

Management of Invasive Fungal Disease – Therapeutic options

Conflict of Interest Disclosure

Research grants – advisory boards – speaker

Management of IFD – Therapeutic options

- **In Haem-Onc**
 - *Guidelines*
 - *Epidemiology*
- **Candida infections**
- **Stewardship**

Managing IFD : Drug Choices in Haem-Onc

Which drug do you use for prophylaxis in AML and allogeneic transplantation?

1. Fluconazole
2. Itraconazole
3. Voriconazole
4. Posaconazole
5. Conventional amphotericin
6. Liposomal Amphotericin
7. Echinocandin
8. None

Managing IFD : Drug Choices in Haem-Onc

Which drug do you use empirically?

1. Fluconazole
2. Itraconazole
3. Voriconazole
4. Posaconazole
5. Conventional amphotericin
6. Liposomal Amphotericin
7. Echinocandin
8. Isavuconazole

Managing IFD : Drug Choices in Haem-Onc

Which drug do you use to treat invasive aspergillosis?

1. Itraconazole
2. Voriconazole
3. Posaconazole
4. Conventional amphotericin
5. Liposomal Amphotericin
6. Echinocandin
7. Isavuconazole

No conventional amphotericin use in UK oncology

Haem-Onco Guidelines From 2007...

Guideline title	Affiliated associations/society	Year
Australian and New Zealand consensus guidelines	Australasian Leukaemia and Lymphoma / Infectious Diseases / NSW Cancer Institute	2008
IFI during therapy for haematological malignancy	British Committee for Standards in Haematology (BCSH)	2008
Primary prophylaxis in patients with haematological malignancies	Infectious Diseases Working Party (AGIHO) of the German Society of Haem-Onc (DGHO)	2009
Treatment of invasive fungal infections in cancer patients	AGIHO of the DGHO	2009
Clinical practice guidelines for candidiasis	Infectious Diseases Society of America (IDSA)	2009
Treatment of aspergillosis: clinical practice guidelines	IDSA (Update anticipated 2015)	2008
Antifungal prophylaxis in leukemia	European Conference on Infections in Leukaemia (ECIL)-3	2010
Empirical antifungal therapy	ECIL-3	2010
Antifungal therapy in leukemia	ECIL-4	2011
Diagnosis and management of Candida diseases	European Society of Clinical Microbiology and Infectious Diseases (ESCMID)	2012
Prevention and treatment of cancer-related infections	National Comprehensive Cancer Network (NCCN)	2012

