



Medical University of Graz

# ESCMID Candida Guidelines

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**Disclosures:**



**Research grant  
(investigator initiated study)**



**Unterstützung Reisekosten**



## ■ ESCMID Candida Guidelines

### Hintergrund

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### • Candida Morbidität und Mortalität

- **400.000 Fälle/Jahr weltweit**

- **Mortalität ca. 40%**

### • Europäische Guidelines für Diagnose und Therapie von Candida Infektionen



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- **25 Europäische Experten unter Leitung von Andrew J. Ullmann**
- **2 Konsensus Meetings**
- **Unzählige Telefonkonferenzen und Emailkorrespondenzen**



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### Rating nach IDSA



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### 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 center); 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:

- ††† meta-analysis (or systematic review of RCT);
- †† transferred evidence i.e. results from different patients' cohorts, or similar immune-status situation;
- † comparator group: historical control;
- uncontrolled trials
- for published abstract (presented at an international symposium or meeting)



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### 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



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## Ausnahme Biomarker für Diagnose

<b>Rationale of Recommendations by Quality of Evidence for Diagnostic Module. BIOMARKERS ONLY</b>	
<b>Accuracy</b>	$\text{accuracy} = \frac{\text{number of true positives} + \text{number of true negatives}}{\text{numbers of true positives} + \text{false positives} + \text{false negatives} + \text{true negatives}}$
Highly recommended	Technique is accurate in >70% of cases (most)
Recommended	Technique accurate in 50 – 70% of cases (reasonable number)
Not Recommended	Technique accurate in <50% of cases (small number)
No recommendation	No data
<b>Quality of evidence accepted</b>	
Level I	Evidence from at least 1 properly designed prospective <b>multicentre</b> cross-sectional or cohort study
Level II	Evidence from (1) at least 1 well-designed prospective single-centre cross-sectional or cohort study or (2) a properly designed retrospective <b>multicentre</b> cross-sectional or cohort study or (3) from case-control studies
Level III	Opinions of respected authorities, clinical experience, descriptive case studies, or reports of expert committees



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### **Candidämie:**

- **Blutkulturen**
- **Interpretation von Katheter/peripher**
- **Sensitivität 50-75%**



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## What are the best tests for diagnosing candidaemia? 1

Specimen	Test	Considerations	Remarks/Recommendations
Blood	Blood culture	<ul style="list-style-type: none"><li>• Number of blood cultures: 3 (2 to 4)</li><li>• Total volume: Children &lt;2kg, 2 to 4 mL, between 2 and 12 kg, 6 mL, between 12 and 36, 20 mL. At least 60 mL for adults</li><li>• Timing: Obtain blood cultures, one right after the other, from different sites following the clinical events that precipitated the blood culture</li><li>• Site: Venipuncture remains the technique of choice. Blood obtained through an indwelling line is twice as likely to yield a contaminant than blood obtained through a properly prepared skin site</li><li>• Frequency: Daily when candidaemia is suspected</li></ul>	<ul style="list-style-type: none"><li>• Essential investigation</li><li>• Separate 20-ml blood samples obtained within a 30- min period, each divided equally between an aerobic and anaerobic blood culture vial in 10-ml aliquots, were considered to represent a single culture</li><li>• Lower sensitivity in neutropenic patients and under antifungal treatment</li><li>• Sensitivity varies depending on the species and system (e.g. lower for BACTEC and <i>C. glabrata</i>)</li><li>• ID is mandatory</li><li>• Caution: Yeast in BC is not always <i>Candida</i></li></ul>

### References:

- 1) Denning et al. Lancet Infect Dis 2003;3:230-40
- 2) Einsele et al. Clin Microbiol Infect 2008;14 Suppl 4:37-45
- 3) Gadea et al. Enf Infect Microbiol Clin 2007;25:336-40
- 4) Lass-Flörl. Clin Microbiol Infect 2009;15 Suppl 5: 60-5
- 5) Richardson M. Hosp Med 2000;61:610-4
- 6) Baron et al. Cumitech 1C. Blood cultures IV



## ■ Guidelines Diagnostik (AK)

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**2x/Woche  
Mannan plus Anti-Mannan**

**β-D- Glukan**

 **Hoher NPV**

**CAVE: unter antifungaler Therapie falsch negativ**



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### What are the best tests for diagnosing candidaemia? 2

