Antifungal Stewardship
Do we need it?

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Melbourne, Australia

Recommended reading:

No conflicts of interest
Case Study 1

You are a general ID physician who has been asked by your hospital executive to address the costs of antifungal agents in your hospital. 3 of the agents, liposomal amphotericin, voriconazole and posaconazole are in the top 10 for hospital drug costs.
Goals of Antimicrobial Stewardship

Judicious use

– Optimal patient outcomes
– Conserve antifungals

1. Antifungal usage surveillance (as costs a major driver)
2. Optimise use (diagnostics, clinical review)
3. Monitor outcomes of program
   – IFI surveillance
   – Establish failure & efficacy (e.g. breakthroughs)
4. Monitor resistance

BUT Fungal infection surveillance is complex!
General Strategies for Stewardship

• Restrictive (rapid impact)
  – Formulary
  – Approval required for use by nominated person (ID, expert)

• Persuasive (more effective long term)
  – Education, educative tools
  – Clinical guidelines
  – Access to experts to discuss case
  – Post prescription review

But evidence for antibiotics...

• Simply monitoring antifungal usage (or cost) data is not appropriate without:
  – An assessment of appropriateness of use (i.e. what was the indication, and for which at-risk group, guideline concordance, preventable infection?)
  – Understanding local epidemiology, new patients at risk (e.g. Campath, myeloma)
  – Using accepted definitions for IFI to enable benchmarking (Revised EORTC/MSG definitions CID 2008)
Implementation barriers and facilitators in the haematology and oncology setting
An Australian Perspective
Fact 1: Cancer patients are complex!

- Oncology vs. Haematology
- Low risk versus high risk haematology
  - HSCT vs. CLL
- Low risk versus high risk oncology
  - Dose intense regimens (e.g. breast, H&N, sarcoma)
- Use of novel agents
  - e.g. rituximab, lenolinamide, Campath, ibrutinib
- Be aware of steroid use (often underestimated)
- Changes in intensity of treatment for elderly:
  - Autologous SCT for myeloma patients >70 yrs
  - Allogeneic SCT for patients 55-80 yrs
  - Standard AML chemotherapy up to 80 yrs
Fact 2: Clinical presentations of infections complex or difficult to Dx

- Altered clinical expression common
- Broader spectrum of pathogen(s)
  - And often >1 (e.g. Aspergillus & Stenotrophomonas, PJP and IFI, CMV & IFI)
- Timing of infection post treatment important
- Require aggressive diagnostic methods (e.g. BAL)
- Early empiric therapy may be necessary
Phases of opportunistic infections among allogeneic hematopoietic cell transplant recipients

- **Phase I: Pre-engraftment**
  - Graft-versus-host-disease: Acute
  - Neutropenia, barrier breakdown (mucositis, central venous access devices)
  - Gram-negative bacilli
  - Gram-positive organisms
  - Gastrointestinal *Streptococcus* species

- **Phase II: Post-engraftment**
  - Impaired cellular and humoral immunity; NK cells recover first, CD8 T cell numbers increasing but restricted T cell repertoire
  - Encapsulated bacteria
  - Herpes simplex virus
  - Respiratory and enteric viruses
  - Cytomegalovirus (seasonal/intermittent)
  - Varicella zoster virus
  - Other viruses eg, HHV6
  - EBV PTLD

- **Phase III: Late phase**
  - Impaired cellular and humoral immunity; B cell & CD4 T cell numbers recover slowly and repertoire diversifies
  - *Aspergillus* species
  - *Candida* species
  - *Aspergillus* species
  - *Pneumocystis*

Day 0 | Day 15-45 | Day 100 | Day 365 and beyond

- More common
- Less common

EBV: Epstein-Barr virus; HHV6: human herpesvirus 6; PTLD: posttransplant lymphoproliferative disease.

Fact 3: Haematologists/oncologists have strong belief systems

- “We are very good at identifying our patients at risk”
- “Our patients are special”
- Still febrile….“we need to escalate just in case”
- “Meropenem is better than pip/taz for neutropenic enterocolitis”
- “We would like to save the (central) line”

Expect evidence to be looked at closely
Need good working relationships to effect change
A fit 60 year old man, diagnosed with Stage III follicular lymphoma receives CHOP chemotherapy (consisting of cyclophosphamide, doxorubicin, vincristine and prednisolone) administered every 21 days. On day 9 of Cycle 2 his ANC is $0.4 \times 10^9$ cells/L and he is febrile with temperatures $> 38.5^\circ$C. He otherwise feels well, has had no rigors, no hypotension, no focal signs or symptoms of infection. He lives close to the hospital and has good supports.

**Do you consider this patient low or high risk for developing medical complications?**

- **Low-risk, 49%**
- **High-risk, 47%**
- **Unsure, 4%**

The answer? **Low risk**

Establishing antifungal stewardship

• Establish clinical governance (i.e. exec support)
• Include antifungals in antimicrobial policy as *highly restricted*
• The formulary should reflect best evidence/published guidelines
• ENGAGE
  – Pharmacists (project management skills)
  – ID/infection prevention colleagues
  – Haematology/oncology clinicians/junior staff
  – Nursing staff (critical to engage)
• An ID fellow embedded within the service optimal (impact day-to-day decision making)
• Opportunities for research will be a driver (this group very keen to publish)
Recommend national or international consensus/expert guidelines

Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting, 2014


Monica Slavin on behalf guidelines writing group and steering committee:
Sharon Chen, Karin Thursky, Orla Morrissey, Leon Worth, Christina Chang, Chris Blyth, Jeff Szer

7 consensus guidelines covering prevention and management of IFI (including PJP)


Adapt recommendations for local use
Consider potential formulary changes

Guidelines for the antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation

1 PURPOSE & SCOPE
These guidelines are based on the national consensus guidelines published in December 2014


The summary recommendations are shown below.

2 INTRODUCTION
Antifungal prophylaxis represents an important ‘preventive’ strategy for managing patients at high risk of developing an invasive fungal disease (IFD), particularly those undergoing intensive treatments. The approach to deciding appropriate prophylaxis for the above population requires consideration of:

- the patient’s risk of acquiring an invasive mould or yeast infection during period of immunosuppression
- an institution’s incidence of invasive fungal infection and an ever evolving fungal ecology of the environment
- drug-related factors such as effectiveness, associated toxicity, potential drug-drug interactions and cost. 

