

# ESCMID Candida Guidelines 2011

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ESCMID

EUROPEAN SOCIETY  
OF CLINICAL MICROBIOLOGY  
AND INFECTIOUS DISEASES

# Disclosure of Potential Conflicts of Interest:

## 1. Employment or Leadership Position

None

## 2. Advisory Role

Basilea, Pfizer, MSD, Astellas, Gilead, Aicuris

## 3. Stock Ownership

None

## 4. Honoraria

Astellas, Gilead, MSD, Astellas, and Pfizer

## 5. Financing of Scientific Research

Aicuris, Astellas, Gilead, MSD, Pfizer, and BioCryst

## 6. Expert Testimony

None

## 7. Other Financial Relationships

none

# Summary Presentation of ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

**Authors:** Murat Akova, Maiken Arendrup, Sevtap Arikan-Akdagli, Matteo Bassetti, Jacque Bille, Thierry Calandra, Elio Castagnola, **Oliver A. Cornely**, **Manuel Cuenca-Estrella**, Peter Donnelly, Jorge Garbino, Andreas Groll, Raoul Herbrecht, **William Hope**, Henrik Elvang Jensen, Bart-Jan Kullberg, Cornelia Lass-Flörl, **Olivier Lortholary**, Wouter Meersseman, Georgios Petrikos, Malcolm Richardson, Emmanuel Roilides, **Andrew J. Ullmann**, **Paul Verweij**, Claudio Viscoli

**Main Coordinator:** Andrew J. Ullmann



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## EXPERT/AUTHOR-GROUP (ESCMID)

Guideline-Coordinator

Coordinator Subgroup

### Expert Group:

- Participation in preparation of draft on subtopics
- Will participate in the weekend working meetings
- Review final presentation and manuscript

Chosen by...

## Representatives (EORTC; EBMT; ESICM, ECMM)

- Members of societies will review final manuscript
- If considered expert and representative as well, this person would count as "expert"

EFISG/  
ESCMID

Societies

# Working Modules

Diagnostic procedure

ICU (medical & surgical)

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

Paediatrics

PICU

Haematology/Oncology

HIV/AIDS

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

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

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

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

**Olivier Lortholary**, Georgios Petrikos

**bold:** working module(s) coordinators

# Quality of Guidelines

Certain qualities are required:

- the scope and purpose of the guidelines
- stakeholder involvement
- rigor of development
- clarity of presentation, applicability
- editorial independence

# GRADE approach

Factors that influence the strength of recommendations

- Magnitude of the difference between the desirable and undesirable consequences,
- Quality of the available supporting evidence,
- Certainty about values and preferences of patients,
- Resource expenditure associated with the compared management options.



# Quality of Guidelines

Three simple questions asked repeatedly:

- What do clinicians want (intention)?
- Which option is better for patients (intervention)?
- Is the chosen option truly better?

# ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

**Authors:** M. ... Arkan-Akdagli, Matteo  
B... , Elio Castagnola, **Oliver A. Cornely**,  
Ma... ter Donnelly, Jorge Garbino , Andreas Groll, Raoul  
He... hope, Henrik Elvang Jensen, Bart-Jan Kullberg, Cornelia  
Las... , **Olivier Lortholary**, Wouter Meersseman, Georgios Petrikos,  
Malcolm Richardson, Emmanuel Roilides, **Andrew J. Ullmann**, **Paul Verweij**,  
Claudio Viscoli

**Main Coordinator:** Andrew J. Ullmann

# Strength of the EFISG Recommendation by Quality of Evidence

## Two Parts:

- Strength of recommendation
- Quality of Evidence

## Strength of recommendation

Grade A	ESCMID (fungal infection study group) <b>strongly</b> supports a recommendation for use
Grade B	ESCMID (fungal infection study group) <b>moderately</b> supports a recommendation for use
Grade C	ESCMID (fungal infection study group) <b>marginally</b> supports a recommendation for use
Grade D	ESCMID (fungal infection study group) <b>supports</b> a recommendation against use

