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ESCMID FUNGAL INFECTION STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

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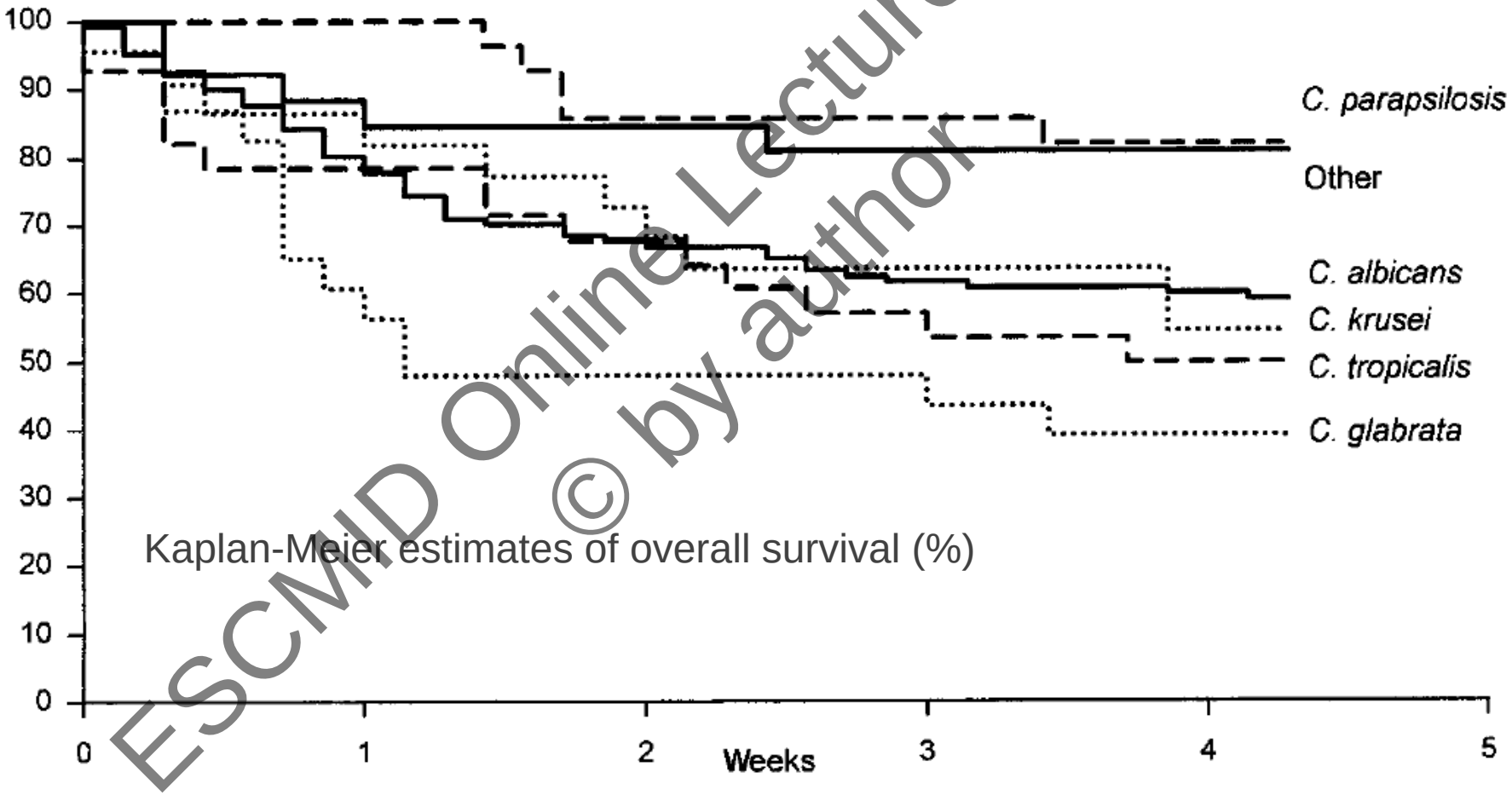
Haematology and Oncology

Disclosure

- In the past 5 years, AJU has received grant support from **Schering Plough Research Institute**
- Advisor/consultant to the **Aicuris, Astellas Pharma, Basilea, Gilead Sciences, Merck Sharp and Dohme, Pfizer, and Schering Plough**.
- Speaker's Bureau of **Gilead Sciences, Merck Sharp and Dohme, Astellas Pharma and Schering Plough**.