No prophylaxis is required for lower risk patients which includes those with solid tumours undergoing chemotherapy.
### 3 INDICATIONS FOR PROPHYLAXIS

**Haematological malignancy**

*First-line prophylactic agent should be posaconazole for mould-active prophylaxis and fluconazole for candida prophylaxis*

<table>
<thead>
<tr>
<th>Risk classification</th>
<th>Clinical examples</th>
<th>Recommended prophylaxis</th>
</tr>
</thead>
</table>
| **High risk (>10% incidence IFD)** | - Acute leukaemia or myelodysplasia, with remission induction and re-induction chemotherapy  
  - Mod - Severe acute GVHD (grade 3-4): steroid dose 0.5-1mg/kg/day +/- 2nd immunosuppressant  
  - Mod - Severe chronic GVHD  
  - Allogeneic HSCT with invasive fungal risk factors (inc. CMV, GVHD, previous IFI)  
  - Alemtuzumab use, especially in highly treatment-refractory patients with CLL or lymphoma  
  - Neutrophils <0.1 x 10^9/L for >3 weeks or <0.5 x 10^9/L for >5 weeks | Mould-active prophylaxis:  
  posaconazole 200mg orally, three times a day  
  (For patients with a BMI >30, doses up to 800 mg may be required) |
<table>
<thead>
<tr>
<th>Low risk (≈2% incidence of IFD)</th>
<th>Very low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Autologous HSCT</td>
<td>o Standard chemotherapy for lymphoma</td>
</tr>
<tr>
<td>o Allogeneic HSCT up to at least Day 100</td>
<td>o Chronic myeloid leukaemia</td>
</tr>
<tr>
<td>o Patients receiving intensive/dose-escalated therapy for lymphoma</td>
<td>o Other myeloproliferative neoplasms</td>
</tr>
</tbody>
</table>

**Anti-Candida prophylaxis:**
fluconazole 200mg orally, daily

**No prophylaxis (unless additional risk factors)**

GVHD, graft-versus-host disease; HSCT, haemopoietic stem cell transplant.

**Additional individual risk factors for invasive candida or mould infection**
*(discuss with Infectious Diseases where appropriate)*

- Prolonged broad spectrum antibiotics (Candida)
- Gastro-intestinal surgery (Candida)
- ICU admission (Candida)
- Central venous catheter (Candida)
- Multiple sites of colonisation (e.g. sputum, skin, drain-tube)
- Iron overload (mould)
- Recent CMV reactivation (mould)
- Ganciclovir use (mould)
- Heavy environmental exposure to moulds
- Corticosteroids >1 mg/kg prednisolone equivalent and neutrophils <1 x 10⁹/L for >1 week
- Corticosteroids >2 mg/kg prednisolone equivalent >2 weeks
- Heavily pre-treated haematology patients
<table>
<thead>
<tr>
<th>Risk group</th>
<th>Agent</th>
<th>Alternative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Posaconazole</td>
<td>Voriconazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Itraconazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liposomal amphotericin B</td>
</tr>
<tr>
<td>Low risk</td>
<td>Fluconazole</td>
<td>Itraconazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caspofungin</td>
</tr>
</tbody>
</table>

Oral *posaconazole* remains the preferred agent for use in high-risk patients due to its broad anti-mould activity and low-breakthrough IFD rates. It is the only mould-active agent to demonstrate a survival advantage in a randomised trial in AML patients.

Oral posaconazole suspension can be difficult to reliably administer in patients with GVHD of the gastrointestinal tract and mucositis, with absorption most questionable in patients experiencing vomiting, diarrhoea or colitis. Further information on optimising posaconazole exposure and monitoring drug levels is available below in PROPHYLAXIS DRUGS AND DOSING or the optimising drug therapy guidelines published by *Chau et al. 2014*.
Use of electronic antimicrobial AMS

- Guidance MS – a computerised assistive decision support tool for AMS (developed at Royal Melbourne Hospital 2005)
- Innovation arm of the National Centre for Antimicrobial Stewardship
- In 60 Australian hospitals (inc. paediatric)
- Unique – supports networks/multi-site programs (NOT only patient centric like EMRs/EMM)
- Fully supports hospital accreditation for AMS
- Supports
  - Formulary/Guideline concordant prescribing
  - Restricted indications/durations of use
  - Post prescription review
  - Flexible implementation
  - Audit/reporting/research
1. Access Guidance MS from the intranet.
An alert approval generated for clinical review

Patients are triaged for review based on drug (e.g. liposomal ampho), indication (e.g. sepsis), or LACK of an approval (i.e. dispensing alert)
Auditing and reports for antimicrobials. Case finding—indications captured more accurate than clinical coding.
A Pilot Study of a Computerized Decision Support System to Detect Invasive Fungal Infection in Pediatric Hematology/Oncology Patients.

Bartlett A¹, Goeman E¹, Vedi A², Mostaghim M³, Trahair T⁴, O'Brien TA⁴, Palasanthiran P¹, McMullan B¹.

Author information
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2School of Women's and Children's Health, University of New South Wales, Sydney, NSW, Australia.
3University of Technology, Sydney, Australia.
4Kids Cancer Centre, Sydney Children's Hospital, Randwick, NSW, Australia.

Abstract

OBJECTIVE: Computerized decision support systems (CDSSs) can provide indication-specific antimicrobial recommendations and approvals as part of hospital antimicrobial stewardship (AMS) programs. The aim of this study was to assess the performance of a CDSS for surveillance of invasive fungal infections (IFIs) in an inpatient hematology/oncology cohort.

METHODS: Between November 1, 2012, and October 31, 2013, pediatric hematology/oncology inpatients diagnosed with an IFI were identified through an audit of the CDSS and confirmed by medical record review. The results were compared to hospital diagnostic-related group (DRG) coding for IFI throughout the same period.

RESULTS: A total of 83 patients were prescribed systemic antifungals according to the CDSS for the 12-month period. The CDSS correctly identified 19 patients with IFI on medical record review, compared with 10 patients identified by DRG coding, of whom 9 were confirmed to have IFI on medical record review.

CONCLUSIONS: CDSS was superior to diagnostic coding in detecting IFI in an inpatient pediatric hematology/oncology cohort. The functionality of CDSS lends itself to inpatient infectious diseases surveillance but depends on prescriber adherence.
What about less well studied populations?

IFI Breakthrough in Non-AML at Peter Mac
A collaborative project between pharmacy, ID and Haem unit. Guidance antimicrobial approvals, chemotherapy and pharmacy dispensing system used to undertake surveillance of IFIs.