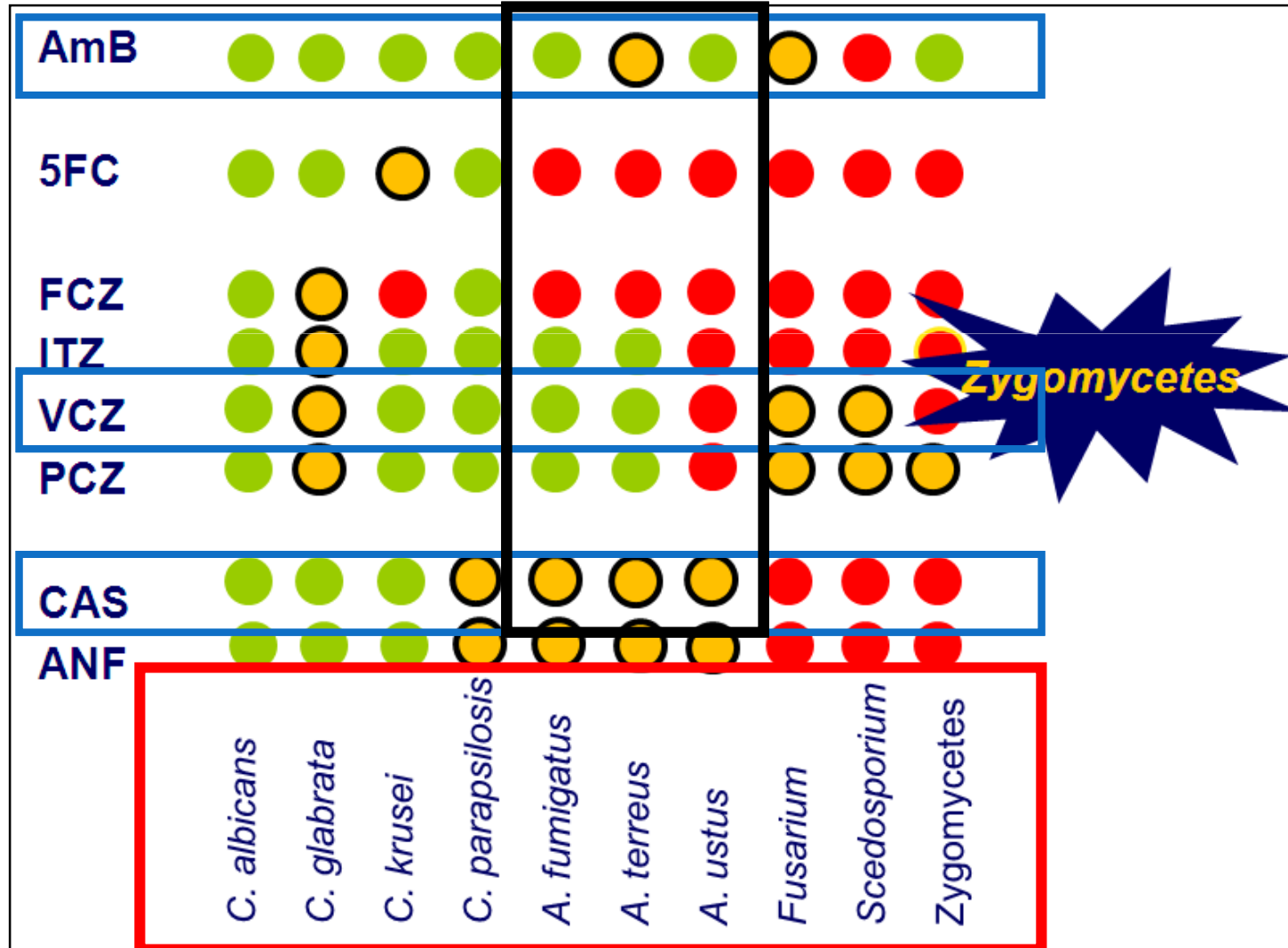
Empirical Therapy

	IDSA 2008	IDSA 2009 ^a	BCSH 2008	ECIL-3 2010
Fluconazole		B^b		C
Itraconazole	A^a	B^b		B
Voriconazole	A^a			B
Amphotericin B	A^a			B^c
Amphotericin B colloidal dispersion	A			B
Amphotericin B lipid complex	A	A^b		B
Liposomal amphotericin B	A^a	A^b	A^d	A
Caspofungin	A^a	A^b	A^d	A
Micafungin				B

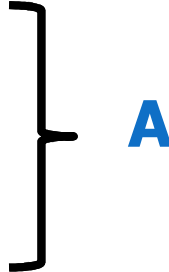
^aSpecific to *Aspergillus*; ^bspecific to suspected invasive *Candida*;
^cnot if risk factors for renal toxicity; ^dempirical therapy discouraged.

Empirical therapy: Epidemiology?

Courtesy of B. de Pauw



Empirical

- LIPOSOMAL AMPHORTERICIN B
 - CASPOFUNGIN
 - Voriconazole
- (A - while waiting for the results of investigations; IDSA)
(B – ECIL)
- 

Treatment 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	^c
Caspofungin	A^a	C	B	C	^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. ^c

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

Candida (ESCMID) guidelines

ESCMID PUBLICATIONS

10.1111/1469-0691.12037

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: developing European guidelines in clinical microbiology and infectious diseases

A. J. Ullmann^{1†}, O. A. Cornely^{2†}, J. P. Donnelly^{3†}, M. Akova⁴, M. C. Arendrup⁵, S. Arican-Akdagli⁶, M. Bassetti⁷, J. Bille⁸, T. Calandra⁹, E. Castagnola⁹, J. Garbino¹⁰, A. H. Groll¹¹, R. Herbrecht¹², W. W. Hope¹³, H. E. Jensen¹⁴, B. J. Kullberg⁵, C. Lass-Flor¹⁵, O. Lortholary^{16,17}, W. Heersseman¹⁸, G. Peotikkos¹⁹, M. D. Richardson²⁰, E. Roilides²¹, P. E. Verweij¹, C. Viscoli²² and M. Cuenca-Estrella^{23†} for the ESCMID Fungal Infection Study Group (EFISG)

ESCMID *Candida* guideline(s)

Diagnostic procedure

ICU (medical & surgical)

