





Petrikkos - Mucormycosis

Mucormycosis



George Petrikkos, 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
Oliver A. Cornely	Germany
Eric Dannaoui	France
Andreas Groll	Germany
Katrien Lagrou	Belgium
Fanny Lanternier	France
Livio Pagano	Italy
Georgios Petrikkos	Greece
Anna Skiada	Greece

Imaging

Population	Intention	Method / Finding	SoR	QoE	Reference	Comment
Hematologic malignancy	To differentiate mucormycosis from invasive pulmonary aspergillosis	CT / reversed halo	B	II _u	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 _h	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 _h	Chamilos CID 2005 Marchiori Chest 2012	

Petrikkos - Mucormycosis

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	

Population		Intention	Intervention/Method	SoR	QoE	Ref.	Comment
Any		To diagnose	Direct microscopy preferably using optical brighteners	A	IIu	Lass-Flörl CID 2007 McDermott OralSurgOralMed OralPathoOralRadiolEndod 2010	Rapid diagnosis No identification to genus level Intraoperative assessment of clear margins
Any		To diagnose	Culture	A	IIIr	Ribes CMR 2000 Wang Mycoses 1990	Avoid grinding
Any		To diagnose	Histopathology	A	IIu	Chakrabarti Postgr Med J 2009 Ben-Ami J Infect 2009 Rüping JAC 2010 Skiada CMI 2011 Frater ArchPathLabMed 2001	
Any		To diagnose	Immunohistochemistry	C	IIu	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	IIu	Bialek J Clin Pathol 2005 Lass-Flörl CID 2007 Rickerts CID 2007	in house fresh material preferred over paraffin embedded
Any		To diagnose	Molecular based studies on <u>paraffin</u> slides	B	IIu	Bialek J Clin Pathol 2005 Dannaoui JCM 2010 Lass-Flörl CID 2007 Rickerts CID 2007 Hammond JCM 2011	in house

Petrikkos - Mucormycosis

Susceptibility Testing		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
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 know-ledge	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	not validated for mucormycosis

Genus and Species Identification		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
Population	Intention	Intervention/Method	SoR	QoE	Reference	Comment
Any	To guide treatment	Identification to genus level	C	IIu	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	IIu	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	IIu	Kontoyiannis JID 2005 Alvarez JCM 2009	N=19; ITS seq. Concordance 79%. Morphology not reliable N=190; ITS seq., Concordance 93%

Prophylaxis		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
Population	Intention	Intervention	SoR	QoE	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



Petrikkos - Mucormycosis

ESCMID		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
Diagnosis-driven Treatment – Timing						
Population	Intention	Intervention	SoR	QoE	Reference	Comm
Immune-compromised	To increase survival	Immediate treatment initiation	A	IIu	Chamilos CID 2008	N=70 Treatment initiation ≥ 6 days after symptoms onset: 2-fold increased week 12 mortality



ESCMID		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
Targeted Treatment – First Line						
Pop	Intention	Intervention	SoR	QoE	Reference	Comment
Any	To increase survival rates	Surgical debridement	A	IIu	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	IIu	Roden CID 2005 Greenberg AAC 2006 Skiada CMI 2010 Zaoutis PIDJ 2007	N=470 N=19 N=59 N=92, paediatric
Any	To cure and to increase survival rates	Amphotericin B, liposomal ≥ 5mg/kg	A	IIu	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



ESCMID		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
Targeted Treatment – First Line						
Pop	Intention	Intervention	SoR	QoE	Reference	Comment
Any, except CNS	To cure	Amphotericin B, lipid complex 5mg/kg	B	IIu	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	IIu	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

Petrikkos - Mucormycosis

 Targeted Treatment – Salvage  ESCMID FUNGAL INFECTION STUDY GROUP European Society of Clinical Microbiology and Infectious Diseases						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Refractory to prior antifungal therapy	To cure	Posaconazole 4x200mg/d or 2x400mg/d	A	II _u	Greenberg AAC 2006 van Burik CID 2006 Skiada CMI 2011 Vehreschild 2012 CRM	N=19 N=81* N=61 N=15*
Intolerant to prior antifungal	To cure	Posaconazole 4x200mg/d or 2x400mg/d	A	II _u	Greenberg AAC 2006 van Burik CID 2006 Vehreschild 2012 CRM	N=5 N=43* N=15*

*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.
*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.

 Targeted Treatment – Salvage  ESCMID FUNGAL INFECTION STUDY GROUP European Society of Clinical Microbiology and Infectious Diseases						
Population	Intent	Intervention	SoR	QoE	Reference	Comm
Intolerant to prior antifungal	To cure	Amphotericin B, liposomal, 5mg/kg	B	II _u	Pagano Haematol 2004	N=8
Refractory to prior antifungal therapy	To cure	Amphotericin B, lipid complex, 5mg/kg	B	II _u	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 _u	Larkin Inf Med 2003	N=12
Intolerant due to pre-existing renal disease	To cure	Amphotericin B, lipid complex, 5mg/kg	B	II _u	Larkin Inf Med 2003	N=18
Intolerant due to pre-existing renal disease	To cure	ABCD 5mg/kg	B	II _u	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  ESCMID FUNGAL INFECTION STUDY GROUP European Society of Clinical Microbiology and Infectious Diseases						
Population	Intention	Intervention	SoR	QoE	Reference	Com m
Haematological malignancy with ongoing neutropenia	To cure infection	gCSF, dose not reported	A	II _u	Pagano BJH 1997 Kontoyiannis CID 2000 Pagano Haematol 2004 Roden CID 2005 Kara IntJClinPract 2007 Pagano JChemoth 2009	N=8 N=12 N=18 N=18 N=5 N=8
Haematological malignancy with ongoing neutropenia	To cure infection	Granulocyte transfusion	C	II	Pagano Haematol 2004 Kontoyiannis CID 2000 Roden CID 2005	N=7 N=8 N=7
Haematological malignancy with ongoing neutropenia	To cure infection	Granulocyte transfusion + IFNy1b	C	III	Safdar Cancer 2006	N=4



Petrikkos - Mucormycosis

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
<ul style="list-style-type: none"> more likely to receive surgery less likely to have disseminated disease shorter treatment duration surgical should follow general rules, debridement until clear margins 							

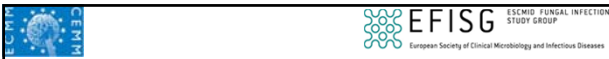
Population		Intent	Intervention	SoR	QoE	Reference	Comment
Uncontrolled diabetes		To cure	Control of hyperglycaemia and ketoacidosis	A	IIu	Lantemier CID 2012 Yohal Surv Ophthal 1994 Chakrabarti PostgradMedJ 2009 Roden CID 2005 Bhansali Postgrad Med J 2004 Rammaert Diabetes Metab 2012	N=23 N=87 N=15 N=337 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 and permanent reversal of immunosuppression achieved	A	III	No reference found.	

Petrikkos - Mucormycosis

  <small>ESCMID FUNGAL INFECTION STUDY GROUP</small> European Society of Clinical Microbiology and Infectious Diseases						
Hyperbaric Oxygen						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Non-haematologic	To cure	Exposure to 100% hyperbaric oxygen	C	II _r	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 _r	John CMI 2005 Roden CID 2005	N=3
poorly controlled diabetes	To cure	Hyperbaric oxygen	C	II _u	Gamba Radiology 1986	N=5

Arendrup - Rare yeast



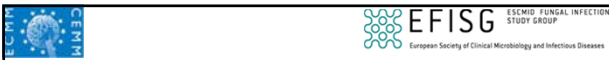
**ESCMID / ECMM Guideline
Diagnosis & Management of
Emerging Invasive Fungal Diseases**

Rare yeasts

Coordinators: Maiken C. Arendrup and Olivier Lortholary
Group members: M Akova & T Boek

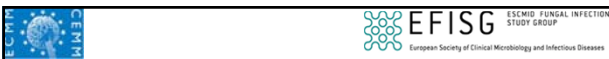
Guideline Conveners: Oliver A. Cornely & Jacques F. Meis

Guideline group participants: William Hope, Andrew J. Ullmann, Jesus Guinea, Sevtap Arikan-Akdagli, Anuradha Chowdhary, Arunaloke Chakrabati, Manuel Cuenca-Estrella¹, Eric Dannaoui, Andreas Groll, Josep Guarro, Sybren de Hoog, Elisabeth Johnson, Katrien Lagrou, Fanny Lanternier, Cornelia Lass-Flörl, Joseph Meletiadis, Patricia Munoz, Livio Pagano, George Petrikos, Malcolm D. Richardson, Emmanuel Roilides, Anna Maria Tortorano, Paul E. Verweij



Included species

- ✓ *Cryptococcus*
 - *adeliensis, albidus, curvatus, flavescens, laurentii* and *uniguttulatum*
- ✓ *Geotrichum*
 - *candidum* and *clavatum*
- ✓ *Kodamaea ohmeri*
- ✓ *Malassezia*
 - *furfur, globosa* , *pachydermatis* and *restricta*
- ✓ *Rhodotorula*
 - *glutinis, minuta* and *muclilaginoso*
- ✓ *Saccharomyces*
 - *cerevisiae* and *boulardii*
- ✓ *Trichosporon*
 - *osahii, asteroides, dermatis, inkin, jirovecii, loubieri, mucooides* and *mycotaxinivorans*
- ✓ *Magnusiomyces capitatus*