Specimen	Test	Considerations	Remarks/Recommendations
Serum	Mannan and Anti-Mannan	•Combined detection	RECOMMENDED Serial determinations may be necessary. High NPV
	Other Ab (such as Serion ELISA classic)	•Limited data for candidemia	No recommendation
	B-D-Glucan	•No specific for <i>Candida</i>	RECOMMENDED (for Fungitell) No recommendation for other tests. Serial determinations are recommended (twice a week). High NPV. Not validated in children
	Septifast	•Limited data for candidemia	No recommendation
	In house PCR	•No third party validation data available	No recommendation



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### What are the best tests for diagnosing invasive candidiasis? 1

Specimen	Test	Considerations	Remarks/Recommendations
Tissue sample/body fluids from normally sterile sites	Direct microscopy and histopathology <b>1.</b>	<ul style="list-style-type: none"> <li>Obtained and collected aseptically</li> <li>Transport to the lab promptly</li> <li>Tissue for histopathology should be placed in fixative as rapid as possible (caution: sample can dry up)</li> <li>Special stains should be use including optical brighteners, silver stains and PAS</li> <li>Morphology cannot be used for definitive ID</li> </ul>	<ul style="list-style-type: none"> <li>Small samples are prone to sampling error</li> <li>Samples for culture must not be placed in chemical fixing fluids</li> <li>Sample must be kept moist</li> <li>Expertise needed for interpretation</li> </ul>
	Culture <b>2.</b>	Include fungal selective media	<ul style="list-style-type: none"> <li>Yeast isolation from normally sterile tissues or fluids is usually indicative of deep seated infection</li> <li>Negative culture results do not exclude Candida infection. Blood cultures have low diagnostic yield</li> <li>Process promptly to avoid multiplication of organisms. If not possible, store at 4-5 degrees</li> <li>Identification is mandatory</li> </ul>



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### What are the best tests for diagnosing invasive candidiasis? 2

Specimen	Test	Considerations	Remarks/Recommendations
Tissue sample/body fluids from normally sterile sites (cont.)	Immunohistochemistry	<ul style="list-style-type: none"><li>Not generally available. If yeast seen in tissue but BC negative then use immunohistochemistry</li></ul>	<ul style="list-style-type: none"><li>Genus specific antibody commercially available only (e.g. Rabbit anti <i>C. albicans</i>, type A: Biotin, Serotec, No.1750-5557)</li><li>Only positive results reliable</li></ul> <ul style="list-style-type: none"><li>Not commercially available</li><li>These techniques might be carried out following Laser microdissection</li></ul>
	Tissue PCR	<ul style="list-style-type: none"><li>Use free DNA materials</li><li>Not generally available</li><li>No third party validation data available</li></ul>	
	In situ hybridization	<ul style="list-style-type: none"><li>Not generally available</li></ul>	
Serum	Mannan and Anti-Mannan	<ul style="list-style-type: none"><li>Combined detection</li><li>Not enough data available</li></ul>	<ul style="list-style-type: none"><li>No recommendation. It can be more useful for chronic disseminated candidosis</li></ul>
	β-D-Glucan	<ul style="list-style-type: none"><li>Not specific for <i>Candida</i></li></ul>	<ul style="list-style-type: none"><li><b>RECOMMENDED.</b> If available (twice a week). Not validated in children</li></ul>
	Septifast and in-house PCR	<ul style="list-style-type: none"><li>No published data available</li></ul>	<ul style="list-style-type: none"><li>No recommendation</li></ul>



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### What are the best tests for diagnosing chronic disseminated candidiasis? 1

Specimen	Test	Considerations	Remarks/recommendations
Tissue sample	Direct microscopy/Histopathology	<ul style="list-style-type: none"><li>• A tissue biopsy is highly recommended</li><li>• Same as invasive candidiasis</li></ul>	<ul style="list-style-type: none"><li>• Same as invasive candidiasis</li></ul>
	Culture Immunohistochemistry Tissue PCR In situ hybridization	} Same as invasive candidiasis	
Blood	Blood culture	Same as invasive candidiasis	
Serum	Mannan and Anti-Mannan	<ul style="list-style-type: none"><li>• Combined detection</li><li>• Not specific for <i>Candida</i></li></ul>	<ul style="list-style-type: none"><li>• RECOMMENDED</li><li>• RECOMMENDED (as supplementary test). Not validated in children</li></ul>
	B-D-Glucan Septifast and in-house PCR	No published data available	<ul style="list-style-type: none"><li>• No recommendation</li></ul>