Other non-immunocompromised (medical & surgical), other immunocompromised situations

Paediatrics

PICU

Haematology/Oncology

HIV/AIDS

ESCMID candida guideline(s) Working Groups

Author panel: EFISG/ESCMID & representatives from EORTC; EBMT; ESICM, ECM
M

Diagnostic procedure

Maiken Cavling Arendrup, Sevtap Arikan-Akdagi, Jacques Bille, **Manuel Cuenca-Estrella**, Peter Donnelly, Henrik Elvang Jensen, Cornelia Lass-Förl, Malcolm Richardson, **Paul Verweij**

ICU (medical & surgical)

Other non-immunocompromised (medical & surgical), other immunocompromised situations

Matteo Bassetti, Thierry Calandra, **Oliver Cornely**, Jorge Garbino, Bart-Jan Kullberg, Wouter Meersseman

Paediatrics

PICU

Elio Castagnola, Andreas Groll, **William Hope**, Emmanuel Roilides

Haematology/Oncology

Murat Akova, Raoul Herbrecht, **Andrew Ullmann**, Claudio Viscoli

HIV/AIDS

Olivier Lortholary, Georgios Petrikkos

Group leaders in bold

Diagnosis of *Candida* infections – Specific comments

- BC (sens 50-75%), 3 sets- then daily
 - Adults: 40-60 mL (Ae, An and Mycosis bottle)
 - Paed: ≤ 2 kg: 2 to 4 mL
 - 2-12 kg: 6 mL
 - 12-36 kg: 20 mL

Species ID mandatory

- Mannan Ag & Ab, serial tests may be necessary
 - Sens: 80%, Spec: 85%, NPV: >85% for candidaemia
 - Sens: 86% in 21 cases of chronic disseminated candidiasis
 - Timing: mean 16 days before positive culture

Candida specific

- β -D-glucan, serial tests recommended (2/week)
 - Sens: >65%, Spec: >80%, NPV: >85%

Pan-fungal

Candida - Prophylaxis, empiric, pre-emptive

❖ Prophylaxis: Fluconazole

- BI: Abd. surgery + Recurrent GI perf. / anastomotic leakage* (Caspo CII_u)
 - AI: Neonates <1 kg/27 week if high local prevalence
 - AI: HSCT w neutropenia/GVHD/↓neutrophil recovery (Posa/Vori AI)
-
- Empiric (fever driven approach)
 - Patient group not defined
 - Compound: dependent on local epidemiology & interactions
-
- Pre-emptive (microbiological markers)
 - Mannan Ag & anti-mannan (may be false positive if heavy colonised)
 - β-D-Glucan (false pos: haemodialysis, gauze, albumin, other inf., contamination)
 - Colonisation (may predict species of subsequent inv infection)
 - *Candida* in airway specimen should not pre-empt antifungal tx (DIT)
 - Compound: dependent on local epidemiology & interactions

Targeted Treatment: Candidaemia

- Initial: Echinocandin (AT)

- Comments: consider *C. parapsilosis* & EMA micafungin warning
- Alternatives: AmBisome (BI), Voriconazole (BI)*, Fluconazole (CI)*