<table>
<thead>
<tr>
<th>Haematological malignancy</th>
<th>Precursor lymphoid neoplasms</th>
<th>Mature B-cell neoplasms</th>
<th>Mature T- &amp; NK-cell neoplasms</th>
<th>Hodgkin lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLL/SLL</td>
<td>DLBCL</td>
<td>Plasma cell neoplasms</td>
<td>Other B-cell NHL</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>17</td>
<td>51</td>
<td>186</td>
<td>251</td>
</tr>
<tr>
<td>No. receiving antifungal prophylaxis</td>
<td>9</td>
<td>9</td>
<td>99</td>
<td>103</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>7</td>
<td>9</td>
<td>99</td>
<td>103</td>
</tr>
<tr>
<td>Mold-active agent</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>IFD episodes</td>
<td>n</td>
<td>4</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>IFD prevalence (95% CI)</td>
<td>29.4% (9.5-68.6%)</td>
<td>7.8% (2.1-20.1%)</td>
<td>4.3% (1.9-8.5%)</td>
<td>2.8% (1.1-5.7%)</td>
</tr>
<tr>
<td>IFD rate per 10,000 treatment days</td>
<td>10.7</td>
<td>4.4</td>
<td>2.8</td>
<td>*</td>
</tr>
</tbody>
</table>

A national audit tool for antimicrobials.
All public and private hospitals
Supports benchmarking
Data for action
Implementation barriers and facilitators in non-hematological patients

A SPANISH Perspective

Patricia Muñoz
Clinical Microbiology and Infectious Disease
Hospital General Universitario Gregorio Marañón
Instituto de Investigación Gregorio Marañón
Centro de investigación biomédica en red en Enfermedades Respiratorias (CIBERES)
Universidad Complutense de Madrid. Spain
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CONFLICT OF INTEREST DISCLOSURE

Within the last 12 months
Consultant and/or speaker for Astellas, Gilead, Merck, Novartis and Pfizer

No conflict of interest related to the contents of this session
Present way of using antifungals

- **Prophylaxis** (guidelines)

- **Targeted** therapy (culture - BMs)

- **Empirical** therapy (based on risk factors and clinical scores such as the ‘Candida score’)

@ ESCMID eLibrary by author
Who prescribes What

- AF use audit (100 patients)
  - Who prescribes what and why

Evaluation of antifungal use in a tertiary care institution: antifungal stewardship urgently needed

Maricela Valerio¹,², Carmen Guadalupe Rodriguez-Gonzalez²,³, Patricia Muñoz¹,²,⁴*, Betsabe Caliz²,³, María Sanjurjo²,³ and Emilio Bouza¹,²,⁴ on behalf of the COMIC Study Group (Collaborative Group on Mycoses)†

ICU patients are also ‘special’

- **Type of patient**
  - Age (newborns, elderly)
  - Obese

- **Comorbidities**
  - Transplantation
  - Neutropenia
  - Other IS
  - Drug interactions
  - Cancer, diabetes

- **Clinical situation**
  - Critical conditions
  - Renal insufficiency
  - Liver insufficiency
  - Hypoalbuminemia

- **External devices**
  - ECMO
  - VAD
Methods: First steps toward AF stewardship

✓ Setting: 1,550-bed tertiary teaching centre serving a population of approximately 715,000 inhabitants

  ▪ Approx. 1,500 patients per year receive systemic AFs, with a cost of ~ €3,000,000

• We identified the main AF prescribing departments: Hematology, ICUs, Oncology, Nephrology, Gastroenterology, Pediatrics, Transplant units

• We conducted surveys to evaluate physicians’ knowledge on the diagnosis and management of Invasive fungal infections (IFI) and AF prescribing practices: EDUCATION

• We created a Collaborative Group on Mycoses (COMIC)

✓ At least: Pharmacists, clinical microbiologists, ID consultants and physicians of the top AF prescribing departments
CLINICAL MICROBIOLOGY
MYCOLOGY LAB
MOLECULAR BIOLOGY LAB

ANTIFUNGAL PRESCRIBERS
Hematology, SOT, intensive care unit, oncology, gastroenterology, internal medicine, surgery, radiology...

COMIC STUDY GROUP

INFECTIOUS DISEASE ATTENDINGS
Emilio Bouza, Patricia Muñoz, Ana Fernández-Cruz, Paloma Gijón, Mar Sánchez-Somolinos, Belén Padilla, Antonio Vena

PHARMACY DEPARTMENT
Maria Sanjurjo, Carmen Rodríguez, Betsabé Cálix
Our Strategy **Has 3 Pillars**

1. **Education**

2. **Diagnosis**

3. **Therapy**

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**Indication**

**Dose**

**TDM**

**Duration**

**DRUG**
Education and Local Guidelines

- **Initiate educational activities**
  - General and particular sessions
  - Use the results of the previous surveys
  - Involve all members of the AFS team

- **Produce your own local consensus guidelines**
  - Intranet and/or pocket leaflets
  - Local epidemiology, diagnostic criteria, indications, dose adjustments
  - General or for specific departments
  - On-site education
  - Members contact information/telephone numbers
# How much European prescribing physicians know about invasive fungal infections management?

Maricela Valerio¹,², Antonio Vena¹,²,³, Emilio Bouza¹,²,³, Nanna Reiter⁴, Pierluigi Viale⁵, Marcel Hochreiter⁶, Maddalena Giannella⁶, Patricia Muñoz¹,²,⁵,⁶ and on behalf the COMIC study group (Collaborative group on Mycosis).

## Table 2 Percentage of adequate answers regarding department and physician category

<table>
<thead>
<tr>
<th>Question</th>
<th>Adequate answer</th>
<th>Overall N = 121</th>
<th>Medical n = 62</th>
<th>ICU N = 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q11. Which do you think is the percentage of fluconazole resistance in <em>Candida</em> strains isolated from blood cultures at your hospital?</td>
<td>Less than 5%.</td>
<td>24</td>
<td>19.4</td>
<td>28.8</td>
</tr>
<tr>
<td>Q12. In which of the following scenarios would you choose L-AmB as your first choice?</td>
<td>In unspecified invasive filamentous fungal infection.</td>
<td>47.1</td>
<td>51.6</td>
<td>44.2</td>
</tr>
<tr>
<td>Q13. Regarding the treatment with azoles and candins, which of the following statements is true:</td>
<td>Candins can be used as empirical treatment before knowing the yeast antifungal susceptibility.</td>
<td>67.8</td>
<td>64.5</td>
<td>75</td>
</tr>
<tr>
<td>Q14. When isolating <em>Aspergillus</em> spp. in a respiratory sample, you would consider:</td>
<td>Treatment in patients who fulfilled criteria of proven or probable invasive aspergillosis</td>
<td>52.1</td>
<td>74.2</td>
<td>26.9</td>
</tr>
<tr>
<td>Q15. Which of the following statements regarding the Galactomannan test is false:</td>
<td>It can only be performed in serum samples.</td>
<td>42</td>
<td>50.8</td>
<td>35.3</td>
</tr>
</tbody>
</table>
### Evaluation of antifungal use in a tertiary care institution: antifungal stewardship urgently needed