Excluded species

- *Cryptococcus*
 - *C. neoformans* & *C. gattii* -----> Not rare
 - *C. albidosimilis, C. diffluens, C. humicola* and *C. uzbekistanensis*
- *Trichosporon*
 - the 34+ other species not associated with human disease
- *Blastobotrys proliferans*
- *Millerozyma farinosa*
- *Ogataea polymorpha*
- *Guehomyces pullulans*
- *Torulaspora delbrueckii*
- *Pneumocystis jirovecii* -----> Not rare
- Rare/emerging *Candida* spp. excluded (Covered in the *Candida* guideline)
 - as defined by the anamorphic name

} Not shown to be relevant human pathogens

Arendrup - Rare yeast

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

Challenges/ limitations

- **Taxonomy and \pm correct species ID**
 - Uncertainty particularly for older literature
 - Eg. *Trichosporon beigeli*
 - Eg. *Magnusiomyces capitatus* >< *Blastoschistomyces capitatus* >< *Trichosporon capitatus* >< *Geotrichum capitatus*
- **No standardised Susceptibility tests or Breakpoints**
- **Case stories and smaller cohorts**
 - Publication bias (successes overrepresented? newer drugs bias'ed?)
 - Rare due to low virulence not rare per se
 - How to interpret "overall" outcome (did the patient die with or because of the inf)
- **Expert opinion...**
 - Despite mycology experts, limited → no personal experience

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

Challenges/ limitations

Common sense and pragmatism
Translated knowledge & experience from other IFI


Caution
Very few "A"s
Some "no recommendations"


- Despite mycology experts, limited → no personal experience


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

Diagnosis

Arendrup - Rare yeast

 Imaging						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
No specific imaging findings for other rare yeast infections. Hence, imaging should be performed following standard infectious disease management guidelines and according to focal symptomatology.						

 Surveillance cultures						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
FUO without response to AB	Early diagnosis of invasive <i>Trichosporon</i> infection	Surveillance culture	C	Ilu	Suzuki Eur J Haem 2010	Only 2/21 <i>Trichosporon</i> fungaemic patients were colonized before inv inf. However, after pos BC, surveillance cultures were also pos.
*Ei essential investigation						

 Direct Microscopy						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Any	To diagnose IFI	Direct microscopy preferably using optical brighteners	A	Ilu	Lass-Flöri CID 2007	Allows rapid (presumptive) diagnosis of fungal infection. Identification to genus and species level not possible.
Any	To diagnose cryptococcal CNS infection	India Ink staining of CSF	A	EI*		Capsule visualised around the cell. Allows rapid diagnosis of cryptococcal meningitis (when the infection organism is capsulate).
*Ei essential investigation						

Arendrup - Rare yeast

ESCM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
ESCM		EFISG		European Society of Clinical Microbiology and Infectious Diseases		
Blood culture						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
FUO without response to AB	Diagnose rare yeast fungaemia	Blood culture	A	EI*	Baron Cumitech 1C 2005, Cockerill CID 2004, Arendrup ECIL-3 BMT 2012, Arendrup SJD 1996	Volume of blood is essential. Adults: 40-60 ml either one venipuncture or separate right after each other. Repeated if signs and symptoms of fungaemia persists.
FUO without response to AB	Diagnose rare yeast fungaemia	Blood culture incl. mycosis bottle	B	II*	Arendrup JCM Jan 2011, Arendrup JCM Sep 2011, Horvath JCM 2004, Ericson DMID 2012, Cateau DMID 2012	Several studies have documented better yield for <i>Candida</i> and BACTEC and BacT/ALERT BC systems if a mycosis medium is included. Not shown specifically for rare yeasts.

EI: Essential investigation

ESCM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
ESCM		EFISG		European Society of Clinical Microbiology and Infectious Diseases		
Species specific culture procedures						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Immuno-compromised	Diagnose other cryptococci (non-neoformans; non-gattli)	Culture: Blood, CSF, respiratory specimen, pleural fluid. Use SDA 30-35 °C.	A	III	McCurdy 2003 Comp. Ther. Dromer, 2012 265 /id	Growt better at lower tp; <i>C. albidus</i> associated w summer-type hypersensitivity pneumonitis
Neonates, children and adults with CVC and lipid supplementation suspected of <i>Malassezia</i> fungaemia	Diagnose <i>Malassezia</i> BSI	BC: Isolator 10 Lysis centrifugation with subculture on lipid containing selective agar Or BC bottle supplemented with palmitic acid with prolonged incubation (2 weeks)	B	III	Marcon JCM 1986, Nelson JCM 1995, A. Velegaki in Tragiannidis et al. 2010	Performance of modern automated blood culture systems is not investigated. <i>M. pachydermatis</i> is not lipid dependent.
Neonates, children and adults with CVC and lipid supplementation suspected of <i>Malassezia</i> fungaemia	Diagnose inv <i>Malassezia</i> inf	Sterile specimens & pos BC: Use Sab overlaid with sterile olive oil, Dixon agar or other lipid containing agar for subculture	A	II	Arendrup 2009, CMI 2009, Gaitanis 2012, Clin. Microbiol. Rev. 25, 106, Kaneko JCM 2007	

ESCM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
ESCM		EFISG		European Society of Clinical Microbiology and Infectious Diseases		
Surrogate markers						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Immuno-compromised	Diagnose other cryptococci (non-neoformans; non-gattli)	Crypto Ag test	C	III	McCurdy Comp Ther 2003 Khawcharoenporn Infection 2007	Low sensitivity (4/17 positive in one cohort); neg test does not exclude cryptococcosis
		Galactomannan Ag	C	III	Dalle JCM 2005	Cross reaction demonstrated in a clin case and in vitro. However, sensitivity not examined.
		β-D-Glucan	D	II	Otabasi Med Mycol 2006	β-D-glucan is not part of the cryptococcal cell wall.

Arendrup - Rare yeast

EFISG		ESCMID FUNGAL INFECTION STUDY GROUP				
European Society of Clinical Microbiology and Infectious Diseases						
Surrogate markers						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
FUO without response to AB	Diagnose Inv. <i>M. capitatus</i>	Galactomannan Ag	C	III	Giacchino JCM 2006; Bonini Diagn Microbiol Infect Dis 2008	Cross reaction in a clinical case and in vitro. However sensitivity not examined.
FUO without response to AB	Diagnose Inv. <i>M. capitatus</i>	β-D-Glucan	C	III	Odabasi Med Mycol 2006	Culture supernatant positive but no clinical data.
FUO without response to AB	Diagnose Inv. <i>Rhodotorula</i>	β-D-Glucan	C	III	Odabasi Med Mycol 2006	<i>R. mucilaginosa</i> culture supernatant positive but no clinical data.

EFISG		ESCMID FUNGAL INFECTION STUDY GROUP				
European Society of Clinical Microbiology and Infectious Diseases						
Surrogate markers						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
FUO without response to AB	Diagnose inv <i>Saccharomyces</i>	β-D-Glucan	C	III	Yoshida J Med Vet Mycol 1997, Odabasi Med Mycol 2006	Single clinical case and culture supernatant positive
FUO without response to AB	Diagnose inv <i>Saccharomyces</i>	Platelia Mannan antigen	C	III	Rimek Mycoses 2004	Single clinical case and antigen similarity
FUO without response to AB	Diagnose Inv. <i>Trichosporon</i>	β-D-Glucan	D	III	Suzuki Eur J Haem 2010, Nakase Int J Inf Dis 2012, Kushima Int J Inf Dis 2012,	Sensitivity app. 50%, so not useful for <i>Trichosporon</i> , however, may be indicated for other reasons.
FUO without response to AB	Diagnose Inv. <i>Trichosporon</i>	Galactomannan Ag	B	II	Fekkar CID 2009	Pos test in clinical cases, in culture supernatant, and in experimental trichosporonosis (Cryp ag) Dual positivity suggestive. Sensitivity not examined
FUO without response to AB	Diagnose Inv. <i>Trichosporon</i>	Crypto Ag test	B	II	Fekkar CID 2009; Melcher JCM 1991, Lyman JCM 1995; Campbell Lancet 1995; MacManus 1985	

EFISG		ESCMID FUNGAL INFECTION STUDY GROUP				
European Society of Clinical Microbiology and Infectious Diseases						
Molecular-based Detection						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
FUO without response to AB	Diagnose Inv. rare yeast infection	ITS PCR and sequencing		No recommendation		No standardised test or external validation of in house tests


Arendrup - Rare yeast

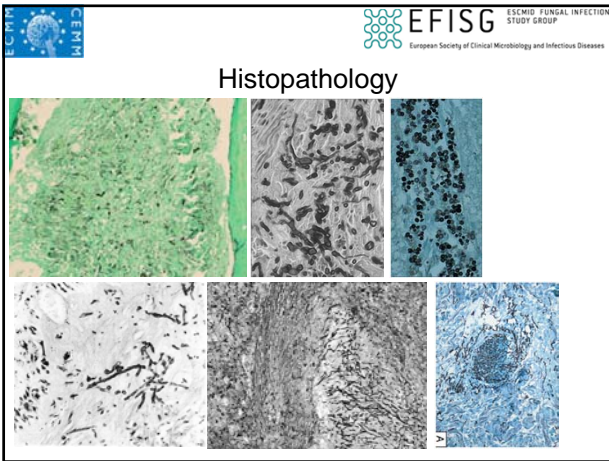
EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		European Society of Clinical Microbiology and Infectious Diseases		
Microbiology Susceptibility Testing 2						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Invasive <i>Cryptococcus</i> infection (other than <i>C. neoformans</i> & <i>C. gattii</i>)	To guide treatment	EUCAST/CLSI ref testing	C	III	McCurdy Comp. Ther. 2003; Rimek JCM 2004; Kordossis 1998; Kantarcioglu Medical Mycol. 2007 and Med. Mycol 2005; Kordossis Med mycol 1998; Burnik Med Mycol 2007; Pan Mycoses 2012; Johnson Mycoses 1998; Bauters Med Mycol 2001; McCurdy South Med J 2001; Averbuch Med Mycol 2002	Species dependent variation in susceptibility to 5-FC and fluconazole. Species ID may be difficult or delayed.
Invasive <i>Cryptococcus</i> infection (other than <i>C. neoformans</i> & <i>C. gattii</i>)	For epidemiological purposes	EUCAST/CLSI ref testing	B	II		

EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		European Society of Clinical Microbiology and Infectious Diseases		
Susceptibility Testing 1						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
<i>Trichosporon</i> Inv infection	To guide treatment	EUCAST/CLSI ref testing	C	II	Rodriguez-Tudela AAC 2005, Araujo Ribeiro Rev Ibero Micol 2008, Zaragoza AAC 2011	Spp. specific susceptibility patterns, ID difficult by conventional methods. But no breakpoints for these spp.
<i>Trichosporon</i> Inv infection	For epidemiological purposes	EUCAST/CLSI ref testing	B	II	Rodriguez-Tudela AAC 2005, Araujo Ribeiro Rev Ibero Micol 2008, Zaragoza AAC 2011	Limited data suggest species specific differences in susceptibility. More data necessary and might help future treatment choice before susceptibility testing is available
<i>Malassezia</i> inv infection	To guide treatment	Modified susceptibility testing	D	II	Tragiannidis 2009; Velegraki in Tragiannidis et al. 2010; Gupta Br J Derm 2000; Garau AAC 2003; Sugita JCM 2005; Rincon JCM 2006; Velegraki JCM 2004; Miranda IJAA 2007; Prado JMM 2008; Jesus Vet Micro 2011.	No standardises susceptibility tests and no breakpoints established. Significant variation and broad MIC ranges. Resistance to azoles for <i>M. pachydermatis</i> also published by Nijima et al. 2011, Vet. Microb. 149, 288-290.

EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		European Society of Clinical Microbiology and Infectious Diseases		
Conventional Species Identification						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
<i>Trichosporon</i> Inv infection	To guide treatment	Phenotypic species ID (Incl commercial systems)	D	II	Rodriguez-Tudela AAC 2005	Only valid to the genus level. Species specific differences in susceptibility
<i>Malassezia</i> Inv infection	To guide treatment and gain more experience with spp related differences	Tween utilization, growth at 32, 37 and 40C, Cremophor EL utilization, beta-glucosidase activity and catalase activity;	C	II	Galatanis Clin Microbiol Rev 2012; Gueho-Kellerman 2010; Sugita 2010; Gupta JCM 2004	Misidentification rate of 13.8% when comparing traditional ID with sequencing methods (Gupta)
<i>Malassezia</i>	Identification <i>M. pachydermatis</i>	Growth on SDA	B	II	Galatanis et al. 2012. Clin. Microbiol. Rev. 25: 106	<i>M. pachydermatis</i> may be less susceptible to azoles

Arendrup - Rare yeast

 EFISG ESCMID FUNGAL INFECTION STUDY GROUP European Society of Clinical Microbiology and Infectious Diseases					
Molecular-based Identification					
Intention	Intervention	SoR	QoE	Reference	Comment
Identify <i>Cryptococcus</i> isolates	D1D2 domains and/or ITS 1+2 regions of rDNA	B	II	Fonseca The yeasts, a taxonomic study 2011; Rimek JCM 2004; Tintelnot JCM 2005	MALDI-TOF is a promising alternative, but performance depend on the database
Identify <i>Trichosporon</i> isolates	IGS1 sequencing	B	II	Araujo Rev Iberoam Micol 2008; Rodriguez-Tudela AAC 2005; Sugita JCM 2002	ITS sequencing sufficient for Genus ID but not species ID.
Identify <i>Malassezia</i> isolates	ITS rDNA sequencing; IIS and restriction analysis; D1D2 sequencing; D1D2 and restriction analysis; or Luminex platform using rDNA sequences	B	II	Galatani Clin Microbiol Rev 2012; Guillot Antonie Van Leeuwenhoek 1995; Sugita Med Mycol 2010; Gupta JCM 2004	Species ID important for epidemiological purposes (particularly in suspected outbreaks). MALDI-TOF is a promising alternative, but performance depend on the database
Identify <i>Geotrichum</i> & <i>Magnusiomyces</i>	D1D2 domains and/or ITS 1+2 regions of rDNA	B	II		MALDI-TOF is promising, but performance depend on the database



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


Arendrup - Rare yeast


Population		Intention	Intervention	SoR	QoE	Reference	Comment
Rare yeasts are rare – thus no indication for specific primary prophylaxis. Most rare yeasts are covered by standard <i>Aspergillus</i> prophylaxis (exception: <i>Rhodotorula</i>). No specific primary prophylaxis against cryptococcosis in Europe.							
Immunosuppressed, prior diagnosis of invasive rare yeast infection	To prevent recurrence, „secondary prophylaxis“	Last drug effective in the same patient					
Immunosuppressed	To prevent <i>S. boulardii</i> infection	Avoid probiotics containing <i>S. boulardii</i>	A	II	Thygesen BMI Case Reports 2012; Stefanatou Mycoses 2011; Bassetti Am J Med 1998; de Llanos International Journal of Food Microbiology 2006; Herbrecht CID 2005; Munoz CID 2005		
	To prevent <i>Malassezia</i> , <i>Rhodotorula</i> , <i>Kodamaea ohmeri</i>	Scrupulous adherence to standard hygienic measure	A	II	Gaitanis et al. 2012 (Mal), Chang NEJM 1998 (Mal); Khodavaisy, J Prev Med Hyg 2011; 52: 215-8. (Rho) Elias. J Egypt Public Health Assoc 2009; 84: 169-81. (Rho); Pernicelli Eur J Clin Micro Inf Dis 2006 (Rho outb), Chakrabarti Submitted	Have been isolates from the hands of health care workers and associated with outbreaks	


Population		Intention	Intervention	SoR	QoE	Reference	Comment
No recommendation can be given because of a lack of evidence.							

Population		Intention	Intervention	SoR	QoE	Reference	Comment
If institutional epidemiology demands rare yeasts to be part of the antifungal spectrum, refer to drugs used for targeted treatment.							

Arendrup - Rare yeast

 Diagnosis-driven Treatment – Timing						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
No data available. Early treatment presumably warranted.						

 Targeted Treatment – Antifungals- first line 1						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
<i>Cryptococcus</i> other than <i>C. neoformans</i> & <i>C. gattii</i>	CNS & severe inf. Induction	Amphotericin (±flucytosine*)	B	III	Khawcharoenporn Infection 2007; McCurdy Compr Ther 2003; Pan Mycoses 2012; Bernal-Martinez Med Mycol 2010; Serena AAC 2004;	MICs for 5-FC, fluco & other azoles often elevated and particularly so for <i>C. albidus</i> , <i>C. laurentii</i> and <i>C. uniguttulatum</i>
	CNS & severe inf. Consolidation	Fluconazole ≥ 400 mg/d	C	III	Quindos Rev Iberoam Micol 2004; Shimokawa JCM 2005; Pedrosa Mem Inst Oswaldo Cruz 2006; Kordosis Med Mycol 1998;	
	Non-CNS, not severe inf.	Fluconazole ≥ 400 mg/d	C	III	Garcia-Martos Med Clin (Barc) 2002;	MICs for 5-FC, fluco & other azoles often elevated and particularly so for <i>C. albidus</i> , <i>C. laurentii</i> and <i>C. uniguttulatum</i> . May be preferable to fluconazole for the less azole susceptible species
	Non-CNS, not severe inf.	Amphotericin	C	III		
	Any	Echinocandins	D	II		Intrinsically resistant

 Targeted Treatment – Antifungals- first line 1						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
<i>Geotrichum</i> inv inf	cure	Amphotericin B ± 5-FC	B	III		Preferred agent is amphotericin B (w/wo 5-FC), but as data is scarce we do not give an A recommendation
<i>Geotrichum</i> inv inf	cure	Fluconazole	-	-		No data
<i>Geotrichum</i> inv inf	cure	Voriconazole	-	-		No data
<i>Geotrichum</i> inv inf	cure	Echinocandins	D	II		Level of evidence based on in vitro susceptibility testing demonstrating intrinsic resistance

Arendrup - Rare yeast

Population		Intention	Intervention	SoR	QoE	Reference	Comment
K. ohmeri inv inf		cure	Amphotericin B	B	III	Taj-Aldeen J Med Microbiol 2006; De Barros Med Mycol 2009; Yang J Infect Dis 2009; Al-Sweih Med Mycol 2011	Most (but limited) clinical experience w amphotericin B;
K. ohmeri inv inf		cure	Fluconazole	C	III	Chakrabarti submitted 2013; Yang J Infect Dis 2009; Santino Mycoses 2013	Elevated MICs for some isolates. Fluconazole successful in 5/6 paediatric cases, in 1/1 adult immunocompromised patient case (fluconazole followed by itraconazole) unsuccessful in one adult case of cellulitis [70,74,78].
K. ohmeri inv inf		cure	Echinocandins	C	III	Chiu Int J Antimicrob Agents 2010; Shaaban Mycopathologia 2010	Two case reports showed successful outcome for one patient each on micafungin and caspofungin respectively (MICs higher than for C. albicans)
K. ohmeri inv inf		cure	Voriconazole	-	-		No data

Population		Intention	Intervention	SoR	QoE	Reference	Comment
M. capitatus inv inf		cure	Amphotericin B ± 5-FC	B	III	Cofrancesco Mycoses 1995; Gadea JCM 2004; DeMaio, CID2000	Most (but limited) experience. In vitro susceptibility of amphotericin B in the intermediate range, failures in hepatosplenic infections reported on amphotericin B monotherapy.
M. capitatus inv inf		cure	Voriconazole	B	III	Gadea JCM 2004	Less data available, but promising in vitro susceptibility
M. capitatus inv inf		cure	Fluconazole	-	-	Serena Int J Antimicrob Agents 2007	In vitro resistant - but animal model data suggest activity
M. capitatus inv inf		cure	Echinocandins	D	II	Chittick AAC 2009; Schuermans Med Mycol 2011	Level of evidence based on in vitro susceptibility testing demonstrating intrinsic resistance and on case reports documenting breakthrough infections on an echinocandin.