- CVC removal

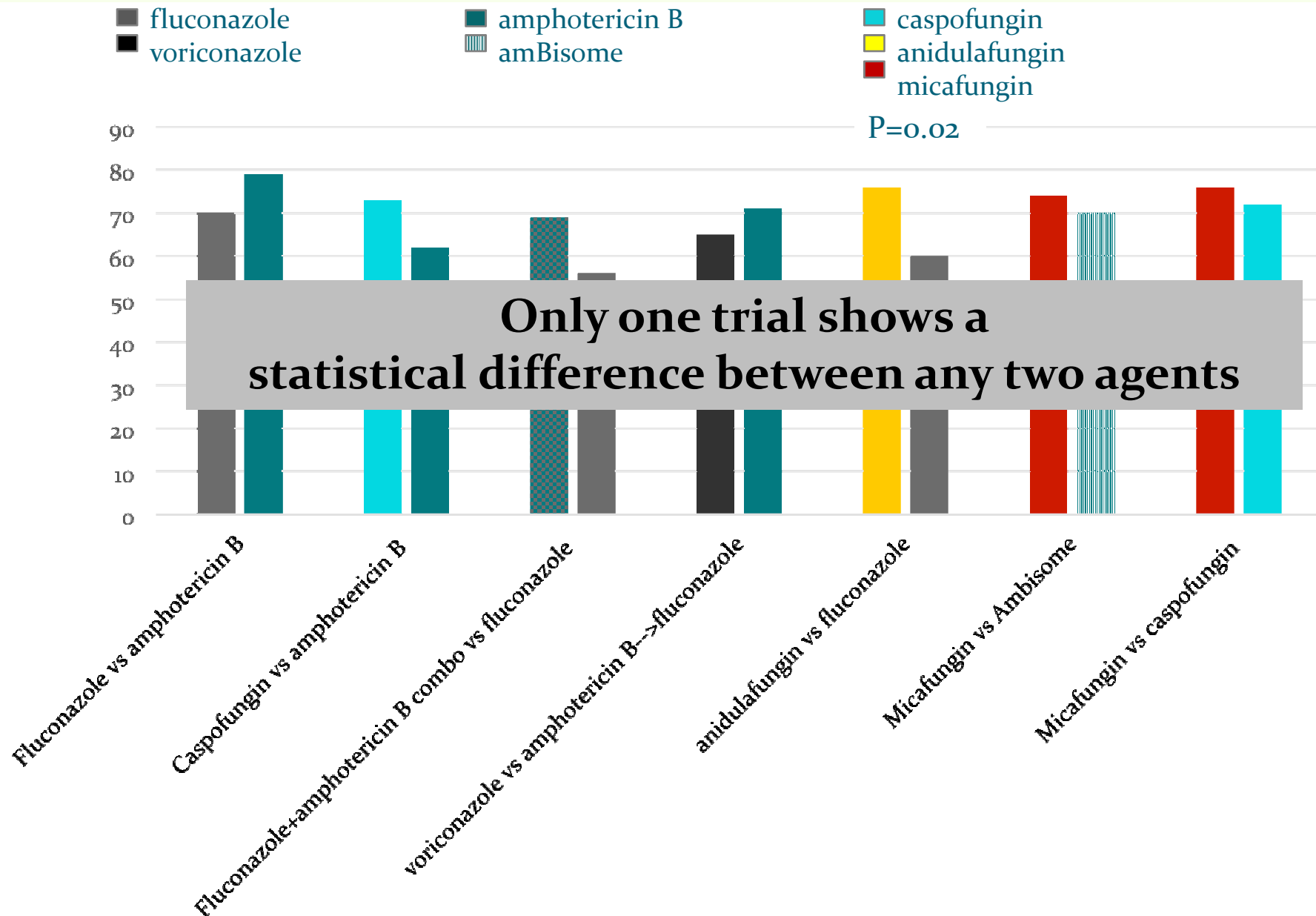
- Whenever possible (AII)
- If contraindicated: Echinocandin/Amphotericin (BII), avoid azole (DII)!

- Step down (day 10*)

- Monitoring

- Species ID and susceptibility test (BII)
- Daily BC until negative (BIII) – then another 14 days therapy

Clinical trials: Success rates



Motivation behind echinocandins as 1st line

Quantitative review of randomized trials*

Species	Success if echinocandin		
	P	OR	95% CI
All organisms (978)	0.01	2.33	1.27-4.35
<i>C. albicans</i> (408)	0.005	3.7	1.49-9.09
<i>C. glabrata</i> (104)	0.05	2.63	1.1-6.25
<i>C. parapsilosis</i> (212)	NS		
<i>C. tropicalis</i> (261)	NS		
Non-albicans (570)	NS		

*Rex 1994; Mora-Duarte 2002, Rex 2003; Kullberg 2005, Reboli 2007; Kuse 2007, Pappas 2007



C. parapsilosis and echinocandins

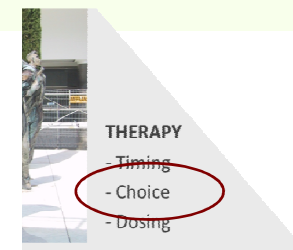


Table 3. Microbiologic and Global Responses at the End of Intravenous Therapy in the Modified Intention-to-Treat Population.*