References: identical as candidaemia



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### **Mannan AK/AG empfohlen bei**

- **Candidämie**
- **Chronisch Disseminierter Candidiasis**
- **Hoher NPV, niedrige Spezifität**

### **β-D-Glucan empfohlen bei**

- **Candidämie**
- **Invasiver Candidiasis**
- **Chronisch Disseminierter Candidiasis**
- **Nicht validiert bei Kindern**
- **Positiv bei Staphylokokken**
- **Cut-off**

### **Keine Empfehlung**

- **Andere AK Tests**
- **Septifast**



# ■ Guidelines Diagnostik (AST)

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## When are AST recommended for patient management and when for epidemiological reasons? 1

Isolated from	FOR patient management	FOR Epidemiology
<b>Blood and other deep sites</b>	<b>All isolates</b> and particularly: <ol style="list-style-type: none"><li>1. Strains from patients exposed to antifungal agents</li><li>2. Clinical failures</li><li>3. Rare and emerging species</li><li>4. Species that are known to be resistant or less-susceptible to antifungal drug(s) in clinical use</li></ol>	<ul style="list-style-type: none"><li>• All isolates should be tested using a <b>reference method or a validated commercial method</b></li></ul>
<b>Superficial sites</b>	<ul style="list-style-type: none"><li>• Failed to respond or relapsing infection</li><li>• Surveillance cultures from patients exposed to antifungal agents</li></ul>	<ul style="list-style-type: none"><li>• Periodical epidemiological studies should be done</li></ul>



## ■ Guidelines Diagnostik (TDM)

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### **TDM empfohlen bei**

- **Voriconazol**

- **Toxizität, fehlendes Therapieansprechen, ECMO**

- **5-Fluorocytosin**

### **Nicht bei Echinocandinen**

- **CAVE: ECMO**



## ■ Guidelines Diagnostik (TDM)

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### Are therapeutic drug monitoring (TDM) indicated for patient management? 1

- TDM must be used for patients treated with 5-fluorocytosine
- TDM is not normally required for drugs used in the treatment of *Candida* infections (ECMO can reduce echinocandin concentration)
- TDM is recommended if voriconazole is prescribed (voriconazole TDM is highly recommended in unsatisfactory response to therapy, suspicion of toxicity or drug interaction(s), impaired liver or renal function an in patients on extracorporeal membrane oxygenation)

#### References:

- 1) Trifilio et al. Cancer 2007;109:1532-5
- 2) Pascual et al. Clin Infect Dis 2008;46:201-11
- 3) Buchkowsky et al. Ther Dr Monit 2005; 27:322-33
- 4) CLSI M27-S3 (itraconazole)
- 5) Andes et al. Antimicrob Agents Chemother 2009;53:24-34



# ■ Guidelines Therapie/Prophylaxe

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**NNT ?  
Lokale  
Inzidenz?**

Prophylaxis: Which Agents?						
 <b>EFISG</b> <small>ESCMID FUNGAL INFECTION STUDY GROUP</small> <small>European Society of Clinical Microbiology and Infectious Diseases</small>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages	To prevent intraabdominal candida infection	Fluconazole 400mg/d	B	I	Eggimann CCM 1999	Placebo, N=43
	As above	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 $\geq$ 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 $\geq$ 72h	To prevent invasive candidiasis / candidaemia	Fluconazole 100mg/d (in the context of SDD)	C	I	Garbino ICM 2002	Placebo, N=204



# ■ Guidelines Therapie/Prophylaxe HM

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**Prophylaxis in allogeneic HCT**  **EFISG** ESCMID FUNGAL INFECTION STUDY GROUP  
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*Intention: morbidity reduction (Candida)*