Population		Intention	Intervention	SoR	QoE	Reference	Comment
Rhodotorula inv infection		To cure	Amphotericin ± 5FC	A	III	Nunes AAC 2013, Diekema JCM 2005, Garcia-Suarez Mycoses 2010	In vitro susceptible, Amphotericin associated with good outcome in clinical practice.
Rhodotorula inv infection		To cure	Echinocandin	D	II	Nunes AAC 2013, Diekema JCM 2005, Mori Transpl Inf Dis 2011, Garcia-Suarez Mycoses 2011a; Garcia-Suarez Mycoses 2011b; Mori transpl Inf Dis 2012	High MICs, breakthrough inf on fluconazole and echinocandin common.
Rhodotorula inv infection		To cure	azoles	D	II	Nunes AAC 2013, Diekema JCM 2005, Mori transpl Inf Dis 2012	High MICs (fluconazole >32 and voriconazole MIC50 of 2 mg/L), breakthrough inf on fluconazole and echinocandin common.

Arendrup - Rare yeast

EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		European Society of Clinical Microbiology and Infectious Diseases		
Targeted Treatment – Antifungals- first line 3						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Saccharomyces inv infection	To cure	amphotericin B	B	III	Enache-Angoulvant CID 2005	Most clinical experience; toxicity risk higher than for echinocandins
Saccharomyces inv infection	To cure	Echinocandin	B	III	Lolis Crit Care 2008, Choi Br J Haem 2012, Enache-Angoulvant CID 2005, Arendrup JCM 2011, Andes CID 2012	Two successful cases in the literature (+&-neutropenic), no emergence of <i>S. cerevisiae</i> after intro of echinocandins as first line agents for candidaemia, two recent failure cases neutropenic (unpublished data)
Saccharomyces inv infection	To cure	amphotericin B + 5-FC	C	III	Tiballi DMID 1995; Hamoud IMAJ 2011; Richter JAM 2004; Tompson JAC 2009; Quindos Rev Ibero Micol 2004	Excellent in vitro susceptibility. May be used in severe cases or when penetration into an infected focus is challenging.
Saccharomyces inv infection	To cure	Fluconazole	D	III	Enache-Angoulvant CID 2005, Arendrup JCM 2011	Lower success rate compared to amphotericin B. Increased occurrence in patients exposed to fluconazole. High fluconazole MICs (similar to those for <i>C. glabrata</i>)

EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		European Society of Clinical Microbiology and Infectious Diseases		
Targeted Treatment – Antifungals- first line 1						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Trichosporon inv inf	cure	Voriconazole	B	III	Suzuki Eur J Haem 2010; Asada CID 2006; Fournier Eur J Clin Micr Inf Dis 2002; Serena AAC 2006; Matsue CID 2006	Survival sign higher in pts receiving azole containing therapy (OR death 4.49 if non azole, P 0.0064). Good in vitro activity. Efficacious in exp trichosporonosis.
Trichosporon inv inf	cure	Fluconazole	C	III	Suzuki Eur J Haem 2010; Girmenia JCM 2005; Ruan CID 2009;	Most experience and data is with fluconazole
Trichosporon inv inf	cure	Echinocandin	D	II	Suzuki Eur J Haem 2010, Araujo Ribeiro Rev Ibero Micol 2008, Rodriguez-Tudela AAC 2005, Bayramoglu Infection 2008, Matsue CID 2006	Breakthroughs on caspofungin and micafungin and as below. No in vitro efficacy.
Trichosporon inv inf	cure	Amphotericin	D	III	Walsh JCM 1990; Hoy Rev Infect Dis. 1986; Girmenia JCM 2005; Serena AAC 2006; Gabriel Med Mycol 2011; Marty JCM 2003; Ruan CID 2009	Several spp. display low in vitro susceptibility. Poor outcome for amphotericin in case series and exp models

EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		European Society of Clinical Microbiology and Infectious Diseases		
Targeted Treatment – Antifungals- first line 4						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Malassezia inv inf in unstable pt	Cure	Amphotericin	B	III	Tragiannidis Mycoses 2009; Gaitanis Clin Microbiol Rev 2012	
Malassezia inv infection	Cure	Fluconazole	B	III	Tragiannidis Mycoses 2009; Gaitanis Clin Microbiol Rev 2012	14 days after last positive blood culture and resolution of symptoms; initial IV to oral therapy depending patient's clinical response
Malassezia inv infection	Cure	Voriconazole	C	III	Tragiannidis Mycoses 2009; Gaitanis Clin Microbiol Rev 2012	No comparison with amphotericin or fluconazole in vivo. In general MICs are lower for voriconazole compared to fluconazole, however, so is the exposure, particularly in the paediatric population. More side effects and interactions and is not licensed for neonates.
Malassezia inv infection	Cure	Echinocandins	D	III	Tragiannidis Mycoses 2009; Gaitanis Clin Microbiol Rev 2012	Intrinsically resistant

Arendrup - Rare yeast

ESCM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		European Society of Clinical Microbiology and Infectious Diseases	
Targeted Treatment – Antifungals- first line 4							
Population	Intention	Intervention	SoR	QoE	Reference	Comment	
Sporobolomyces inv inf	Cure	Amphotericin	-	-	Serena AAC 2004; Espinel-Ingroff JCM 1998	Insufficient data, scarce in vitro testing suggests susceptibility but no clinical data in the literature	
Sporobolomyces inv inf	Cure	Voriconazole	-	-	Serena AAC 2004; Espinel-Ingroff JCM 1998	Insufficient data, scarce in vitro testing suggests susceptibility but no clinical data in the literature	
Sporobolomyces inv inf	Cure	Fluconazole	D	II	Serena AAC 2004; Espinel-Ingroff JCM 1998	Level of evidence based on in vitro susceptibility testing demonstrating intrinsic resistance	
Sporobolomyces inv inf	Cure	Echinocandins	D	II	Serena AAC 2004; Espinel-Ingroff JCM 1998	Level of evidence based on in vitro susceptibility testing demonstrating intrinsic resistance	



ESCM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		European Society of Clinical Microbiology and Infectious Diseases	
"non-drug-related interventions"							
Population	Intention	Intervention	SoR	QoE	Reference	Comment	
CVC related rare yeast	Clear the infection	CVC removal		II	Galtanis et al. 2012; Tragiannidis et al. 2009, Mycoses 53, 187-195 (Malassezia)	Rare yeast inf except <i>C. neoformans</i> have been strongly associated with CVC in place	

TIMM Trends in Medical Mycology
www.TIMM2013.org

6th TRENDS IN MEDICAL MYCOLOGY

11-14 October 2013, Copenhagen, Denmark



Tortorano - Hyalohyphomycosis

Working Module on Hyalohyphomycosis



1. Epidemiology & Prevention
2. Diagnosis & In vitro susceptibility
3. Antifungal treatment
4. Adjunctive treatment

Tortorano Anna Maria, Richardson Malcolm, Roilides Emmanuel, van Diepeningen Anne, Caira Morena, Muñoz Patricia, Johnson Elizabeth, Meletiadiis Joseph, Pana Zoe-Dorothea, Lackner Michaela, Paul Verweij, Thomas Freiburger, Lass-Flörl Cornelia

Laboratory diagnosis/Conventional Methods/*Fusarium species*

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Any	To diagnose	Direct microscopy	A	III	Nucci CMR 2007	Positive direct microscopy supports growth in culture
Any	To diagnose	Culture	A	III	Nucci CMR 2007 Dignani CMI 2004	<i>Fusarium spp.</i> easily recovered on routine mycological media without cycloheximide. Caution in interpretation of growth (possible contamination) Blood cultures have a high yield. Easily isolated from skin biopsy (frequent metastatic skin lesions) Isolation of <i>Fusarium</i> in culture needed for a definitive diagnosis in presence of hyphae in tissue.

Laboratory diagnosis/Conventional and molecular methods/*Fusarium species*

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Any	To diagnose	Histopathology	A	III	Guarner CMR 2011	Hyaline septate acute angle branching hyphae similar to those of <i>Aspergillus</i> . Histopathology cannot provide fungal genus and species.
Any	To diagnose	Immuno-histochemistry	C*	III*	Guarner CMR 2011	Reagents for detection of <i>Fusarium spp.</i> in tissue are not commercially available Not yet evaluated (for specialised Labs)
Any	To diagnose	FFPE in situ hybridization	C	III	Hayden, 2003 Montone 2009	In house; SE low. Differentiate <i>Aspergillus</i> from <i>Fusarium</i>

* It is difficult to recommend a technique that is not validated/commercially available, but additional methods are welcome.

