ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

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ICU (medical & surgical)

Other non-immunocompromised, other immunocompromised situations

Disclosure

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  Astellas, Basilea, F2G, Genzyme, Gilead, Merck/Schering, Pfizer

Prophylaxis: Which Agents?

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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_u	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

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**

Pre-emptive Therapy: ß-D-Glucan

Popu-lation	Intention	Inter-vention	SoR	QoE	Reference	Comments
ICU	Early treatment of invasive candidiasis / candidaemia	To treat when ß-D-glucan test is positive	C	II_u	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	•Low specificity •Low sensitivity •High NPV •False positives with •Haemodialysis •Other fungal or •Bacterial infection •Wound gauze •Maybe useful in PCP

Pre-emptive Therapy: *Candida* sp. isolated from respiratory secretions

Popula-tion	Intention	Intervention	SoR	QoE	Reference	Comment
Any	Cure	Any antifungal	D	II_u	Meersseman Int Care Med 2009	• No data from ICU populations • Case series with haematological malignancy

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 EJCMID 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.

Targeted Treatment of Candidaemia
Polyenes

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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_a	Anaissie ICAAC 1995 Ito CID 2005	
Amphotericin B, colloidal dispersion	D	II_u	Noskin CID 1998	•Mostly immunocompromised patients (HCT, haematology/oncology or SOT) rather than ICU patients

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

Targeted Treatment of Candidaemia
Echinocandins

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Compound	SoR	QoE	Reference	Comment
Anidulafungin 200/100	A	I	Reboli NEJM 2007	• Broad spectrum • Resistance rare • Fungicidal • Local epidemiology • *C. parapsilosis, C. krusei* • Safety profile • Less drug-drug interactions than caspofungin
Caspofungin 70/50	A	I	Mora-Duarte NEJM 2002 Pappas CID 2007	• Largely as above
Micafungin 100	A	I	Kuse Lancet 2007 Pappas CID 2007	• Largely as above • Consider EMA warning label

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 Gafter-Gvili Mayo Clin Proc 2008	• Limited spectrum • Inferiority to anidulafungin (especially in the subgroup with high APACHE scores), • *C. parapsilosis*
Itraconazole	D	II_a	Tuil CCM 2003 (abstract)	
Posaconazole	D	III	No reference found	• PO only
Voriconazole	B	I	Kullberg Lancet 2005 Ostrosky EJCMID 2003 Perfect CID 2003	• Limited spectrum compared to echinocandins • Drug-drug interactions • IV in renal impairment • Need for TDM

TDM, Therapeutic drug monitoring.

Targeted Treatment of Candidaemia Combinations

Compound	SoR	QoE	Reference	Comment
Efungumab + Lipid-associated amphotericin B	D	II	Pachl CID 2006	
Amphotericin B deoxycholate + Fluconazole	D	I	Rex CID 2003	Efficacious, but • Increased risk of toxicity in ICU patients • No survival benefit
Amphotericin B deoxycholate + 5-fluorocytosine	D	II	Abele-Horn Infect 1996	
other two-drug combinations	D	III	Leroy CCM 2009	

Targeted Treatment of Candidaemia: Duration & Diagnostics

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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_a	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 • Species is susceptible • Patient tolerates PO • Patient is stable	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

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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

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.

Chorioretinitis/Endophthalmitis
Azoles & Surgery

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Population	Intervention	SoR	QoE	Reference
Chorioretinitis/ Endophthalmitis, susceptible species	Fluconazole	A	II_u	Essman Ophth Surg Lasers 1997 Luttrull AmJOphth 1995 Laatikainen AmJ Ophth 1992 Akler CID 1995 Riddell CID 2011
	Voriconazole	A	II_u	Thiel AAC 2007 Oude-Lashof CID 2011 Breit Am J Ophth 2005 Hakki AAC 2006 Riddell CID 2011
Endophthalmitis, i.e. vitreal involvement	Amphotericin B deoxycholate intraocular injection	B	II_u	Essman Ophth Surg Lasers 1997 Grueb Cornea 2006 Payne Arch Ophthalmol 2010
	Vitrectomy	B	II_u	Essman Ophth Surg Lasers 1997

Chorioretinitis/Endophthalmitis Polyenes & Echinocandins

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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_u	Gauthier CID 2005 Cornely JAC 2007 Sarria CID 2005 Hakki AAC 2006 Spriet JAC 2009

Central Nervous System

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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_u	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 EJCMID 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)

Endocarditis

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Population	Intention	Intervention	SoR	QoE	Reference
Native valve	Decrease mortality	Surgery within 1 week	A	II_u	Falcone Medicine 2009 Ellis CID 2001 Lefort ICAAC 2009
		Liposomal Ampho B +/- 5-fluorocytosine	B	II_a	Lefort ICAAC 2009
		Caspofungin +/- 5-fluorocytosine	C	II_a	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

Joint Infection

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Population	Intention	Intervention	SoR	QoE	Reference
Arthritis	Cure	Fluconazole 400, ≥6 wks	A	II_u	Pérez-Gómez Sem Arth Rheum 1998 Hansen Scand JID 1995
		Liposomal Ampho B / ABLC 2 wks, followed by Fluconazole 400, total ≥6 wks	A	II_u	Hansen Scand JID 1995
		Echinocandin ≈2 weeks followed by Fluconazole 400, total ≥6 wks	B	III	Cornely JAC 2007 Sim Hon Kon Med J 2005
		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 suppres-sion	Fluconazole life long	A	III	Merrer J Infect 2001 Kelesdis Scand JID 2010 Levine Clin Orthop Relat Res 1986

Urinary Tract Infection

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Population	Intention	Intervention	SoR	QoE	Reference
Asympto-matic	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_r	Tuon IJID 2009 Kauffman CID 2000
Pyelo-nephritis	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.

Bone Infection

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Population	Inten-tion	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_u	Hennequin CID 1996 Sugar DMID 1990 Miller CID 2001
	Cure	Liposomal Ampho B / ABLC 2-6 wks followed by fluco-nazole 400 mg, total 6-12 months	A	II_u	Hennequin CID 1996 Miller CID 2001
	Cure	Echinocandin 2-6 wks follow-ed 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.