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European Fungal Management Guidelines – Applicable to My Patients in My Hospital?

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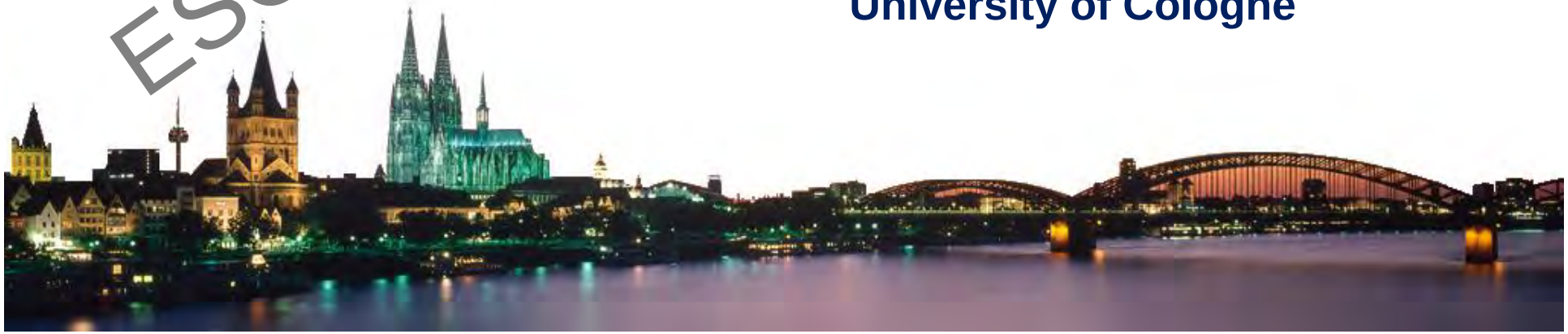

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Transparency Declaration

- European Commission
  - FP7, IMI-JU 6 (COMBACTE), 8 (APC), 9 (CARE)
- European Organisation for Research and Treatment of Cancer (EORTC)
- European Society for Clinical Microbiology and Infectious Diseases (ESCMID)
- European Confederation of Medical Mycology (ECMM)
- German Federal Ministry of Research and Education
  - BMBF 01KN1106, 01KN0706, 01GH1001E, 01EZ0931, 01EK1422
- German Center for Infection Research (DZIF)
- German Research Foundation (DFG)
- German José Carreras Leukaemia Foundation (DJCLS)
- SME & Industry Research Grants, Trial Design, or Presenting for
  - 3M, Actelion, Astellas, Basilea, Bayer, Celgene, Cidara, Cubist/Optimer, Da Volterra, F2G, Genentech, Genzyme, Gilead, GSK, Merck Serono, MSD, Miltenyi, NanoMR, Parexel, Pfizer, Quintiles, Sanofi Pasteur, Summit/Vifor, Viropharma

Definition of the Strength of Recommendation

Grade	ESCMID EFISG
A	strongly supports a recommendation for use
B	moderately supports a recommendation for use
C	marginally supports a recommendation for use
D	supports a recommendation against use

Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37.

Definition of the Quality of Evidence

Level	ESCMID EFISG
I	Evidence from at least 1 properly designed randomized, controlled trial
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
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37.

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Definition of the Quality of Evidence

Index	ESCMID EFISG
r	Meta-analysis or systematic review of randomised controlled trials
t	Transferred evidence i.e. results from different patients‘ cohorts, or similar immune-status situation
h	Comparator group is a historical control
u	Uncontrolled trial
a	Abstract published at an international meeting

Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37.

Applicability in India

ESCMID Phaeohyphomycosis Guideline

ESCMID AND ECMM PUBLICATIONS

10.1111/1469-0691.12515

ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi

A. Chowdhary[1], J. F. Meis[2,3], J. Guarro[4], G. S. de Hoog[5], S. Kathuria[1], M. C. Arendrup[6], S. Arikan-Akdagli[7], M. Akova[8], T. Boekhout[5,9], M. Caira[10], J. Guinea[11,12,13], A. Chakrabarti[14], E. Dannaoui[15], A. van Diepeningen[5], T. Freiberger[16], A. H. Groll[17], W. W. Hope[18], E. Johnson[19], M. Lackner[20], K. Lagrou[21], F. Lanternier[22,23], C. Lass-Flörl[20], O. Lortholary[22,23], J. Meletiadis[24], P. Muñoz[11,12,13], L. Pagano[10], G. Petrikkos[25], M. D. Richardson[26], E. Roilides[27], A. Skiada[28], A. M. Tortorano[29], A. J. Ullmann[30], P. E. Verweij[3], O. A. Cornely[31] and M. Cuenca-Estrella[32]

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Clin Microbiol Infect 2014; 20 (Suppl. 3): 47-75.

