

Management of Invasive Mould Infections



Barts Health 
NHS Trust

 Barts and The London
Queen Mary's School of Medicine and Dentistry



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Disclosures



Research grants – advisory boards – speaker

Background: Epidemiology

Richardson M, Lass-Flörl. C Clin Microbiol Infect 2008;14 :5-24.

Warnock D. Jpn J Med Mycol 2007;48:1-12.

- Mycoses in Europe...

Invasive Candidosis

Invasive Aspergillosis

PCP (*P. jiroveci*)

Cryptococcosis

Zygomycosis

Scedosporium infection

Fusarium infection

Histoplasmosis

Penicilliosis

Coccidioidomycosis

Blastomycosis

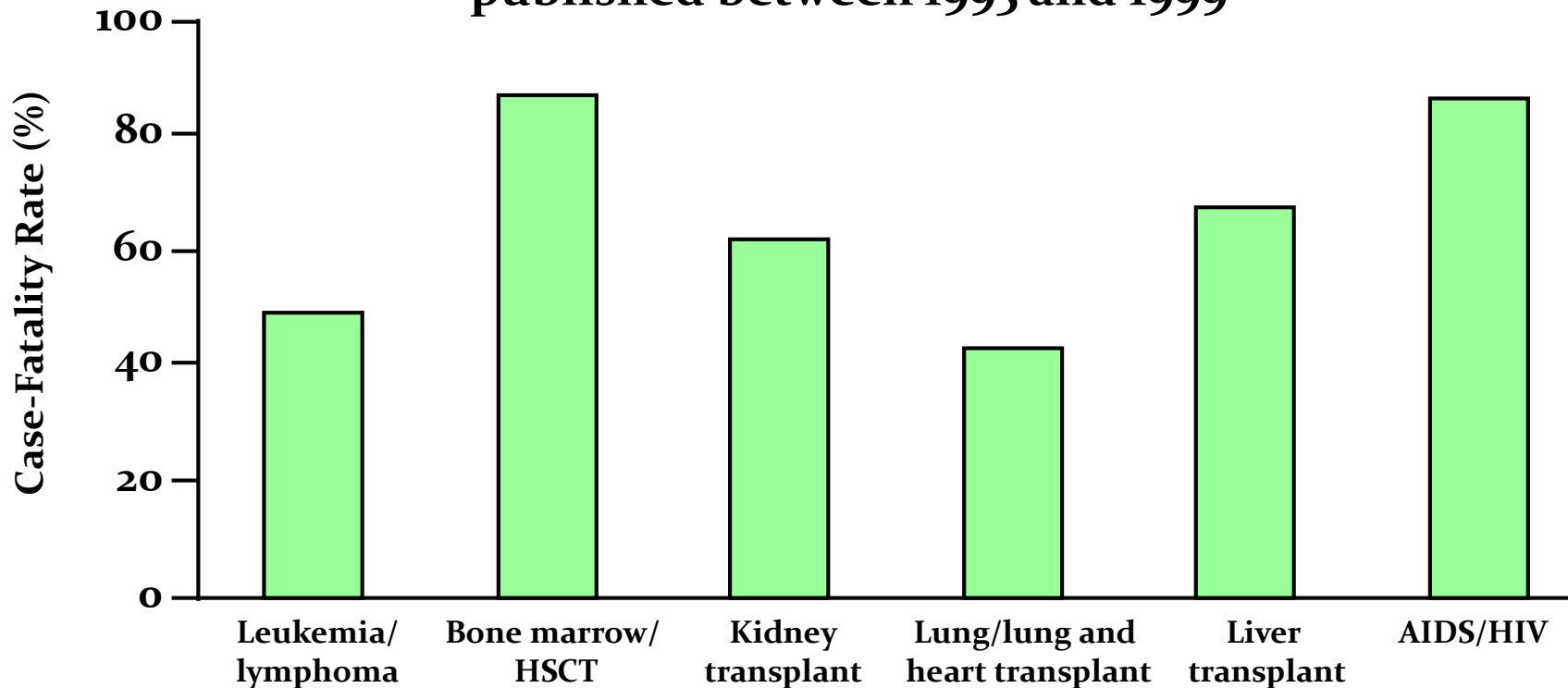
Background: Scale of the problem

| Disease (most common species) | Location | Estimated life-threatening infections/ year at that location* | Mortality rates (% in infected populations)* |
|---|---------------------------------------|---|--|
| Opportunistic invasive mycoses | | | |
| Aspergillosis (<i>Aspergillus fumigatus</i>) | Worldwide | >200,000 | 30–95 |
| Candidiasis (<i>Candida albicans</i>) | Worldwide | >400,000 | 46–75 |
| Cryptococcosis (<i>Cryptococcus neoformans</i>) | Worldwide | >1,000,000 | 20–70 |
| Mucormycosis (<i>Rhizopus oryzae</i>) | Worldwide | >10,000 | 30–90 |
| Pneumocystis (<i>Pneumocystis jirovecii</i>) | Worldwide | >400,000 | 20–80 |
| Endemic dimorphic mycoses*† | | | |
| Blastomycosis (<i>Blastomyces dermatitidis</i>) | Midwestern and Atlantic United States | ~3,000 | <2–68 |
| Coccidioidomycosis (<i>Coccidioides immitis</i>) | Southwestern United States | ~25,000 | <1–70 |
| Histoplasmosis (<i>Histoplasma capsulatum</i>) | Midwestern United States | ~25,000 | 28–50 |
| Paracoccidioidomycosis (<i>Paracoccidioides brasiliensis</i>) | Brazil | ~4,000 | 5–27 |
| Penicilliosis (<i>Penicillium marneffeii</i>) | Southeast Asia | >8,000 | 2–75 |

*Most of these figures are estimates based on available data, and the logic behind these estimates can be found in the text and in the Supplementary Materials. †Endemic dimorphic mycoses can occur at many locations throughout the world. However, data for most of those locations are severely limited. For these mycoses, we have estimated the infections per year and the mortality at a specific location, where the most data are available.