Tortorano - Hyalohyphomycosis

Population		Intention	Intervention	SoR	QoE	Reference	Comment
Any		To diagnose	Glucan test/ Galactomannan	B	III	Tortorano JCM 2012	Glucan usually positive in case of invasive infection, but cannot distinguish <i>Fusarium</i> infection from other mycoses <i>Aspergillus</i> galactomannan is sometimes positive in patients with fusariosis, GM may be useful to follow pts


Population		Intention	Intervention/Method	SoR	QoE	Reference	Comment
Immunocompromised pts		To diagnose	Panfungal qPCR ; 28S target	B	II	Landlinger Leukemia 2010	In house; SE 96%, SP 77%
Any		To diagnose	Panfungal semi-nested ITS2 PCR + AFLP	B	III	Landlinger EJCMID 2009	In house
Neutropenic patients		To diagnose	Multiplex ITS1 PCR + DNA microarray hybridization	C	III	Spies JCM 2007	In house
Any		To diagnose	Multiplex tandem PCR on blood	C	III	Lau JCM 2008	In house
Any		To diagnose	Nested PCR on tissue, BAL, serum	C	III	Ahmad Mycoses 2008	In house, mouse model
Any		To diagnose	Specific PCR	C	III	Hue JCM 1999	In house; not sufficiently specific
Any		To diagnose	Duplex qPCR on tissue and serum	C	III	BernaMartinez Med Myc 2012	Mouse model, lower sensitivity for <i>F. oxysporum</i>

* It is difficult to recommend a technique that is not validated/commercially available.


Population		Intention	Intervention/Method	SoR	QoE	Reference	Comment
Any		Species identification	Morphology	A	III	Alcazar-Fuoli 2008	Identify to the genus or 'species-complex' level
Any		Species identification	MALDI-TOF	C	III	Marinach CMI 2009 DeCarolis CMI 2012	Identification highly dependent of database
Any		Species identification	DNA MLST (EF-1alpha, RPB1, RPB2 targets)	A	II	O'Donnell JCM 2010	Web-accessible database, 69 species covered
Any		Species identification	Genus specific PCR 28S rDNA sequencing	C*	III	Hennequin JCM 1999	In house


* It is difficult to recommend a technique that is not validated/commercially available.

Tortorano - Hyalohyphomycosis

 ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES						
Microbiology Susceptibility Testing/ <i>Fusarium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Any	In vitro susceptibility	MIC: EUCAST ref. method	B*	III	EUCAST website	Validated only for <i>Candida</i> and <i>Aspergillus</i>
Any	In vitro susceptibility	MIC: CLSI ref. method	B*	II	M38-A2	<i>Fusarium</i> can be tested.
Any	In vitro susceptibility	MIC: Etest	B*	III	Debourgogne EJCMI 2012	AmB and VCZ vs. CLSI: Agreement 73% AmB and 92% VCZ.
Any	In vitro susceptibility	MIC: Sensititre	B*	III	Linares JCM 2005	97-98% agreement with CLSI (few isolates).
Any	In vitro susceptibility	Clinical breakpoint determination	B*	III	M38-A2	Yet to be identified or approved by CLSI or any regulatory agency.

* MIC gives an overview of in vitro resistance and therefore may support choice of antifungals. CLSI method for guidance on treatment; other tests for epidemiology only

 ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES						
Treatment/ <i>Fusarium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Immunocompromised pts (Hematol. & HSCT) with disseminated infection	First line treatment	Voriconazole ADULTS Loading dose 6 mg/kg q12h IV (first 24 h) then 4 mg/kg q12h (3 days), then possible oral therapy (200 mg q12) CHILDREN <13 yrs 7 mg/kg q12h >12yrs 200mg q12h	A	II	Perfect CID 2003 Lortholary AAC 2010 Campo J Infect 2010 Rojas MJHID 2012 Peman Ther Clin Risk Manag 2006 ECIL 4 Guidelines 2011	Initial or salvage treatment: 47% complete/partial response. Breakthrough infection reported in pts receiving prophylaxis. Therapeutic drug monitoring required

 ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES						
Treatment/ <i>Fusarium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Immunocompromised pts	First line treatment	Liposomal AMB	B	II	Nucci Cancer 2003 Jensen CMI 2004 Musa Br J Haematol 2000	Isolates often AMB resistant Reported superior to AMB Consider higher doses
Immunocompromised pts	First line treatment	AMB lipid complex	C	III	Patterson Clin Pediatr 1996	Isolates often AMB resistant Limited case reports
Immunocompromised pts	First line treatment	Conventional AMB	D	II	Nucci Cancer 2003 Jensen CMI 2004 Musa Br J Haematol 2000	Isolates often AMB resistant Breakthrough infections during empirical treatment Prognosis dismal unless PMN count recovers
Immunocompromised pts	First line treatment	Candins	D	III	Nucci CID 2004 Rojas MJHID 2012	Intrinsically resistant
Immunocompromised pts	First or second line treatment	Combination Therapy: LAMB + CAS LAMB + VOR VORI + CAS	C	III	Rojas MJHID 2012 Campo J Infect 2010 Lortholary AAC 2010	LAMB + candin or triazole: unclear if combination is more effective than drug alone Combination no better than VORI alone

Tortorano - Hyalohyphomycosis

ESCMID		ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES				
Treatment/ <i>Fusarium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Immunocompromised pts (hematological malignancies & HSCT)	Second line treatment	Posaconazole: 800 mg/d in 2 or 4 divided doses TDM	A	II	Raad CID 2006 Campo J Infection 2010	Approved for salvage treatment (48% complete/partial response). Breakthrough infection during prophylaxis.
Immunocompromised pts	Second line treatment	Voriconazole TDM	A	III	Baden Transplantation 2003	Substantial efficacy and acceptable level of toxicity

ESCMID		ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES				
Granulocyte Transfusions/Cytokine Treatment/ <i>Fusarium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Hematological Cancer	To improve response to infection	Cytokine-stimulated granulocyte transfusion + antifungals	B	II _t	Boutati EI Blood 1997	Resolution only in pts who recovered of myelosuppression
Neutropenic patients	To improve response to infection	Granulocyte transfusion	B	III _t	Dignani Leukemia 1997	3 pts included
Granulocytopenic patients	To improve response to infection	Granulocyte transfusion + other interventions	B	III _t	Spielberger Clin Infect Dis 1993	1 patient only
Leukemia	To improve response to infection	Granulocyte transfusion	B	III _t	Helm Am Acad Dermatol 1990	1 patient only

ESCMID		ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES				
Granulocyte Transfusions/Cytokine Treatment/ <i>Fusarium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Granulocytopenic patients	To improve response to infection	GM-CSF (combined with antifungals)	B	III _t	Spielberger Clin Infect Dis 1993	1 patient
Leukemia	To improve response to infection	GM-CSF (combined with antifungals)	B	III _t	Helm J Am Acad Dermatol 1990	1 patient

Tortorano - Hyalohyphomycosis

ESCMI		ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES				
Surgical Debridement/ <i>Fusarium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Leukemia/BM TX	To cure infection	Surgey	A	III ₁	Lupinetti, Ann Thorac Surg 1990 Lupinetti, J Thorac Card Surg 1992	Successful outcome in pulmonary infections
Any	To cure solitary lung nodules	Surgery	A	II _r	Nucci CMR 2007	Independent protective factor
Any	To cure osteomyelitis	surgical debridement	A	III	Many case reports	Aggressive surgical debridement of necrotic tissue needed Poor outcome
Any	To cure catheter-related infection	Catheter removal + DAMB or LAMB	A	II	Velasco Eur. J. Clin. Micro. Infect. Dis. 1995	4/4 survival

ESCMI		ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES				
Laboratory diagnosis/Conventional Methods/ <i>Scedosporium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
All	To diagnose	Direct microscopy	A	III	Cortez CMR 2008	Positive direct microscopy supports significance of growth in culture
Immunocompromised pts	To diagnose	Culture	A	III	Cortez CMR 2008	Isolation (growth in 3-4 days) from respiratory tract and sinuses; soft tissues (hematogenous dissemination), bone, blood; mainly <i>S. prolificans</i>
Near-drowning victims	To diagnose	Culture	A	III	Cortez CMR 2008	<i>S. apiospermum</i> / <i>P. boydii</i> isolated from aspiration or surgical drainage of brain abscesses (rarely from respiratory secretions or CSF)

ESCMI		ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES				
Laboratory diagnosis/Conventional Methods/ <i>scedosporium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Cystic fibrosis pts	To diagnose	Culture	A	III	Borman MedMyc 2010	Repeated isolation of <i>Scedosporium</i> accepted as indicator of colonization <i>S. apiospermum</i> may contribute to inflammatory reaction and progressive deterioration of lung function. Disseminated infection if pts are immunosuppressed (lung transplant)
			A	III	Horré Mycoses 2010	
Cystic fibrosis pts	To diagnose	Culture	A	III	Cimon EJCMID 2000	Selective media supplemented with cycloheximide or benomyl (10 µg/ml, Sce-Sel+) allows growth of <i>Scedosporium</i> over other filamentous fungi from bronchial secretions
					Summerbell JCM 1993	
					Rainer AVanLeeu 2008	
					Horré Mycoses 2010	
					Borman MM 2010	
						SceSel+ agar (supplemented with benomyl and dichloran)

Tortorano - Hyalohyphomycosis

ESCMID		ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGISTS AND INFECTIOUS DISEASES					
Laboratory diagnosis/ <i>Scedosporium species</i>							
Population	Intention	Intervention	SoR	QoE	Reference	Comment	
Any	To diagnose	Histopathology	A	III	Guarner CMR 2011	Hyaline thin-walled septate hyphae, 2-5 µm wide similar to those seen with aspergillosis and other agents of hyalohyphomycosis.	
Any	To diagnose	In situ hybridization on FFPE	C*	III	Hayden Diagn Mol Pathol 2003 Montone Am J Clin Pathol 2009	In house; diff. <i>Aspergillus</i> spp., <i>Fusarium</i> spp. and <i>Pseudallescheria</i> spp., but low sensitivity for <i>Fusarium</i> and <i>Pseudall.</i> In house; diff. <i>Aspergillus</i> spp. from <i>Fusarium</i> spp.	
* It is difficult to recommend a technique that is not validated/commercially available, but additional investigational methods can be helpful when available.							