Applicability in Europe

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ESCMID Candida Guideline

ESCMID PUBLICATIONS 10.1111/1469-0691.12039

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients

O. A. Cornely[1†], M. Bassetti[2†], T. Calandra[3†], J. Garbino[4†], B.-J. Kullberg[5†], O. Lortholary[6,7†], W. Meersseman[8†], M. Akova[9], M. C. Arendrup[10], S. Arikan-Akdagli[11], J. Bille[3], E. Castagnola[12], M. Cuenca-Estrella[13], J. P. Donnelly[14], A. H. Groll[15], R. Herbrecht[16], W. W. Hope[17], H. E. Jensen[18], C. Lass-Flörl[19], G. Petrikkos[20], M. D. Richardson[21], E. Roilides[22], P. E. Verweij[5], C. Viscoli[23] and A. J. Ullmann[24]

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Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37.

Applicability in My Patients

Series in the ECMM-Journal *Mycoses*

Our 2014 approach to candidaemia

Philipp Koehler,[1,2] Daniela Tacke[1] and Oliver A. Cornely[1,2,3]

[1]Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany, [2]CEC

Our 2014 approach to mucormycosis

Daniela Tacke,[1] Philipp Koehler,[1,2] Birgid Markiefka[3] and Oliver A. Cornely[1,4,5,6,7]

[1]Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany, [2]Cologne Excellence Cluster on Cellular

Our 2015 approach to invasive pulmonary aspergillosis

B. Liss,[1,2] J. J. Vehreschild,[1,2,3] C. Bangard,[4] D. Maintz,[4] K. Frank,[5] S. Grönke,[5] G. Michels,[5] A. Hamprecht,[6] H. Wisplinghoff,[6] B. Markiefka,[7] K. Hekmat,[8] M. J. G. T. Vehreschild[1,2,3] and O. A. Cornely[1,2,3,9,10]