Background: Impact of invasive aspergillosis

MORTALITY
Determined from 1,941 patients in 50 studies
published between 1995 and 1999

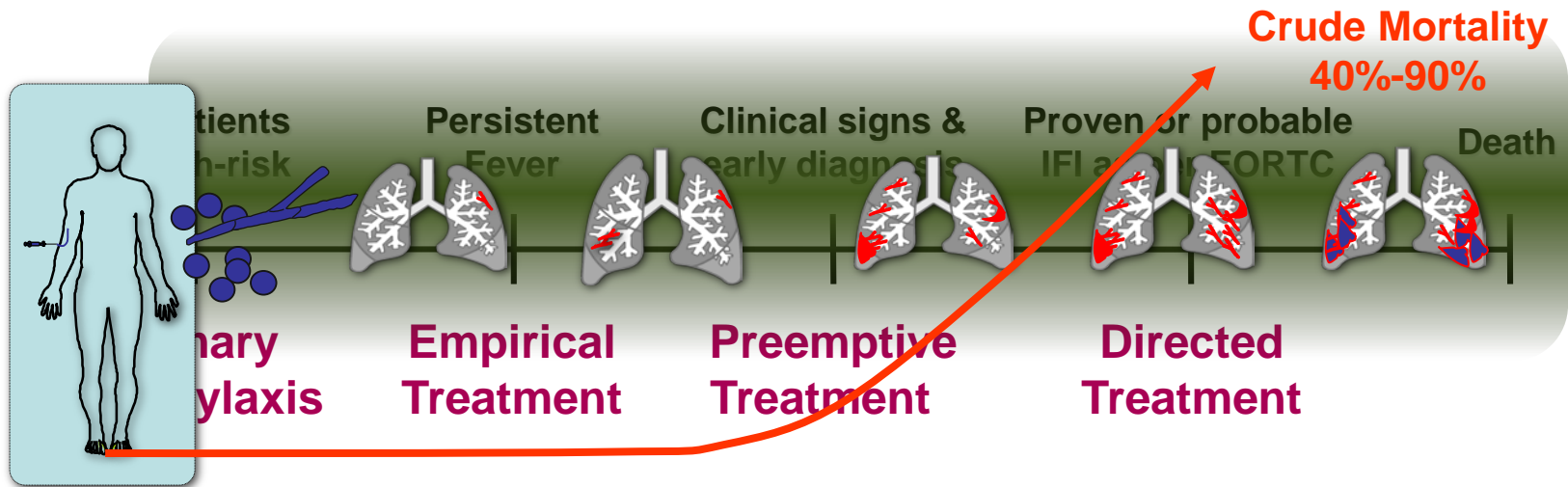


HSCT indicates hematopoietic stem cell transplant.
Lin SJ et al. *Clin Infect Dis.* 2001;32:358-366.

Management of Invasive Mould Infections

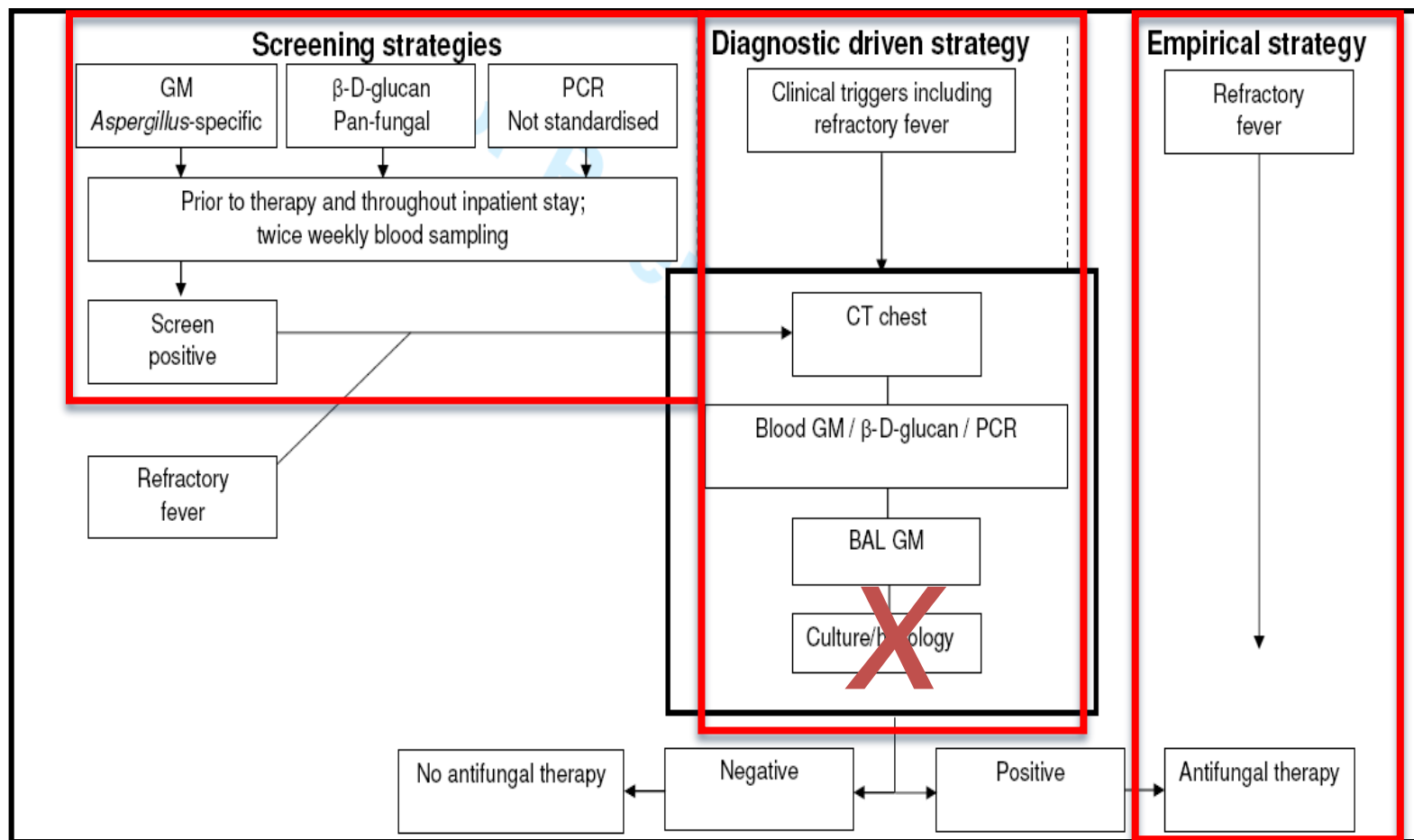
- **Management Strategies**
- **Current challenges**
 - *Diagnosis*
 - *Resistance*
- **Current Treatment Options**
 - *Guidelines - Study data*
- **Isavuconazole Data**
 - *Aspergillosis – Mucormycosis*
- **Antifungal Stewardship**

