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# Prevention of invasive fungal infections in solid organ transplant recipients: Universal or Targeted Prophylaxis?

Paolo Grossi

4th Trends in Medical Mycology
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## Patients at greatest risk of invasive fungal infection

- Haematopoietic stem cell recipients
- Neutropenic patients with leukaemia treated by intensive chemotherapy
- **Solid organ transplant recipients**
- Critically ill patients
- Preterm babies admitted to neonatology units
- Patients receiving chronic treatment with corticosteroids
- Patients with acquired immune deficiency syndrome (AIDS)

# Invasive Fungal Infections in Solid Organ Transplant Recipients

- Frequency and pathogens vary with type of transplant
- Major center-to-center variation in frequency of IFIs
- Substantial differences in IFIs between SOT and HSCT recipients

# Invasive fungal infections in transplant recipients

## TransNet Surveillance Program 2001-2006

## 1181 IFI

| Solid organ transplant (n = 292) | | Hematopoietic stem cell transplant (n= 829) | |
|---|---|---|---|
| Candidiasis | 53% | Aspergillosis | 44% |
| Aspergillosis | 19% | Candidiasis | 29% |
| Cryptococcosis | 8% | Other moulds | 11% |
| Other moulds | 6% | Zygomycoses | 6% |
| Endemics | 5% | | |
| Zygomycoses | 2% | | |

Pappas P., et al. ICAAC 2007

# Epidemiologic characteristics of invasive aspergillosis in transplant recipients

| | Incidence range % (mean) | Mean days to onset (range) | % *Mortality* |
|---|---|---|---|
| Liver | 1-8 (2) | 17 (6-1107) | 87 |
| Lung | 3-14 (6) | 120 (4-1410) | 68 |
| Heart | 1-15 (5.2) | 45 (12-365) | 78 |
| Kidney | 0-4 (.7) | 82 (20-801) | 77 |
| Pancreas | 1.1-2.9 | NA | 100 |
| Small bowel | 0-10 (2.2) | 289 (10-956) | 66 |

Modified from Singh N., et al. CMR 2005;18:44–69

# Antifungal agents for invasive mycoses

- **Amphotericin B**
- **Lipid associated polyenes**
  - ABLC, ABCD, Ambisome
- **Azoles**
  - Fluconazole
  - Itraconazole (cyclodextrin/intravenous)
  - Voriconazole
  - Posaconazole
- **Echinocandins**
  - Caspofungin
  - Anidulafungin
  - Micafungin

# Use of antifungal drugs in immunocompromised patients

Limited evidence of optimal strategies for utilizing the available antifungal armamentarium

# Strategies to prevent fungal infections in SOT

## Universal prophylaxis

Administration of an agent to all recipients to prevent infection

# Potential prevention strategies for invasive fungal infections in OLTX

| Candida spp. | Aspergillus spp. | Cryptococcus spp. |
|---|---|---|
| •Fluconazole, 100–400 mg per os q.d. for 4–8 weeks after tx (A-I) | •Lipid-associated amphotericin B, 1 mg/kg, or itraconazole (iv or per os) before and after (4 weeks) OLTX in patients with AFH (C-III) | •Prevention of CMV disease (C-III) |
| •Lipid-associated amphotericin B, 1 mg/kg for 5 days after transplantation (B-I) | •Microbiological surveillance and antifungal preemptive treatment in immunocompromised individuals (C-II) | •High index of suspicion in severely immunocompromised individuals (C-III) |
| •Prevention of CMV disease (B-I)<br>•SBD (B-III)<br>•Targeted therapy with fluconazole based on presence of risk factors (C-III) | •Prevention of CMV disease (C-III) | |

Paya CV. CID 2001;33:S47-S52

# Prophylactic fluconazole in OLTX (400 mg/day i.v. or p.o for 10 weeks)

| Variable | Placebo | Fluconazole |
|---|---|---|
| Patients n. | 104 | 108 |
| Pts with proven FI, n (%) | 45 (43) | 10 (9) * |
| Pts with superficial infection, GI tract, wound or UTI, n (%) | 29 (28) | 4 (4%) * |
| Pts with invasive infection of blood, lungs, intra-abdominal, sinuses or multiple organs, n (%) | 24 (23) | 6 (6%) * |

* P <0.001 compared with placebo

Winston DJ, et al. Ann Intern Med 1999;131:729-737

# Antifungal Prophylaxis in Liver Transplant Patients: A Systematic Review and Meta-analysis

**Mario Cruciani,[1] Carlo Mengoli,[2] Marina Malena,[1] Oliviero Bosco,[1] Giovanni Serpelloni,[1] and Paolo Grossi[3]**

