

Working Module

Phaeohyphomycosis

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

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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



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

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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

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	

Microbiology Serology

Population	Intention	Intervention	SoF	QoE	Reference	Comment
ANY	Detect infection	Beta-D-Glucan	C	III	Koo CID 2009 Onishi JCM 2011 Cuetara 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

Microbiology Molecular-based Procedures

Population	Intention	Intervention	SoF	QoE	Reference	Comment
ANY	Detect infection in tissues	PCR-based methods	C	III	Lau JCM 2007 Castelli 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

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Microbiology Susceptibility Testing

Population	Intention	Intervention	SoR	OoE	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

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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

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)

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Treatment

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Prophylaxis

Population	Intention	Intervention	SoP	QoE	Reference	Comment
NO DATA						

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Fever-driven Treatment – Antifungals

Population	Intention	Intervention	SoP	QoE	Reference	Comment
NO DATA						

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Diagnosis-driven Treatment – Antifungals

Population	Intention	Intervention	SoP	QoE	Reference	Comment
NO DATA						

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Targeted Treatment – Antifungals

Population	Intention	Intervention	SoP	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 Capoor JMM 2007 Castro IJD 2008	Dramatic results of uncontrolled cases
Mycetoma	As above	VORI or POSA plus SURGERY	A	III	Lacroix BJD 2005 Lee JFAS 2007 Louergue 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 BJD 1997	Surgery when possible

Targeted Treatment – Antifungals

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Chromoblastomycosis (<i>Fonsecaea</i> , <i>Phialophora</i> , <i>Rhinocladiella</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 IJD 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

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	McAler 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 JOHNS 2008 Erwin JAsthma 2007	Case reports

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

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 IJD 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

Targeted Treatment – Antifungals

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Keratitis (<i>Curvularia</i> , <i>Bipolaris</i> , <i>Exserohilum</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

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 Karuppal JFAS 2009 Shigemura, Infection 2009	Case reports

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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

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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 Elinav JCM 2009 Al-Aidaros 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

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 Oztas JMM 2009 Al-Obaid EJCMI 2006 Barron JCM 2003 Negrone 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 EJCMI 2003 Tong TID 2007 Whyte PID 2005	Expert opinion based on cases of disseminated infection by <i>Scedosporium</i> spp.

Summary

- Efforts to detect and ID species
- No new diagnostic techniques available yet
- Treatment based on surgery plus antifungal agents (triazoles or AmB)
- If surgery is not possible, bad prognosis
- Disseminated infection, combination therapy, aggressive approach since mortality >75%