

# Mucormycosis

**George Petrikos, MD, PhD.**

Professor of Internal Medicine  
and Infectious Diseases

**National and Kapodistrian University of Athens,**

**“ATTIKON” University Hospital**

**petrikos@hol.gr**



## Author Experts of the Guideline on Emerging Fungal Diseases Working Module Mucormycosis

Author	Country
Sevtap Arikan-Akdagli	Turkey
Arunaloke Chakrabarti	India
<b>Oliver A. Cornely</b>	<b>Germany</b>
Eric Dannaoui	France
Andreas Groll	Germany
Katrien Lagrou	Belgium
Fanny Lanternier	France
Livio Pagano	Italy
<b>Georgios Petrikos</b>	<b>Greece</b>
Anna Skiada	Greece

Population	Intention	Method / Finding	SoR	QoE	Reference	Comment
Hematologic malignancy	To differentiate mucormycosis from invasive pulmonary aspergillosis	CT / reversed halo	B	II <sub>u</sub>	Wahba CID 2008 Marchiori Chest 2012	value depends on pre-test probability
Hematologic malignancy	To differentiate mucormycosis from invasive pulmonary aspergillosis	CT / pleural effusion	C	II <sub>h</sub>	Chamilos CID 2005 Marchiori Chest 2012	N=16 N=18
Hematologic malignancy	To differentiate mucormycosis from invasive pulmonary aspergillosis	CT / >10 nodular infiltrates	C	II <sub>h</sub>	Chamilos CID 2005 Marchiori Chest 2012	

Population	Intention	Method	SoR	QoE	Reference	Comm
Any	Staging	CT cranial, sinus, chest, abd.	B	III	Pagano Haematol 2004 Chamilos CID 2005	IM more acute than IA
Diabetic, facial pain, sinusitis, amaurosis	To diagnose mucormycosis	Cranial CT	A	IIu	Centeno Radiology 1981 Gamba Radiology 1986	
As above, but with bone destruction on CT	To determine extent of disease	Cranial MRI	A	IIu	Mohindra Mycoses 2007 Koc Int J Neurosci 2007 Herrera Skull Base 2009	
Asia (China and India): No underlying diseases, flank pain, fever, haematuria, renal infarct	To diagnose renal mucormycosis	CT or MRI	A	IIu	Chugh Am J Kid Dis 1993 Sharma Br J Radiol 2006 Marak Med Mycol 2010	N=4 N=1 N=2
Any	To diagnose mucormycosis	CT-biopsy	A	IIu	Lass-Flörl CID 2007 Rickerts CID 2007	

Popu- lation	Intention	Intervention/ Method	SoR	QoE	Ref.	Comment
Any	To diagnose	Direct microscopy preferably using optical brighteners	A	Ilu	Lass-Flörl CID 2007 McDermott OralSurgOralMed OralPathoOralRadiolEndo d 2010	Rapid diagnosis No identification to genus level Intraoperative assessment of clear margins
Any	To diagnose	Culture	A	IIIr	Ribes CMR 2000 Kontoyiannis AmJClinPathol 2007	Avoid grinding, preferred temp. 37 C
Any	To diagnose	Histopatho- logy	A	Ilu	Chakrabarti Postgr Med J 2009 Ben-Ami J Infect 2009 Rüping JAC 2010 Skiada CMI 2011 Frater ArchPathLabMed 2001	
Any	To diagnose	Immuno- histochemistry	C	Ilu	Jensen J Pathol 1997	In house

Population	Intention	Intervention/Method	SoR	QoE	Ref.	Comment
Any	To diagnose	Molecular based studies on <u>fresh</u> clinical material	B	Ilu	Lass-Flörl CID 2007 Rickerts CID 2007 Millon CID 2013	in house fresh material preferred over paraffin embedded
Any	To diagnose	Molecular based studies on <u>paraffin</u> slides	B	Ilu	Bialek J Clin Pathol 2005 Dannaoui JCM 2010 Hammond JCM 2011	in house test systems; Dannaoui paper is on animal model

Population	Intention	Intervention/ Method	SoR	QoE	Reference	Comment
Any	To guide treatment	EUCAST / CLSI	C	IIu	CLSI M38-A2 EUCAST Definitive Doc. E.Def. 9.1 Chakrabarti JCM 2010	Clinical relevance uncertain No clear correlation no breakpoint
Any	To guide treatment	Correlation of MIC with in vivo outcome	C	IIu	Chakrabarti JCM 2010	A. elegans, limited retrospective data, suggests correlation
Any	To establish epidemiologic knowledge	Susceptibility testing	A	IIu	Vitale JCM 2012 Almyroudis AAC 2007 Dannaoui JAC 2003 Sun AAC 2002 Torres-Narbona AAC 2007 Alastruey-Izquierdo AAC 2009 Chakrabarti JCM 2010 Alastruey-Izquierdo CMI 2009	N=66 N=217 N=36 N=37 N=45 N=77 N=18 A. elegans Review
Any	To establish epidemiologic knowledge	MIC by reference method	A	III	CLSI 2008. M38-A2 EUCAST CMI 2008	other methods not validated for mucormycosis