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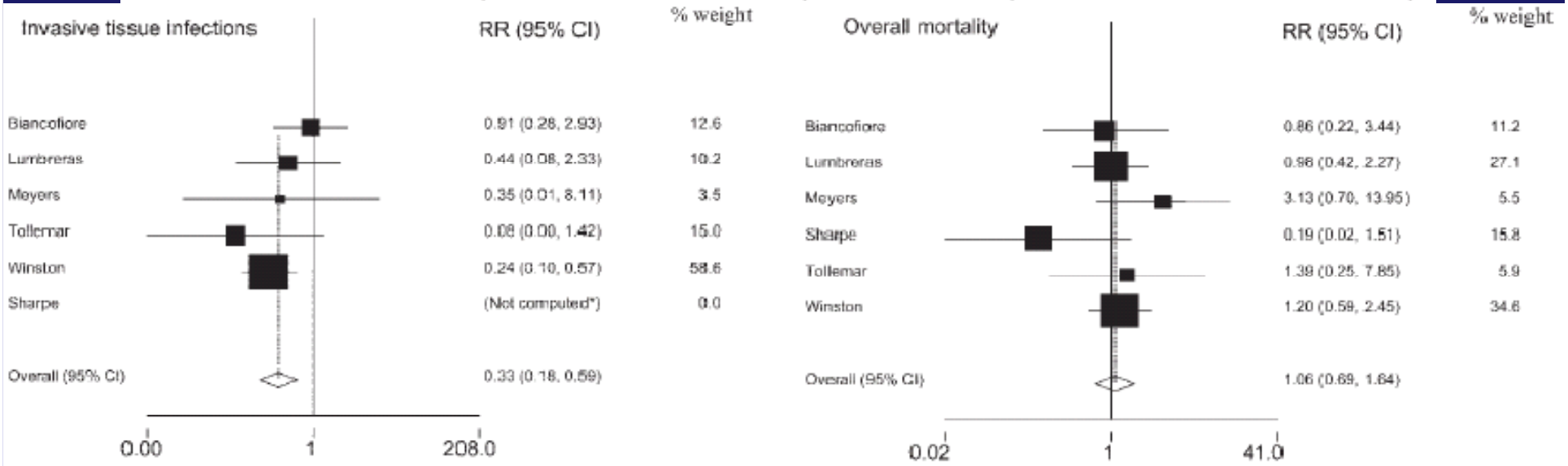



**Empiric treatment for suspected fungal infections and overall mortality were not affected by antifungal prophylaxis. *Emergence of non-Candida albicans species in patients receiving prophylaxis***

Liver Transpl 2006;12:850-858

# Antifungal Prophylactic Practices in Liver Transplant Recipients

| Centers responding to the survey | 67/106 (63%) |
|---|---|
| Centers using prophylaxis | 91% |
| Universal | 28% |
| Targeted | 72% |
| Retransplantation | 81% |
| Reexploration | 65% |
| Renal replacement therapy | 44% |

N.SINGH, et al. AJT 2008; 8: 426–431

# Antifungal Prophylactic Practices in Liver Transplant Recipients.

| | |
|---|---|
| **Candida prophylaxis** | **88%** |
| Fluconazole | 86% |
| **Mould directed prophylaxis** | |
| Echinocandins | 41% |
| Voriconazole | 25% |
| Polyene | 18% |

Fluconazole vs non-fluconazole use was associated with higher reported rate of mould infections (aspergillosis, zygomycosis, and scedosporiosis, RR 1.5, 95% CI, 1.0-2.2, p=.04)

N.SINGH, et al. AJT 2008; 8: 426–431

# Antifungal prophylaxis according to risk profile Multicenter European Survey

| Risk factor | Antifungal agent | No. of centers | % |
|---|---|---|---|
| No risk factors present | No prophylaxis | 39 | 65 |
| | Fluconazole | 15 | 25 |
| | Itraconazole | 1 | 1.7 |
| | Amphotericin B | 2 | 3.3 |
| | Lipid formulation of Amphotericin B | 1 | 1.7 |
| | Nystatin | 1 | 1.7 |
| | Not known | 1 | 1.7 |
| Any risk factor present | No prophylaxis | 7 | 12 |
| | Fluconazole | 30 | 50 |
| | Caspofungin | 3 | 5 |
| | Fluconazole OR Itraconazole | 2 | 3.3 |
| | Amphotericin B | 5 | 8.3 |
| | Lipid formulation of Amphotericin B | 8 | 13.3 |
| | Voriconazole | 1 | 1.7 |
| | Not known | 2 | 3.3 |
| | Amphotericin B OR Caspofungin | 1 | 1.7 |
| | Fluco OR Vorico OR Caspofungin | 1 | 1.7 |

Els Vandecasteele, et al. Transplant International 2009;:1-9

| Risk factor | No. of centers | Antifungal agent | No. of centers | % |
|---|---|---|---|---|
| Re-operation (redo or revision) | 22 | Fluconazole | 12 | 54.5 |
| | | Caspofungin | 2 | 9.1 |
| | | Amphotericin B | 2 | 9.1 |
| | | Lipid formulation of Amphotericin B | 3 | 13.6 |
| | | Voriconazole | 1 | 4.5 |
| | | Not known | 1 | 4.5 |
| | | Fluconazole OR caspofungin | 1 | 4.5 |
| Primary graft dysfunction | 17 | Fluconazole | 11 | 64.7 |
| | | Caspofungin | 1 | 5.9 |
| | | Lipid formulation of Amphotericin B | 2 | 11.7 |
| | | Fluconazole OR itraconazole | 1 | 5.9 |
| | | Not known | 1 | 5.9 |
| | | Itraconazole | 1 | 5.9 |
| Large volume transfusion | 15 | Fluconazole | 10 | 66.6 |
| | | Caspofungin | 1 | 6.7 |
| | | Lipid formulation of Amphotericin B | 1 | 6.7 |
| | | Fluconazole or voriconazole | 1 | 6.7 |
| | | Not known | 2 | 13.3 |
| Fulminant liver failure | 10 | Fluconazole | 7 | 70 |
| | | Amphotercin B | 1 | 10 |
| | | Amphotercin B OR caspofungin | 1 | 10 |
| | | Not known | 1 | 10 |
| Anti rejection therapy | 7 | Fluconazole | 7 | 100 |
| Positive culture for fungi | 4 | Fluconazole | 2 | 50 |
| | | Not known | 1 | 25 |
| | | Caspofungin | 1 | 25 |
| AB >5 days | 4 | Fluconazole | 4 | 100 |
| Renal failure/dialysis | 3 | Lipid formulation of Amphotericin B | 1 | 33.3 |
| | | Amphotercin B | 1 | 33.3 |
| | | Caspofungin | 1 | 33.3 |