Epidemiology

European Data

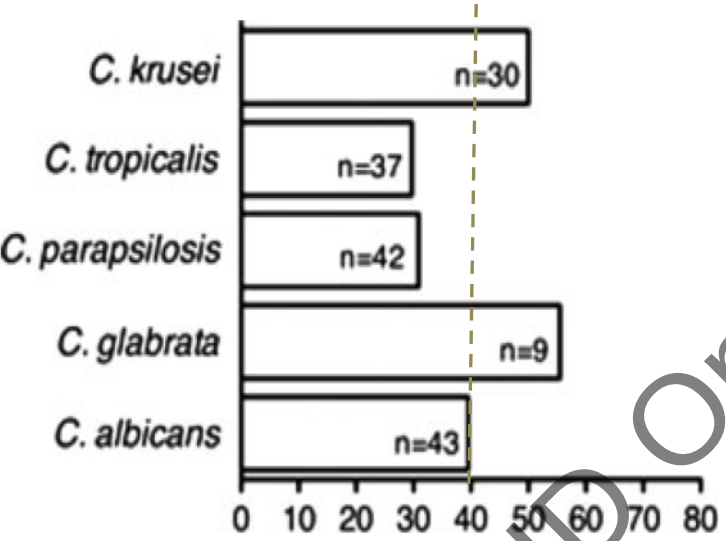


Kaplan-Meier estimates of overall survival (%)

Viscoli et al. CID 1999

Epidemiology

USA Data



Crude mortality rates at Day 30

Factors associated with crude mortality at day 30

Variable	Bivariate Analysis		Multivariate Analysis	
	Pearson	*P*	OR* (95% CI)	*P*
Age >50 years	0.160	.03	1.64 (1.09-1.99)	.02
Neutrophils <100/mL	0.188	.06	3.36 (1.07-10.55)	.03
APACHE II score	0.421	.0001	1.37 (1.16-1.61)	.001
Breakthrough infection	0.229	.003		
Neutrophil recovery	−0.352	.0001	0.18 (0.05-0.54)	.05
New antifungal therapy	−0.204	.01		
Intercurrent bacterial infection	0.241	.001		
Prior use of antibiotics	0.268	.0001		

Sipsas et al Cancer 2009

Epidemiology

USA Data

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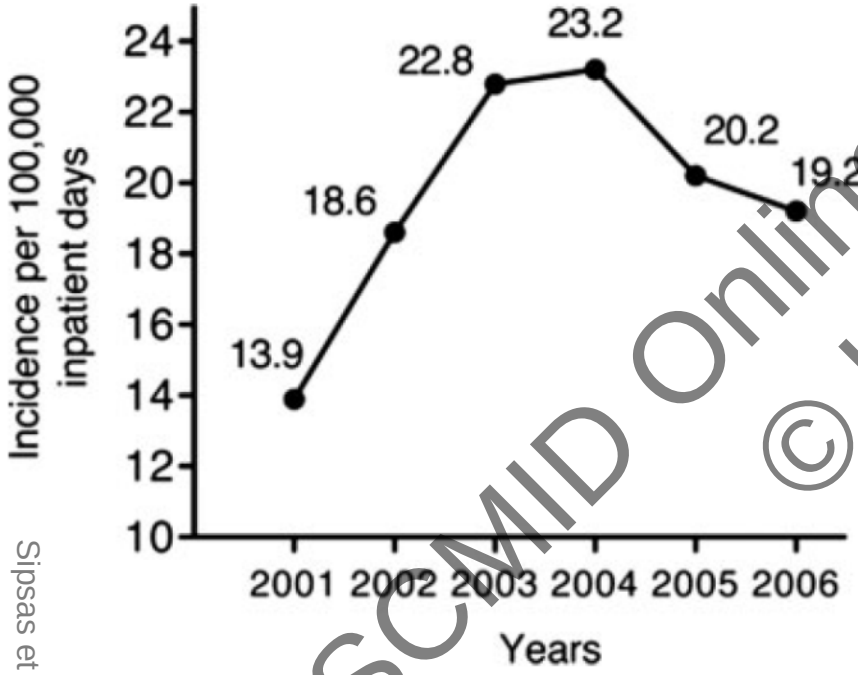
Incidence of candidaemia among patients with haematological malignancies