# Genus and Species Identification



Population	Intention	Intervention/Method	SoR	QoE	Reference	Comment
Any	To guide treatment	Identification to genus level	C	Ilu	Alastruey-Izquierdo AAC 2009 van Burik CID 2006 Greenberg AAC 2006 Petraitis Med Mycol 2012 Roden CID 2005	Cunninghamella: more virulent higher mortality POS less effective
Any	To establish epidemiologic knowledge and for outbreak investigation	Identification to species level	A	Ilu	Alvarez JCM 2009 Roden CID 2005 Skiada CMI 2011 Balajee JCM 2009	Different species may have different clinical syndromes and different treatment approaches
Any	To establish epidemiologic knowledge	Molecular identification to species level	A	Ilu	Kontoyiannis JID 2005  Alvarez JCM 2009	N=19; ITS seq. Concordance 79%, Morphology not reliable N=190; ITS seq., Concordance 93%



# Prophylaxis

Population	Intention	Intervention	SoR	OoE	Reference	Comm
Neutropenic or GvHD, in outbreak	To prevent	Posaconazole 3x200mg/d	C	III	Cornely NEJM 2007 Ullmann NEJM 2007 Pagano CID 2012	N=1 N=1 N=0
Neutropenic or GvHD, in outbreak	To prevent	Fluconazole, itraconazole, voriconazole	D	II	Lass-Flörl Drugs 2011	
Immunosuppressed, prior diagnosis of mucormycosis	To prevent recurrence, „secondary prophylaxis“	Surgical resection and last drug effective in the same patient	A	III	Nosari BMT 2007 Hoover MedPedOnc 1997	N=3 N=1

# Diagnosis-driven Treatment – Timing

Population	Intention	Intervention	SoR	QoE	Reference	Comm
Immune-compromised	To increase survival	Immediate treatment initiation	A	Ilu	Chamilos CID 2008	N=70 Treatment initiation $\geq$ 6 days after symptoms onset: 2-fold increased week 12 mortality

ESCMID

Online Lecture Library  
 © by author

Pop	Intention	Intervention	SoR	QoE	Reference	Comment
Any	To increase survival rates	Surgical debridement	A	II <sub>u</sub>	Tedder Ann Thor Surg 1994 Roden CID 2005 Chakrabarti PostMedJ 2009 Skiada CMI 2011 Lanternier CID 2012 Zaoutis PIDJ 2007	N=90 N=45 N=59 N=92, paediatric
Any	To cure and to increase survival rates	Surgery in addition to antifungal treatment	A	II <sub>u</sub>	Roden CID 2005 Greenberg AAC 2006 Skiada CMI 2010 Zaoutis PIDJ 2007	N=470 N=19 N=99 N=92, paediatric
Any	To cure and to increase survival rates	Amphotericin B, liposomal ≥ 5mg/kg	A	II <sub>u</sub>	Pagano Haematologica 2004 Cornely CID 2007 Rüping JAC 2010 Shoham Med Mycol 2010 Skiada CMI 2011 Lanternier ICAAC 2012 Ibrahim AAC 2003 Lewis AAC 2010	N=4 N=5 N=21 N=28 N=130 N=40 Animal model Animal model
CNS	To cure	Amphotericin B, liposomal 10 mg/kg, initial 28 days	A	III	Ibrahim AAC 2008 Groll JID 2000	Animal model Animal model

Pop	Intention	Intervention	SoR	QoE	Reference	Comment
Any, except CNS	To cure	Amphotericin B, lipid complex 5mg/kg	B	II <sub>u</sub>	Larkin Inf Med 2003 Skiada CMI 2011 Ibrahim AAC 2008 Groll JID 2000	N=10 N=7 animal model animal CNS levels
Any	To cure	Posaconazole 4x200mg/d or 2x400mg/d	B	II <sub>u</sub>	Rüping JAC 2010 Skiada CMI 2011 Dannaoui AAC 2003	N=8 N=17 Animal, small N
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

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Refractory to prior antifungal therapy	To cure	Posaconazole 4x200mg/d or 2x400mg/d	A	II <sub>u</sub>	Greenberg AAC 2006 van Burik CID 2006 Skiada CMI 2011 Vehreschild 2012 CRM	N=19 N=81* N=61 N=15 <sup>#</sup>
Intolerant to prior antifungal	To cure	Posaconazole 4x200mg/d or 2x400mg/d	A	II <sub>u</sub>	Greenberg AAC 2006 van Burik CID 2006 Vehreschild 2012 CRM	N=5 N=43* N=15 <sup>#</sup>

\*in the van Burik study 33 patients had refractory disease and were intolerant; 11 individuals are part of both reports, i.e. van Burik and Greenberg.