# A Survey of Anti-fungal Management in Lung Tx
## Post-Tx Prophylaxis for Fungal Infection

| Post-transplant prophylaxis | Number of programs (%) |
|---|---|
| Prophylaxis performed | 28 (76) |
| Sub-groups prophylaxed | |
| Cystic fibrosis | 26 (70) |
| COPD | 21 (57) |
| Bronchiectasis | 17 (46) |
| Sarcoidosis | 16 (43) |
| IPF | 17 (46) |
| No prophylaxis performed | 9 (24) |

COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis.

Dummer S. et al. J Heart Lung Transplant 2004;23:1376-81

# A Survey of Anti-fungal Management in Lung Tx
## Duration of Post-transplant Prophylaxis

| Duration of prophylaxis | Number of programs (%) |
|---|---|
| During initial hospitalization | 1 (4) |
| 1 month | 6 (21) |
| 2 months | 3 (11) |
| 3 months | 6 (21) |
| 6 months | 4 (14) |
| 6 to 12 months | 1 (4) |
| 12 months | 2 (7) |
| >12 months | 1 (4) |
| Lifetime | 4 (14) |
| Total | 28 (100) |

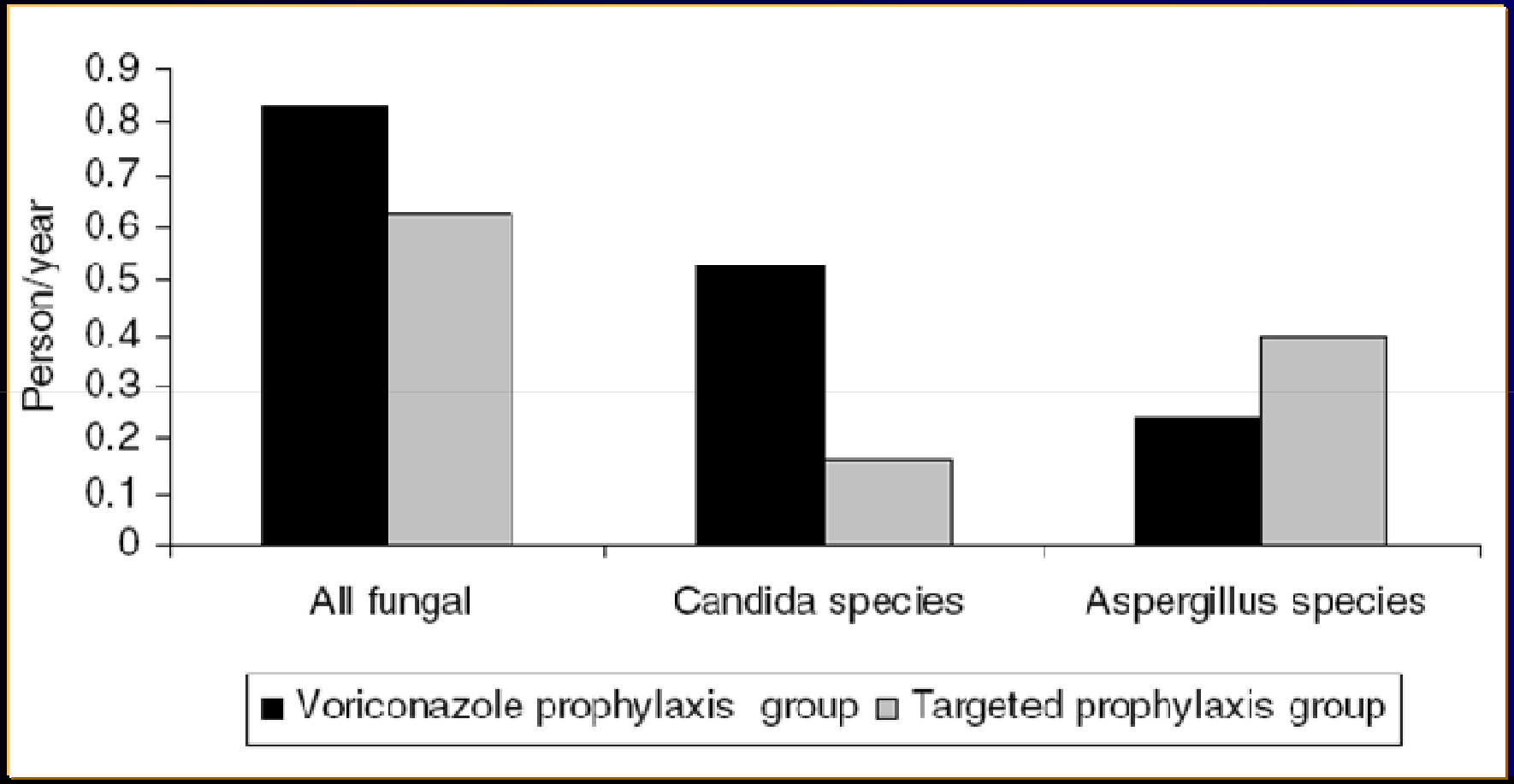
Dummer S. et al. J Heart Lung Transplant 2004;23:1376-81