Antifungal Strategies



X

Management of IMD - Strategies in Haem-Onc



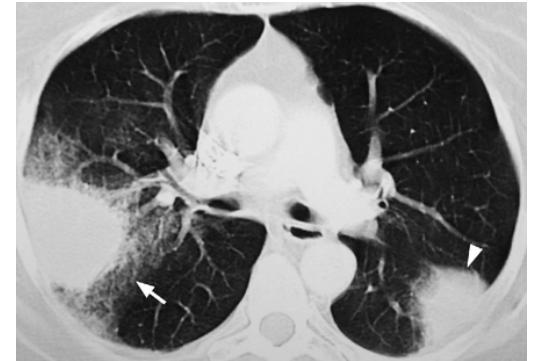
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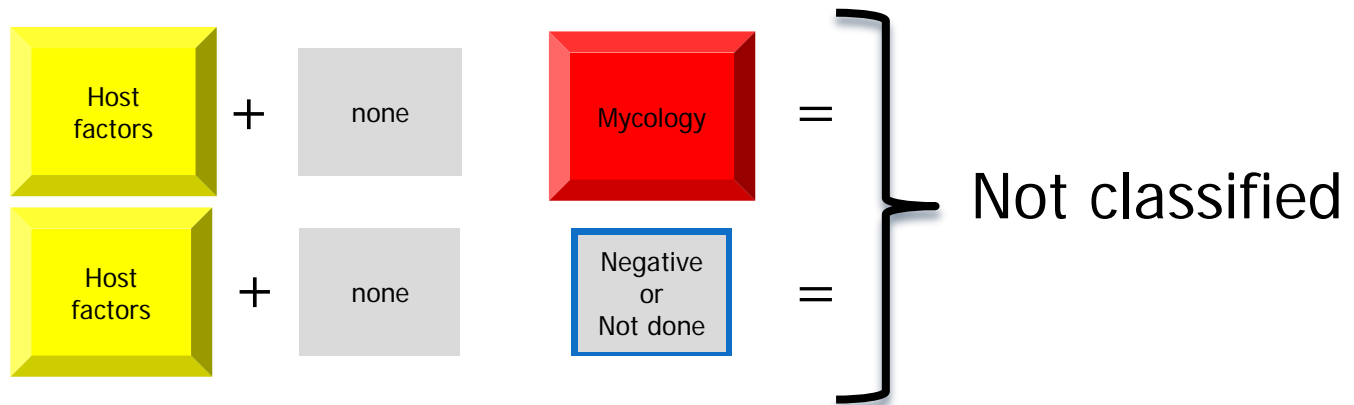
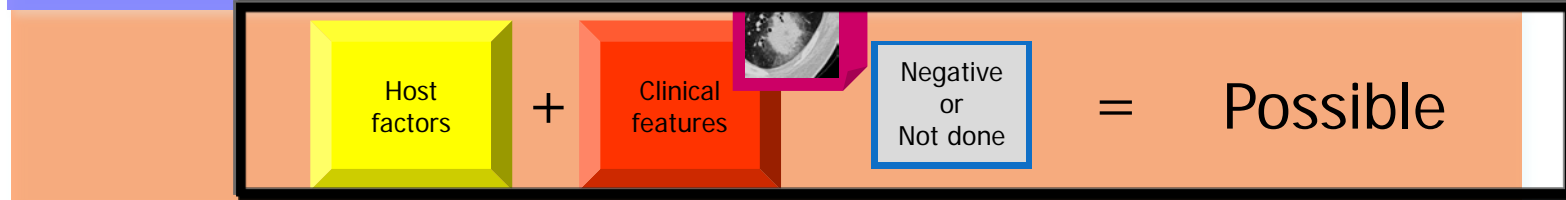
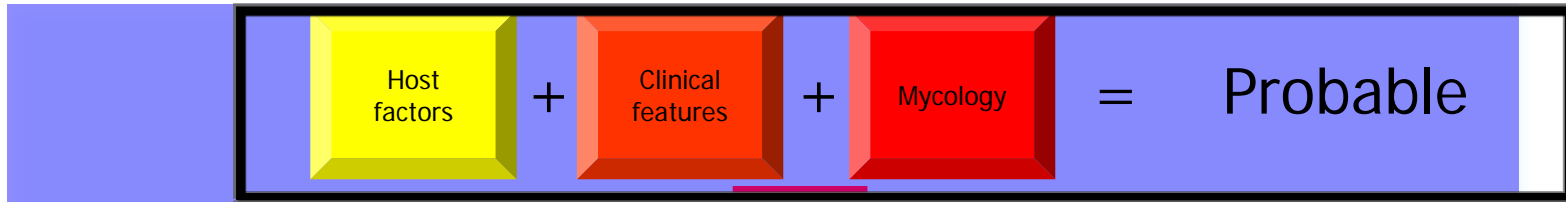
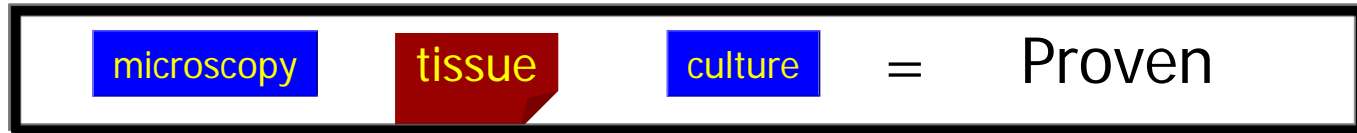
Management of IMD - Diagnosis

Diagnosis is THE CHALLENGE...

- **Host factors** - high-risk?
- **Imaging** - what is the pathogen?
- **Laboratory tests**
 - blood culture
 - culture/microscopy (other)
 - biomarkers