Maricela Valerio¹,², Carmen Guadalupe Rodriguez-Gonzalez²,³, Patricia Muñoz¹,²,⁴*, Betsabe Caliz²,³, Maria Sanjurjo²,³ and Emilio Bouza¹,²,⁴ on behalf of the COMIC Study Group (Collaborative Group on Mycoses)†

<table>
<thead>
<tr>
<th>Inappropriate Prescription, n (%)</th>
<th>Prophylaxis (n=15)</th>
<th>Empirical (n=42)</th>
<th>Pre-emptive (n=20)</th>
<th>Tailored (n=20)</th>
<th>Overall (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score, mean ± SD</td>
<td>9.1 ± 1.3</td>
<td>6.6 ± 2.7</td>
<td>8.3 ± 2.2</td>
<td>9.5 ± 1.9</td>
<td>7.7 ± 2.6</td>
</tr>
<tr>
<td>Inappropriate prescription, n (%)</td>
<td>6 (40)</td>
<td>33 (78.6)</td>
<td>10 (50)</td>
<td>5 (25)</td>
<td>57 (57)</td>
</tr>
<tr>
<td>Reason for inappropriate prescription, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no microbiological adjustment</td>
<td>1 (6.7)</td>
<td>21 (50.0)</td>
<td>7 (35.0)</td>
<td>3 (15.0)</td>
<td>35 (35.0)</td>
</tr>
<tr>
<td>inappropriate antifungal selection</td>
<td>1 (6.7)</td>
<td>20 (47.6)</td>
<td>3 (15.0)</td>
<td>4 (20.0)</td>
<td>31 (31.0)</td>
</tr>
<tr>
<td>inappropriate duration</td>
<td>2 (13.3)</td>
<td>18 (42.9)</td>
<td>4 (20.0)</td>
<td>2 (10.0)</td>
<td>27 (27.0)</td>
</tr>
<tr>
<td>inappropriate administration route</td>
<td>1 (6.7)</td>
<td>12 (28.6)</td>
<td>4 (20.0)</td>
<td>3 (15.0)</td>
<td>20 (20.0)</td>
</tr>
<tr>
<td>unnecessary prescription (incorrect indication)</td>
<td>1 (6.7)</td>
<td>9 (21.4)</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
<td>16 (16.0)</td>
</tr>
<tr>
<td>inappropriate dosage</td>
<td>2 (13.3)</td>
<td>9 (21.4)</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
<td>16 (16.0)</td>
</tr>
</tbody>
</table>
3. Identify the *magnitude of the problem* and specific targets

- **AF use audit (100 patients)**

  - **Score of adequacy** (0-10) evaluating: indication, drug, dose, via, adjustment, duration.
    - 52.6% optimal, **23.4% not optimal** and **24% incorrect**

  - Inadequate DOTs in intensive care unit 48% (**>50% of overall cost**)
Pharmacy department

- AF alerts, prescription tools, interactions, iv fluco to PO
- Monitor cost. Overall and at unit level
- Price negotiation !!!
- Expert Pharm: mentor prescribing physicians or daily audit of agreed protocols
Methods: AF stewardship structure

4. Local guidelines for diagnosis and management of IFI based on the local epidemiology

5. Annual course and pocket guidelines

6. Detection of all the patients receiving high cost AFs based on an electronic prescription system

6. ID physician bedside intervention

Valerio et al. ICAAC 2013; Poster No. 1610
Muñoz P. Mycoses. 2015 Jun;58 Suppl 2:14-25
Infectious diseases

ID physicians
- Daily bedside intervention
  - Prescribing etiquette:
    - Different healthcare models
    - Perceived loss of autonomy, local leaders in charge
  - Consultation
Methods: Bedside intervention

Ongoing intervention since Oct 2011

Pharmacy dept identifies new AF prescriptions each day
- Pharmacy department sends the list of patients to ID physicians in the programme
- ID specialists visit the patients and review the clinical charts
- ID specialists interview the prescribing physician
- ID specialists give diagnostic and treatment recommendations based on local guidelines

Patients’ records are re-reviewed after discharge

Staff attitudes to the recommendations, daily defined doses (DDDs) and the cost (€) of AFs are monitored monthly

Muñoz P. Mycoses. 2015 Jun;58 Suppl 2:14-25
Bedside intervention (5 years!)

2011–2012
N=156

31%

11%

2013–2015
N=243

85%

4%

15%

Some therapeutic advice

Stop antifungal

Change drug

Change administration route

Change dose

Advice in haematology

%
Multidisciplinary interventions

Pneumologist, Radiologists, ......

Hematologists
- More Dx workout
- Share knowledge
- Accept AFS Team decisions

Ego = 1
Knowledge

“More the Knowledge
Lesser the Ego,
Lesser the Knowledge
More the Ego...”

-Albert Einstein.
Clinical Microbiology

- Rapid turnover of lab results (streamlining)
- Help clinicians with Dx investigations
- TDM
- New diagnostic tools
IFIs are hard to prove and to exclude Biomarkers

Behavourial vs Technical changes

Muñoz P. Personal opinion
Biomarkers alone: low S (58-84%); Sp: 65.8-92.0%

Combinations:
- CAGTA80+BDG80: S 96.8% and Sp 84%
- CAGTA80 + MN75: S 93.5% and Sp 86%
- S 100% for C. albicans, C. tropicalis, and C. parapsilosis
- Only combinations including BDG detected C. krusei

<table>
<thead>
<tr>
<th>Candidemia prevalence</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.6% (present study)</td>
<td>97.7%</td>
</tr>
<tr>
<td>10%</td>
<td>99.6%</td>
</tr>
<tr>
<td>5%</td>
<td>99.8%</td>
</tr>
</tbody>
</table>
Combination of *Candida* Biomarkers in Patients Receiving Empirical Antifungal Therapy

- Prospective, observational study
- 100 patients included
  - 63 ICU (44 surgical and 19 medical)
  - 37 non-ICU (13 surgical and 24 medical)
- Antifungals indication
  - High-risk gastrointestinal surgery
  - Sepsis in non-surgical patients
- Final classification
  - No-IC 58%, proven IC 30%, probable IC 12%