Candida species isolated from hematologic malignancy or stem cell transplantation patients with candidaemia over 3 consecutive periods

Species	No. of Patients (%)		
	1988-1992,[17] n=230	1993-2002,[18] n=281	2001-2007, n=173
C. albicans	79 (34)	38 (13)	41 (24)
Non-*albicans* species	139 (60)	227 (81)	129 (75)
C. glabrata	28 (12)	86 (31)	8 (5)
C. krusei	17 (7)	68 (24)	30 (17)
C. parapsilosis	33 (14)	39 (14)	42 (24)
C. tropicalis	53 (23)	27 (10)	37 (21)
C. guilliermondii	2 (1)	4 (1)	4 (2)
C. lusitaniae	3 (1)	3 (1)	2 (1)
Other*	—	—	6 (3)
Mixed *Candida* spp.	12 (5)	16 (6)	3 (2)

**C. kefyr* (1), *Torulopsis famata* (1), and nonspecified non-*albicans Candida* spp. (4).

Sipsas et al Cancer 2009

Treatment (Dose) of invasive disease/candidaemia in Neutropenia/HCT

Intention: success including survival

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Agent	Rec	Duration	References
Fluconazole	BII_t		Rex NEJM 1994, Anaissie CID 1996, Anaissie Am J Med 1996 (Caution regarding resistance) Because of old data, FLUC should rather be considered as a step-down treatment option.
Itraconazole	DIII		Only one abstract in non-neutropenics published 2003 in CCM (O. Tuil & Y. Cohen)
Posaconazole	DIII		One case report in non neutropenic (Anstead GM
Voriconazole	CII_t		
Anidulafungin	BII_t		
Micafungin	AII_t		
Caspofungin	AII_t		
Liposomal Amphotericin B	BII_t		Micafungin)
AmB lipid complex	CII_a		Anaissie ICAAC 2005, Ito CID 2005
AmB colloid dispersion	CIII		Noskin CID 1998
Deoxycholate Amphotericin B	DII_t		Anaissie CID 1996, Muarte Duarte NEJM 2002, Walsh NEJM 1999, Ullmann CID 2006

As per study design: at least 14 days after last BC positivity, recovery from severe neutropenia and resolution of clinical signs including exclusion of endocarditis and endophthalmitis by appropriate examination (Rex NEJM 1994) BII_t,

Treatment (Combinations) of invasive disease/candidaemia in Neutropenia

Intention: success including survival

Agent	Rec	Duration	References
Deoxycholate amphotericin B & 5-fluorocytosine	DIII	N/A	Too toxic and erratic PK
Deoxycholate amphotericin B & fluconazole (sequential therapy only)	CII_t	N/A	Rex CID 2003 (study regarding non-antagonism, value in comparison to safer echinocandins unclear, therefore only an option), Kullberg et al (Lancet 2005) studied voriconazole vs. sequential D-AmB and fluconazole No difference in main endpoints; more toxicity in the AmB arm, despite only 3 days AmB median.
Efungumab & lipid formulation of amphotericin B	DIII	N/A	Pachl J et al. 2006, flaws in the design of study

Other combinations not studied; expert opinion say combination might be useful in severe deep-seated infections (abdominal infection, CNS, endocarditis) CIII

Prophylaxis in Neutropenia
WHEN? Dose?