ESCMID		ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGISTS AND INFECTIOUS DISEASES					
Laboratory diagnosis/Adjunctive Assays/ <i>Scedosporium species</i>							
Population	Intention	Intervention/Method	SoR	QoE	Reference	Comment	
Any	To diagnose	Panfungal PCR (ITS1 target) + sequencing on fresh tissues/FFPE	B*	III	Lau JCM 2007	In house	
Immunocompromised pts	To diagnose	Panfungal qPCR ; 28S target	B	II	Landlinger Leukemia 2010	In house; SE 96%, SP 77%	
Any	To diagnose	Panfungal semi-nested ITS2 PCR + AFLP	B	III	Landlinger EJCMI 2009	In house	
Neutropenic patients	To diagnose	Multiplex ITS1 PCR + DNA microarray hybridization	C	III	Spieß JCM 2007	In house	
Any	To diagnose	Multiplex tandem PCR on blood	C	III	Lau JCM 2008	In house	
Any	To diagnose	Multiplex PCR + liquid-phase array	C*	III	Buelow Med Myc 2012	Lower specificity due to primer cross-reactivity	
* It is difficult to recommend a technique that is not validated/commercially available, but additional investigational methods can be helpful when available.							
There are panfungal molecular studies in which agents of hyalohyphomycosis are reported to be covered. Molecular tests should be used in combination with conventional laboratory tests; possibility of 2 consecutive samples required; careful check for							

ESCMID		ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGISTS AND INFECTIOUS DISEASES					
Laboratory diagnosis/Identification/ <i>Scedosporium species</i>							
Population	Intention	Intervention/Method	SoR	QoE	Reference	Comment	
Any	Species identification	Morphological and physiological key characters	A	III	Gilgado JCM 2008	Morphology + carbohydrates assimilation: differentiate <i>P. boydii</i> and relative (clade 5), <i>P. minutispora</i> , <i>S. apiospermum</i> , <i>S. aurantiacum</i> , <i>S. dehoogii</i> , <i>S. prolificans</i>	
Any	Species identification	MALDI-TOF	C	III	DelChierico Proteomics 2012 Coulibaly Med Mycol 2011	Highly dependent of database	

Tortorano - Hyalohyphomycosis

Laboratory diagnosis/Molecular-based Identification/ <i>Scedosporium</i> species						
Population	Intention	Intervention/Method	SoR	QoE	Reference	Comment
Any	Species identification	ITS and β -tubulin sequencing	A	III	deHoog, Mycoses '11	Needed for a reliable identification
Any	Species identification	Rolling circle amplification (ITS target)	C*	III	Lackner Appl Env Microb 2011 Zhou JCM 2008	<i>P. ellipsoidea</i> , <i>P. fusoides</i> not distinguished. <i>S. apiospermum</i> and <i>S. prolificans</i> included
Any	Species identification	AFLP	C*	III	Lackner Mycoses '11	60 clinical isolates tested*
Any	Species identification	LAMP vs. qPCR vs. PCR-based reverse line blot (RBL); BT2 target	C*	III	Lu JCM 2011	LAMP the best for species distinguishing*
Any	Species identification	Repetitive sequence-based PCR	C*	III	Steinmann Med Myc 2011	Not sufficiently specific for <i>P. boydii</i> and <i>S. apiospermum</i> *
Any	Species identification	AFLP vs. species-specific PCR-RFLP; ITS and BT2 targets	C*	III	Lackner Med Myc 2012	New taxonomy of <i>P. boydii</i> complex considered

* It is difficult to recommend a technique not commercially available, but additional investigational methods can be helpful: for use in specialised laboratories
*New taxonomy of *P. boydii* complex considered

Microbiology Susceptibility Testing/ <i>Scedosporium</i> species						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Any	In vitro susceptibility	MIC distribution according to spp.	A	III	Lackner AAC 2012 Castanheira AAC 2012	In vitro susceptibility may differ within and between <i>Scedosporium</i> sp.
Any	In vitro susceptibility	MIC: EUCAST ref. method	A	III	EUCAST website	Validated only for <i>Candida</i> and <i>Aspergillus</i>
Any	In vitro susceptibility	MIC: CLSI ref. method	A	II	CLSI M38-A2 document	<i>P. boydii</i> (<i>S. apiospermum</i>) and <i>S. prolificans</i> can be tested.
Any	In vitro susceptibility	MIC: Sensititre	B	III	CarrilloMuñoz Mycoses 2006 JC 2004 Linares JCM 05	98% agreement with CLSI M38-A, (few isolates tested)
Any	In vitro susceptibility	Breakpoint determination	B	III	M38-A2 document	Yet to be identified.
Any	Correlation MIC - outcome	In vivo models of infection	C	III	Rodríguez AAC 2010 Guarro IAC 11	VCT, POS: good in vitro-in vivo correlation

Susceptibility testing gives an overview of in vitro resistance and therefore may support choice of antifungals.

Treatment/ <i>Scedosporium</i> species						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Immunocompromised pts	First line treatment	Voriconazole	A	II	Many case reports	Success in 66%. Lowest response in CNS or disseminated infections. TDM recommended!
Immunocompromised pts	First line treatment	Combined therapy: VOR+ LAMB VOR +CASPO	C	III	Case reports	Unclear if combination is more effective than either drug alone
Immunocompromised pts	First or second line treatment	LAMB	C	III	Husain CID 2005 Heath CMI 2009	AMB lower efficacy compared to VOR LAMB less active in vitro against all three <i>Scedosporium</i> spp. compared to VOR
Immunocompromised pts	First or second line treatment	AMB	D	III	Heath CMI 2009	<i>S. apiospermum</i> and related species are usually resistant. Prognosis poor unless neutrophil count recovers

Tortorano - Hyalohyphomycosis

ESCMID		Treatment/ <i>Scedosporium species</i>					
Population	Intention	Intervention	SoR	QoE	Reference	Comment	
Near-drowning victims	First line Treatment	Voriconazole	A	II	Many case reports	VOR good penetration into CSF. Good response in pediatric patient with CNS <i>S. apiospermum</i> infection. Combination of surgery and voriconazole. TDM recommended	
CF patients	First line treatment as for invasive disease	Voriconazole	B	III	Symoens HLT 2006 Borghì MMycol 2010 Luijk Case Rep Infect Dis '11	Infection or colonization? If critically ill azole +LAMB TDM recommended	
CF patients	First line treatment	VOR + LAMB	C	III	Vázquez-Tsuji Rev Iberoam Micol 2006 Guignard J Cyst Fibros 2008		

ESCMID		Treatment/ <i>Scedosporium species</i>					
Population	Intention	Intervention	SoR	QoE	Reference	Comment	
Cerebral abscess	First line treatment	Voriconazole	A	III	Chakraborty J Neurosurg 2005 Buzina Med Mycol 2006 Leechawengwongs Mycoses 2007	Case reports. Excellent CNS penetration Surgery if possible	
Cerebral abscess	Second line treatment	LAMB + POS CAS + VOR	C	III	Caggiano Mycopathol 2011 Satirapoj Transp Proceed 2008 Mursch Childs Nerv Syst 2006	Although echinocandins lack CNS penetration, CASPO + VOR significantly reduced colony counts. Beneficial effect of radical surgical debridement.	
Trauma: Skin/soft tissue infections	First line treatment	Voriconazole	A	III	Azofra CID 2010 Schaenman J Clin Microbiol 2005 Yoneda J Dermatol 2012	Surgical debridement is crucial	

ESCMID		Treatment/ <i>Scedosporium prolificans</i>					
Population	Intention	Intervention	SoR	QoE	Reference	Comment	
Immunocompromised pts (pulmonary/ disseminated)	To cure	Voriconazole	B	II	Husain CID 2005 Nishio Kan Zasshi 2012 Troke AAC 2008	Independent protective factor in tx recipients 40% survival (8/20)	
Immunocompromised pts (pulmonary)	To cure	Voriconazole plus terbinafine	B	III	Many case reports	In vitro data and animal models. 50% survival (3/6)	
Immunocompromised pts (pulmonary)	To cure	Itraconazole	C	III	Many case reports	15% survival (3/12)	
Immunocompromised pts (pulmonary)	To cure	AMB	D	III	Many case reports	4% survival (1/26)	
Immunocompromised pts (pulmonary)	To cure	AMB+ triazole (s) (not VCZ) or AMB+5FC	C	III	Many case reports	6% survival (1/17)	