Martinez-Jimenez MC JAC 2015; 70(11):3107-15
Microbiology and AFS

- Patients with suspected IC treated empirically
- CAGTA + BDG: **NPV 97%** (100% in ICU patients)

### Sensitivity, specificity, PPV and NPV of the combination of CAGTA + BDG in critical and non-critical patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>S (%)</th>
<th>SP (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (100)</td>
<td>96.7 (80.9-99.8)</td>
<td>47.1 (35.4-59.4)</td>
<td>43.9 (31.9-56.6)</td>
<td>97.1 (82.9-99.8)</td>
</tr>
<tr>
<td>ICUs (63)</td>
<td>100.0 (62.9-99.0)</td>
<td>42.6 (29.5-56.7)</td>
<td>22.5 (11.4-38.9)</td>
<td>100 (82.2-99.6)</td>
</tr>
<tr>
<td>Non ICUs (37)</td>
<td>95.2 (74.1-99.7)</td>
<td>62.5 (35.9-83.7)</td>
<td>76.9 (55.9-90.2)</td>
<td>90.9 (57.1-99.5)</td>
</tr>
</tbody>
</table>

Martinez-Jimenez MC JAC 2015; 70(11):3107-15
Annual cost of antifungals (USD)

-4: 3057202
-3: 3031328
-2: 3773189
-1: 3817455
1: 3288292
2: 2871497
3: 2419774

~≈ half a million USD per year
**AFS program: Clinical and Microbiological results**

<table>
<thead>
<tr>
<th>Incidence of candidemia /1000 adm</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>0.87</td>
<td>0.83</td>
<td>0.66</td>
<td>0.48</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>0.27</td>
<td>0.53</td>
<td>0.38</td>
<td>0.35</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>0.09</td>
<td>0.13</td>
<td>0.24</td>
<td>0.12</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>0.16</td>
<td>0.22</td>
<td>0.16</td>
<td>0.08</td>
</tr>
</tbody>
</table>

% non albicans Candida

| 58.5 | 52.8 | 53.8 | 57.1 |

% Fluconazole Resistance (Candida spp.)

| 6.3 | 4.7 | 4.1 | 3.4 |

### Health results

<table>
<thead>
<tr>
<th>Voriconazole levels out of range (%)</th>
<th>2011</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF toxicity (%)</td>
<td>NA</td>
<td>28</td>
</tr>
<tr>
<td>Candidemia related mortality (%)</td>
<td>21.8</td>
<td>13.9</td>
</tr>
</tbody>
</table>
Targeted therapy
The Impact of Guidelines-concordant Management on the Outcomes of Candidemia

- Prospective multicenter study of hospitalized adults with candidemia in 10 hospitals from Spain (2010-2011).

- We analyzed the compliance with the following recommendations of the guidelines:
  1. Early **appropriate antifungal** therapy
  2. **Use of echinocandin or amphotericin B therapy** in patients with neutropenia or septic shock
  3. Administration of a different class of antifungal drug in patients with breakthrough candidemia
  4. **Source control, follow-up blood cultures, performing an ophthalmoscopic evaluation or an echocardiogram, and treatment duration** according the complexity of the infection.

The impact of guidelines implementation on clinical outcomes was analyzed by univariate and multivariate analysis, comparing adherent with non-adherent patients.
The Impact of Guidelines-concordant Management on the Outcomes of Candidemia

- **376 episodes of candidemia.** A full compliance of the recommendations was performed in <15% of the episodes.
- Within 2 days of candidemia 56% of patients received an appropriate antifungal treatment.
- 42% of patients with septic shock and 65% with neutropenia received echinocandin or amphotericin B therapy.
- Venous catheters were removed in 79% of cases (98% in whom it was considered the source of the infection).
- 71% of patients had follow-up blood cultures.
- Ophthalmoscopy and Echocardiogram were performed in 47% and 49% of cases.

Adherence with less than 50% of the recommendations was independently associated with a higher early (AOR=160.5; 95% CI, 18.8–1368; \( p < .001 \)) and overall mortality (AOR=21.1; 95% CI, 9.4–47.4; \( p < .001 \)).
Clinical Impact of a *Candida* bundle on management of candidemia in adults


- **Aim:** Evaluate the effectiveness of a comprehensive care bundle to increase compliance with the overall management of adult patients with candidemia.

- Management of candidemia was compared between the group receiving the care bundle and historical controls, using a pretest-posttest design.

- **Patients who died within the first 72 h from BC collection were excluded from the primary analysis,** as these patients would not have the opportunity to complete all the elements of the care bundle.

Clinical Impact of a *Candida* bundle on management of candidemia

### PRELIMINARY RESULTS

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Intervention group N=50 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bundle elements successfully completed</td>
<td>49 (98)</td>
</tr>
<tr>
<td>Patients with more than 1 element not completed successfully</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Appropriate therapy after culture and susceptibility results</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Intravenous catheter removed*</td>
<td>42/42 (100)</td>
</tr>
<tr>
<td>Blood cultures every 48 hrs until negative</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Appropriate duration of therapy</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Ophthalmologic examination performed</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Echocardiogram (TTE or ETE) performed</td>
<td>49 (100)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Vena A, Muñoz P
Aims of our study

- Evaluate the inter-patients variability in antifungal pharmacokinetics
- Examine whether recommended doses of antifungal drugs accurately predict serum concentrations in non-selected hospitalized patients.

Prospective study performed at Gregorio Marañon hospital including all hospitalized patients who received a systemic azole or an echinocandin for prophylaxis or treatment (either empirical or targeted) for an IFI.
Each patient had one blood sample taken at the end of a dosing interval (within 30 minutes of the next dose), at least 3 days post-initiation of treatment.

Adequate concentrations:
- Fluconazole >11 µg/ml
- Echinocandins >1 µg/ml
- Voriconazole 1-5.5 µg/ml
- Posaconazole >0.7 µg/ml

Outcome was considered favorable when the following criteria were fulfilled: completion of treatment course without change or addition of another antifungal drug; no evidence of breakthrough IFI or of attributable mortality.
Therapeutic drug monitoring of antifungal drugs: another tool to improve patients outcome?

- 84 patients (65.4% male, median age of 61 years)
- Indication: prophylaxis (40.5%), empirical (31%) and targeted (28.5%) therapy.
- Main AFs prescribed: micafungin (28 patients), fluconazole (23) and voriconazole (15).
Therapeutic drug monitoring of antifungal drugs: another tool to improve patients outcome?

- According to current guidelines, doses were considered adequate in 76 patients (90.5%), but only 67.1% of them attained an adequate serum concentrations.
- 8 patients received inadequate doses and 3 had good levels.
- Favorable clinical outcome was observed in 51 patients with empirical or targeted therapy.