# Voriconazole Prophylaxis in Lung Transplant Recipients

| | Voriconazole | Targeted itraconazole/ inhaled ampho B prophylaxis | p-value |
|---|---|---|---|
| Number of invasive fungal infections | 1/65 (1.5%) | 7/30 (23%) | 0.001 |
| Rate of non-aspergillus infections at 1 year | 2/65 (3%) | 7/30 (23%) | 0.004 |

*Husain S, et al. AJT 2006;6: 3008–3016*

# Comparison of incidences (person years) of colonization in lung transplant recipients between voriconazole and targeted prophylaxis group.




Patient receiving voriconazole prophylaxis had significantly higher incidence of *Candida colonization* 0.53/person-year versus 0.16/person-year (p = 0.006).

*Husain S, et al. AJT 2006;6: 3008–3016*

# Comparison of the rate of elevated liver enzymes (≥3 times upper limit of normal) between targeted prophylaxis group and voriconazole group

| | Voriconazole prophylaxis group %(n) (n = 65) | Targeted prophylaxis group %(n) (n = 27) | p values |
|---|---|---|---|
| GGTP[1] | 60% (39/65) | 41% (11/27) | 0.07 |
| ALT[2] | 45% (29/65) | 15% (4/27) | 0.005 |
| AST[3] | 37% (25/65) | 15% (4/27) | 0.02 |

*Husain S, et al. AJT 2006;6: 3008–3016*

# Drug interactions with voriconazole

| Type of interaction, drug | Recommendation |
|---|---|
| Decreases voriconazole levels | |
| Carbamazepine | Contraindicated |
| Long-acting barbiturates | Contraindicated |
| Rifampin | Contraindicated |
| Levels increased by voriconazole | |
| Astemizole | Contraindicated |
| Cisapride | Contraindicated |
| Cyclosporine | Reduce dosage by one-half and monitor levels |
| Ergot alkaloids | Contraindicated |
| Omeprazole | Reduce dosage by one-half |
| Quinidine | Contraindicated |
| Sirolimus | Contraindicated |
| Tacrolimus | Reduce dosage to one-third of its original level and monitor levels |
| Terfenadine | Contraindicated |
| Warfarin | Monitor prothrombin time |
| Decreases voriconazole levels and increases other drug levels | |
| Rifabutin | Contraindicated |
| Phenytoin | Double voriconazole dosage and monitor for increased phenytoin levels |
| Levels likely increased by voriconazole: sulfonylureas, statins, vinca alkaloids, calcium channel blockers, benzodiazepines | Monitor effects of drug and consider decreasing dosage when voriconazole is added |