Candida Pathogen	Successful Microbiologic Response			Successful Global Response†		
	Anidulafungin Group no. of isolates/total no. (%)	Fluconazole Group no. of isolates/total no. (%)	P Value	Anidulafungin Group no. of patients/total no. (%)	Fluconazole Group no. of patients/total no. (%)	P Value
<i>Candida albicans</i>	77/81 (95)	57/70 (81)	0.01	60/74 (81)	38/61 (62)	0.02
<i>C. glabrata</i>	15/20 (75)	18/30 (60)	0.37	9/16 (56)	11/22 (50)	0.75
<i>C. parapsilosis</i>	9/13 (69)	14/16 (88)	0.36	7/11 (64)	10/12 (83)	0.37
<i>C. tropicalis</i>	13/15 (87)	7/11 (64)	0.35	13/14 (93)	4/8 (50)	0.04
Other candida species	5/6 (83)	3/3 (100)	1.00	3/4 (75)	2/3 (67)	1.00
All candida species	119/135 (88)	99/130 (76)	0.02	92/119 (77)	65/106 (61)	0.01

C. parapsilosis: fluconazole numerically superior

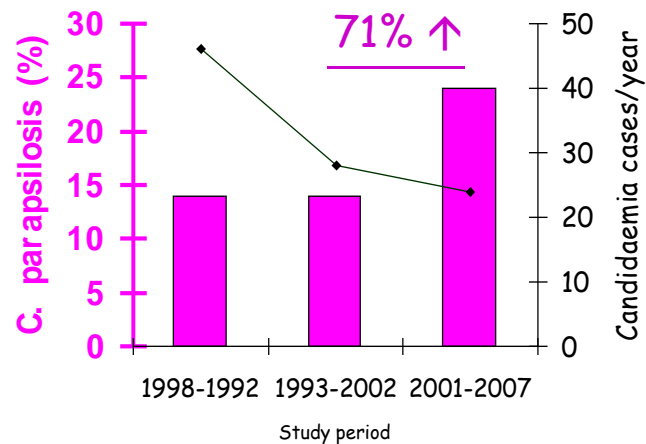
Echinocandin use and *C. parapsilosis*

Post marketing experiences

Single centre Haem US

2001-7 vs earlier 173 cases

- *C. parapsilosis* candidaemia

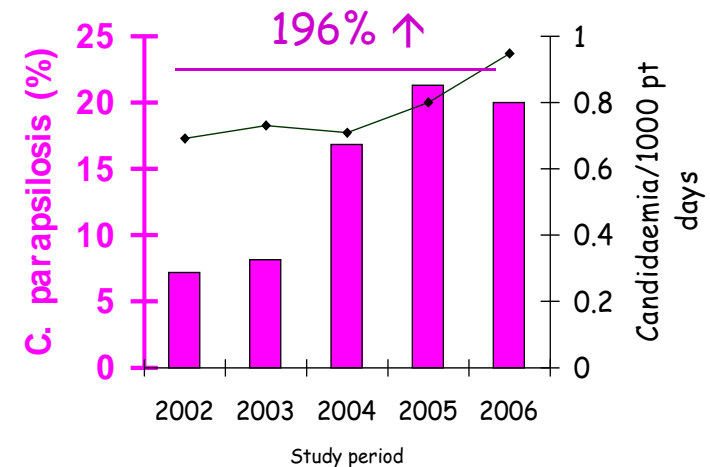


- Breakthrough during Caspo
 - 52% *C. parapsilosis* (P 0.0016)

Single Tertiary Centre US

2002 → 2006 469 cases

- *C. parapsilosis* candidaemia



- Echinocandin use
 - 4 → 10 DDD/1000 pt days

Conclusions

- ESCMID guidelines
 - better diagnostics
 - optimised treatment strategies

- Adaption to local epidemiology
 - incidence rate
 - species distribution
 - case mix

Management of IFD – Therapeutic options

- **In Haem-Onc**
 - *Guidelines*
 - *Epidemiology*
- **Candida infections**
- **Stewardship**

What is Antimicrobial Stewardship?

Bulletin of the World Health Organization 2011;89:390-392.
Infection Control and Hospital Epidemiology; 33; . 322-327, 2012



The right antibiotic
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

"Antimicrobial stewardship:

- ▶ is an **inter-professional effort**, across the continuum of care
- ▶ involves timely and optimal selection, dose and duration of an antimicrobial
- ▶ for the best clinical outcome for the treatment or prevention of infection
- ▶ with minimal toxicity to the patient
- ▶ and minimal impact on resistance and other ecological adverse events such as *C. difficile*"

[Nathwani et al., 2012]

What is Antifungal 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

antifungal **stewardship:**

- ▶ is an **inter-professional effort**, across the continuum of care
- ▶ involves timely and optimal selection, dose and duration of an *antifungal*
- ▶ for the best clinical outcome for the treatment or prevention of infection
- ▶ with minimal toxicity to the patient
- ▶ and minimal impact on resistance and other ecological adverse events such as *C. difficile*"

[Nathwani et al., 2012]

Stewardship

- Control and stopping antimicrobial therapy ?