Intention: morbidity reduction including survival advantage

Situation	Recommendation	References
Early neutropenic phase	Fluconazole (CI), Itraconazole (CI), Voriconazole (ND), Posaconazole (CII_t), Caspofungin (ND), Micafungin (CI), Anidulafungin (ND), L-Amphotericin B (DI)	1) Glasmacher , 2006;JAC;57:317 2) Menichetti ,CID 1999;28:250 3) Gøtzche , BMJ 1997;314:1238 4) Harousseau AAC 2000;44:1887 5) Boogaerts, JAC 2001 6) Oren, BMT, 2006;38:127 7) Penack, Ann Oncol 2006;17:1306 8) Cornely, NEJM 2007;356:335 9) Hirata, Leuk Lymphoma 2010;51:853
Duration of prophylaxis	No prophylaxis recommended (BII)	Gøtzche , BMJ 1997;314:1238
Different decision in antibody treatment?	No evidence for prophylaxis (BIII)	ND

ND: no data

Explanation/Issues: A study showed no diff. between flu and itra (1). But, it was open-label and no placebo. Another randomized,placebo controlled study showed superiority for itra for preventing Candida (2), but no overall mortality advantage (less mortality due to Candida, n.s.). In the Penack trial (7) low dose L-AmB was ineffective for Candida disease.

Prophylaxis in autologous HCT WHEN? Dose?

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Intention: morbidity reduction including survival advantage

Situation	Recommendation	References
Early neutropenic phase	Fluconazole (ND), Itraconazole (CII), Voriconazole (ND), Posaconazole (CII_t), Caspofungin (ND), Micafungin (ND), Anidulafungin (ND), any amphotericin B formulation (ND)	1) Jathavedam A, et al. Biol Blood Marrow Transplant. 2008 May;14(5):595-600 2) Nucci M, et al. CID 2000;30:300 3) Cornely NEJM 2007
Duration of prophylaxis	No prophylaxis recommended (BIII)	
Different decision in antibody treatment?	No evidence for prophylaxis (BIII)	

ND: no data

Explanation/Reason/Issues:

Indirect evidence for survival advantage in prophylaxis for invasive candida is only available from Cornely seen in the NEJM article. None was studied for other drugs for candidiasis.

Prophylaxis in allogeneic HCT

Intention : morbidity & survival advantage

Commentary:

The group recognizes that other fungal infections possibly play a more important role on the outcome and mortality in this patient population (e.g. filamentous fungi).

Various antifungal agents had similar outcomes as fluconazole and have received strength of recommendation due to this finding.

The strength of recommendation when including all possible fungal infections would be most likely different by EFISG and a prescribing physician must be aware of this.

Prophylaxis in allogeneic HCT

Intention: morbidity reduction (Candida)

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Situation	Recommendation	References
During early neutropenic phase	Fluconazole (AI); Itraconazole (BI); Posaconazole (AII_t), Voriconazole (AI); Micafungin (AI), Caspofungin (CII_u), Anidulafungin (ND), Liposomal AmB (BII)	Goodman JL NEJM 1992; Morgenstern 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 SM BMT 1999; Penack O Ann Onco 2006
During later phase within first 100 days	Fluconazole (AI); Itraconazole (BI); Posaconazole (CIII), Voriconazole (AI); Micafungin (CIII), Caspofungin (CII_u), 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)

Prophylaxis in allogeneic HCT

Intention : survival advantage (Candida)