Situation	Recommendation	References
During early neutropenic phase	Fluconazole (AI); Itraconazole (BI); Posaconazole (AII <sub>1</sub> ), Voriconazole (AI); Micafungin (AI), Caspofungin (CII <sub>1</sub> ), Anidulafungin (ND), Liposomal AmB (BII)	Goodmann JL NEJM 1992; Morgenstein G Brit J Haema 1999; Marr KA Blood 2004 (180 days); Cornely OA NEJM 2007; Wingard JR (100-180 days) Blood 2010; van Burik CID 2004; Chou LS Pharmacotherapy 2007; Kelsey S MBMT 1999; Penack O Ann Onco 2006
During later phase within first 100 days	Fluconazole (AI); Itraconazole (BI); Posaconazole (CII), Voriconazole (AI); Micafungin (CII), Caspofungin (CII <sub>1</sub> ), Anidulafungin (ND), Liposomal AmB (CIII)	Slavin M JID 1995; Winston DJ Ann Intern Med 2003 (180 days); Marr KA Blood 2004 (180 days); Cornely OA NEJM 2007; Wingard JR Blood 2010; van Burik CID 2004; Chou LS (up to 100 days) Pharmacotherapy 2007
During GVHD (moderate to severe)	Fluconazole (AI); Itraconazole (CI); Posaconazole (AI), Voriconazole (BI), others (ND)	Ullmann NEJM 2007; Wingard JR Blood 2010; Chou LS Pharmacotherapy 2007

**Explanation/Reason/Issues/Comments:**  
Due to safety issues with itraconazole and amphotericin B, those drugs received a weaker strength of recommendation (Marr Blood 2004; Chou LS Pharmacotherapy 2007; Ullmann CID 2006)



# ■ Guidelines Therapie - Empirisch

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## Empiric Therapy: When is it Indicated?

Population	Intention	Intervention	SoR	QoE	Reference
At risk + persistent FUO	Reduce overall mortality	Antifungal treatment (unspecified)	C	III	Garey CID 2004 Morrell AAC 2005 Parkins JAC 2007 Kumar Chest 2009
Adult ICU patients with fever despite broad-spectrum antibiotics, APACHE II >16	Resolution of fever	Fluconazole 400mg/d	D	I	Schuster Ann Int Med 2008

### Definitions:

- Empiric = persistent FUO / **Fever driven approach**
- Pre-emptive = treatment based on a validated marker / **Diagnosis driven approach**



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Empiric treatment in Neutropenia incl. HCT		
Dosage & Intention: morbidity reduction		
Agents // Situation (trial included allo HCT)	Rec	References
Liposomal amphotericin B (3mg/kg/d) (Allo= yes)	A1	Walsh NEM 2000; Prentice Br J Haematol 1997; Wingard CID 2000; Walsh NEM 2002; Walsh NEM 2004; Maertens Pediatr Inf Dis J 2010
Caspofungin (70 mg on D1 then 50 mg) (Allo=yes)	A1	Walsh NEM 2004; Maertens Pediatr Inf Dis J 2010
Amphotericin B colloidal dispersion (4 mg/kg/d) (Allo=yes)	B1	White GD 1998
Amphotericin B lipid complex (5 mg/kg/d) (Allo=yes)	B1	Wingard CID 2000
Itraconazole (200 mg iv Q12h on D1 & D2 then 200 mg iv/d) (Allogeneic HCT=not reported)	B1	Boogaarts Ann Intern Med 2001; Ehninger Onkologie 2007
Voriconazole (2 x 6 mg/kg on D1 then 2x3 mg/kg/d) (Allo=yes)	B1	Walsh NEM 2002
Fluconazole (400 mg/d) (Allo=not reported)	CI*	Winston Am J Med 2000; Viscdi C, Eur J Cancer 1998 May;32A(5):814-20
Amphotericin B deoxycholate (0.5 – 1.0 mg/kg/d) (Allo=yes)	C1	White GD 1998; Walsh NEM 1999; Boogaarts Ann Intern Med 2001; Ehninger Onkologie 2007
Micafungin (100 mg) (AlloH SCT = yes)	BII	Tamura Leuk Lymphoma 2009; Kubiak Clin Ther 2010
Anidulafungin	NR	No data

**Explanation/Issues:**  
\*Limitation for fluconazole due to lack of anti-mould activity; need to rule out a mould infection with aspergillus GM test and chest and sinus CT scan.  
Only B1 for amphotericin B colloidal dispersion due to safety issue with this agent; amphotericin B lipid complex more toxic in a direct comparison to liposomal AmB.  
For micafungin: Tamura = non-comparative trial (dose 50-100 mg); Kubiak = 323 pts, retrospective, observational, sequential cohort (dose 100 mg)



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### Pre-emptive Therapy: β-D-Glucan