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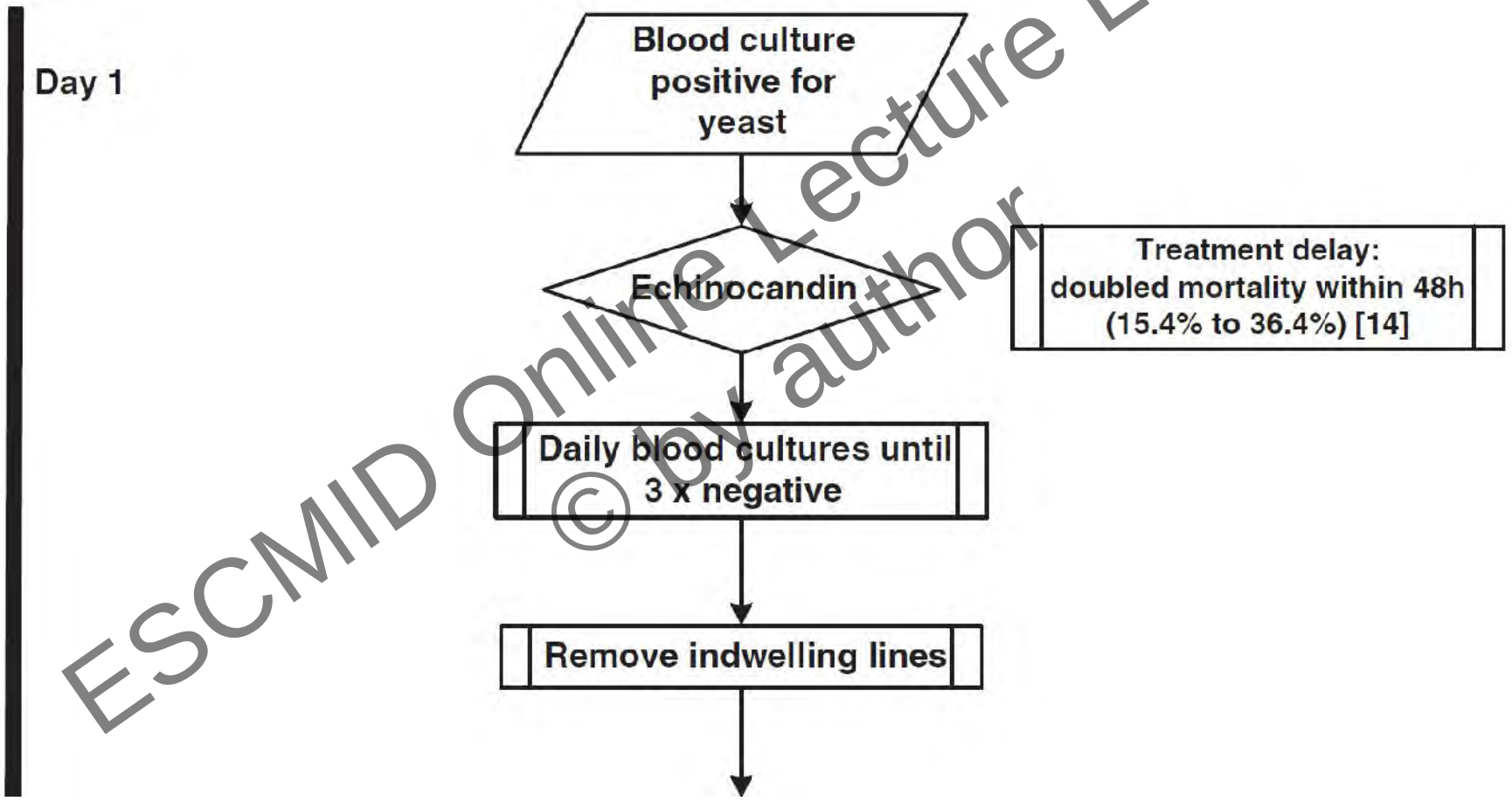
Candidemia Management



Koehler P et al. Mycoses 2014.

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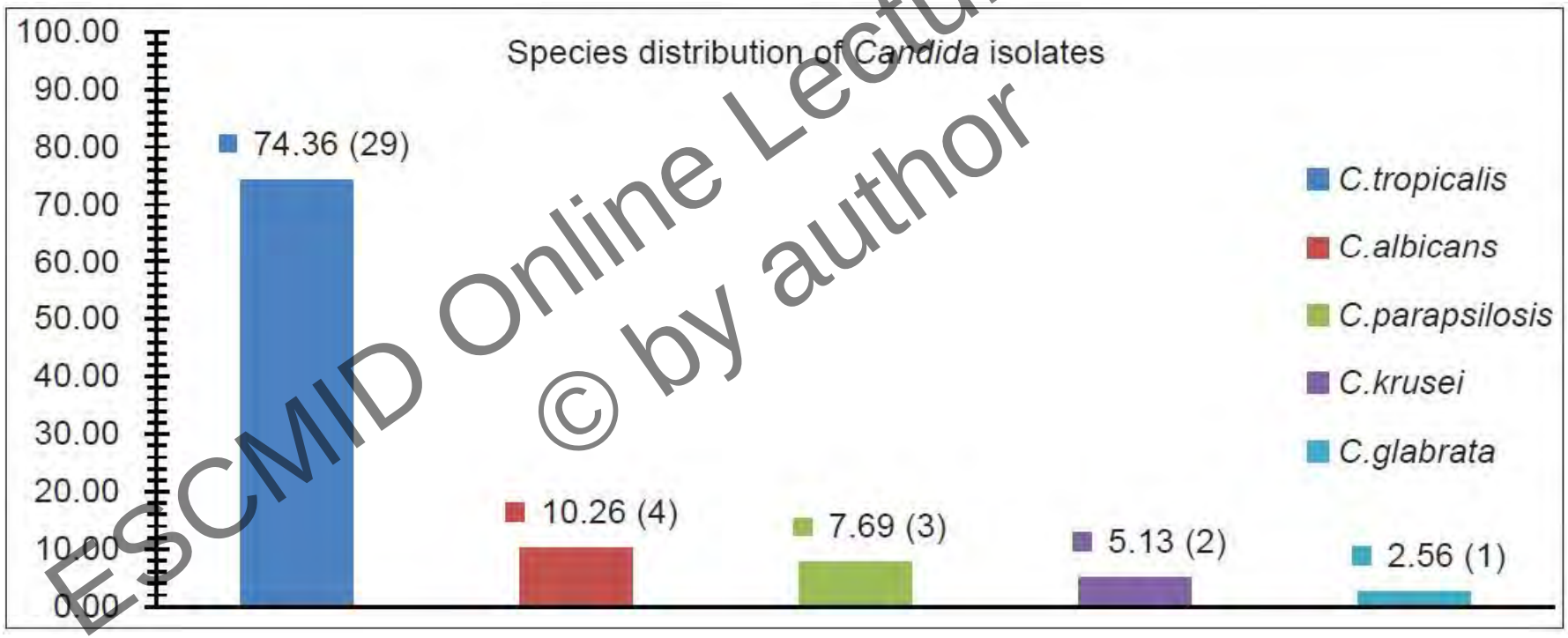
Epidemiology of Candidemia in India
An Example from the South