Tortorano - Hyalohyphomycosis



ESCMM		ESCMIID EUROPEAN SOCIETY OF CLINICAL MYCOLOGY AND INFECTIOUS DISEASES					
Treatment/ <i>Scedosporium prolificans</i>							
Population	Intention	Intervention	SoR	QoE	Reference	Comment	
Intrabronchial infection (Lung transplant)	To cure	Intrabronchial ABLC instillation	C	III	Morales Transpl Proc 2009	Endobronchial prosthesis infection	
Intrabronchial infection (Lung transplant)	To cure	VOR or POSA plus TERBINAFINE plus GM-CSF/leukocyte transfusions	B	III	Howden EJCMIID 2003 Tong TID 2007 Whyte PID 2005	Expert opinion based on cases of disseminated infection by <i>Scedosporium spp</i>	
Solitary pulmonary nodule	To cure	Surgery	A	II	Rodriguez-Tudela Med Mycol 2009	Independent protective factor	



ESCMM		ESCMIID EUROPEAN SOCIETY OF CLINICAL MYCOLOGY AND INFECTIOUS DISEASES					
Treatment/ <i>Scedosporium prolificans</i>							
Population	Intention	Intervention	SoR	QoE	Reference	Comment	
Cerebral abscess	To cure	Complete excision (when possible)	A	II	RodriguezTudela Med Mycol 2009	Improved outcome	
CNS or disseminated	To cure	Voriconazole	B	II	Troke AAC 2008		
CNS or disseminated	To cure	VOR plus TERB	B	III	Many case reports		
CNS or disseminated	To cure	VORI or POSA or LAMB plus ECHINO plus TERB	B	III	Revankar CMR 2010	Expert opinion, some animal models and case reports	

ESCMM		ESCMIID EUROPEAN SOCIETY OF CLINICAL MYCOLOGY AND INFECTIOUS DISEASES					
Treatment/ <i>Scedosporium prolificans</i>							
Population	Intention	Intervention	SoR	QoE	Reference	Comment	
Osteomyelitis/s eptic arthritis	First line treatment	Voriconazole	B	III	Garcia-Vidal SpineJ09 Troke AAC 2008	Cases Good response	
Osteomyelitis/s eptic arthritis	Second line treatment	VOR + CAS + surgery	B	III	Steinbach JCM 2003	1 Case Good response	
Osteomyelitis/s eptic arthritis	First line treatment	VOR + TBF	B	III	Gosbell Myc 2003 Kesson CID 2009 Li JY TID 2008	2 Cases ± surgery. Good response	
Osteomyelitis/s eptic arthritis	Adjunctive therapy	Surgery	A	III	Many reports	Increased recovery rates	

Tortorano - Hyalohyphomycosis

 						
Treatment/ <i>Scedosporium prolificans</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Skin and subcutaneous infections	To cure	Voriconazole	B	II	Troke AAC 2008	91% success rate
Skin and subcutaneous infections	To cure	Surgery	C	III	Wood CID 1992 Kumar ANZIO 1997	Recovery

 						
Cytokine Treatment/ <i>Scedosporium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
HSCT recipients Neutropenic patients	To cure	GM-CSF (combined with antifungals)	B	III	Antachopoulos Immunother 2012	Independent protective factor
Chronic granulomatous disease	To cure	GM-CSF (combined with antifungals)	A	II	Rodriguez Tudela Med Mycol 2009 Bouza CID 1996	
Immuno-compromised patients	To cure	G-CSF (300 µg/kg/day); LAMB (40 mg/kg/day) and G-CSF (150 or 300 µg/kg/day) doses from murine model	C	III	Ortoneda Diagn Microbiol Infect Dis 2004	Only murine model data available; current clinical evidence is not sufficient to allow firm recommendation

 						
Surgical debridement/ <i>Scedosporium species</i>						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Immunocompetent/immunocompromised patients	To cure osteomyelitis	Surgical debridement of infected bone and soft tissue	B	III	Many case reports	Evidence based only on case reports
HSCT and SOT recipients	To cure	Surgical debridement of pulmonary lesions or CNS lesions and surrounding inflamed tissue.	C	III	Husain CID 2005	23 HSCT, 57 SOT Lower mortality, (potential bias)
HIV-positive pts with a strongly impaired immune system	To cure	surgery	C	III	Tammer Int J Infe Dis 2011	Case series and review (N= 22)

Cuenca-Estrella - Phaeohyphomycosis

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

Working Module

Phaeohyphomycosis

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


Author Experts of the Guideline on Emerging Fungal Diseases Working Module Phaeohyphomycosis

Author	Country
Anuradha Chowdhary	India
Manuel Cuenca-Estrella	Spain
Josep Guarro	Spain
Sybren de Hoog	The Netherlands
Jacques F. Meis	The Netherlands



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

Phaeohyphomycosis

- Fungal infections caused by black fungi (around one hundred species): dark pigmented organisms with thick cell wall
- Ubiquitous organism. More common in subtropical areas.
- Plant pathogens
- Soil, sewer...
- Animal infections





Cuenca-Estrella - Phaeohyphomycosis

Phaeohyphomycosis


- Colonization (some species in cystic fibrosis and fungus ball)
- Allergy, Allergic bronchopulmonary pneumonia???
- Superficial and subcutaneous infections:
 - Rino-sinusitis
 - **Mycetoma (specific entity)**
 - **Chromoblastomycosis (sclerotic bodies)**
 - Other subcutaneous phaeohyphomycosis
 - Onychomycosis, otitis...
 - Local and disseminated deep infections: arthritis, osteomyelitis, endophthalmitis, endocarditis, pneumonia, **CNS infections**
 - Related to hospital infections (device colonization and conidia inhalation)

AST of Black Fungi (others than *Scedosporium*)

Data from Spanish reference center and several papers

SPECIES	Nb. Isolates	AMB		ITC		VRC		POS		ECHINO	
		MIC50	MIC90	MIC50	MIC90	MIC50	MIC90	MIC50	MIC90	MIC50	MIC90
<i>Alternaria</i> spp.	35	0.25	0.50	0.25	>8.0	1.0	>8.0	0.12	>8.0	1.0	>16.0
Other black fungi: <i>Bipolaris</i> <i>Curvularia</i> <i>Exophiala</i> <i>Exserohilum</i> <i>Fonsecaea</i> <i>Phialophora</i> <i>Rhinocladiella</i>	31	0.12	0.50	0.25	>8.0	0.12	>8.0	0.06	>8.0	1.0	>16.0

Diagnosis



Cuenca-Estrella - Phaeohyphomycosis



ECMM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
European Society of Clinical Microbiology and Infectious Diseases						
Imaging						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Local infections and sinusitis	Detect and localize infection	Conventional radiology, CT-SCAN and MRI	A	III	Revankar CMR 2010 Cherian BJR 2009	No specific signs, except the dot-in-circle sign (MRI) in mycetoma
Pulmonary infection	Detect pneumonia, pulmonary nodules or endobronchial lesions	Conventional radiology, CT-SCAN and MRI	A	III	Kumar IJPM 2008 De Pawn CID 2008	No specific signs
Intracranial infection (including immunocompetent patients with signs of cerebral lesions)	Detect cerebral abscess	CT-SCAN, MRI	A	III	Revankar CID 2004 Koo MM 2010 Taj-Aldeen MM 2010	No specific signs
Intracranial infection	Detect cerebral granuloma, intracranial mass, or infarctions	MRI	A	III	Madhugiri JNP 2011 Revankar CMR 2010	No specific signs



ECMM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
European Society of Clinical Microbiology and Infectious Diseases						
Microbiology Conventional Methods						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
All cases	Definitive diagnosis and species ID	Microscopical examination (Gram, KOH, clacofluor) and cultures	A	III	Cuenca-Estrella JAC 2011 Revankar CMR 2010	Visualization of melanized fungi Conventional isolation media. BHI can help to recover some species
Cerebral abscess and other localized infections	Definitive diagnosis and species ID	Specimen at the sources of infection	A	III	Cuenca-Estrella JAC 2011 Revankar CMR 2010	<i>C. bantiana</i> and <i>R. mackenziei</i> (most common in cerebral abscess)
Disseminated infections	Definitive diagnosis and species ID	Blood cultures and other specimens	A	III	Cuenca-Estrella JAC 2011 Revankar CMR 2010	

ECMM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
European Society of Clinical Microbiology and Infectious Diseases						
Microbiology Serology						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
ANY	Detect infection	Beta-D-Glucan	C	III	Koo CID 2009 Onishi JCM 2011 Cuertara CVI 2009	Panfungal, no enough data
ANY		Galactomannan	D	III	Cuenca-Estrella JAC 2011	Cross reactivity in some cases
Infections by <i>F. pedrosoi</i> and <i>C. carrioni</i>	Detect infection	ELISA	C	III	Revankar CMR 2010	No validated

Cuenca-Estrella - Phaeohyphomycosis

 						
Microbiology Molecular-based Procedures						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
ANY	Detect infection in tissues	PCR-based methods	C	III	Lau JCM 2007 Castell JCM 2008 Buitrago CMI 2013	No enough data
ANY	Detect infection in CSF, BAL and other liquids	PCR-based methods	C	III	Revankar CMR 2010	No data

 						
Microbiology Susceptibility Testing						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Isolates from deep sites	To know resistance in vitro and recommend best therapy	MIC determination	A	III	CLSI M27-A3, M27-S3, M44-A2 EUCAST Document 9.2	Reference or validated commercial methods
All isolates	To know local epidemiology	Periodical epidemiological surveys	A	III	Cuenca-Estrella ERAIT 2010 Cuenca-Estrella AAC 2009	Reference or validated commercial methods

 						
Microbiology Species Identification						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Isolates from deep sites	Species ID to recommend most adequate treatment	Conventional methods	A	III	Cuenca-Estrella JAC 2011 Revankar CMR 2010	Experience required
All isolates	To know local epidemiology	Periodical epidemiological surveys	A	III	Cuenca-Estrella JAC 2011 Revankar CMR 2010	
Isolates difficult to ID by conventional methods and sibling/cryptic species	Definitive species ID	Molecular ID (DNA target sequencing)	B	III	Balajee JCM 2009	Rare species. Essential investigation in some cases