EORTC/MSG 2008 - Definitions



Audit of IFD in 531 AML / allograft episodes 2005–9

- EORTC 2008

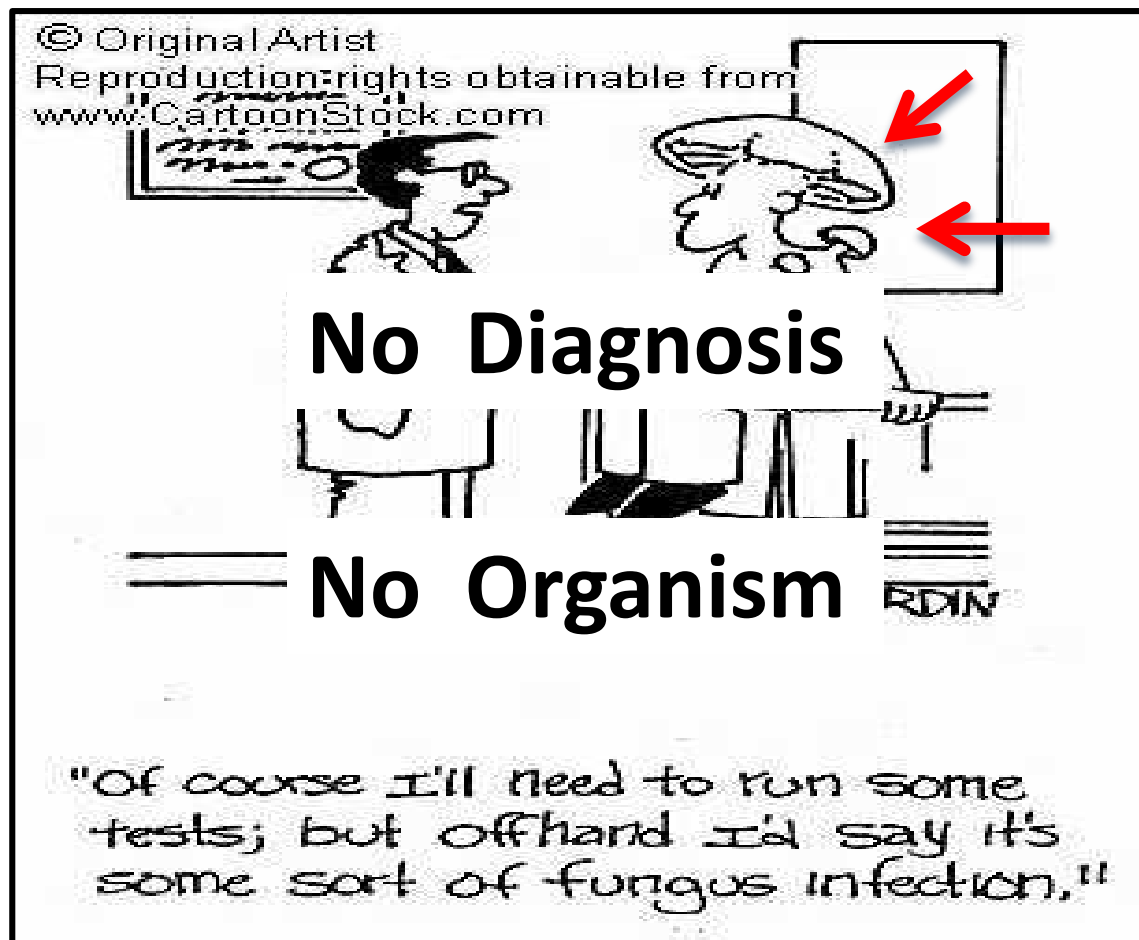
- Evidence of IFD in 235 (44%)

- Proven IFD (2.1%)

FEAR FACTOR vs true IFD

44%

Empirical reality of clinical practice



Antifungal Drug Costs 2005 - 9

- EORTC scores (2008)
- 408/528 episodes - AML or MDS
- 123/528 allogeneic transplants:
 - no IFD (n=489) £1.35M
 - possible (n=28) £0.12M
 - probable (n=4) £0.035M
 - proven (n=7) £0.036M

85% of antifungal drug cost in cases without EORTC/MSG evidence of IFD !

Management of IMD - Resistance

Table 3. General patterns of susceptibility of *Candida* species.

| Species | Fluconazole | Itraconazole | Voriconazole | Posaconazole | Flucytosine | Amphotericin B | Candins |
|-----------------------------|-------------|--------------|--------------|--------------|-------------|----------------|---------------------|
| <i>Candida albicans</i> | S | S | S | S | S | S | S |
| <i>Candida tropicalis</i> | S | S | S | S | S | S | S |
| <i>Candida parapsilosis</i> | S | S | S | S | S | S | S to R ^a |
| <i>Candida glabrata</i> | S-DD to R | S-DD to R | S-DD to R | S-DD to R | S | S to I | S |
| <i>Candida krusei</i> | R | S-DD to R | S | S | I to R | S to I | S |
| <i>Candida lusitanae</i> | S | S | S | S | S | S to R | S |

I, intermediately susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent.

^a Echinocandin resistance among *C. parapsilosis* isolates is uncommon vs. ESCMID 2012 !

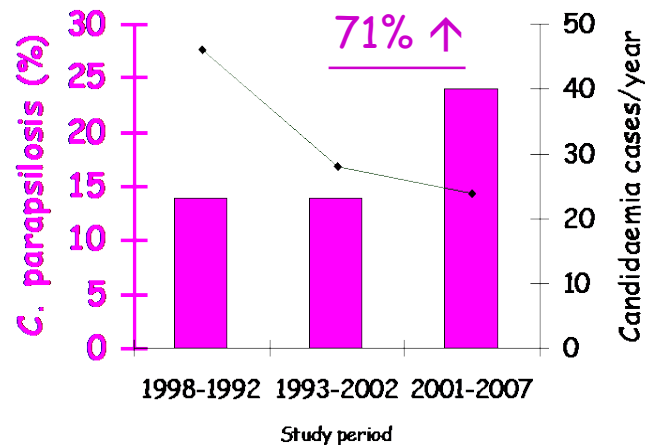
Management of IMD - Resistance

Echinocandin - Post marketing experiences

Single centre Haem US

2001-7 vs earlier 173 cases

- *C. parapsilosis* candidaemia



- Breakthrough during Caspo
 - 52% *C. parapsilosis* (P 0.0016)