Popu- lation	Intention	Inter- vention	SoR	QoE	Reference	Comments
ICU	Early treatment of invasive candidiasis / candidaemia	To treat when β-D-glucan test is positive	C	II <sub>u</sub>	Desmet JCM 2009 Digby Clin Diagn Lab Immunol 2003 Koo CID 2009 Mohr JCM 2011 Presterl Int JID 2009 Takesue WJSurg 2004 Pickering JCM 2005	<ul style="list-style-type: none"><li>• Low specificity</li><li>• Low sensitivity</li><li>• High NPV</li><li>• False positives with<ul style="list-style-type: none"><li>• Haemodialysis</li><li>• Other fungal or</li><li>• Bacterial infection</li><li>• Wound gauze</li></ul></li><li>• Maybe useful in PCP</li></ul>



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### Targeted Treatment: Yeast in Blood Cultures

Population	Intention	Intervention	SoR	QoE	Reference
Candida isolated from one (peripheral blood or central line) blood culture defines candidaemia	Cure	Antifungal treatment	A	II	De Pauw CID 2008 Lecciones CID 1992 Kullberg Lancet 2006
Candidaemia	Cure	Antifungal treatment	A	III	Bodey EJCMI 1992 Edwards ICAAC 1982 Groll J Infect 1996 Kume Pathol Int 2003

#### Comment:

- Previous definitions described **asymptomatic patients** with a blood culture positive for candida. It has been debated whether such patients need antifungal treatment.
- This is a very rare clinical situation, since usually a blood culture would be triggered by a clinical sign (e.g. fever)
- Even surveillance blood cultures positive for candida should prompt immediate treatment.



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## Targeted Treatment of Candidaemia Echinocandins



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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>



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Targeted Treatment of Candidaemia		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP
Azoles		European Society of Clinical Microbiology and Infectious Diseases		
Compound	SoP	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>

TDM. Therapeutic drug monitoring.



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## 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	•Similar efficacy as micafungin •Higher toxicity than micafungin
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	•Mostly immunocompromised patients (HCT, haem/onc or SOT) rather than ICU patients

HCT, haematopoietic stem cell transplantation; SOT, solid organ transplantation.



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### **Empirische Initialtherapie (nicht neutropenisch)**

**ESCMID:**

**Echinocandine**

**fungizid vs fungistatisch  
Biofilm-Aktivität**

**IDSA:**

**Fluconazol**

**mild to moderate severe**

### **Jedenfalls Echinocandine**

- **Vorherige Azol-Exposition**
- **Kritisch Kranke**
- **Neutropenie**



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**C. glabrata:**

**IDSA:**

**Echinocandine (BIII)**

**CAVE: 14% der Fluconazol resistenten  
Isolate auch I / R auf Echinocandine**

**C. krusei:**

**Echinocandine**

**C. parapsilosis:**

**IDSA:**

**Fluconazol**

**C. albicans:**

**IDSA:**

**Fluconazol**



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Catheter-Related Blood Stream Infection		 EFISG ESCMID-FUNGAL INFECTION STUDY GROUP European Society of Clinical Microbiology and Infectious Diseases			
Population	Intention	Intervention	SoR	QoE	Reference
Candidaemia if treated with azoles or deoxycholate amphotericin B	To clear candidemia 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
<b>Comment:</b> 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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**Augenuntersuchung bei allen PatientInnen  
mit Candidämie (innerhalb 1 Woche)**

**Oude Lashof et al CID 2011:  
370 Candidämien (nicht-neutropenisch)**

**16,2% Läsionen auf Retina**

**9,2% Chorioretinitis**

**1,6% Endophthalmitis**



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Chorioretinitis/Endophthalmitis Azoles & Surgery		EFISG ESCMID Fungal Infection Study Group European Society of Clinical Microbiology and Infectious Diseases		
Population	Intervention	SoR	QoE	Reference
Chorioretinitis/ Endophthalmitis, susceptible species	Fluconazole	A	II <sub>u</sub>	Essman Ophth Surg Lasers 1997 Luttrull AmJOpht 1995 Laatikainen AmJ Opht 1992 Akler CID 1995 Riddell CID 2011
	Voriconazole	A	II <sub>u</sub>	Thiel AAC 2007 Oude-Lashof CID 2011 Breit Am J Opht 2005 Hakki AAC 2006 Riddell CID 2011
Endophthalmitis, i.e. vitreal involvement	Amphotericin B deoxycholate intraocular injection	B	II <sub>u</sub>	Essman Ophth Surg Lasers 1997 Grueb Cornea 2006 Payne Arch Ophthalmol 2010
	Vitreotomy	B	II <sub>u</sub>	Essman Ophth Surg Lasers 1997