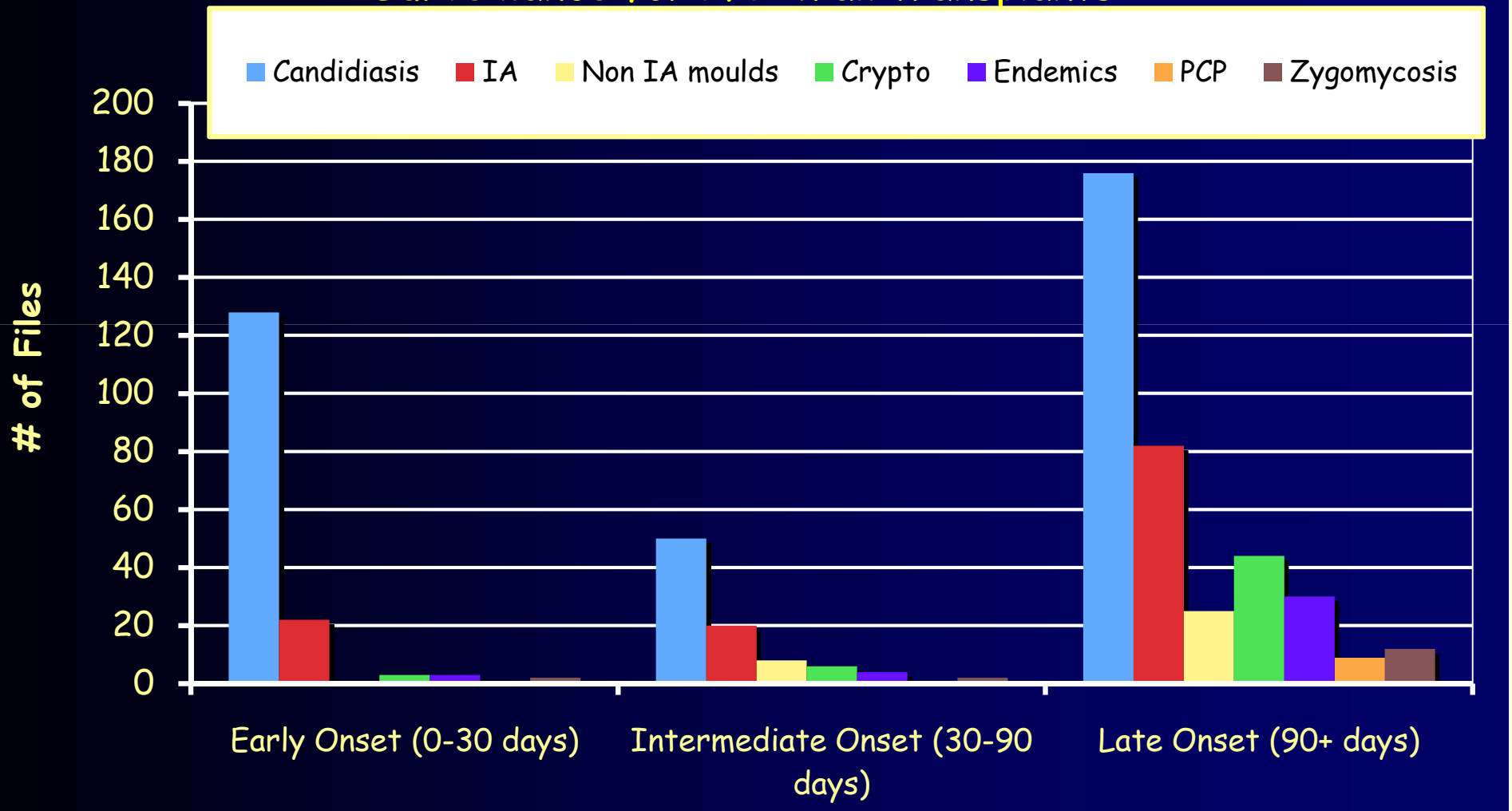
# VORICONAZOLE BLOOD LEVELS EFFICACY AND TOXICITY

| EFFICACY | | TOXICITY | |
|---|---|---|---|
| < 1 ug/Ml | 7/13 (54%) | < 5.5 ug/mL | CNS: 0/36 (0%)<br>Liver: 3/36 (8%) |
| > 1 ug/mL | 34/39 (88%) | > 5.5 ug/mL | CNS: 5/16 (31%)<br>Liver: 3/16 (19%) |

Pascual et al, Clin Infect Dis 2008;46:201-211

# Time to Onset of IFI in SOTs (TransNet Data)

25 academic medical centers, March 2001 to March 2006
Surveillance for IFI in all transplants




Pappas P., et al. ICAAC 2007

## Risk Factors for Zygomycosis In Solid Organ Transplant (SOT) Recipients: A Prospective, Case-Controlled, Multicenter, International Study.

- In a multivariate cox regression model:
- diabetes (HR 2.6,p=.02) was independently associated with zygomycosis;
- **the association of prior azole/caspofungin use approached significance (HR 3.3, p=.053)**
- retransplantation (HR 1.91,p=.09) and baseline renal failure (HR 1.93, p=.10) were not significantly associated with zygomycosis.
- **Conclusions:** Whether use of newer antifungal agents portends a risk beyond that posed by traditional risk factors such as diabetes, remains to be determined.

N.SINGH, et al. ICAAC 2007

# Targeted prophylaxis

Treatment of a subgroup of recipients determined to be high risk as defined by clinical, laboratory, or epidemiological characteristics

# Specific Risk Factors for IFI in SOT

## LIVER

- Pretransplant fulminant hepatic failure
- Primary allograft failure or severe dysfunction
- Retransplantation (acute retransplantation); delayed or repeat transplantation for chronic graft dysfunction should be assessed individually
- Renal failure and hemodialysis
- High transfusion requirement
- Use of OKT3 monoclonal antibody preparations
- 'UNOS status 1, 2a'.

## LUNG

- Hyperacute rejection, acute graft failure, or severe dysfunction.
- Severe lung dysfunction from lung injury or reimplantation response; in this context, enhanced immunosuppression and mechanical ventilation increase the risks of IFI.
- Bronchial ischemic or poorly vascularized bronchial segments especially with mucosal sloughing or necrosis.
- Early recovery of *Aspergillus* on respiratory culture.
- Anastomotic dehiscence.
- CMV infection.
- Retransplantation (early reexploration).

## Invasive Fungal Infections in Low-Risk Liver Transplant Recipients: A Multi-Center Prospective Observational Study

Patients were considered **low risk** if they had ≤ 1 of the following conditions:

- Choledocho-jejunostomy anastomosis;
- Retransplantation;
- Intra-operative administration of ≥ 40 units of blood products, or return to the operating room for intra-abdominal bleeding;
- Return to the operating room for anastomotic leak or vascular insufficiency;
- Preoperative serum creatinine of ≥ 2 mg/dl or need for any form of dialysis within 48 h prior to OLT;
- Perioperative *candida* colonization

Liver transplant recipients at low risk for IFI can be identified utilizing pre-determined criteria, and post-tx antifungal prophylaxis can be routinely withheld in these patients.