Why is stewardship important?

- Resistance
- Changing epidemiology of fungal infection
- Toxicity/ side effects
- Cost

Candida Resistance – Role for Stewardship

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 !

Candida Resistance – Role for Stewardship

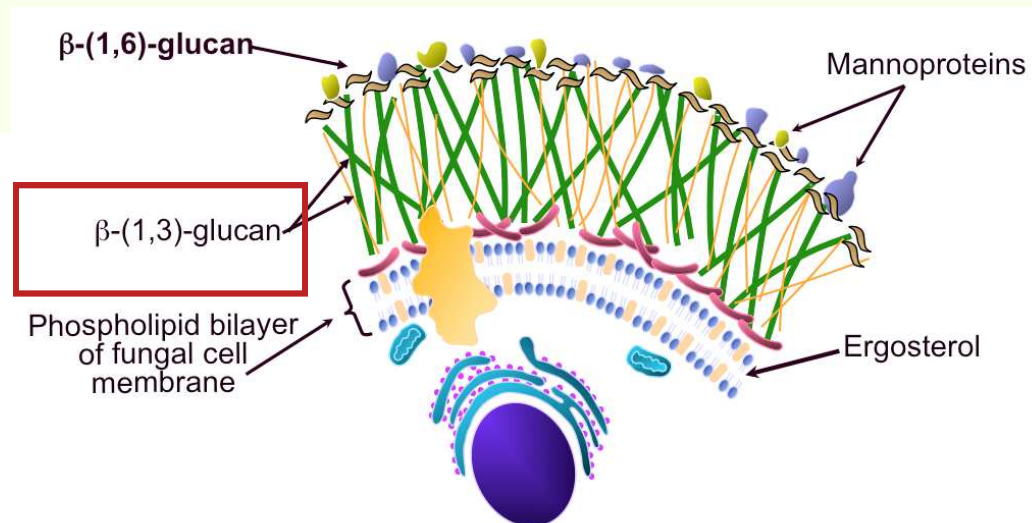
- High rates of echinocandin resistance (>12%)
 - Fluconazole-resistant *Candida glabrata* clinical isolates
- Epidemiology of *Candida spp* changes with selective pressure.
 - Fluconazole-resistant *Candida spp*
- Emergence of rare, multidrug-resistant *Candida species*

Alexander et al. Clin Infect Dis 2013; 56:1724–32.

Chow et al. Clin Infect Dis 2008; 46:1206–13

Chowdhary et al. Eur J Clin Microbiol Infect Dis. 2014 Jun;33(6):919-26. doi:

β-D-GLUCAN

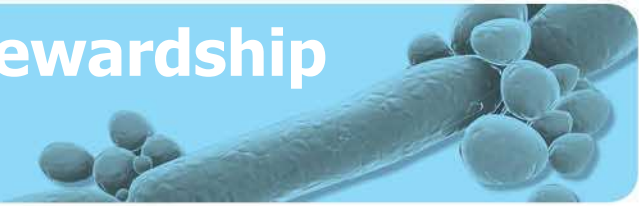


- β-D-glucan (BG) is a panfungal cell wall component
- Excluding mucorales, crypto and blasto
- NPV 95 to 99%; PPV around 50% (= rule out test).
- Cross reactivity with other beta glucans
- False positives - cellulose filters, surgery gauzes, ?betalactams, severe mucosistis, etc.
- False negatives - elevated triglycerides / bilirubin and haemolysed blood

Feasibility studies

- Two Spanish studies
 - Combination of biomarkers
 - Beta- D- glucan, germ tube Ab, mannan Ag, antimannan Ab
 - High sensitivity and NPV
 - Particularly with Beta-D-glucan & germ tube Ab
- Up to 30% of antifungal therapy in ICU could be discontinued by such an approach

Implementation of antifungal stewardship

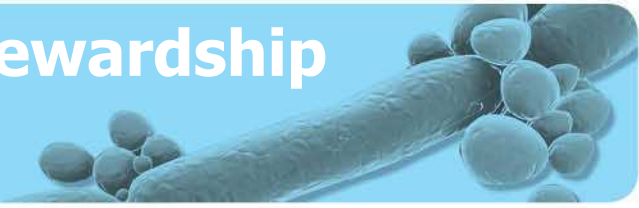


- Question: how to implement AF stewardship?