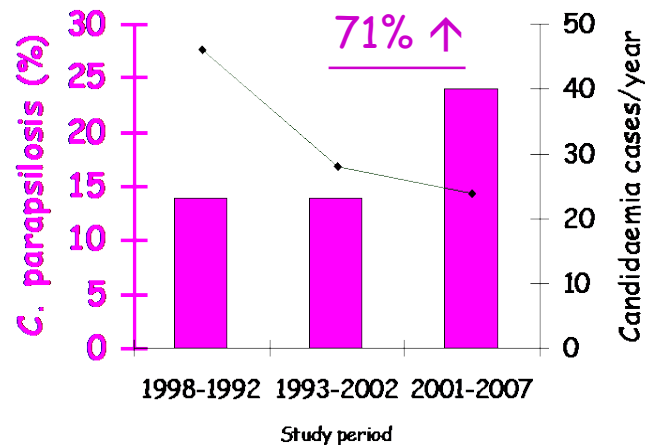
Management of IMD - Resistance

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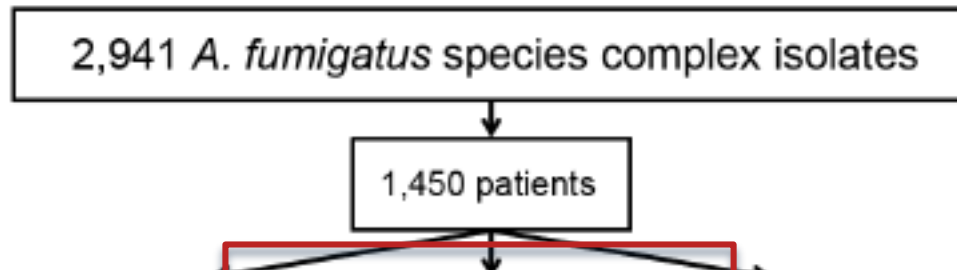
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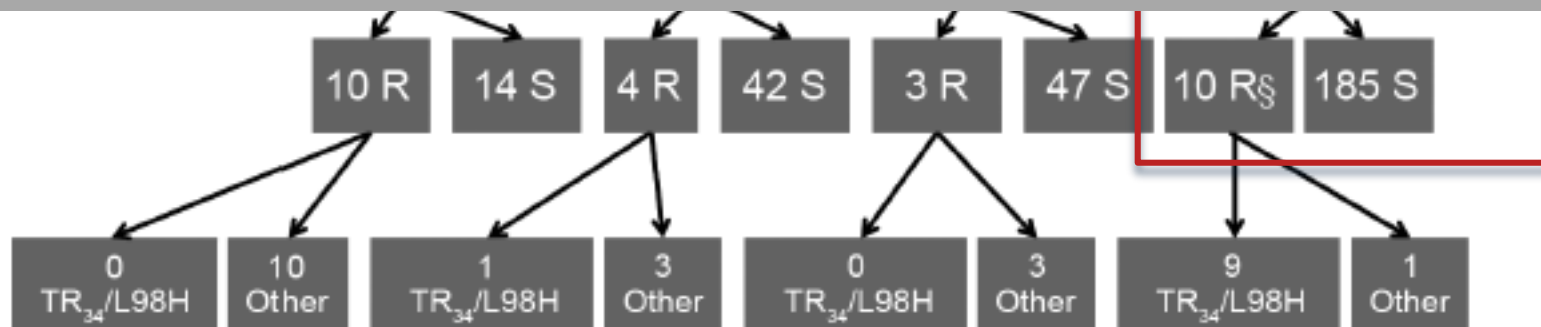
Management of IMD - Resistance



- Azole-resistant *A. fumigatus* in IFD = 5.1%

Azole resistance is widespread in Europe.

Azole resistance associated with a worse outcome



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Management of IMD - Treatment

Guidelines for probable/proven IA

| | DGHO 2009 | ASID 2008 | IDSA 2008 | ECIL-3 2010 | BCSH 2008 |
|------------------------------|----------------------|--------------|--------------|------------------------|----------------------|
| Itraconazole | B | | B | | |
| Posaconazole | A^a | C | B | B | |
| Voriconazole | A | B | A | A/B^a | A^d |
| Amphotericin B | | C | | | A |
| Amphotericin B lipid complex | B | | A | B | |
| Liposomal amphotericin B | A | B | A | B | |
| Caspofungin | A^a | C | B | C | |
| Micafungin | C | | B | | |

^aFor salvage therapy; ^bfor CNS IA – restrict to proven;

^cno grading for IA treatment – both have A for empirical;

^dempirical therapy discouraged in patients with febrile neutropenia.

Management of IMD - Treatment

Invasive aspergillosis: first line therapy

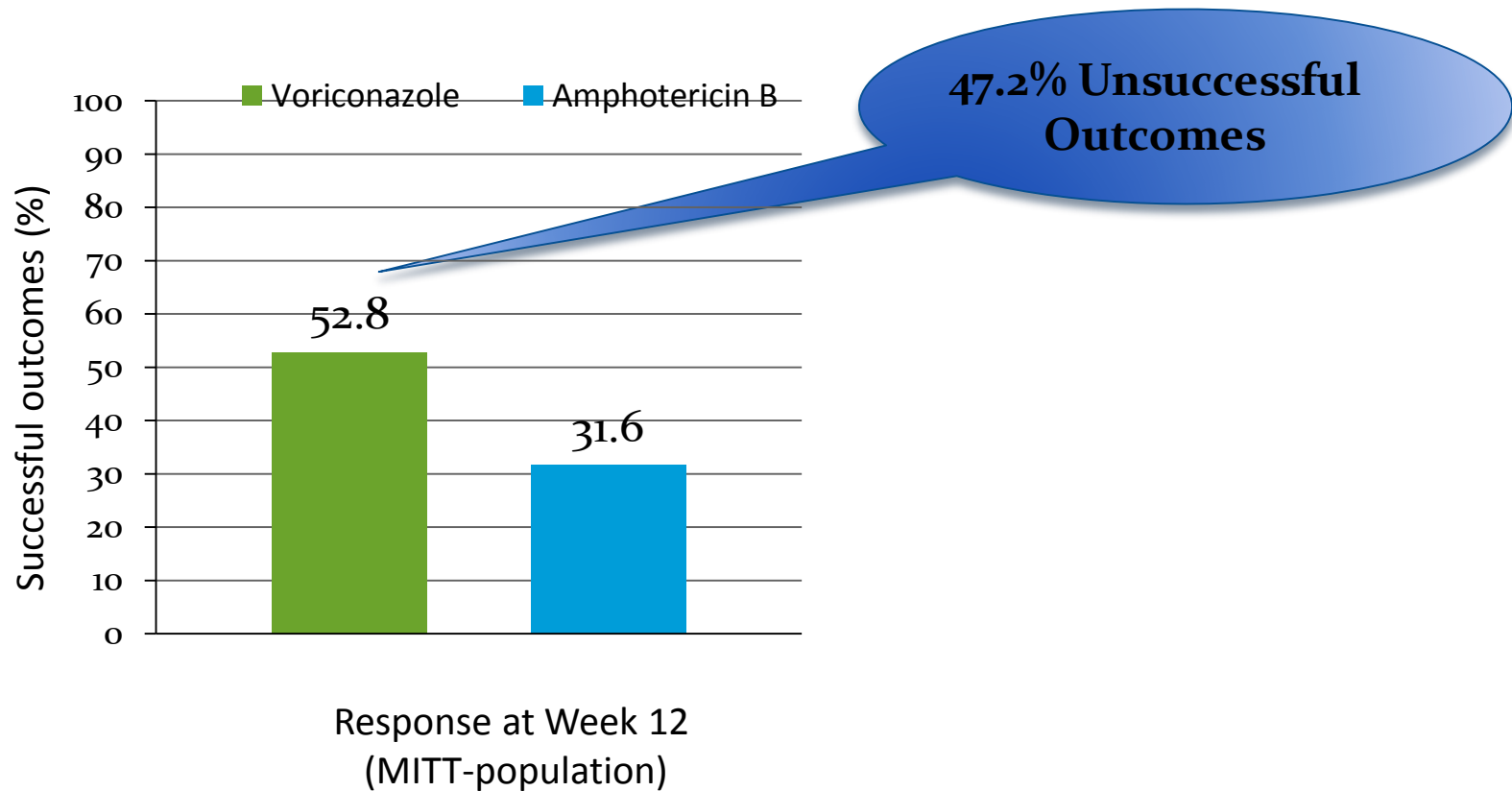
- **RCT - Voriconazole vs. Amphotericin B deoxycholate**
- 277 probable / proven IA* for 391 patients randomized
- Allo HSCT \approx 25%; Leukaemia \approx 43%

| | Vorico | C Ampho B | Significant |
|--------------------|--------|-----------|-------------|
| Patients (No.) | 144 | 133 | |
| Dose (mg/kg/d) | 7.87 | 0.97 | |
| CR + PR @ week 12 | 53% | 32% | Yes |
| Survival @ week 12 | 71% | 58% | Yes |
| Serious AEs | 13% | 24% | Yes |
| Most frequent SAE | liver | renal | |