EFISG ESCMID FUNGAL INFECTION STUDY GROUP
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Situation	Recommendation	References
During early neutropenic phase	Fluconazole (AI); Itraconazole (CI); Posaconazole (BII_t)*, Voriconazole (CI); Micafungin (CI), Caspofungin (CIII), Anidulafungin (ND), Liposomal AmB (CIII) *: identical outcome regarding Candida infection compared to flu/itra but the overall death rate in the Cornely trial was lower with posaconazole.	Goodmann JL NEJM 1992; Morgenstern 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; Kelsey SM BMT 1999; Penack O Ann Onco 2006
During later phase within first 100 days	Fluconazole (AI); Itraconazole (CI); Posaconazole (CIII), Voriconazole (CI); Micafungin (CIII), Caspofungin (CII_u), Anidulafungin (ND), Liposomal AmB (CIII)	Slavin M JID 1995 (day 110); 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;
During GVHD (moderate to severe)	Fluconazole (CI); Itraconazole (CI); Posaconazole (BI)*, Voriconazole (CI)*, others (ND) *: identical outcome regarding Candida infection compared to fluconazole but the rate of fungal related death in the Ullmann trial was lower with posaconazole.	Ullmann NEJM 2007; Wingard JR Blood 2010

Secondary Prophylaxis

- Secondary prophylaxis is not indicated in case of prior candidaemia without any sign of deep seated infection– including situations in which the patient is exposed to a new immunosuppressive condition such as prolonged neutropenia induced by chemotherapy, autologous or allogeneic HCT (CIII)

Empiric treatment in Neutropenia incl HCT

WHEN: 3 to 4 days of persistent fever in all major trials (AII), not defined for relapsing fever

Issues: Recommendations only apply to patients with expected prolonged duration of neutropenia (>10 days) e.g.

- induction/consolidation chemotherapy of AML-MDS, autologous or allogeneic HCT;
- extensive diagnosis work-up is required to exclude a clinically or mycologically documented infection which might require specific therapy

Empiric treatment in Neutropenia incl. HCT

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Dosage & *Intention: morbidity reduction*

Agents // Situation (trial included allo HCT)	Rec	References
Liposomal amphotericin B (3mg/kg/d) (Allo= yes)	AI	Walsh NEJM 1999; Prentice Br J Haematol 1997; Wingard CID 2000; Walsh NEJM 2002; Walsh NEJM 2004; Maertens Pediatr Inf Dis J 2010
Caspofungin (70 mg on D1 then 50 mg) (Allo=yes)	AI	Walsh NEJM 2004; Maertens Pediatr Inf Dis J 2010
Amphotericin B colloidal dispersion (4 mg/kg/d) (Allo=yes)	BI	White CID 1998
Amphotericin B lipid complex (5 mg/kg/d) (Allo=yes)	BI	Wingard CID 2000
Itraconazole (200 mg iv Q12h on D1 & D2 then 200 mg iv/d) (Allogeneic HCT=not reported)	BI	Boogaerts Ann Intern Med 2001; Ehninger Onkologie 2007
Voriconazole (2 x 6 mg/kg on D1 then 2x3 mg/kg/d) (Allo=yes)	BI	Walsh NEJM 2002
Fluconazole (400 mg/d) (Allo=not reported)	CI*	Winston Am J Med 2000; Viscoli C, Eur J Cancer. 1996 May;32A(5):814-20.
Amphotericin B deoxycholate (0.5 – 1.0 mg/kg/d) (Allo=yes)	CI	White CID 1998; Walsh NEJM 1999; Boogaerts Ann Intern Med 2001; Ehninger Onkologie 2007
Micafungin (100 mg) (AlloHSCT = 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 BI for amphotericin B colloidal dispersion due to safety issue with this agent; amphotericin B lipid complex more toxicity in a direct comparison to liposomal AmB.
For micafungin: Tamura = non comparative trial (dose 50-150 mg) ; Kubiak = 323 pts, retrospective, observational, sequential cohort (dose 100 mg)