Engagement with colleagues

Implementation of antifungal stewardship



Question: how to implement AF stewardship?

- It needs to be a priority. A collaborative effort is required.
 - Managerial support (medical director / infection control officer?)
 - Pharmacy, microbiology/ID, haemato-oncology/ICU etc
 - Other departments – radiology, respiratory service...
 - Administrative support
 - Funding?

Implementation of antifungal stewardship



Roles of the “Stewardship Team”:

•GUIDELINES

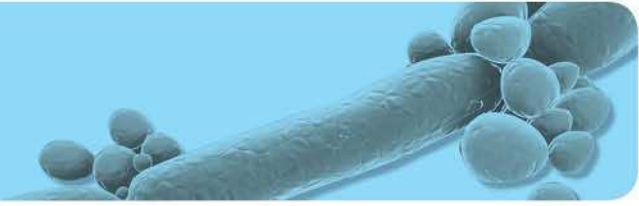
- review and update
- Infrastructure (eg HEPA filtration)
- Drug prophylaxis and treatment
- Strategy, diagnostic tests and follow-up

•EDUCATION

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

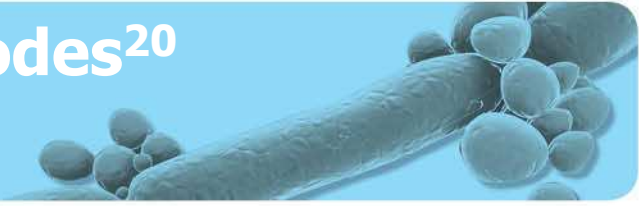
- Review guidelines...

Know your local data



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

Audit of 531 AML/allograft episodes²⁰



- Using EORTC/MSG criteria
 - Evidence of IFD, 39 (7.4%)
 - Probable/proven, 11 (2.1%)
- 44% of patients treated for “IFD”

- To consider:
 - “Physician fear” versus true rate of IFD
 - Low rates of IFD impact on screening strategies
 - Diagnostic-driven approach

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

**GM -
CT +**

- Investigate

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

- Treat

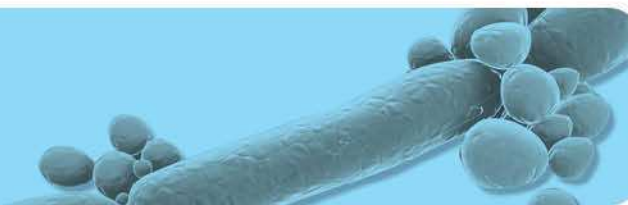
Non pulmonary IFI?

- Imaging -sinus/head/abdomen

Pulmonary IFD?

- Bronchoscopy
- BAL

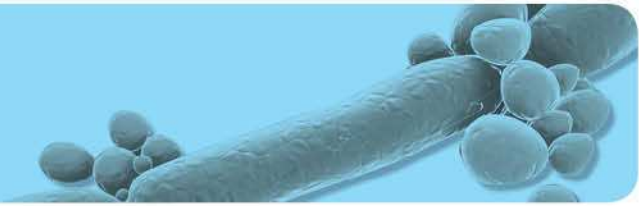
Audit of IFD diagnostics



Analysis of IFD diagnostic use in haemto-oncology patients receiving Micafungin

- 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%)
 - Overall, in 15/19 of patients there was **no evidence of IFD** using EORTC/MSG criteria (CT/GM/cultures)

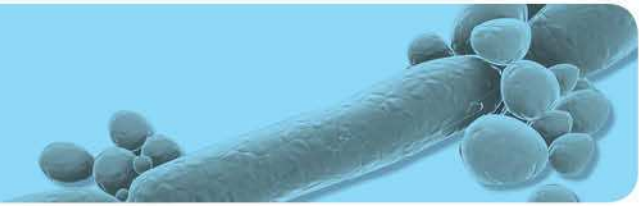
Audit of IFD diagnostics



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?