# Strength of the EFISG Recommendation by Quality of Evidence

## Quality of evidence

- Level I Evidence from at least 1 properly designed randomized, controlled trial
- Level II\* Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
- Level III Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

### \*: added index:

- r: meta-analysis (or systematic review of RCT);
- t: transferred evidence i.e. results from different patients' cohorts, or similar immune-status situation;
- h: comparator group: historical control;
- u: uncontrolled trials
- a: for published abstract (presented at an international symposium or meeting)

# **ESCMID Diagnostic & Management Guideline for Candida Diseases 2011**

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**Main Coordinator:** Andrew J. Ullmann

# Management (incl. Treatment)

- Interpretation of positive results from secretions
- Types of treatment (e.g. ICU):
  - Prophylaxis
  - Empirical therapy
  - Pre-emptive therapy
  - Targeted treatment
    - Catheter-related infections
    - Treatment of chorioretinitis/endophthalmitis
    - CNS
    - Endocarditis
    - UTI
    - Bone and joint infections

# Management (incl. Treatment)

Focusing on special host groups

- SOT
- Children
  - NICU: prophylaxis, targeted treatment
  - Neonates
  - Bezoars
  - HCT & AL: prophylaxis, empirical treatment
  - PICU
  - Paediatric HIV and primary immunodeficiency



# Management (incl. Treatment)

Focusing on special host groups

- HIV and AIDS
  - OPC
  - Oesophagitis: incl. secondary prophylaxis
  - Vulvovaginal candidiasis
  - Interactions
- Haematology and oncology
  - Prophylaxis
  - Empirical treatment
  - Issues about targeted treatment and pre-emptive therapy
  - Chronic disseminated candidiasis; CVC issues
  - Cytokines, Granulocyte Infusions



# Selected Topics

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# Treatments of oesophageal candidiasis [HIV/AIDS]

## Summary

Recommendation	SoR/QoE	References
Start treatment without endoscopy	AIII	
No local treatments; only systemic agents	DIII	
Oral fluconazole (200-400 mg/d for 14-21d): 1st line therapy	A1	De Wit 1989
Deoxycholate amphotericin i.v.(0.3-0.7 mg/kg/d) should no longer be used	CIII	
Echinocandins can be used in patients who cannot swallow but not better than fluconazole (or favour micafungin 150 mg/d as it is the only EMEA approved echinocandin? But higher relapse rate than fluconazole also true for anidulafungin	B1	De Wet CID 2004 Krause CID 2004
Itraconazole oral solution as an alternative	B1	
Posaconazole (400 mg bid) or voriconazole (200 mg bid) or any echinocandin not considered 1st line therapy but considered in refractory or fluconazole resistant cases	AII(posa)/ CII(echino)/ CIII (vori)	Ally CID 2001
Suppressive therapy (Fluconazole 100-200 mg 3x/w) if recurrent infections	B1	

# Targeted Treatment of Candidaemia

## Polyenes

Compound	SoR	QoE	Reference	Comment
Amphotericin B, deoxycholate, any dose	D	I	Ullmann CID 2006 Bates CID 2001 Anaissie CID 1996 Rex NEJM 1994 Philips EJCMID 1995 Mora-Duarte NEJM 2002	
Amphotericin B, liposomal	B	I	Kuse Lancet 2007 Dupont Crit Care 2009	<ul style="list-style-type: none"> <li>• Similar efficacy as micafungin</li> <li>• Higher toxicity than micafungin</li> </ul>
Amphotericin B, lipid complex	C	II <sub>a</sub>	Anaissie ICAAC 1995 Ito CID 2005	
Amphotericin B, colloidal dispersion	D	II <sub>u</sub>	Noskin CID 1998	<ul style="list-style-type: none"> <li>• Mostly immunocompromised patients (HCT, haematology/oncology or SOT) rather than ICU patients</li> </ul>