Pre-emptive treatment:

No real data on Candida diseases

No recommendation

- Candida colonization does not play a role in this patient population
- Criteria defining pre-emptive treatment of fungal infection in cancer patients are poorly defined and associated more to filamentous fungi infections

Autologous/allogeneic HCT/Neutropenia

How to treat if intolerant or not responding

Recommendation	Reference
If receiving fluconazole or L-Amp B switch to echinocandin (BII_t)	Mora-Duarte NEJM 2007, Kuse ER Lancet 2007, Reboli NEJM 2007, Pappas CID 2007

Explanation/Issues:

No adequately powered, randomized trials for candidaemia in either neutropenics or HCT recipients….Identification of *Candida* species may be helpful (e.g. *C. krusei*).

Mucosal Candidiasis

Sites

Diseases	Agents/Recommendation
Oropharyngeal	Nystatin susp (non-neutropenic, mild) (BII), miconazole buccal (BII_t), flu (AI), itra solution (AII), posa (AII), vori (BII) echinocandin (BII), Amp B (BII) [i.v. echinocandins and lipid AmB possible in very severe and refractory cases (BII)]
Oesophageal	Flu (AI), itra (AIII), posa (AI) vori (AIII), echinocandin (BII), [i.v. echinocandins and lipid AmB possible in very severe and refractory cases (BII)]

References:
Reminder: Identify species
Wilcox JID 1997, Ally R CID 2001, Gligorov 2010

Chronic Disseminated Candidiasis

Intention: Diagnosis

Recommendation	Recommendation	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)

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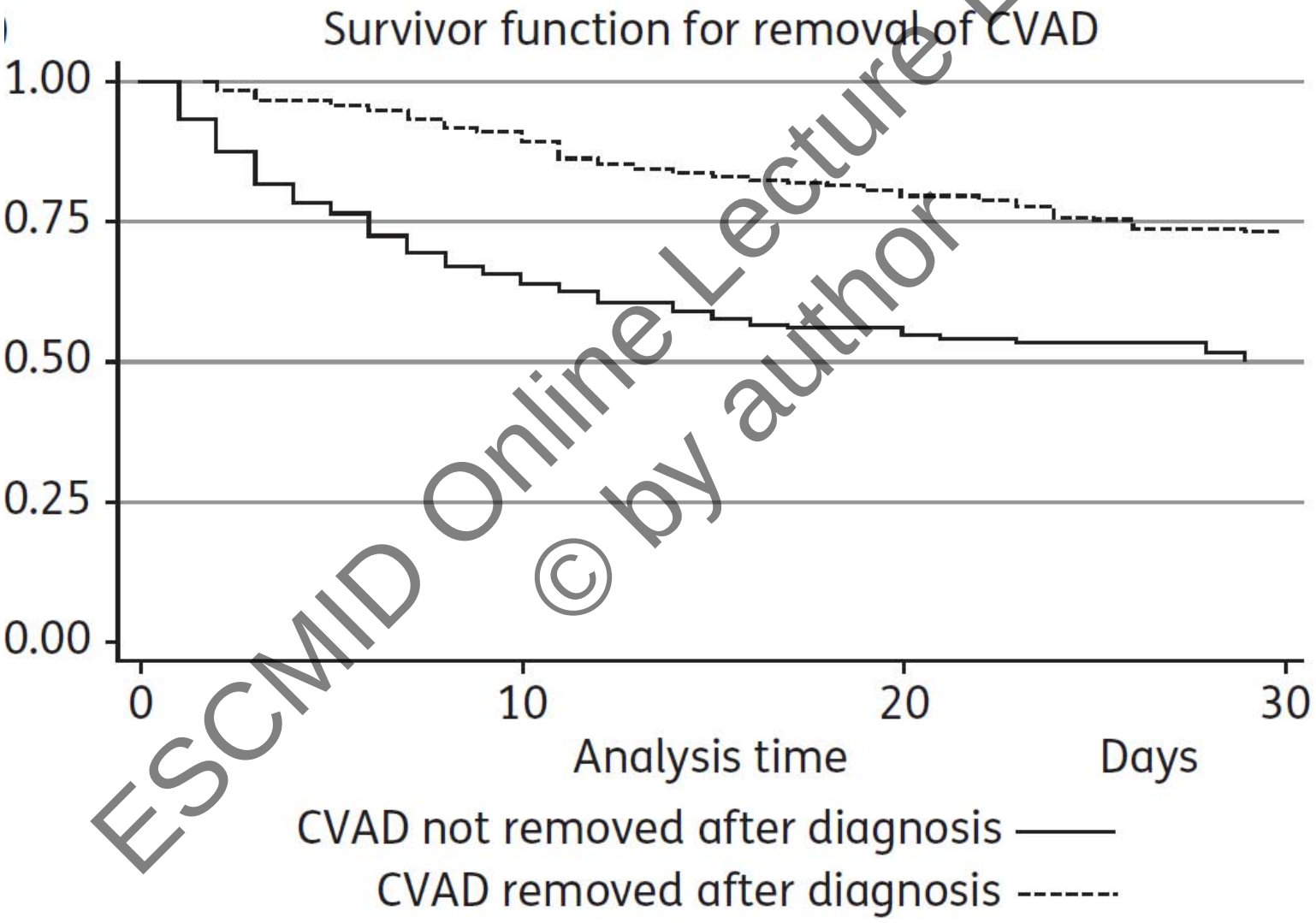
Recommendation	Duration	Reference
Fluconazole (BIII)	Reported duration minimum 3 months	L.-M. Poon, H.-Y. Chia, L.-K. Tan, T.-C. Liu,-P. Koh Successful intensive chemotherapy followed by autologous hematopoietic cell transplantation in a patient with acute myeloid leukemia and hepatosplenic candidiasis: 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, Rohrlich PS, Lortholary O.Adjuvant Corticosteroid Therapy for Chronic Disseminated Candidiasis. Clinical Infectious Diseases 2008; 46:696–702