Giri S et al. J Postgrad Med 2013;59:190-5.

Targeted Treatment of Candidaemia
Polyenes

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

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, haem/onc or SOT) rather than ICU patients

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

Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37.

Targeted Treatment of Candidaemia
Azoles

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

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	IIa	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.

Clin Microbiol Infect 2012; 18 (Suppl. 7): 19–37.

Targeted Treatment of Candidaemia
Echinocandins

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

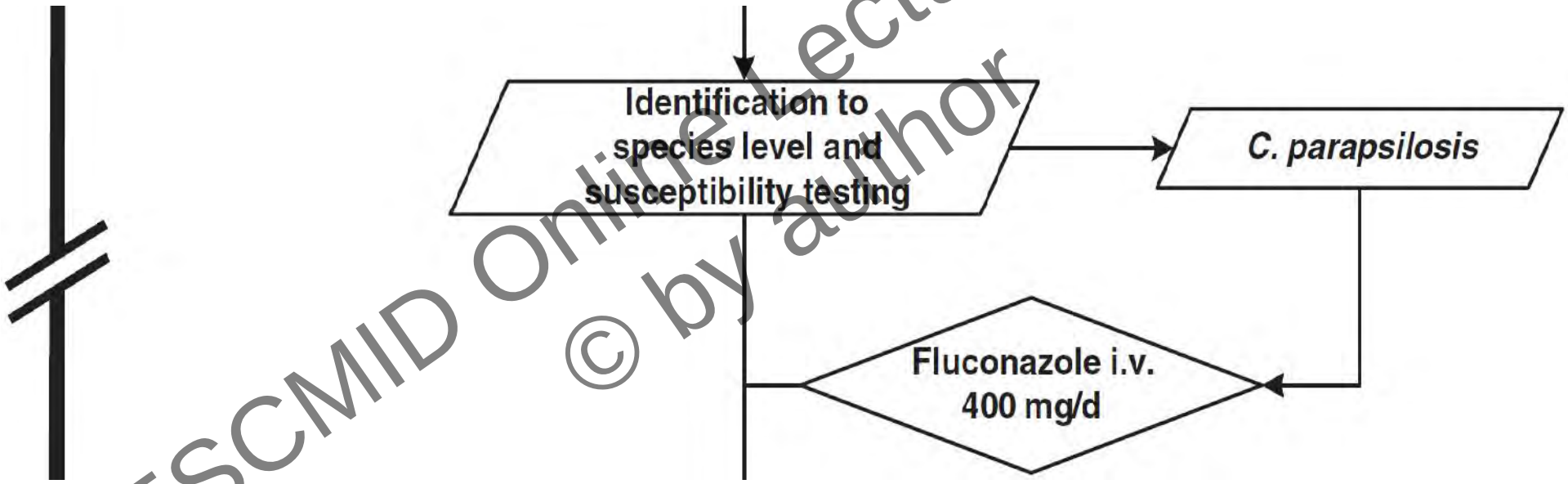
Compound	SoR	QoE	Reference	Comment
Anidulafungin 200/100	A	I	Reboli NEJM 2007	• Broad spectrum • Resistance rare • Fungicidal • Local epidemiology • C. parapsilosis, C. krusei • Safety profile • Less drug-drug interactions than caspofungin
Caspofungin 70/50	A	I	Mora-Duarte NEJM 2002 Pappas CID 2007	•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

Anidulafungin was superior over fluconazole.
Success rate in *C. albicans* higher with anidulafungin.