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Chorioretinitis/Endophthalmitis Polyenes & Echinocandins		 <b>EFISG</b> ESCMID FUNGAL INFECTION STUDY GROUP <small>European Society of Clinical Microbiology and Infectious Diseases</small>		
Population	Intervention	SoR	QoE	Reference
Chorioretinitis/ Endophthalmitis	Amphotericin B deoxycholate	C	II	Oude-Lashof CID 2011
	Amphotericin B deoxycholate + 5-fluorocytosine	C	III	Edwards Medicine 1974 Parke Ophth 1982 McQuillen CID 1992 Essman Ophth Surg Lasers 1997
	Liposomal amphotericin B	B	III	Oude-Lashof CID 2011 Goldblum Ophth Res 2004 Neppert Klin Mbl Augheilk 1992
	Liposomal amphotericin B + 5-fluorocytosine	B	III	No reference found
	Amphotericin B deoxycholate	C	III	Virata CID 1999
	Amphotericin B lipid complex + 5-fluorocytosine	B	III	Darling J Infect 2000
	Caspofungin	D	II <sub>u</sub>	Gauthier CID 2005 Comely JAC 2007 Sarría CID 2005 Hakki AAC 2006 Spriet JAC 2009



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Urinary Tract Infection		EFISG ESCMID FUNGAL INFECTION STUDY GROUP European Society of Clinical Microbiology and Infectious Diseases			
Population	Intention	Intervention	SoR	QoE	Reference
Asymptomatic	Eliminate candiduria	None	A	III	Revankar 2010 Kauffman CID 2000
		Fluconazole 200mg d1-14*	C	I	Sobel CID 2000 Kauffman CID 2000
		Removal of urinary catheter	B	I	Sobel CID 2000
		Ampho B bladder irrigation	C	II <sub>r</sub>	Tuon IJID 2009 Kauffman CID 2000
Pyelonephritis	Cure	Caspofungin 70/50mg for 9-28d	C	III	Sobel CID 2007
		Fluconazole +/- 5-FC**	A	III	No reference
		Ampho B deoxycholate +/- 5-FC	A	III	No reference
Cystitis	Cure	Fluconazole	A	III	Sobel CID 2000 Kauffman CID 2000
		Amphotericin B +/- 5-fluorocytosine	B	III	Sobel CID 2000 Kauffman CID 2000
Fungus balls	Cure	Surgical intervention	A	III	Bartone J Urol 1988 Shih Urol 2005

\*In pre-operative patients treatment is indicated to suppress candiduria; \*\*if species is susceptible.



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Endocarditis		EFISG ESCMID FUNGAL INFECTION STUDY GROUP European Society of Clinical Microbiology and Infectious Diseases			
Population	Intention	Intervention	SoR	QoE	Reference
Native valve	Decrease mortality	Surgery within 1 week	A	II <sub>u</sub>	Falcone Medicine 2009 Ellis CID 2001 Lefort ICAAC 2009
		Liposomal Ampho B +/- 5-fluorocytosine	B	II <sub>b</sub>	Lefort ICAAC 2009
		Caspofungin +/- 5-fluorocytosine	C	II <sub>b</sub>	Lefort ICAAC 2009
Prosthetic valve	Decrease mortality	Early surgery	A	III	Falcone Medicine 2009 Boland Mycoses 2010
Prosthetic valve, if surgery contra-indicated	Suppression of infection	Fluconazole	C	III	Boland Mycoses 2010
	Cure	Liposomal Ampho B	B	III	Boland Mycoses 2010
	Cure	Caspofungin	B	III	Boland Mycoses 2010
Pacemaker, ICD, VAD	Cure	Removal	A	III	Baddley EJCMID 2008 Aslam CID 2010