Impact of IFD diagnostics



Stewardship with enhanced diagnostics

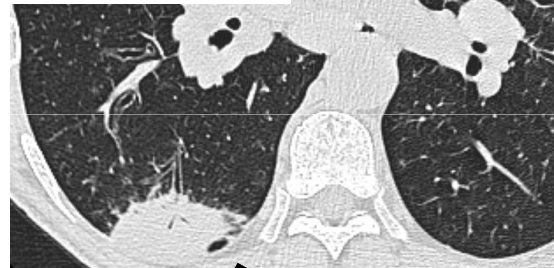
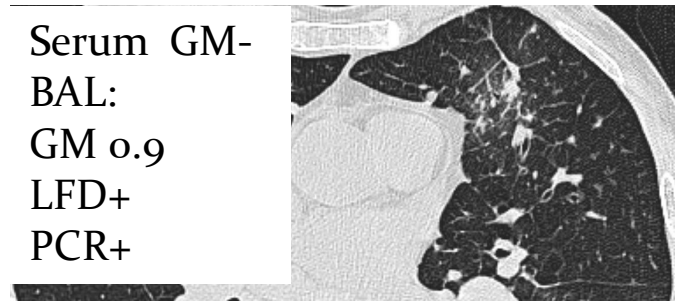
- Fungal Audit Tool F.A.T.(s) – online audit tool



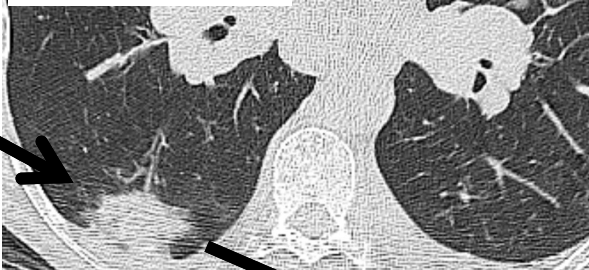
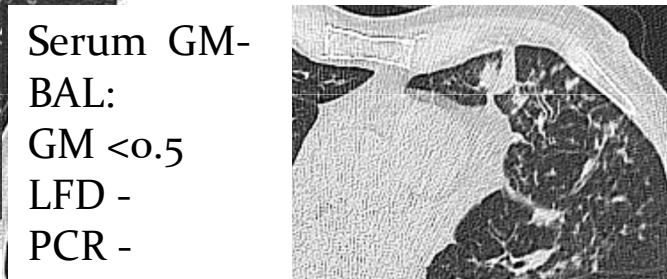
A Team Approach - "Stewardship"

A Case study

Clinical Deterioration
BUT "fungal" lesions resolving



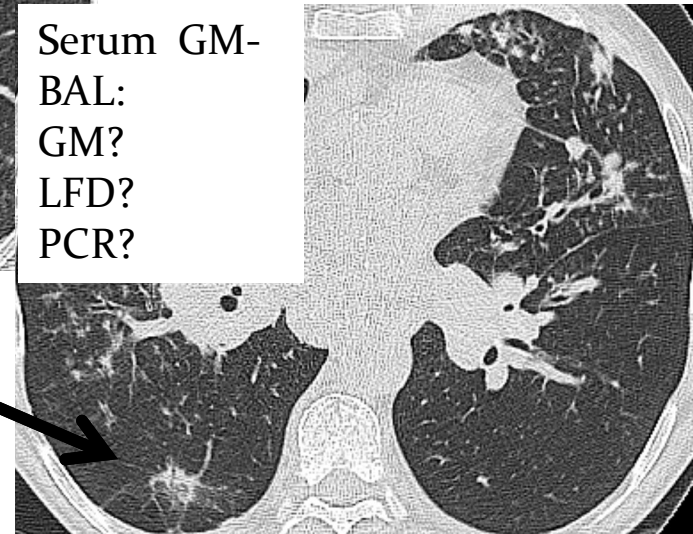
EORTC - Probable
Liposomal Ampho
Voriconazole



EORTC - Possible
Voriconazole to
Combination!

No IFD

Sept



Management of IFD – Therapeutic options

Summary

- Guidelines
- Diagnostics – CT; biomarkers
- Local epidemiology

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



11th ANNUAL
FUNGAL UPDATE

PROGRAMME & REGISTRATION INFORMATION

Royal College of Pathologists – CPD approved – 9 credits

Registering to attend the meeting

If you would like to attend the 11th Annual Fungal Update, please visit our website below where you will be able to find more information and register.

www.fungalupdate.org

- Fungal Update 2015 - 10th Anniversary Meeting
- Podcasts of meeting available
- F.A.T.(s) and Stewardship