* Not using 2008 EORTC-MSG consensus definitions

Management of IMD - Treatment

Primary treatment of IA - response rate / survival



Management of IMD - Treatment

Isavuconazole (Cresemba)

EMA-approved indications

In adults for the treatment of:

- Invasive Aspergillosis
- Mucormycosis (when amphotericin B is inappropriate)

Management of IMD - Treatment

Isavuconazole: new kid on the block

| | Voriconazole | Isavuconazole* |
|--------------------------|--------------------------------|-------------------------------|
| Active against Mucorales | No | Some |
| Food effect | Yes | No |
| β -cyclodextrin | Yes | No |
| Administration | Twice/d following loading dose | Once/d following loading dose |
| Predictable PK in adults | No | Yes |
| Need for TDM | Yes | ? |
| Drug Interactions | +++ | ++ |
| Safety (visual) | ++ | + (no visual) |
| Clinical experience | Extensive | Limited |

*Miceli MH and Kauffman CA. Clin Infect Dis 2015 Jul 15

Management of IMD - Treatment

RCT: Isavuconazole versus voriconazole (SECURE)

Study design

- A phase 3, randomized, double-blind trial
- Primary treatment of IFD

Study size

- 527 patients randomized
- 516 received at least one dose of study drug

Indication

- IFD caused by *Aspergillus* species or other filamentous fungi

Primary objective

- Non-inferiority, all-cause mortality at Day 42, ITT population

Primary endpoint (ITT)

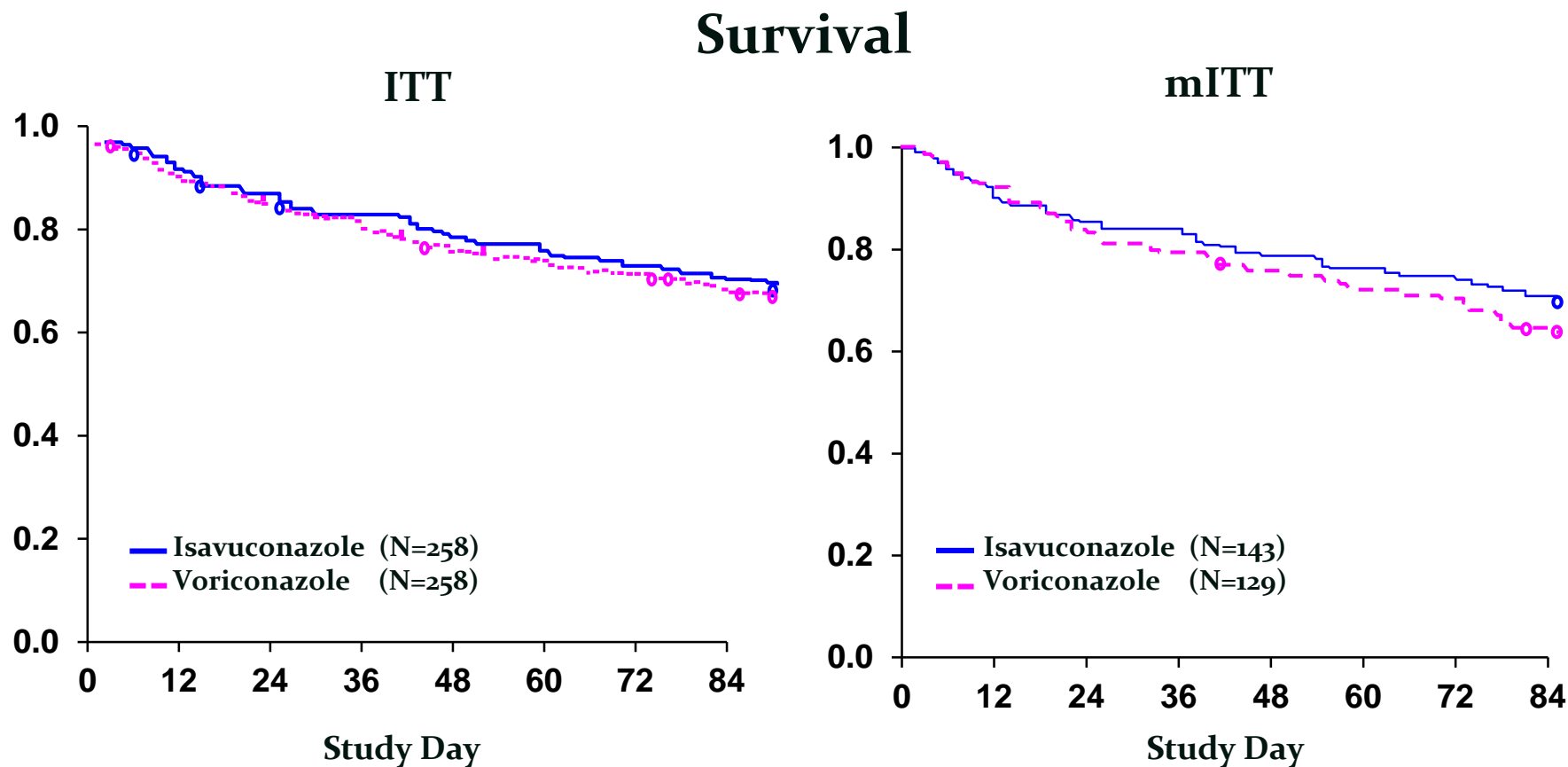
All-cause mortality through Day 42 (ITT population)

| | Isavuconazole N = 258 | Voriconazole N = 258 |
|--|--------------------------|-------------------------|
| All-cause mortality, n (%) | 48 (18.6) | 52 (20.2) |
| Adjusted treatment difference % (95% CI) ^a | -1.0 (-7.8, 5.7) | |
| Deaths, n (%) | 45 (17.4) | 50 (19.4) |
| Unknown survival status, n (%) ^b | 3 (1.2) | 2 (0.8) |

^aIsavuconazole–voriconazole calculated by a stratified Cochran–Mantel–Haenszel method (strata: Geographic region, Allogeneic BMT/HSCT, and uncontrolled malignancy status)

^bPatients with unknown survival status were counted as deaths

Survival consistent for ITT and mITT



Treatment-emergent Adverse Events (TEAE)

| Patients with TEAEs | Isavuconazole N = 257 % | Voriconazole N = 259 % | P-value |
|---|-------------------------------|------------------------------|-----------------|
| Patients with any TEAE | 96.1 | 98.5 | NS |
| Study drug-related TEAEs | c 42.4 | 59.8 | <0.05 |
| Serious TEAEs | 52.1 | 57.5 | NS |
| Study drug-related serious TEAEs | 10.9 | 11.2 | NS |
| TEAEs leading to study drug discontinuation | 14.4 | 22.8 | <0.05 |
| Study drug-related TEAEs leading to discontinuation | 8.2 | 13.5 | NS |
| Death | 31.5 | 33.6 | NS |