Pappas PG et al. *Am J Transplan 2006; 6: 386–391*

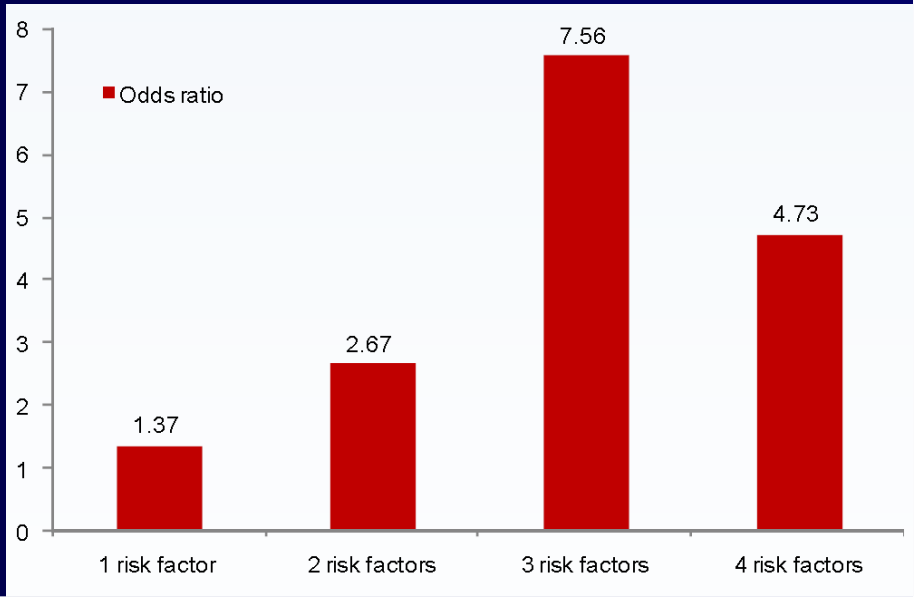
# Identifying a Targeted Population at High Risk for Infections after Liver Transplantation in the MELD Era

"High-risk" factors for infections were defined as:

- MELD >30
- ICU stay >48 hrs prior to transplant
- Intraoperative transfusion >15 units
- Retransplantation
- Posttransplant dialysis or reoperation

**The odds ratio for a post-transplant major infection were 1.37, 2.67, 7.56, and 4.73 in recipients with 1, 2, 3, and 4 high-risk factors, respectively (*x2 for trend, p<.001*)**

Hsin-YunSun, et al.ATC 2009



# In univariate analysis, all pre-definded high-risk factors were significantly associated with infections within 90 days posttransplant, and so was age at transplant

| Factors | Reference | OR (95% CI) | P value |
|---|---|---|---|
| Components of high-risk factor | | | |
| Retransplant | No retransplant | 3.36 (1.19-9.48) | .022 |
| Posttransplant dialysis | No dialysis | 2.45 (1.02-5.89) | .045 |
| Posttransplant reoperation | No posttransplant reoperation | 2.45 (1.22-4.90) | .011 |
| ICU stay >48hr prior to transplant | ICU stay ≤48hr prior to transplant | 4.51 (1.69-11.98) | .002 |
| Intraoperative transfusion ≥15 units | Intraoperative transfusion <15 units | 2.02 (1.03-3.96) | .039 |
| MELD score >30 | MELD score ≤30 | 3.48 (1.65-7.32) | .001 |
| Age at transplant | Continuous variable | 1.09 (1.03-1.16) | .001 |
| Donor age | Continuous variable | 1.00 (.98-1.02) | .638 |
| Hepatocelluar carcinoma | No hepatocelluar carcinoma | .87 (.44-1.75) | .717 |
| CMV R-D+ | No CMV R-D+ | .99 (.49-2.04) | .996 |
| CMV infection | No CMV infection | 1.14 (.63-2.05) | .662 |
| Current era | Prior era | .84 (.44-1.63) | .623 |

Hsin-YunSun, et al.ATC 2009

# A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization*

Cristóbal León, et al. Crit Care Med 2006; 34:730–737

| Risk factor | Candida score |
|---|---|
| Parenteral nutrition | +0.908 |
| Surgery | +0.997 |
| Multifocal colonization | +1.112 |
| Severe sepsis | +2.038 |

*Conclusions: In a large cohort of nonneutropenic critically ill* patients in whom *Candida colonization was prospectively assessed,* a "Candida score" >2.5 accurately selected patients who would benefit from early antifungal treatment.

# Usefulness of the "*Candida* score" for discriminating between *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients: A prospective multicenter study

| | Colonized and Invasive Candidiasis (No. Patients) | Invasive Candidiasis No. (%) | Patients to be Included[a] |
|---|---|---|---|
| *Candida* score <3 | 565 | 13 ( 2.3) | 8.7 |
| *Candida* score ≥3 | 327 | 45 (13.8) | |
| Colonization index <0.5 | 411 | 16 ( 3.9) | 20.8 |
| Colonization index ≥0.5 | 481 | 42 (8.7) | |

[a]Number of patients with *Candida* score ≥3 to predict one infection attributable to the increase of the score.

- ***Conclusions: In this cohort of colonized patients (834/1107) staying >7 days, with a CS <3 and not receiving antifungal treatment, the rate of IC was <5%. Therefore, IC is highly improbable if a Candida-colonized non-neutropenic critically ill patient has a CS <3.***

**Leon C. et al. Crit Care Med 2009; 37:1624 -1633**

# Risk factors for infections caused by Aspergillus spp., recommended agent for prophylaxis and duration

| Organ | Risk factors | Antifungal prophylaxis | Duration |
|---|---|---|---|
| Liver* | | | |
| | Pre-transplant fulminant hepatic failure<br>Primary allograft failure<br>Retransplantation<br>Requirement of renal replacement therapy<br>High transfusion requirements<br>Use of monoclonal antibodies | Lipid formulation of amphotericin B 2.5–5 mg/kg/day<br>Or<br>Voriconazole 400 mg/day | 4 weeks<br>or until resolution of risk factors |
| Lung | | | |
| | Airway ischemia<br>Reperfusion injury<br>Receipt of single lung transplant<br>Presence of bronchial stents<br>Acquired hypogammaglobulinemia<br>*Aspergillus* colonization | Inhaled amphotericin B 6–30 mg/day<br>Or<br>Voriconazole 400 mg/day<br>Or<br>Itraconazole 400 mg/day | 2 weeks to lifelong |

*These are risk factors for *Candida* as well, however, prophylaxis with an agent without anti-*Aspergillus* activity is not appropriate. Antifungal prophylaxis may be warranted whenever more than one risk factor is present.