ICD = implantable cardioverter defibrillator, VAD = ventricular assist device



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Bone Infection		EFISG ESCMO Fungal Infection Study Group European Society of Clinical Microbiology and Infectious Diseases			
Population	Intention	Intervention	SoR	QoE	Reference
Osteomyelitis / spondylodiscitis	Cure	Surgical debridement*	C	III	Hendricks CID 2001 Miller CID 2001
	Cure	Fluconazole 400 mg 6-12 months	A	II <sub>u</sub>	Hennequin CID 1996 Sugar DMID 1990 Miller CID 2001
	Cure	Liposomal Ampho B / ABLC 2-6 wks followed by Fluconazole 400 mg, total 6-12 months	A	II <sub>u</sub>	Hennequin CID 1996 Miller CID 2001
	Cure	Echinocandin 2-6 wks followed by Fluconazole 400 mg total 6-12 months	B	III	Cornely JAC 2007 Legout Scand JID 2006
	Cure	Voriconazole 2x3 mg/kg ≥6 weeks	B	III	Schilling Med Mycol 2008

\*Indications for surgery are instability, or e.g. large abscess.



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Joint Infection		EFISG <small>ESCMID FUNGAL INFECTION STUDY GROUP</small> <small>European Society of Clinical Microbiology and Infectious Diseases</small>			
Population	Intention	Intervention	SoR	QoE	Reference
Arthritis	Cure	Fluconazole 400, ≥6 wks	A	II <sub>u</sub>	Pérez-Gómez Sem Arth Rheum 1998 Hansen Scand JID 1995
	Cure	Liposomal Ampho B / ABLC 2 wks, followed by Fluconazole 400, total ≥6 wks	A	II <sub>u</sub>	Hansen Scand JID 1995
	Cure	Echinocandin =2 weeks followed by Fluconazole 400, total ≥6 wks	B	III	Cornely JAC 2007 Sim Hon Kon Med J 2005
	Cure	Voriconazole 2x3 mg/kg ≥6 wks	B	III	Sili CID 2007
Prosthetic joint infection	Cure	Prosthesis removal	A	III	Tunkel AJM 1993
Prosthetic joint infection with prosthesis retention	Chronic suppression	Fluconazole life long	A	III	Merrer J Infect 2001 Kelesdis Scand JID 2010 Levine Clin Orthop Relat Res 1986



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Central Nervous System		 <b>EFISG</b> <small>ESCMID FUNGAL INFECTION STUDY GROUP</small> <small>European Society of Clinical Microbiology and Infectious Diseases</small>		
Population	Intervention	SoR	QoE	Reference
Meningitis	Liposomal amphotericin B +/- 5-fluorocytosine	B	III	Houmeau Arch Fr Pediatr 1993 Ng Arch Int Med 1995 Jarlov ScandJID 1995
	Amphotericin B deoxycholate +/- 5-fluorocytosine	D	II <sub>u</sub>	Casado CID 1997 Chen ScandJID 2004 Smego Rev Inf Dis 1984 Chen ScandJID 2004
	Amphotericin B deoxycholate +/- 5-fluorocytosine	D	III	Perfect JAC 1994 (animal model)
	Fluconazole	C	III	Aleixo J Infect 2000 Chen ScandJID 2004 Cruciani EJCMI 1992
	Voriconazole	C	III	Schwartz Blood 2005 Weiler AAC 2011 Kullberg Lancet 2005
	Caspofungin	D	III	Liu JCM 2004 (case) van Hal EIC 2008 (case)



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**14 Tage Minimum!!**



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Targeted Treatment of Candidaemia: Duration & Diagnostics					
			EFISG European Society of Clinical Microbiology and Infectious Diseases		
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 CID 2011
		Take 1 blood culture per day until negative	B	III	No reference found
	Detect organ involvement	Transoesophageal echocardiography	B	II <sub>s</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.



## ■ Diskussion

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- **Guidelines für Europa**

- **Lokale Epidemiologie von non-albicans Spezies <10%**



**Trotzdem empirisch Beginn mit Echinocandin??**



## ■ Take home message

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- **Echinocandine empirische Therapie der Wahl bei**
  - **Kritisch Kranken**
  - **vorheriger Azol-Exposition**
  - **Neutropenie**
- **Bei milder bis moderater Verlaufsform UND niedriger lokaler Epidemiologie von non-albicans Candida spp.**
  - **Fluconazol erwägen**
- **Step-down approach**
  - **Nach Spezies Identifikation**



Medizinische Universität Graz



**Thank you for your attention!!**