# Targeted Treatment of Candidaemia

## Echinocandins

Compound	SoR	QoE	Reference	Comment
Anidulafungin 200/100	A	I	Reboli NEJM 2007	<ul style="list-style-type: none"> <li>• Broad spectrum</li> <li>• Resistance rare</li> <li>• Fungicidal</li> <li>• Local epidemiology</li> <li>• <i>C. parapsilosis</i>, <i>C. krusei</i></li> <li>• Safety profile</li> <li>• Less drug-drug interactions than caspofungin</li> </ul>
Caspofungin 70/50	A	I	Mora-Duarte NEJM 2002 Pappas CID 2007	<ul style="list-style-type: none"> <li>• Largely as above</li> </ul>
Micafungin 100	A	I	Kuse Lancet 2007 Pappas CID 2007	<ul style="list-style-type: none"> <li>• Largely as above</li> <li>• Consider EMA warning label</li> </ul>

# Targeted Treatment of Candidaemia

## Azoles

Compound	SoR	QoE	Reference	Comment
Fluconazole	C	I	Anaissie CID 1996 Rex NEJM 1994 Rex CID 2003 Philips EJCMID 1995 Reboli NEJM 2007 Tuil CCM 2003 Abele-Horn Infect 1996 Leroy CCM 2009 Gafer-Gvili Mayo Clin Proc 2008	<ul style="list-style-type: none"> <li>• Limited spectrum</li> <li>• Inferiority to anidulafungin (<u>especially</u> in the subgroup with high APACHE scores),</li> <li>• <i>C. parapsilosis</i></li> </ul>
Itraconazole	D	II <sub>a</sub>	Tuil CCM 2003 (abstract)	
Posaconazole	D	III	No reference found	<ul style="list-style-type: none"> <li>• PO only</li> </ul>
Voriconazole	B	I	Kullberg Lancet 2005 Ostrosky EJCMID 2003 Perfect CID 2003	<ul style="list-style-type: none"> <li>• Limited spectrum compared to echinocandins</li> <li>• Drug-drug interactions</li> <li>• IV in renal impairment</li> <li>• Need for TDM</li> </ul>

# Targeted Treatment of Candidaemia: Duration & Diagnostics

Population	Intention	Intervention	SoR	QoE	Reference	
No organ involvement	Avoid organ involvement	Treat for 14 days after the end of candidaemia	B	II	Oude-Lashof Eur J Clin Microbiol Infect 2003	
		Take 1 blood culture per day until negative	B	III	No reference found	
	Detect organ involvement	Transoesophageal echocardiography		B	II <sub>a</sub>	Fernández-Cruz ICAAC 2010
		Fundoscopy		B	II	Oude-Lashof CID 2011 Rodriguez Med 2003 Brooks Arch Int Med 1989 Parke Ophthalmol 1982
		If CVC, PICC, or intravascular devices, search for thrombus		B	III	No reference found
Any	To simplify treatment	Step down to fluconazole after 10 days of IV, if <ul style="list-style-type: none"> <li>• Species is susceptible</li> <li>• Patient tolerates PO</li> <li>• Patient is stable</li> </ul>	B	II	Reboli NEJM 2007 Mora-Duarte NEJM 2002 Pappas CID 2007	

CVC, Central venous catheter; PICC, Peripherally inserted central catheter.

# Catheter-Related Blood Stream Infection

Population	Intention	Intervention	SoR	QoE	Reference
Candidaemia if treated with azoles or deoxycholate amphotericin B	To clear candidaemia To improve survival	Remove indwelling lines	B	II	Liu J Infect 2009 Weinberger J Hosp Inf 2005 Leroy CCM 2009 Rex CID 1995 Almirante JCM 2005 Rodriguez CMI 2007
if treated with liposomal amphotericin B or echinocandin			D	II	Nucci CID 2010 Kucharikova AAC 2010 Kuhn AAC 2002 Mukherjee IJAA 2009

## Comment:

In patients treated with liposomal amphotericin B, caspofungin or micafungin removal of indwelling lines within 48 hours after treatment initiation was not associated with a higher survival rate neither at 28 nor 42 days.