According to serum concentration

According to current guidelines

$\rho = 0.02$

Adequate AF exposure
Non adequate fungal exposure

$\rho = 1$
Some of our recent references in the field


- **Antifungal use audit:** identifies how AF are used and targets for intervention. Valerio M, *JAC* 2014

- **Non restrictive bed-side intervention:** safe and very cost-effective. Valerio M. *JAC* 2015


- **Monitoring AF levels:** *Guinea J Med Mycol.* 2016

- **A review:** Muñoz P. *Mycoses.* 2015;58(Suppl 2):14–25

- **Bundle for management of candidemia.** In Press
Case study 2
Karin Thursky

Peter MacCallum Cancer Centre has had an effective AMS program in place since 2009 with

1. Dedicated ID physician and pharmacist for AMS
3. Policies and guidelines for adapted to PMAC
4. An electronic AMS program (Guidance MS) to monitor indications, survey infections/AMT rounds and post prescription review
5. Availability of early bronchoscopy 24-72 hours, BAL galactomannan and aspergillus PCR

We evaluated the role of PET/CT in the management of IFIs
But rising costs of antifungals!!

Expenditure: >$1,000,000 in 2012
Positron emission tomography (PET)

- Radio-isotope: $^{18}$F-FluoroDeoxyGlucose (FDG)
  - Glucose analogue
  - Actively transported into cells via GLUT

- FDG-PET:
  - Functional *plus* semi-quantitative image

- FDG-PET/CT:
  - As above *plus* more precise anatomical information
  - Effective radiation dose: 13 to 30 mSv
    - Background radiation: 2.4 mSv per yr
    - AP and lateral CXR: 0.1 mSv
    - HRCT Dose 2-8 mSv
    - Standard CT 5-10 mSv
Positron emission tomography (PET)

Use in malignancy:

• False positive
  – Infection (granulocytes & macrophages use glucose as energy source)
    ....TB, IFI, bacterial, viral infections
  – Inflammation (e.g. sarcoid)
  – Other – brown fat, thymic tissue, brain, heart

• False negative
  – Tumours with slow growth and low metabolism – carcinoid tumours, well differentiated adenoCa, pseudomyxoma
  – Small tumours <7mm
  – Hyperglycaemia

FDG PET/CT and IFI

• PET/CT used to monitor response to Rx in 3 AML patients with chronic disseminated candidiasis (Xu et al Clin Nuc Med 2010)

• Retrospective review 16 pts with IFI: occult sites of identified by PET/CT (Ho et al, Brit J Haem 1998)

• Prospective study 30 consecutive pts with proven/probable IFI- PET/CT done within 48 hrs of AF RX
  – PET matched finding from conventional scans
  – Identified occult infection in 4/10 cases candidiasis (splenic abscesses) (Hot et al, Clin Micro and Infection 2010)

• Prospective study (n=28) (Vos 2012):
  – Abnormal uptake in 93% of pts with profound neutropenia and CRP >50 mg/L
  – Early detection of IFI and thrombophlebitis
FDG-PET/CT:
*Prolonged febrile neutropenia*

- Prospective study at PMCC of FDG-PET/CT for evaluation of D+5 fever (adult pts with AML) despite broad-spectrum antibiotics (n=20)
  - 16 (80%) positive scans:
    - Sensitivity 92.9% compared to conventional Ix (1 URTI not found)
  - Located 8 additional sites of infection
    - Altered antimicrobial therapy in 9 pts
    - Prolonged Ab for liver abscess 1
    - Antifungal commenced 1
    - Other directed therapy 2
    - Antifungal withheld 5

FDG-PET/CT: 
*Prolonged febrile neutropenia*

• Prospective study at PMCC of FDG-PET/CT for evaluation of D+5 fever despite antibiotics (n=20)

• 16 (80%) positive scans:
  – Sensitivity 92.9% compared to conventional Ix (1 URTI not found)

• Located 8 additional sites of infection

• Contributed to the management of 15/20 (75%) pts, inc:
  – Altered antimicrobial therapy in 9 pts
    • Prolonged Ab for liver abscess 1
    • Antifungal commenced 1
    • Other directed therapy 2
    • Antifungal withheld 5

Example 1: Localisation

52 y.o woman
Precursor B-lymphoblastic leukaemia (Philadelphia chr negative) 2010
  • Hyper-CVAD
  • Sibling matched allo-HSCT 18/12 ago.
Complicated by chronic GvHD involving skin, eye, liver and lung
  (requiring home oxygen)
  • Severe mixed restrictive/obstructive deficit
Long term immunosuppressive therapy with cyclosporine (ceased end
Jan) and prednisolone (15 mg/day).
No previous IFI

Prophylaxis
  • Bactrim DS daily/Azithromycin 3x wk/Pen V daily /Valacyclovir
    500mg daily
  • Posaconazole 400mg BD
Posaconazole prophylaxis changed to fluconazole following cessation of cyclosporine.

3 mths later:
- Increased cough and sputum production
- Increased SOB and home O2 r/ment for symptomatic relief
- No fevers
Recently renovated kitchen.
HRCT chest (23/4) small cavitating lesion seen and multiple new pulmonary nodules with ground glass changes.
### Posaconazole prophylaxis changed to fluconazole following cessation of cyclosporine

**Hx**
- 3 mths later:
  - Increased cough and sputum production
  - Increased SOB and home O2 r/ment for symptomatic relief
  - No fevers

Recently renovated kitchen.

**Ix**
- Sputum culture: Aspergillus fumigatus
  - Serum ASP PCR and Galactomannan NEG

**Mx**
- Probable pulmonary aspergillosis in high risk patient.
  - Start voriconazole treatment – load with 400 mg bd then 250mg bd thereafter (wt 65kg)
  - Levels 4-5
Apr

Aspergillus isolated
Patchy nodular infiltrates, occ
cavitation
Improved on HRCT at 4 weeks

May

Definite progression of lesions
Changed to Ambisome 300 mg
daily. Cx Renal failure

July

Progression. Bronchoscopy
BAL: No organisms cultured
Galacto negative, Asp PCR positive

Aug

PET scan shows LUL avid nodule
BAL and EBUS
Only LUL washings grow Scedosporium
prolificans. Asp PCR neg
Voriconazole + terbinafine added

Sep

Oct

Jan

Mild progression of irreg nodules.
Ground glass opacities. Worsening
bronchiectasis.
Parainfluenza, E.coli
Piptaz infusion for co-infection