<sup>#</sup>The reason for salvage treatment, i.e. refractoriness vs intolerance, was not reported in this study.

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

Population	Intent	Intervention	SoR	QoE	Reference	Comm
Intolerant to prior antifungal	To cure	Amphotericin B, liposomal, 5mg/kg	B	II <sub>u</sub>	Pagano Haematol 2004	N=8
Refractory to prior antifungal therapy	To cure	Amphotericin B, lipid complex, 5mg/kg	B	II <sub>u</sub>	Walsh CID 1998 Larkin Inf Med 2003	N=16 N=23
Intolerant to prior antifungal	To cure	Amphotericin B, lipid complex, 5mg/kg	B	II <sub>u</sub>	Larkin Inf Med 2003	N=12
Intolerant due to pre-existing renal disease	To cure	Amphotericin B, lipid complex, 5mg/kg	B	II <sub>u</sub>	Larkin Inf Med 2003	N=18
Intolerant due to pre-existing renal disease	To cure	ABCD 5mg/kg	B	II <sub>u</sub>	Herbrecht EJCMI 2001	N=21
Refractory disease or intolerant to prior antifungal therapy	To cure	Polyene plus caspofungin	C	III	Reed CID 2008	N=2
Any	To cure	Polyene plus posaconazole	C	III	Ibrahim AAC 2009	Animal

# Haematology/Oncology

Population	Intention	Intervention	SoR	QoE	Reference	Com m
Haematological malignancy with on-going neutropenia	To cure infection	gCSF, dose not reported	A	IIu	Pagano BJH 1997 Kontoyiannis CID 2000 Pagano Haematol 2004 Rodan CID 2005 Kara IntJClinPract 2007 Pagano JChemoth 2009	N=8 N=12 N=18 N=18 N=5 N=8
Haematological malignancy with on-going neutropenia	To cure infection	Granulocyte transfusion	C	II	Pagano Haematol 2004 Kontoyiannis CID 2000 Rodan CID 2005	N=? N=8 N=7
Haematological malignancy with on-going neutropenia	To cure infection	Granulocyte transfusion + IFNy1b	C	III	Safdar Cancer 2006	N=4



Population	Intention	Intervention	SoR	QoE	Reference	Comm
Pediatric	To cure	Amphotericin B and surgery	A	II	Zaoutis PIDJ 2007 Dehority JPHO 2009 Roilides AmJPerinatol 2009	
Pediatric beyond neonatal period	To cure	Amphotericin B, lipid complex 5mg/kg/d	A	II <sup>t</sup>	Walsh PIDJ 1999 Wiley PIDJ 2005 Walsh CID 1998 Walsh AAC 1997	safety safety Adult PK
Pediatric beyond neonatal period	To cure	Amphotericin B, liposomal ≥5mg/kg/d	A	II <sup>t</sup>	Hong AAC 2006 Dehority JPHO 2009 Kolve JAC 2009 Rüping JAC 2010 Shoham Med Myc 2010 Skiada CMI 2011	PK n=20; safety Adult Adult Adult
Pediatric beyond neonatal period and ≥2 y/o	To cure	Posaconazole 4x200 or 2x400 mg/d; <13 y/o: body-weight based	C	III <sup>t</sup>	Krishna AAC 2007 Welzen PIDJ 2011 Lehrnbecher EJCMID 2010 Döring BMC 2012 Rüping JAC 2010 Skiada CMI 2011 Walsh CID 2007	PK PK N=5 Safety Adult N<17 Adult <sup>TDM</sup>
Pediatric patients beyond the neonatal period	To cure	Amphotericin B lipid-based plus caspofungin	C	III <sup>t</sup>	Reed CID 2008 Walsh 05; Neely 09, Zaoutis 09	N=7 PK <sup>cas</sup> Safety <sup>cas</sup>