Silveira F, et al Medical Mycology 2007;45:305-320

# Prophylaxis With Caspofungin for Invasive Fungal Infections in High-Risk Liver Transplant Recipients

**One of these criteria (major criteria):**

a. Redo caused by severe dysfunction of a previous graft,

b. need for any renal replacement therapy, including dialysis or venous hemofiltration within a maximum time period of 30 days,

c. prior history of fulminant hepatitis leading to LT, or

**Two of these criteria (minor criteria):**

a. a. prior postoperative renal failure (defined as creatinine clearance <50 mL/min) within a maximum time period of 30 days,

b. transfusion intraoperatively of ≥40 units cellular blood products

c. presence of a choledocojejunostomy,

d. ≥ two positive clinical site surveillance culture (nasal, pharyngeal, or rectal) for *Candida* from 48 hr before to 48 hr after LT,

e. reoperation (laparotomy) within 5 days of LT.

Fortun J., et al. Transplantation 2009; 87: 424-435

# Prophylaxis With Caspofungin for Invasive Fungal Infections in High-Risk Liver Transplant Recipients

## Efficacy and safety of caspofungin prophylaxis

| Event | No. (%) patients |
|---|---|
| IFI | 2/71 (2.8%) |
| • Surgical infection by *Mucor spp, 41 d after ending a course of 21 d of caspofungin* | 1 |
| • Surgical infection by *Candida albicans, 19 d after ending a course of 21 d of caspofungin* | 1 |
| Favorable response (MITT analysis) (primary objective) | 63/71 (88.7%) |
| Favorable response (EP analysis) (secondary objective) | |
| • Absence of invasive Fungal infection (IFI) | 54/56 (96.4%) |
| • Absence of invasive aspergillosis (IA) | 56/56 (100%) |

Fortun J., et al. Transplantation 2009; 87: 424–435

# Preemptive therapy

Based on an accurate detection method to identify patients at risk for disease as an essential component of this strategy

# Current diagnostic methods

- **Classic**
  - Microscopy
  - Histopathology
  - Culture
  - Radiographic (HR-CT)
- **Biomarkers**
  - Cell wall components
    - Galactomannan
      - Aspergillus EIA
    - 1,3-ß-D-Glucan
      - Limulus lysate
  - Nucleic acid
    - PCR

# Galctomannan as a Marker for Aspergillosis Results from a meta-analysis

- 27 studies from 1996 – 2005
  - Overall sensitivity 71%, specificty 89%
  - Assay performance varied by patient population

| Population | % Sensitivity | % Specificity |
|---|---|---|
| Hematologic malignancy | 70 | 92 |
| Bone marrow transplant | 82 | 86 |
| Pediatric (hema malign /BMT) | 89 | 85 |
| **Solid organ transplant** | **22** | **84** |

Pfeiffer CD, et al. CID 2006;42:1417-1427

# Utility of Galactomannan Detection in BAL Samples

| # pt<br>160 | Sens<br>(%) | Spec<br>(%) | PPV<br>(%) | NPV<br>(%) |
|---|---|---|---|---|
| Serum | 47 | 93 | 73 | 82 |
| BAL | 85 | 100 | 100 | 88 |

TABLE 4. Sensitivity relative to BAL fluid culture positivity for *Aspergillus species*[a]

| Test | BAL fluid culture positive | | | BAL fluid culture negative | | | *P* value[b] |
|---|---|---|---|---|---|---|---|
| | No. | Sensitivity (%) | 95% CI | No. | Sensitivity (%) | 95% CI | |
| GM EIA with index of 0.5 | 27 | 89 | 71–98 | 22 | 59 | 36–79 | 0.02 |
| GM EIA with index of 1.0 | 27 | 78 | 58–91 | 22 | 41 | 21–64 | 0.02 |
| qPCR | 24 | 96 | 79–100 | 22 | 36 | 17–59 | <0.001 |
| qPCR or GM EIA with index of 0.5 | 23 | 100 | 85–100 | 22 | 64 | 41–83 | 0.001 |

[a] Among patients with proven or probable aspergillosis.
[b] *P* value from Fisher's exact test comparing sensitivities between patients with BAL fluid cultures that revealed growth of *Aspergillus* species (positive) and those with culture-negative BAL fluid cultures.