Most frequent AEs by System Organ Class (SECURE)

| AEs by System Organ Class | Isavuconazole (N=257) | Voriconazole (N=259) |
|--|--------------------------|-------------------------|
| Patients with any AE | 96.1 | 98.5 |
| Gastrointestinal disorders | 67.7 | 69.5 |
| Infections and infestations | 59.1 | 61.0 |
| General disorders and administration site conditions | 57.6 | 55.6 |
| Respiratory, thoracic and mediastinal disorders | 55.6 | 56.8 |
| Metabolism and nutrition disorders | 42.0 | 46.7 |
| Nervous system disorders | 37.0 | 34.4 |
| Skin and subcutaneous tissue disorders | 33.5[#] | 42.5 |
| Investigations | 33.1 | 37.1 |
| Blood and lymphatic system disorders | 30.0 | 31.7 |
| Psychiatric disorders | 27.2 | 33.2 |
| Musculoskeletal and connective tissue disorders | 26.8 | 29.7 |
| Vascular disorders | 26.1 | 29.7 |
| Renal and urinary disorders | 21.4 | 22.4 |
| Cardiac disorders | 16.7 | 22.0 |
| Eye disorders | 15.2[#] | 26.6 |
| Injury, poisoning and procedural complications | 12.8 | 15.1 |
| Hepatobiliary disorders | 8.9[#] | 16.2 |
| Neoplasms benign, malignant and unspecified | 7.4 | 12.0 |

*sorted in descending order in isavuconazole column; [#]p<0.05

Treatment For “probable/proven” IA

- VORICONAZOLE
 - LIPOSOMAL AMPHOTERICIN B
 - ISAVUCONAZOLE^a
- } AI
B1*
AI**

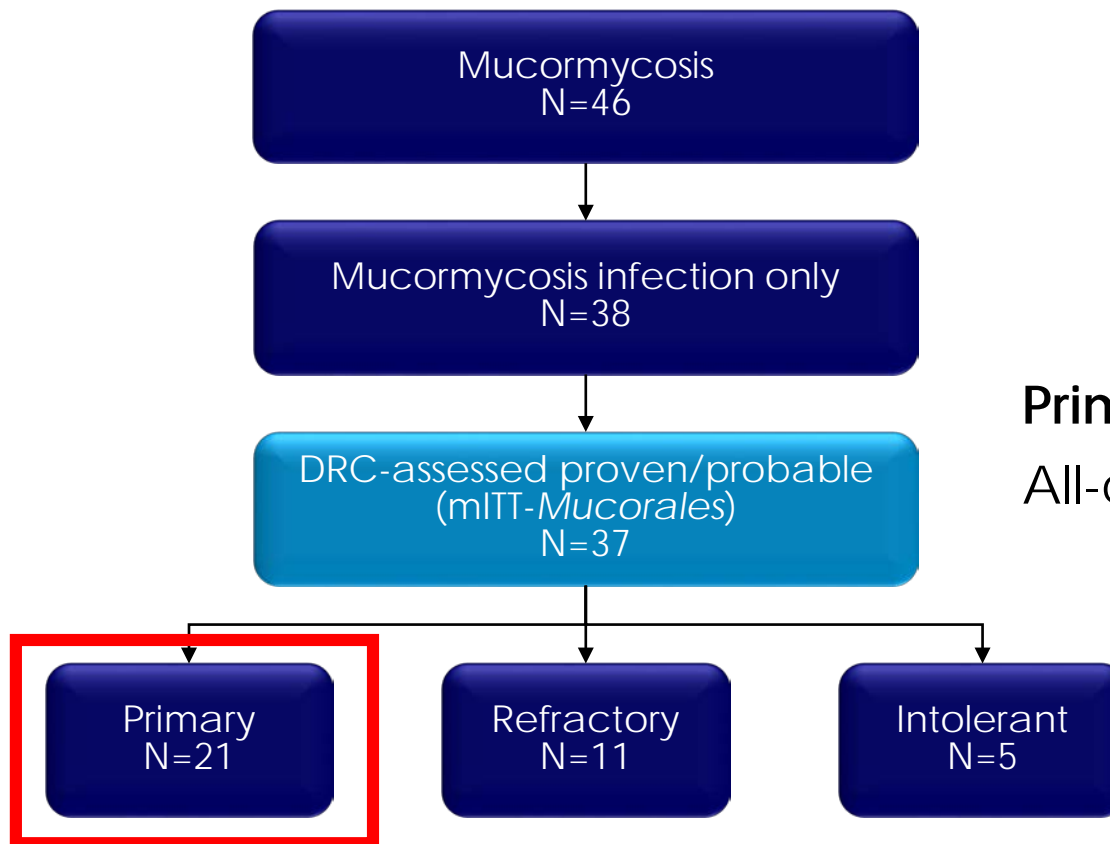
* B1 is an ECIL rating as the pivotal study compared AmBisome against itself !