No rule without exception: *C. parapsilosis*

Cornely OA et al. Clin Microbiol Infect 2012.

Candidemia Management



Koehler P et al. Mycoses 2014.

Recommendations on Catheter Management in Candidaemia

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

Population	Intervention	SoR	QoE	Reference
Central venous catheter can be removed	Remove indwelling lines (not over a guide wire)	A	IIr	Andes CID 2012
Central venous catheter cannot be removed	Echinocandin, liposomal amphotericin B, or amphotericin B lipid complex	B	IIr	Andes CID 2012 Kucharikova AAC 2010 Kuhn AAC 2002 Mukherjee IJAA 2009 Nucci CID 2010 Rex CID 1995
	Azole, or amphotericin B deoxycholate	D	IIr	Almirante JCM 2005 Andes CID 2012 Leroy CCM 2009 Liu J Infect 2009 Rodriguez CMI 2007 Weinberger JHI 2005

Cornely OA et al. Clin Microbiol Infect 2012.

ESCMID Mucormycosis Guideline

ESCMID AND ECMM PUBLICATIONS

10.1111/1469-0691.12371

ESCMID† and ECMM‡ joint clinical guidelines for the diagnosis and management of mucormycosis 2013

O. A. Cornely[1,†,‡,§], S. Arikan-Akdagli[2,‡,§], E. Dannaoui[3,§], A. H. Groll[4,†,‡,§], K. Lagrou[5,‡,§], A. Chakrabarti[6,§], F. Lanternier[7,8], L. Pagano[9], A. Skiada[10], M. Akova[2], M. C. Arendrup[11], T. Boekhout[12,13,14], A. Chowdhary[15], M. Cuenca-Estrella[16,†,‡], T. Freiberger[17,18,†], J. Guinea[19,†,‡], J. Guarro[20,‡], S. de Hoog[12,‡], W. Hope[21,†], E. Johnson[22,‡], S. Kathuria[15], M. Lackner[23,†], C. Lass-Flörl[23,†,‡], O. Lortholary[7,†,‡], J. F. Meis[24,25,†,‡], J. Meletiadis[26,‡], P. Muñoz[19,†], M. Richardson[27,28,†,‡], E. Roilides[29,†,‡], A. M. Tortorano[30,‡], A. J. Ullmann[31,†,‡], A. van Diepeningen[12], P. Verweij[25,32,†,‡] and G. Petrikkos[33,†,‡,§]

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5) Clinical Department of Laboratory Medicine, Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium, 6) Department of Medical Microbiology, Postgraduate Institute of Medical Education & Research, Chandigarh, India, 7) Institut Pasteur, Centre National de Référence Mycoses Invasives et Antifongiques, CNRS, Unité de Mycologie Moléculaire, 8) Service des Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants malades, APHP, Centre d'Infectiologie Necker-Pasteur, IHU Imagine, Université Paris Descartes, Paris, France, 9) Dipartimento di Ematologia, Universita Cattolica del Sacro Cuore, Roma, Italy, 10) 1st Department of Propaedeutic Medicine, Laikon Hospital, National and Kapodistrian University of Athens, Athens, Greece, 11) Unit of Mycology, Department Microbiology & Infection Control, Statens Serum Institut, Copenhagen, Denmark, 12) CBS Fungal Biodiversity Centre [CBS-KNAW], 13) Department of Internal Medicine and Infectious Diseases, University Medical Centre, Utrecht, the Netherlands, 14) Shanghai Key Laboratory of Molecular Medical Mycology, Institute of Dermatology and Medical Mycology, Changzheng Hospital, Second Military Medical University, Shanghai, China, 15) Department of Medical Mycology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India, 16) Instituto de Salud Carlos III, Centro Nacional de Microbiología, Madrid, Spain, 17) Centre for Cardiovascular Surgery and Transplantation, Molecular Genetics Lab, 18) Molecular Immunology and Microbiology RG, Central European Institute of Technology (CEITEC), Masaryk University, Brno, Czech Republic, 19) Departamento de Medicina, Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Universidad

