. (PVE-C)

- 46 cases
- *C. parapsilosis*: 41%, *C. albicans*: 35%
- All yeasts were susceptible to conventional antifungal agents
- 19 patients (41%) underwent surgery
- Cardiac surgery was independently associated (by multivariate analysis) with:
  - Age <66 years
  - Absence of cardiac failure
Prosthetic valve endocarditis caused by *Candida* spp. (PVE-C)

- 68% received maintenance treatment with fluconazole
- Relapse: 4/21 (19%) with maintenance treatment
  
  5/10 (59%) without maintenance treatment
- Mortality rate at 6 months: 37%
- 6-month mortality rate in:
  - patients who received L-amb-based therapy alone: 6%
  - Patients who received echinocandin-based treatment alone: 44%
Conclusions of the ESCAPE study

- By multivariate analysis, the 6-month survival rate was better in patients who received L-amb-based monotherapy.
- 6-month mortality outcomes in patients not operated on were similar to those in patients who underwent operation.
- The results do not support the recommendation of early surgery for all patients with PVE-C.
- “Patients who are not good surgical candidates based on age and/or underlying heart failure can do fairly well with L-amb-based induction therapy followed by long-term azole maintenance therapy.”
A new azole, with high efficacy in the treatment of RVVC
RVVC: very high burden of disease

- No drugs approved for the treatment of RVVC
- IDSA recommendation: maintenance fluconazole therapy
- 2004 study: >55% of patients experienced an acute VVC recurrence within 6 months of ending the maintenance therapy

VT-1161: a new tetrazole

- Metalloenzyme inhibitor that targets the biosynthesis of ergosterol by selectively inhibiting fungal Cyp51
- High oral bioavailability and long plasma half-life.
- May avoid the toxicities and drug interactions that occur with the azoles secondary to cross-reactivity with human cytochrome P450 enzymes
- Broad-spectrum activity against yeast, dermatophytes, endemic fungi and some molds.

Documented history of RVVC (≥ 3 episodes of acute VVC in the past 12 months)

Induction phase: 3 doses of oral fluconazole (150mg/72 hours)

Randomization to 1 of 5 regimens:
1. VT-1161 150mg/d/7days – 150mg/wk/11 weeks – placebo 12 wks
2. VT-1161 300mg/d/7days – 300mg/wk/11 weeks – placebo 12 wks
3. VT-1161 150mg/d/7days – 150mg/wk/23 weeks
4. VT-1161 300mg/d/7days – 300mg/wk/23 weeks
5. Only placebo
The results of this study suggest that VT-1161 is a promising agent to treat RVVC. Further clinical investigation must be undertaken.
Encouraging data for a new antifungal agent
In prophylaxis and continuous-therapy models, VT-1161 outperformed posaconazole in prolonging survival.

P = 0.03 vs placebo, POS-C or POS-D
Thank you!