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STUDY GROUP

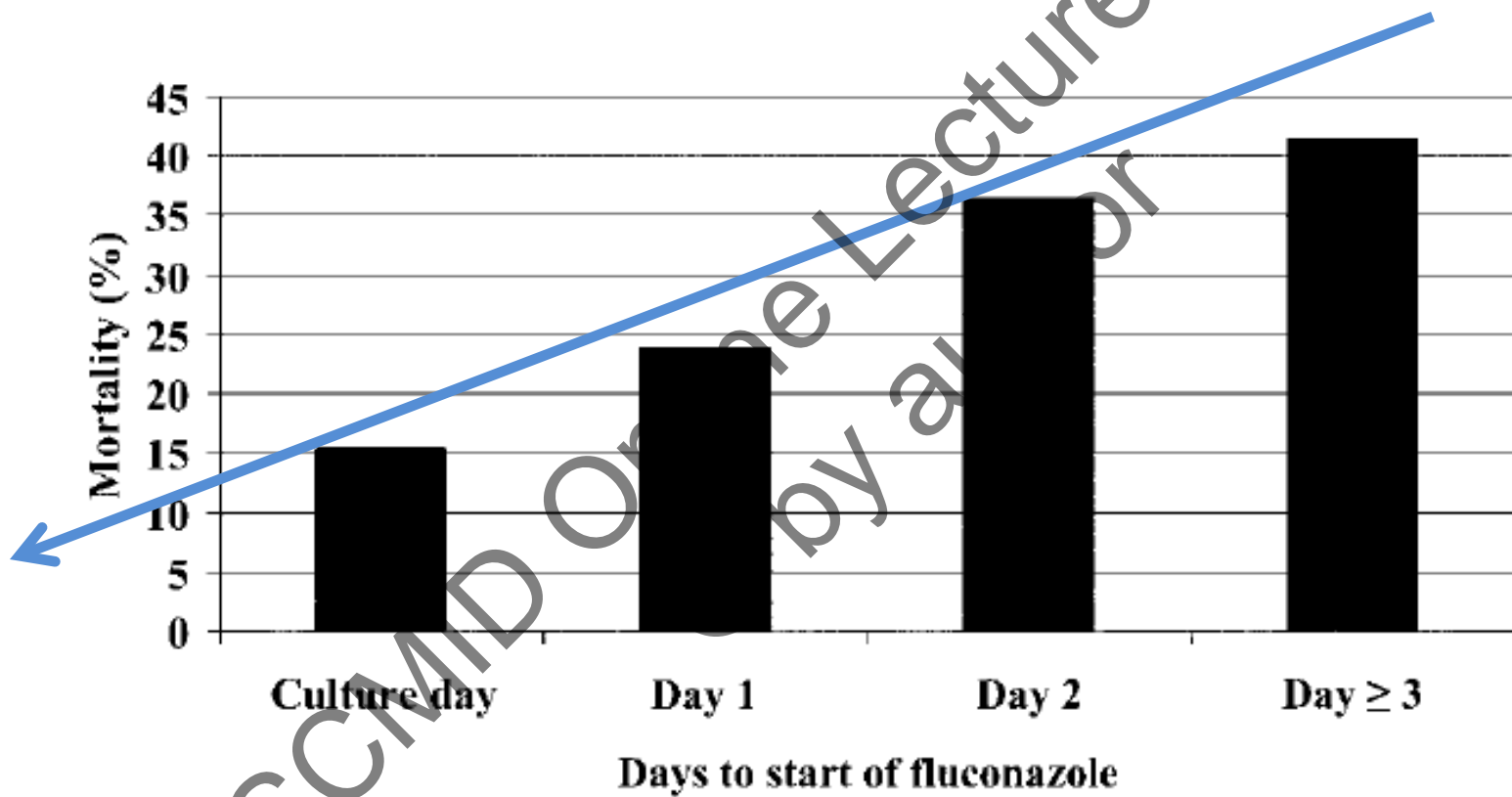
# Risk Profiling

Prophylaxis

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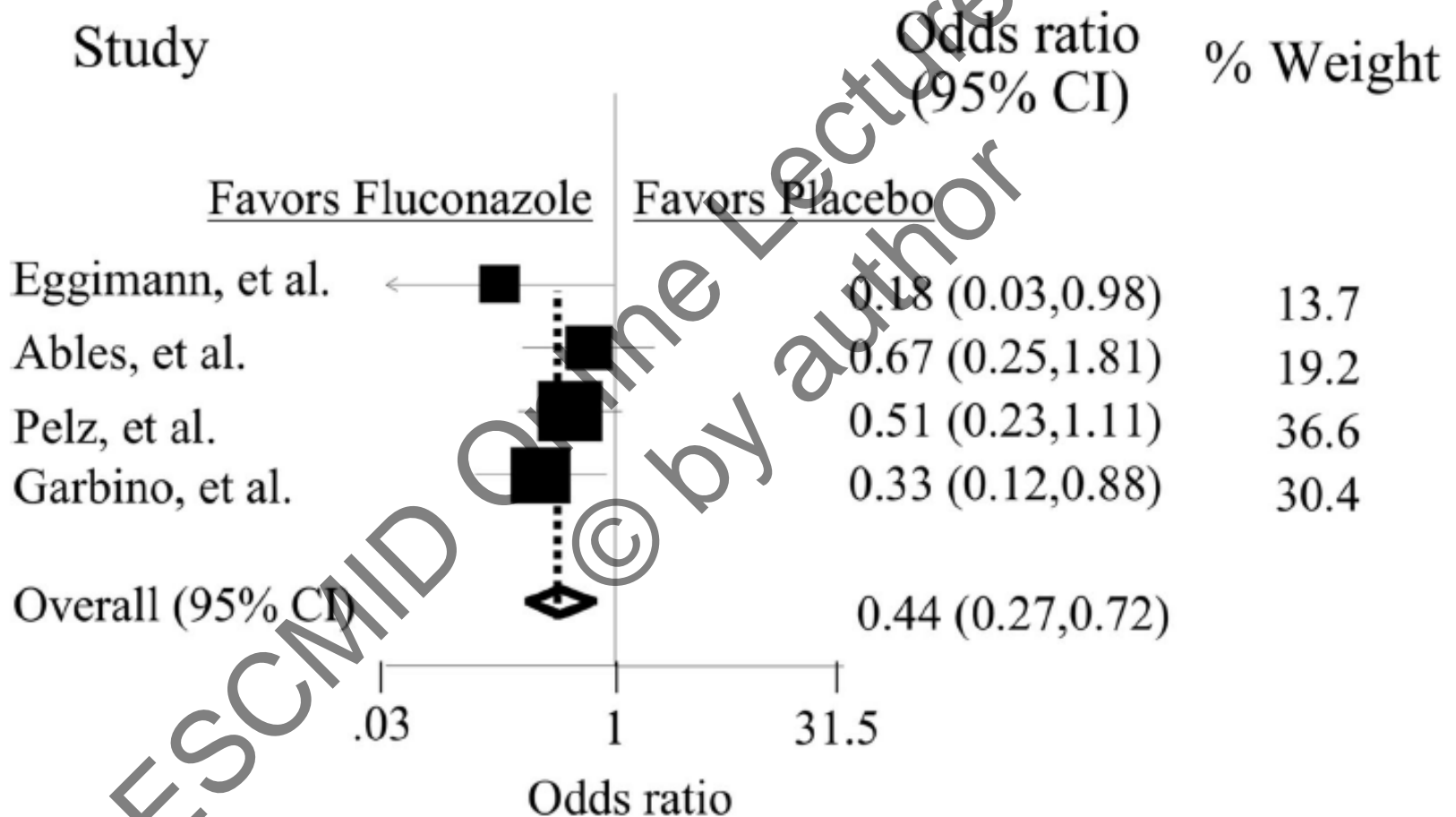


# Relationship Between Hospital Mortality and Number of Days to Initiate Therapy



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# Impact of fluconazole prophylaxis on candidal infections: SICU