Repeat PET shows resolution
New problems with multidrug resistant
pseudomonas
Monitoring Rx with PET/CT

- 50 y.o Hodgkins lymphoma. Penicillin allergy
- **Heavily treated**
  - ABVD
  - Standford BCNU autograft 2010: relapsed after 3 months coeliac plexus
  - Inverted Y radiotherapy (rendered asplenic)
  - Salvage chemo gemcitabine/vinorelbine then brentuximab (anti CD30 monoclonal Ab-drug conjugate)
  - Allogeneic SCT 2011
- Moderate GVHD: Liver, skin, ?? lung. Off all immunosuppressives
- Severe peripheral neuropathy
- Hypogammaglobinaemic, pancytopaenic
- Bactrim Px, monthly IG, **fluconazole**, PPI
PET Jan 2012 (12 months post Tx)
- c/w Fungal lesions
BAL: *Aspergillus Flavus* & *Ps. Aeruginosa*
Aspergillus PCR and galacto neg
Plan: Voriconazole 12 weeks  Ciprofloxacin 3 weeks
PET Jan 2012 (12 months post)
Fungal lesions
BAL: Aspergillus flavus & Ps. Aeruginosa
Aspergillus PCR and galacto neg
Rx: Voriconazole 12 weeks Ciprofloxacin 3 weeks

Repeat PET at 6 weeks
- Recurrent lymphoma rather than infection
Rx Brentuximab chemotherapy 4 cycles
Voriconazole changed to posaconazole due to risk of neuropathy
( theoretical interaction with brentuximab)

PET/CT showed complete remission
Back onto posaconazole secondary prophylaxis
Pulmonary: There is resolution of pulmonary metabolic abnormalities, consistent with interval response of aspergillosis to antimicrobial therapy. Residual ill-defined parenchymal changes demonstrate no metabolic abnormality. Format chest CT also performed today will be reported separately.

Further findings: There is no PET evidence of active graft vs host disease. The distribution of FDG elsewhere is physiologic.

Conclusion: Findings are consistent with a complete metabolic and anatomic response to brentuximab therapy. Metabolic abnormalities related to pulmonary aspergillosis have also resolved.
Worsening cough +++
Active pulmonary infective changes R upper lobe.

Moderate FDG uptake is seen in new areas of peribronchial thickening and peripheral consolidatory changes in the anterior segment of the right upper lobe. Note is also made of FDG avid nodule in the right upper lobe and in the left upper lobe that were not noted in the previous PET scan. These lesions likely represent changes of the infective process that was documented in this patient. Note is also made of septal thickening in the right lower lobe with patchy FDG uptake.
Bronchoscopy
ESBL E.coli Rx Ertapenem (HIH)

BAL:
PJP PCR neg
Asp PCR weak pos, galactomannan 0.65 (>0.5)

Posaconazole increased to treatment dose
Steady state level 0.57 mg/ml (LOW)
Stopped ranitidine ------ rechecked and incr. to 1.3 mg/ml
Significant improvement : CRP normalised

Resolution of all infective changes
BUT......Persistent mild activity left lingula
May 2013 & July 2013: Progressive increase in size and intensity of left lingular node. Low grade uptake through lungs.

? Resistant fungus?
? Alternate pathogen
Bronchoscopy and EBUS
-galactomannan neg
-Asp PCR neg
-few atypical cells

CT guided biopsy
Recurrent Hodgkins lymphoma
FDG-PET and antimicrobial use

Retrospective case control study at PMCC (matched for underlying haem malig, FN >10 days, time period of admission)

• Compared antimicrobial usage following FDG-PET/CT (n=37) vs conventional imaging (n=76) for high risk FN

• FDG-PET/CT had a significant impact on:
  – Antimicrobial utilisation (35.1% vs 11.8%, p=0.003)
  – Duration of liposomal amphotericin B (median 4.0 days vs 10 days; p=0.001)
    • Equated to cost savings of AUD 7,440 – 14,455 per pt
      (cost of FDG-PET/CT approx AUD 1,000 per scan)

Interventions?
Routine PET to decide systemic antifungal therapy.
Adoption of BAL galactomannan and aspergillus PCR/pan fungal PCR rather than serum.
Summary

• Emerging evidence for routine use of FDG-PET/CT in high risk patients
  – 60-80% of scans will influence management
  – Diagnosis – esp. exclusion of bacterial or fungal infections, (very high negative predictive value)
  – Monitoring therapy, and assisting with de-escalation or cessation of Rx
  – Screening for IFI in prolonged NF or PUO in high risk patients is cost-effective
Aspergillosis

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Instituto de Investigación Gregorio Marañón
Centro de investigación biomédica en red en Enfermedades Respiratorias (CIBERES)
Universidad Complutense de Madrid. Spain
pmunoz@hggm.es
Underlying condition of patients with culture proven IA (HGUGM hospital)

Culture positive

<table>
<thead>
<tr>
<th>Year</th>
<th>Others</th>
<th>Hematological</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
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</tr>
<tr>
<td>2014</td>
<td></td>
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</tr>
</tbody>
</table>
Workload Due to *Aspergillus fumigatus* and Significance of the Organism in the Microbiology Laboratory of a General Hospital

E. Bouza, J. Guinea, T. Peláez, J. Pérez-Molina, L. Alcalá, and P. Muñoz

*Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain*

We obtained a score with the five variables selected by the multivariate model. A proportional value was assigned to each variable according to the RR values: “sample obtained by invasive procedures” was assigned a value of 1 (RR, 3.85), “two or more correlative positive samples” was assigned a value of 1 (RR, 3.07), “leukemia” was assigned a value of 2 (RR, 6.38), “corticosteroid treatment” was assigned a value of 2 (RR, 5.45), and “neutropenia” was assigned a value of 5 (RR, 16.21).