Cuenca-Estrella - Phaeohyphomycosis

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

Histopathology

Population	Intention	Intervention	SoR	QoE	Reference	Comment
ANY	Detect infection	Microscopical examination (H&E, Fontana-Masson, PAS, Gomori)	A	III	Lass-Floerl CMI 2009 Richardson HM 2000 Jensen JP 1997	No species ID. Melanized hyphae or yeast (only). No specific structures apart from chromoblastomycosis (sclerotic bodies, Medlar bodies or copper pennies)

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

Treatment

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

Targeted Treatment – Antifungals

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Mycetoma (<i>Madurella</i> , <i>Pyrenochaetae</i> , <i>Leptosphaeria</i>)	Cure (reduce lesions in advanced cases)	KETO or ITRA, 3 months (two years some cases) plus SURGERY	A	II	Ahmed LID 2004 Al-Tawfiq MM 2009 Cajapor JMM 2007 Castro IUD 2008	Dramatic results of uncontrolled cases
Mycetoma	As above	VORI or POSA plus SURGERY	A	III	Lacroix BID 2005 Lee JFAS 2007 Loulergue AJTMH 2006	Less experience
Mycetoma	As above	AMB	D	III	Revankar CMR 2010	Impractical given the duration of therapy
Refractory mycetoma	Reduce lesions	Combination therapy (azoles plus terbinafine or flucytosine)	B	III	Lee JFAS 2007 Hood BID 1997	Surgery when possible



Cuenca-Estrella - Phaeohyphomycosis



ECMM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
European Society of Clinical Microbiology and Infectious Diseases						
Targeted Treatment – Antifungals						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Chromoblastomycosis (<i>Fonsecaea</i> , <i>Phialophora</i> , <i>Rhinoctadella</i>)	Cure (reduce lesions in advanced cases)	ITRA months to years plus SURGERY	A	II	Bonifaz Mycoses 2001 Queiroz-Telles MM 2009 Restrepo ANYAS 1988	Multiple time series
Chromoblastomycosis	As above	Other antifungal agents (azoles, AMB) plus surgery	B	III	Attapattu Mycopathologia 2003 Minotto JAAD 2001	Case reports and reviews
Chromoblastomycosis	As above	Cryotherapy and laser therapy	B	III	Castro IJID 2003	Used in areas where antifungals are not available
Refractory chromoblastomycosis or severe disease	Reduce lesions	Combination therapy (ITRA plus terbinafine)	B	III	Queiroz-Telles MM 2009 Gupta MM 2002 Bonifaz EOP 2004	Surgery when possible



ECMM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
European Society of Clinical Microbiology and Infectious Diseases						
Targeted Treatment – Antifungals						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Allergic sinusitis (<i>Bipolaris</i> , <i>Curvularia</i>)	Remove the mucin and reduce symptoms	Surgery plus systemic steroids	B	III	McAleer Thorax 1981 Rinaldi DMID 1987 Taj-Aldeen AJO 2004	Case reports and reviews
Allergic sinusitis	Reducing the requirement of steroids	Add ITRA	C	III	Kuhn OCNA 2000 Rupa Mycoses 2002	Case reports
Allergic sinusitis, refractory	Reduce symptoms	Add ITRA (VORI in some cases)	B	III	Seiberling AJRA 2009 Chan JHNS 2008 Erwin J Asthma 2007	Case reports

ECMM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
European Society of Clinical Microbiology and Infectious Diseases						
Targeted Treatment – Antifungals						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Allergic bronchopulmonary mycosis (<i>Bipolaris</i> and <i>Curvularia</i>)	Reduce symptoms	Steroids	B	III	Halwig ARRD 1985 Rinaldi DMID 1987 Saenz AJMS 2001 Revankar CMR 2010	Case reports
Allergic bronchopulmonary mycosis	As above	Add ITRA	D	III	Agrawal Chest 2009	Expert opinion



Cuenca-Estrella - Phaeohyphomycosis



  <small>ESCMID FUNGAL INFECTION STUDY GROUP</small> European Society of Clinical Microbiology and Infectious Diseases						
Targeted Treatment – Antifungals						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Subcutaneous nodules (<i>Alternaria</i> , <i>Exophiala</i> , <i>Phialophora</i>)	Cure	Surgery	A	II	Diaz, Lancet 1990 Gene JCM 1995 Revankar CMR 2010 Bogle DS 2004 Farina TID 2007 Kondo IJ 2007	Multiple time series and case reports
Subcutaneous nodules	As above	Cryotherapy, laser therapy, or potassium iodide	B	III	Gugnani MM2006 Torres-Rodriguez AD 2005	Used in areas where antifungals are not available
Subcutaneous nodules	To prevent dissemination (particularly in immunocompromised patients, haematological and SOT)	Add oral azoles	B	III	Revankar CMR 2010	Expert opinion
Multiple subcutaneous nodules	Cure	Azol therapy	B	III	Foulet CID 1999 Miele AJT 2002	Case reports



  <small>ESCMID FUNGAL INFECTION STUDY GROUP</small> European Society of Clinical Microbiology and Infectious Diseases						
Targeted Treatment – Antifungals						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Keratitis (<i>Curvularia</i> , <i>Bipolaris</i> , <i>Exserchilum</i>)	Cure	Topical agents (natamycin mainly) w/wo azoles	A	II	Garg: Ophthalmology 2000 Wilhelmus TAOS 2001	88 cases, retrospective 43 cases by <i>Curvularia</i>
Keratitis	Cure	Topical azoles only (ITRA or VORI)	B	III	Tu, Cornea 2009 Ozbek, Cornea 2006	Case reports
Refractory keratitis	Cure	Oral triazole plus surgery if needed	B	III	Garg: Ophthalmology 2000 Wilhelmus TAOS 2001	Case reports

  <small>ESCMID FUNGAL INFECTION STUDY GROUP</small> European Society of Clinical Microbiology and Infectious Diseases						
Targeted Treatment – Antifungals						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Joint and bone infections (<i>Alternaria</i> and others)	Cure	Surgery plus azoles (ITRA 6 to 24 months)	B	III	Revankar CIMR 2010 Karuppel JFAS 2009 Shigemura, Infection 2009	Case reports

Cuenca-Estrella - Phaeohyphomycosis

 						
Targeted Treatment – Antifungals						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Peritonitis (associated to peritoneal dialysis) (<i>Curvularia</i> , <i>Exophiala</i> , <i>Alternaria</i>)	Cure	Catheter removal and systemic antifungal therapy	A	II	Shin JCM 1998 Reiss-Levy MJA 1981 Kerr AIM 1983 Revankar CMR 2010	Dramatic results removing the catheter. Case reports

 						
Targeted Treatment – Antifungals						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Pulmonary infection (immunocompromised or underlying pulmonary disease) (Many species)	Cure (infection control until recovering immune status)	Systemic antifungal therapy (AMB or ITRA)	B	III	Lastoria JHLT 2009 Woo JCM 2008 Revankar CMR 2010	Case reports
As above	As above	Systemic voriconazole	B	III	Hollinsworth, Infection 2007 Elnav JCM 2009 Al-Aidarous PID 2007	Short number of case reports
As above	As above	Posaconazole	C	III	Mullane TID 2007	Case report
Solitary pulmonary nodule (immunocompetent)	Cure	Surgery	B	III	Greig JI 2001 Borges APLM 1991	Case reports

 						
Targeted Treatment – Antifungals						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Cerebral abscess (<i>C. bantiana</i> and <i>R. mackenziei</i>) (many immunocompetents)	Cure	Complete excision (when possible)	A	II	Delfino MM 2006 Garg NI 2007	Dramatic positive results when possible
As above	Cure	Antifungal combination therapy (AMB, ITRA plus Flucytosine)	C	II	Revankar CID 2004 Koo MM 2010 Taj-Aldeen MM 2010 Revankar CMR 2010	101 cases 50 cases more (70% mortality)
As above	Cure	Monotherapy (VORI, POSA)	C	III	Al-Abdely MM 2005 Nesky CID 2000	Short number of cases
As above	Cure	New combination therapy (VORI or POSA plus ECHINO plus flucytosine)	B	III	Revankar CMR 2010	Expert opinion, some animal models and case reports

Cuenca-Estrella - Phaeohyphomycosis

ESCM		EFISG		ESCMID FUNGAL INFECTION STUDY GROUP		
European Society of Clinical Microbiology and Infectious Diseases						
Targeted Treatment – Antifungals						
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Disseminated infection (<i>Bipolaris</i> , <i>Exophiala</i>) (immunocompromised, HIV+, haematological)	Cure (infection control until recovering immune status)	Monotherapy with AMB or ITRA, VORI, POSA	C	III	Revankar CID 2002 Boggild MM 2006 Brandt JC 2003 Alabaz MM 2009 Hong JMM 2009 Oztaş JMM 2009 Al-Obeid EICMID 2006 Barron JCM 2003 Negróni CID 2004 Revankar CMR 2010	Around 50 cases (mortality >75%). A couple of cases, good evolution with POSA
As above	As above	VORI or POSA plus TERBINAFINE plus CSF/leukocyte infusions	B	III	Bouza CID 1996 Howden EICMID 2003 Tong TID 2007 Whyte PID 2005	Expert opinion based on cases of disseminated infection by <i>Scedosporium</i> spp.