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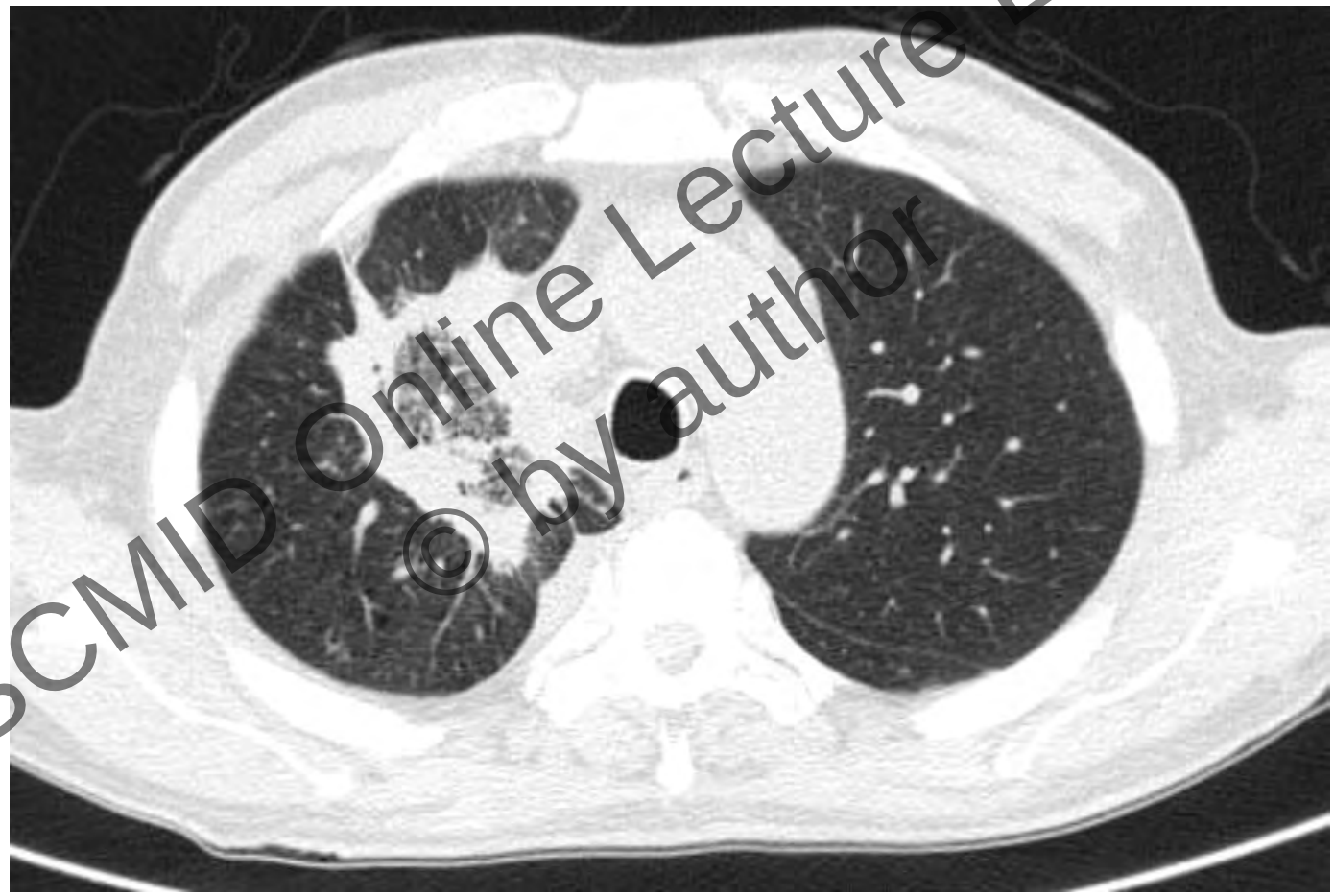
Mucormycosis – Inverse Halo Sign



Clin Microbiol Infect 2014; 20 (Suppl. 3): 5-26.