Becker et al. *Br J Haematol* 2003; 121: 448



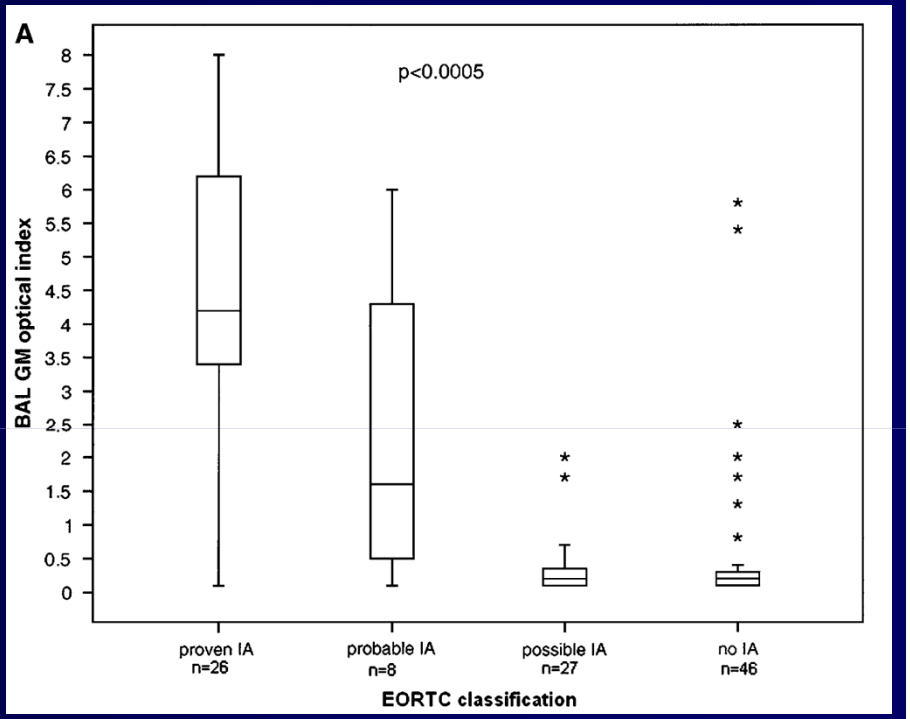
Musher et al. *J Clin Microbiol* 2004: 42(12): 5517-22

# Galactomannan in Bronchoalveolar Lavage Fluid

## A Tool for Diagnosing Aspergillosis in Intensive Care Unit Patients

TABLE 3. GALACTOMANNAN AND CULTURE RESULTS IN 72 PATHOLOGY-CONTROLLED CASES*

| | No. of Patients | | |
|---|---|---|---|
| | Invasive Aspergillosis (*n* = 26) | No Invasive Aspergillosis† (*n* = 46) | Total |
| Serum galactomannan, no.‡ | | | |
| Positive | 11 | 3 | 14 |
| Negative | 15 | 43 | 58 |
| Total | 26 | 46 | 72 |
| BAL galactomannan, no.‡ | | | |
| Positive | 23 | 6 | 29 |
| Negative | 3 | 40 | 43 |
| Total | 26 | 46 | 72 |
| BAL culture, direct examination, no.§ | | | |
| Positive (%) | 15 (58) | 14 (30) | 29 |
| Negative (%) | 11 (42) | 32 (70) | 43 |
| Total | 26 | 46 | 72 |




- The use of galactomannan in bronchoalveolar lavage fluid as a means of establishing early diagnosis of invasive aspergillosis in critically ill patients at risk is promising.

Meersseman W., et al. Am J Respir Crit Care Med 2008;177:27-34,

# (1-3)β-D-Glucan as a marker for invasive fungal infection

**Cell wall component of yeast and moulds**

- *Candida* spp.
- *Acremonium*
- *Aspergillus* spp.
- *Coccidioides immitis*
- *Fusarium* spp.
- *Histoplasma capsulatum*
- *Trichosporon* spp.
- *Sporothrix schenckii*
- *Saccaromyces cerevisiae*
- *Penumocystis jiroveci*

**Exceptions**

- *Cryptococcus*
- *Zygomycetes*
- *Scedosporium*

Fungitell package insert; Odabasi et al. Medical Mycology 2006;44:267-272

# (1→3)β-D-Glucan to Detect Invasive Fungal Infection (IFI)

- 6 US Centers
  - 170 Controls (mostly healthy)
  - 163 Proven/Probable IFIs
    - 111 *Candida*, 22 *Aspergillus*, 3 *Fusarium*,
    - 3 *Zygomycetes*, 12 *Cryptococcus*, 12 Others
  - Serum collected within 72 hours of diagnosis

| Cutoff (pg/ml) | % SN | % SP | PPV | NPV |
|---|---|---|---|---|
| 60* | 70 | 87 | 84 | 75 |
| 80 | 64 | 92 | 89 | 73 |

* Proven candidiasis 81% SN at 60 pg/ml cut-off

Ostrosky-Zeichner et al. CID 2005;41(5):654-659.

# PCR for the diagnosis of invasive fungal infections

Aspergillus meta-analysis 2000 – 2008

- 16 studies assessing serial blood collection (>10,000 samples from 1618 patients)
- **Lack of standardization in PCR methods is a Major problem**
- Contamination of collection devices, reagents, disposables

| Variable | Number |
|---|---|
| Sample type | 3 |
| Volumes tested | 200μL to 10 mL |
| Cell wall disruption | 5 |
| DNA extractions | 3 |
| Target genes | 4 |
| PCR methods | 5 |

Mengoli et al. Lancet Infect Dis 2009; Harrison et al. ICAAC 2008

# Conclusions

- Recent studies have demonstrated that universal prophylaxis probably is not the best available strategy and it is associated to an increase of toxicity, is not cost-effective, and may have an ecological impact in selection of resistant strains.
- The administration of a targeted prophylaxis according to the presence of high risk factors for IFI has demonstrated to be a more efficient strategy
- The transplant community should conduct well-designed clinical trials to provide solid evidence in support of best practice standards for the diagnosis, management and prevention of fungal infections.