Australian Data on CVC Removal



Slavin et al JAC 2010

BIOFILM CVC

Biofilm formation issues on CVC and other hardware

Recommendation	Intention	Comment	Reference
Early catheter removal (BII_u)	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_t)	Morbidity advantage	Pat in the echinocandin trails with CVC retention had equal outcome (low numbers)	Murate Duarte NEJM 2002, Pappas CID 2007, Kuse Lancet 2007, Riboli NEJM 2007
If catheter retention use echinocandins not azoles or LAmB (CII_t)	Morbidity advantage	Worse outcome in non echinocandin trials	Muarte 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 candidemia. No published data available	

Cytokines, Colony-stimulating Factors, Granulocyte Infusions

Recommendation	Reference
G-CSF **Granulocytes Infusions with antifungal agents (Data from paeds)** (CIII)	Grigull L, Support Care Cancer 2006, very weak recommendation for desperate situations , no dischoragement due to desperation therefore due to low data output no recommendation
Immunomodulation for (*primary or other)* refractory cases, G-CSF (CIII)	Ofran Y, Vox Sanguinis 2007; Safdar A, Cancer 2006 (IFNγ1b); Sachs UJ Transfusion 2006; Dignani MC, Cancer 2005; Lee JJ, Leukemia 2001; Di Mario A, Haematologica 1997; Dignani MC Leukemia 1997

Explanation/Issues:
No controlled trials, only anecdotal data with small numbers of patients exist. Since persistent neutropenia is related with treatment failure, recovery from neutropenia substantiates the efficacy of antifungals (Annaise AJM 1998). A recent Cochrane review indicates no mortality difference for all infections in neutropenics (Massey E, Cochrane Database Syst Rev 2009; Jan 21).

Thank You to the Team!