# Prophylaxis: Which Agents?

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages	To prevent intraabdominal <i>Candida</i> infection	Fluconazole 400mg/d	B	I	Eggimann CCM 1999	Placebo, N=43
		Caspofungin 70/50mg/d	C	II <sub>u</sub>	Senn ICM 2009	Single arm, N=19
Critically ill surgical patients with an expected length of ICU stay ≥ 3d	To delay the time to fungal infection	Fluconazole 400mg/d	C	I	Pelz Ann Surg 2001	Placebo, N=260
Ventilated for 48h and expected to be ventilated for another ≥72h	To prevent invasive candidiasis / candidaemia	Fluconazole 100mg/d (in the context of SDD)	C	I	Garbino ICM 2002	Placebo, N=204



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# Strange things

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# Chronic Disseminated Candidiasis in Haem/Onc

## Intention: Diagnosis

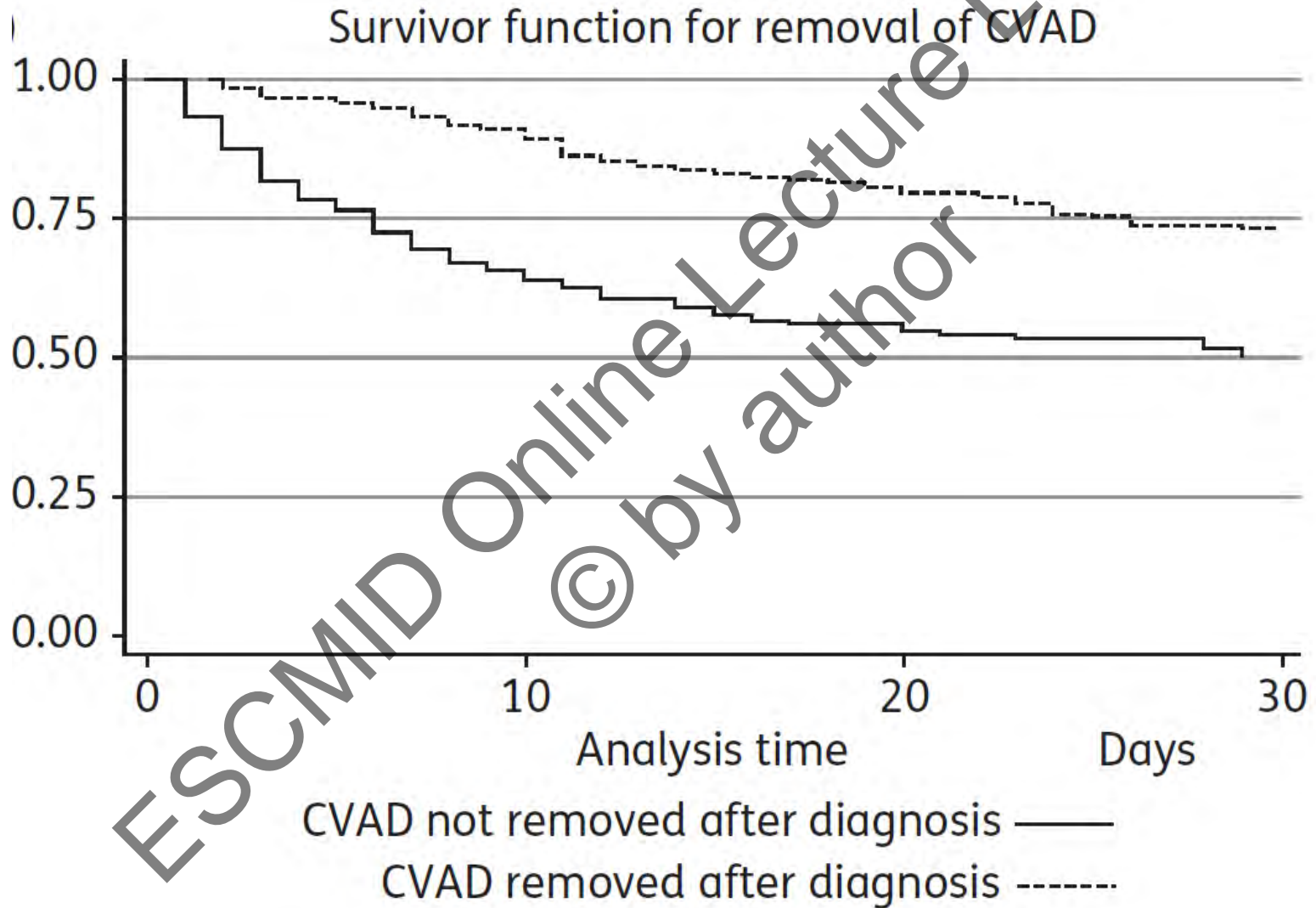
Recommendation	SoR/QoE	Reference
Ultrasound abdomen	BIII	Pagano L et al. Haematologica 2002
CT- abdomen	BIII	If ultrasound is negative, Pagano L et al. Haematologica 2002
MRI abdomen	BII	MRI: high accuracy: Semelka et al. Am J Roentgenl 1997 Hepatosplenic fungal disease: diagnostic accuracy and spectrum of appearances on MR imaging Sallah et al. Acta Haematol 1998 Diagnosis and monitoring response to treatment of hepatosplenic candidiasis in patients with acute leukemia using magnetic resonance imaging