** Unpublished – ECIL6 and ESCMID guidelines

^a Maertens J et al. Lancet Online 9th Dec 2015

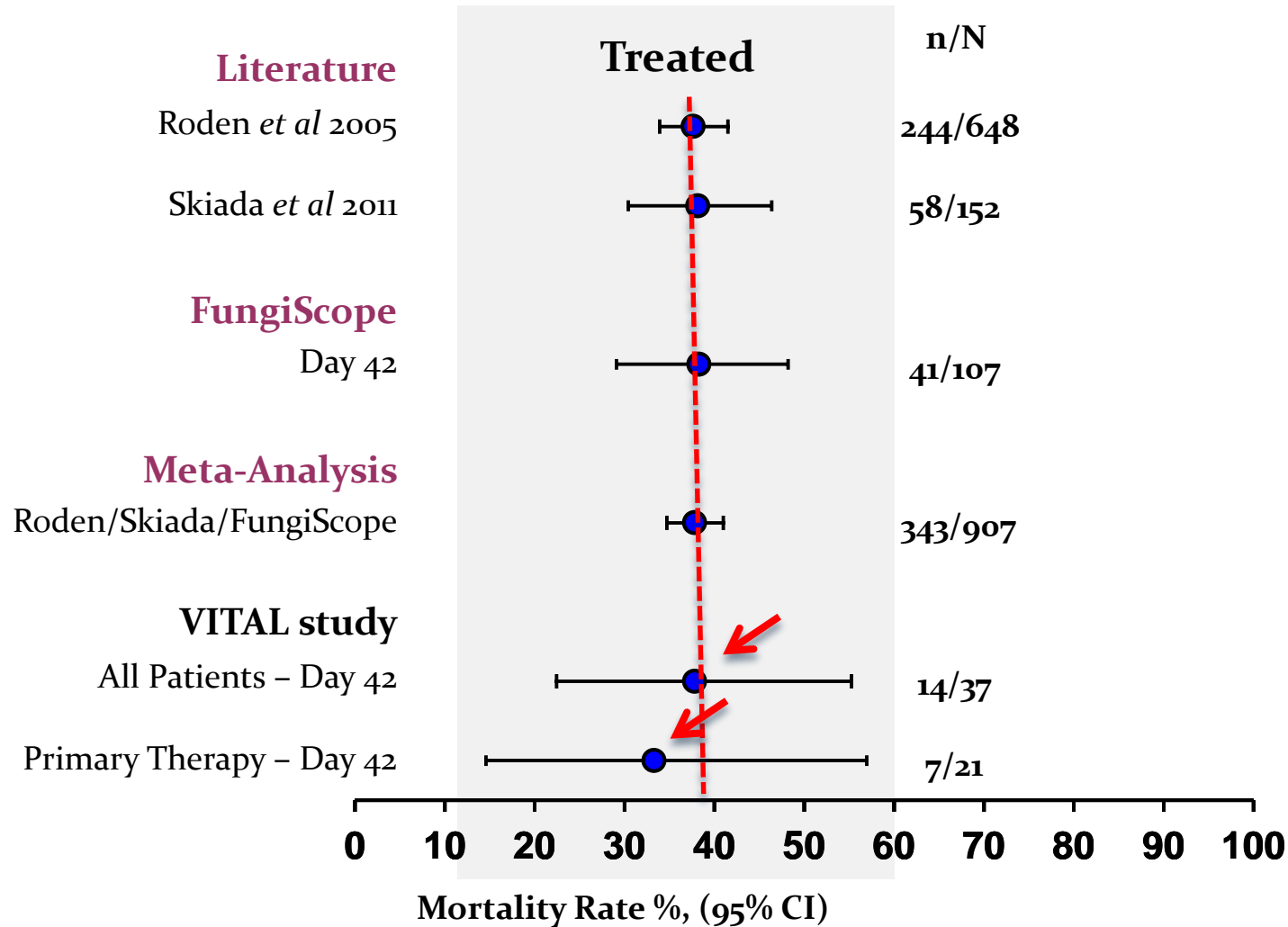
Isavuconazole and Mucormycosis

- Open-label (VITAL study)
- Treatment of IA, rare moulds, yeasts or dimorphic fungi



Primary efficacy end point
All-cause mortality at Day 42

Mortality and Mucormycosis




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Management of IMD - Stewardship

What is Antifungal Stewardship?

A graphic with a white background and a faint grid pattern. It features two blue double-slash symbols (//) at the top left and bottom right. The text is centered and reads: "The right ANTIFUNGAL for the right patient, at the right time, with the right dose, and the right route, causing the least harm to the patient and future patients". At the bottom, there is a URL: "www.cdc.gov/getsmart/healthcare/inpatient-stewardship".

//

The right ANTIFUNGAL
for the right patient,
at the right time,
with the right dose, and
the right route, causing
the least harm to
the patient and future patients //

www.cdc.gov/getsmart/healthcare/inpatient-stewardship

Implementation of antifungal stewardship



Roles of the “Stewardship Team”:

- GUIDELINES

- review and update
- Infrastructure (eg HEPA filtration)
- Drug prophylaxis and treatment
- Strategy, diagnostic tests and follow-up, resistance...

- EDUCATION

- Department seminars, infection control meetings
- Know and present your LOCAL DATA
- Implement guidance
- Audit and feedback

- Review guidelines...

Know your local data



- Do have data on your AF management?
- Many centres do not
- Barts audit data...

At risk

Diagnostic Strategy 2012 with CT + GM; no screening

Primary Prophylaxis

AML/ALL

Auto/Allograft

R-CODOX-M/ IVAC

- Fluconazole 400mg PO daily

UKALL 14 induction I only

- AmBisome 50mg IV daily
- 2nd choice- micafungin 50mg IV daily

72 h

CT / GM

Clinical suspicion of IFI;

- Persistent >72 hrs or relapsing fever +/- clinical signs AND
- No other positive cultures

- Order CT Chest
- Other imaging, e.g. sinus/head/abdomen, if clinically indicated
- Order Serum Galactomannan (GM) for 2 consecutive days

Awaiting results

**GM -
CT normal/non-sp**

- Do not treat

**GM +
CT normal**

- Investigate

Non pulmonary IFI?

- Imaging - sinus/head/abdomen

**GM -
CT +**

- Investigate

Pulmonary IFD?

- Bronchoscopy
- BAL

**GM +
CT + or non-sp**

- Treat

Audit of IFD diagnostics



Analysis of IFD diagnostic use in haemto-oncology (Micafungin subset)

- Jan–Dec 2013 ; 41 episodes (40 patients)
- 19 treatment episodes of suspected IFD:

- *CT/GM not done*, 4 (21%)
- *AF started before CT/GM*, 4 (21%)

- 15/19 of patients there was **no evidence of IFD**

Audit of IFD diagnostics



Conclusions

- Patients receiving AF for suspected IFD
 - 80% had CT/GM
 - 80% no CT/GM/culture evidence of IFD!
= fever-driven management!
- How can we do better?



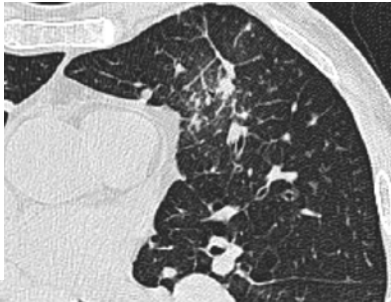
Stewardship with enhanced diagnostics

- Fungal Audit Tool [F.A.T.(s)] – online audit tool

A Team Approach - "Stewardship"

A Case study

Serum GM-
BAL:
GM 0.9
LFD+
PCR+



Clinical Deterioration
BUT "fungal" lesions resolving

Serum GM-
BAL:
GM <0.5
LFD -
PCR -



June

EORTC - Probable
Liposomal Ampho
Voriconazole

EORTC - Possible
Voriconazole to
Combination!

Aug

Serum GM-
BAL:
GM?
LFD?
PCR?



No IFD

Sept

Management of Invasive Mould Infections

Summary

- IFD is a life-threatening disease in the immunocompromised
- Diagnostic vs Empirical Management
- Local epidemiology - resistance

- AF Stewardship
 - team
 - pharmacist / ID / micro / haem-onc
 - data (F.A.T.s)



Thank-you