<table>
<thead>
<tr>
<th>Invasive procedure</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1 correlative sample</td>
<td>1</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5</td>
</tr>
</tbody>
</table>
Host factors

Prolonged use of **steroids** (> 21 days) at the average dose of **0.3 mg / Kg / day** of methylprednisolone (or equivalent)

Recent history of **neutropenia** (<500 PMN / mL) for > 10 days with temporal correlation between fungal infection and neutropenia

**Not enough!!!**

Allogenic stem cell transplantation

Treatment with **drugs** which depress T lymphocyte activity (cyclosporin / tacrolimus / anti-TNF-α monoclonal antibodies / nucleoside analogues) during the previous 90 days

Severe hereditary **immunodeficiency**
Solid neoplasia

- 84 year-old man with brain cancer. Surgery and corticosteroids (Dec 4) - Dexamethasone 8 mg/d)
- Dec 16 pneumonia. Empirical Abs. Progression of infiltrates
- Sputum A. fumigatus. Platelia 0.59. BDG 2538
- Voriconazole. High levels. Liver toxicity
- Died Jan 18

Dexametasona dosis de 8 mg/día (equivalente prednisona 50 mg/día --> 0,8 mg/día/kg
COPD patient

- 60 y-old, COPD
- Previous smoker (50 c/day)
- Admission due to exacerbation Dec 19
  - X-ray: COPD, no clear infiltrate
  - Levofloxacin, systemic and inhaled corticosteroids, bronchodilators

Jan 23:
- Worsening of clinical and radiological features
- Sputum culture (X3) *A. fumigatus*. GM: 0.18 y 0.23; Sputum PCR: positive
- Blood PCR: negative
- Caspofungin + Voriconazole 4 weeks. Voriconazole 3 months
Challenges in IFI diagnosis in SOT

37% of IPA in HT recipients present airway-invasive radiological pattern.

It is associated to a delayed diagnosis:
- mechanical ventilation (AIR 90% vs ANG 23.5%, p < 0.01)
- related mortality rate (AIR 70% vs ANG 23.5%, p = 0.04)
Host factors

- Prolonged use of **steroids** (> 21 days) at the average dose of 0.3 mg/Kg/day of methylprednisolone (or equivalent)
- Recent history of **neutropenia** (< 500 PMN/mL) for > 10 days with temporal correlation between fungal infection and neutropenia
- **Allogenic stem cell transplantation**
- Treatment with drugs which depress T lymphocyte activity (cyclosporin / tacrolimus / anti-TNF-α monoclonal antibodies / nucleoside analogues) during the previous 90 days
- **Severe liver disease** with high risk of IFI (e.g., acute liver failure, severe liver insufficiency with lung infiltrates, Abs, corticosteroids, etc)
- **ICU patient** with prolonged admission, antimicrobials, corticosteroids with lung infiltrates with no alternate diagnosis
- **Severe hereditary immunodeficiency**

Other criteria ??

HIV with high risk of IFI (e.g., CD4 ≤ 200 cells/µL, poor nutritional state, severe liver disease etc., etc.)
Aspergillus IN THE HOSPITAL AIR

Outdoor air
Range 0-105 c.f.u. / m³

Unprotected hospital air
5-25 c.f.u. / m³

HEPA filtered air
<0.1 c.f.u. / m³

Ruiz-Camps et al. *CMI*
2011;17 Suppl 2:1-24

Ruiz-Camps et al. *EIMC*
2010;28:172.e1-172.e21
Outbreak of Invasive Aspergillosis After Major Heart Surgery Caused by Spores in the Air of the Intensive Care Unit

T. Peláez,1,2,3 P. Muñoz,1,2,3 J. Guinep,1,2,3 M. Valerio,1,2 M. Gianella,1,2 C. H. W. Klaassen,4 and E. Bouza1,2,3

1Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, 2Department of Medicine, Faculty of Medicine, Universidad Complutense, Madrid, 3Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERSER CO06/06/2010), Pinar de Aranda, 4Department of Medical Microbiology and Infectious Diseases, Carolina Wilhelmina Hospital, Nijmegen, The Netherlands

Molecular Epidemiology of Aspergillus fumigatus: an In-Depth Genotypic Analysis of Isolates Involved in an Outbreak of Invasive Aspergillosis

Jesús Guinea,1,2,3,4 Dario García de Viedma,1,2,3 Teresa Peláez,1,2,3 Pilar Escribano,1,2,3 Patricia Muñoz,1,2,3,4 Jacques F. Meis,5 Corné H. W. Klaassen,5 and Emilio Bouza1,2,3,4

High levels of airborne filamentous fungal conidia may induce the appearance of nosocomial IA even in patients without the classical risk factors for IA.

Accordingly, we support environmental monitoring of filamentous fungal spores, not only in hematological units, but also in areas where potentially susceptible hosts are admitted (ICU, oncology, gastroenterology, HIV ward).

Due to high risk of liver toxicity or drug interaction, L-AMB was used in 42.8% of the patients. Related mortality was 35.7%.
Voriconazole levels monitoring

- 107 patients (n = 258 samples) at 6 hospitals in Madrid
  - Subtherapeutic (<1μg/ml): 18.2%
  - On-target (1-5.5): 71.3%
  - High (>5.5): 10.5%

- Predictors vori ≥1 μg/ml:
  - Subsequent samples
  - Admission in non-pediatric wards
  - Voriconazole for IA treatment
  - Use of proton pump inhibitors

False-positive *Aspergillus* Antigenemia Due to Blood Product Conditioning Fluids

Pablo Martín-Rabadán,1,2,3,4 Paloma Gijón,1,4 Roberto Alonso Fernández,1 Mónica Ballesteros,5 Javier Anguita,5 and Emilio Bouza1,2,3,4

Table 2. Galactomannan Optical Density Index Readings of Blood Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Blood Collection Bag Manufacturer</th>
<th>Number of Samples Tested</th>
<th>GM-ODI Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed red cells</td>
<td>MacoPharma</td>
<td>4</td>
<td>0.18 (0.11–0.28)</td>
</tr>
<tr>
<td></td>
<td>Fenwal</td>
<td>2</td>
<td>0.22–0.30</td>
</tr>
<tr>
<td>Frozen fresh plasma</td>
<td>Fresenius Kabi</td>
<td>13</td>
<td>0.95 (0.31–4.43)</td>
</tr>
<tr>
<td>Pooled platelets</td>
<td>Fresenius Kabi</td>
<td>18</td>
<td>&gt;5.00 (&gt;5.00)</td>
</tr>
<tr>
<td>Apheresis platelets</td>
<td>Haemonetics</td>
<td>10</td>
<td>0.25 (0.09–0.47)</td>
</tr>
</tbody>
</table>

*False + GM*

- Other fungi (Fusarium, Penicillium, Histoplasma)
- Plasmalyte
- GVHD
- Multiple myeloma
- Antibiotics
- GI tract mucositis
- Bifidobacteria (gut)

Martín-Rabadán. *CID* 2013

Ambasta A. *Medical Mycology* 2015;53:531-57
Impact of micafungin prophylaxis on GM

1738 GM determinations!!! in 254 risk episodes

- 54 positive
- 200 Negative

- 4 IFI *
- 50 FALSE POSITIVES

• 3/4 Clinically driven and 1 surveillance
• NO related deaths

Only 7% of GM + are true positives

Muñoz P. ECCMID 2016
Thank you