Targeted Treatment – First Line

Pop	Intention	Intervention	SoR	QoE	Reference	Comment
Any	To decrease fungal burden & mortality	Surgical debridement	A	II_u	Tedder Ann Thor Surg 1994 Roden CID 2005 Chakrabarti PostMedJ 2009 Skiada CMI 2011 Vironneau ICAAC 2012 Zaoutis PID 2007	N=90 N=45 N=22, rhinocerebral N=92, paediatric
Any	To cure	Surgery in addition to antifungal treatment	A	II_u	Roden CID 2005 Greenberg AAC 2006 Skiada CMI 2010 Zaoutis PIDJ 2007	N=470 N=19 N=99 N=92, paediatric
Any	To cure	Amphotericin B, liposomal ≥ 5mg/kg	A	II_u	Pagano Haematologica 2004 Roden CID 2005 Cornely CID 2007 Rüping JAC 2010 Shoham Med Mycol 2010 Skiada CMI 2011 Ibrahim AAC 2003 Lewis AAC 2010 Lanternier ICAAC 2012	N=4 N=? N=5 N=21 N=28 N=130 Animal model Animal model N=40
CNS	To cure	Amphotericin B, liposomal 10 mg/kg, initial 28 days	A	IIa	Lanternier ICAAC 2012 Ibrahim AAC 2008 Groll JID 2000	N=40, toxicity Animal model Animal model

Treatment duration is being determined on a case-by-case basis and depends, e.g. on extent of surgery and organs involved.

Targeted Treatment – First Line

Pop	Intention	Intervention	SoR	QoE	Reference	Comment
Any, except CNS	To cure	Amphotericin B, lipid complex 5mg/kg	B	II_u	Walsh CID 1998 Larkin Inf Med 2003 Roden CID 2005 Skiada CMI 2011 Ibrahim AAC 2008 Groll JID 2000	N=6 N=10 N=? N=7 animal model animal model/CNS levels
Any	To cure	Posaconazole 4x200mg/d or 2x400mg/d	B	II_u	Rüping JAC 2010 Skiada CMI 2011 Dannaoui AAC 2003	N=8 N=17 Animal model, small N, absorption, emphasizes preference of L-AmB
Any	To cure	Polyene plus caspofungin	C	III	Reed CID 2008	N=7 (6/7 diabetic)
Any	To cure	Amphotericin B, deoxycholate, any dose	D	I	Walsh NEJM 1999 Pagano Haematologica 2004 Roden CID 2005 Ullmann CID 2006 Chakrabarti PostMedJ 2009 Skiada CMI 2011	Renal toxicity N=9 N=532 Renal toxicity N=10 N=21

Treatment duration is being determined on a case-by-case basis and depends, e.g. on extent of surgery and organs involved.

Adjunctive Drugs and General Management

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Haematology patients	To cure infection	Deferasirox 20 mg/kg/d, d1-14	Votes: C 4 D 9 Abstain 3	II	Spellberg AAC 2009 Ibrahim JAC 2010 Spellberg JAC 2012	N=8 Animal N=20 increased mortality
Other than haematology	To cure infection	Deferasirox, any dose	C	III	No reference found.	
Any	To cure infection	Statins	C	III	Lukacs JCM 2004 Chamilos AAC 2006	Animal model and in vitro
Glucocorticosteroids	To cure infection	Stop if feasible, if not: reduce dose of glucocorticosteroids to minimum required dose	A	IIr	Lionakis Lancet 2003	
Any	To cure infection	Continue treatment until complete response (on imaging) and permanent reversal of immunosuppression are achieved	A	III	No reference found.	Optimal duration of treatment has not been studied prospectively

ESCMID-ECMM Guidelines Usefulness

ESCMID-ECMM guidance documents

- Summarise current evidence
- Identify unmet medical needs
- Help develop hospital guidlines → Strategy

ESCMID-ECMM Guidelines Usefulness

ESCMID-ECMM guidance documents should be used in the light of

- Local epidemiology
- Individual patient → Tactics

ESCMID-ECMM guidance are advice, but don‘t determine diagnostic or treatment decisions in the individual patient