# Treatment in Chronic Disseminated Candidiasis

## Intention: Success (incl. Survival)

Recommendation	Duration	Reference
Fluconazole (BIII)	Reported duration minimum 3 months	L.-M. Poon, H.-Y. Chia, L.-K. Tan, T.-C. Liu,-P. Koh Successful intensive chemotherapy followed by autologous hematopoietic cell transplantation in a patient with acute myeloid leukemia and hepatosplenic candidiasis: case report and review of literature. Transpl Infect Dis 2009; 11: 160–166 Pagano L et al. Haematologica 2002
Other azoles effective (BIII)		Lacking Data
Deoxycholate AmB (DIII)		Toxicity issues
Lipid formulations of AmB (AIII)	8 weeks	Better exposure, duration recommendation: Queiroz-Telles F, et al. Pediatr Infect Dis J 2008 Sep; 27 (9): 820-6, Kuse ER et al Lancet 2007
Steroid therapy (CIII)	Until defervesced	Legrand F,Lecuit M, Dupont B, Bellaton E, Huerre R, Rohrllich PS, Lortholary O.Adjuvant Corticosteroid Therapy for Chronic Disseminated Candidiasis. Clinical Infectious Diseases 2008; 46:696–702

# Australian Data on CVC Removal



# BIOFILM CVC

Biofilm formation issues on CVC and other hardware

Recommendation	Intention	Comment	Reference
Early catheter removal (BII <sub>u</sub> )	Survival	Retention and high APACHE and thrombocytopenia also associated with higher mortality (Liu)	Liu CY J Infect 2009, Munoz P Clin Microbiol Infect 2010
Catheter retention (CII <sub>t</sub> )	Morbidity advantage	Pat in the echinocandin trials with CVC retention had equal outcome (low numbers)	Mura-Duarte NEJM 2002, Pappas CID 2007, Kuse Lancet 2007, Riboli NEJM 2007
If catheter retention use echinocandins not azoles or LAmB (CII <sub>t</sub> )	Morbidity advantage	Worse outcome in non echinocandin trials	Mura-Duarte NEJM 2002, Kuse Lancet 2007, Riboli NEJM 2007
Other implanted hardware (pace-maker, port-a-cath) (CIII)	Morbidity advantage	Keep unless proven associated to candidaemia. No published data available	



# SUMMARY

- ESCMID guidelines:
  - Independence
  - Evidence-based medicine
  - Different grading system
  - Including diagnostic procedures
  - Including various European experts in the field
  - Easy availability (presentation online: [www.escmid.org](http://www.escmid.org))
  - Full publication submission planned for early 2012: CMI-Supplement
- Diagnostic procedures:
- Host groups:
  - ICU, others
  - Paeds
  - HIV/AIDS
  - Haem/Onc
- Treatment issues:
  - Role of echinocandins and azoles
  - Conventional AmB: obsolete
  - Hardware removal



# THE TEAM:

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# TEŞEKKÜRLER