Population	Intent	Intervention	SoR	QoE	Reference	Comment
Neonates, in particular premature neonates	To cure	Amphotericin B, lipid complex 5mg/kg/d	A	II <sub>t</sub>	Walsh PIDJ 1999 Wiley PIDJ 2005 Walsh CID 1998 Larkin InfMed 2003 Würthwein AAC 2005	Paediatric safety Paediatric safety Adult Adult Paediatric PK
	To cure	Amphotericin B, liposomal ≥ 5mg/kg/d	A	II <sub>t</sub>	Juster-Reicher 2003 Dehority JPHO 2009 Kolve JAC 2009 Rüping JAC 2010 Shoham Med Myc 2010 Skiada CMI 2011	No neonatal PK Pediatric Safety Adult Adult Adult
	To cure	Amphotericin B, lipid based plus caspofungin	C	III <sub>t</sub>	Reed CID 2008 Saez-Llorens AAC 2009	
	To cure	Amphotericin B, deoxycholate 1-1.5mg/kg/d	D	III	Ibrahim AAC 2003	Animal
CNS involved	To cure	Amphotericin B, liposomal 5-10mg/kg/d	A	II <sub>t</sub>	Groll JID 2000	Animal

Population	Intent	Intervention	SoR	QoE	Reference	Comment
Pediatric beyond neonatal period and $\geq 2$ y/o	To cure	Posaconazole 4x200 or 2x400 mg/d; <13 y/o: body-weight based	A	IIt	Krishna AAC 2007 Welzen PIDJ 2011 Lehmbecher EJCMID 2010 Döring 2012 Greenberg AAC 2006 van Burik CID 2006 Walsh CID 2007	Paediatric PK study Paediatric PK study Paediatric Safety Adult Adult Adult; TDM No established paediatric dose; consider TDM
Paediatric including neonates	To cure	Amphotericin B, lipid-based, plus caspofungin	C	IIIIt	Reed CID 2008 Ibrahim AAC 2008 Saez-Llorens AAC2009 Walsh 05; Neely 09, Zaoutis 09	Adult Animal model Paediatric PK study cas PK cas Safety cas
Pediatric beyond neonatal period and $\geq 13$ y/o	To cure	Amphotericin B, lipid-based, plus posaconazole	C	IIIIt	Ibrahim AAC 2009 Rodriguez AAC 2008	Animal model Animal model

# Non immunocompromised – Trauma



Population	Intention	Intervention	SoR	QoE	Reference	Comment
Trauma	To cure	Surgical debridement and antifungal treatment	A	II	Patino World J Surg Chakrabarti J Inf 2001 Chakrabarti JCM 2003 Roden CID 2005 Skiada CMI 2011 Fanfair NEJM 2012	N=38, necessity of early radical debridement N=5/129 N=3/8 N=44/929 N=39/230 N=13/13

- more likely to receive surgery
- less likely to have disseminated disease
- shorter treatment duration
- surgical should follow general rules, debridement until clear margins

# Diabetes

Population	Intent	Intervention	SoR	QoE	Reference	Comment
Uncontrolled diabetes	To cure	Control of hyperglycaemia and ketoacidosis	A	IIu	Lanternier CID 2012 Yohai Surv Ophthal 1994 Chakrabarti PostgradMedJ 2009 Roden CID 2005 Bhansali Postgrad Med J 2004 Rammaert Diabetes Metab 2012	N=23 N=87 N=15 N=337 N=35 Review
Uncontrolled diabetes with rhino-cerebral	To cure	Surgery	A	III	Chakrabarti PostMedJ 2009 Vironneau ICAAC 2012	N=14 N=14
Uncontrolled diabetes	To cure	gmCSF 250-425µg/d	C	III	Garcia-Diaz CID 2001	N=3, adjunctive to medical and surgical treatment

Population	Intent	Intervention	SoR	QoE	Reference	Comment
Haematology patients	To cure	Deferasirox 20 mg/kg/d, d1-14	4 C 9 D 3 abstain	II	Spellberg AAC 2009 Ibrahim JAC 2010 Spellberg JAC 2012	N=8 Animal N=20
Other than haematology	To cure	Deferasirox, any dose	C	III	No reference found.	
Any	To cure	Statins	C	III	Lukacs JCM 2004 Chamilos AAC 2006	Animal and in vitro
Glucocorticosteroids	To cure	Stop if feasible, if not: reduce steroid dose to minimum required	A	IIr	Lionakis Lancet 2003	
Any	To cure	Continue treatment until CR on imaging <u>and</u> permanent reversal of immunosuppression achieved	A	III	No reference found.	

# Hyperbaric Oxygen

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Non-haematologic	To cure	Exposure to 100% hyperbaric oxygen	C	II <sub>r</sub>	John CMI 2005 Roden CID 2005	N=28, primarily patients with correctable risk factors, i.e. diabetes, trauma
Haematologic	To cure	Exposure to 100% hyperbaric oxygen	C	III <sub>r</sub>	John CMI 2005 Roden CID 2005	N=3
poorly controlled diabetes	To cure	Hyperbaric oxygen	C	II <sub>u</sub>	Gamba Radiology 1986	N=5





# 6<sup>th</sup> TRENDS IN MEDICAL MYCOLOGY

11-14 October 2013, Copenhagen, Denmark