

Working Module on Hyalohyphomycosis

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

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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.

Laboratory diagnosis/Serology/*Fusarium species*

Population	Intention	Intervention	SoR	OoE	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	Spiess 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.

Laboratory diagnosis/Identification/*Fusarium* species

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.

Microbiology Susceptibility Testing/*Fusarium* species

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 EJCMID 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

Treatment/*Fusarium species*

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

Treatment/*Fusarium species*

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

Treatment/*Fusarium* species

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

Granulocyte Transfusions/Cytokine Treatment/*Fusarium species*

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

Granulocyte Transfusions/Cytokine Treatment/*Fusarium species*

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

Surgical Debridement/*Fusarium species*

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Leukemia/BM TX	To cure infection	Surgey	A	III _t	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

Laboratory diagnosis/Conventional Methods/*Scedosporium species*

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/P.boydii</i> isolated from aspiration or surgical drainage of brain abscesses (rarely from respiratory secretions or CSF)

Laboratory diagnosis/Conventional Methods/*Scedosporium species*

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 Summerbell JCM 1993 Rainer AVanLeeu 2008 Horré Mycoses 2010 Borman MM 2010	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 SceSel+ agar (supplemented with benomyl and dichloran)

Laboratory diagnosis/*Scedosporium* species

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.

Laboratory diagnosis/Adjunctive Assays/*Scedosporium* species

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 EJCMID 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; positivity of 2 consecutive samples required; careful check for

Laboratory diagnosis/Identification/*Scedosporium* species

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

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

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 sp.</i>
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 JAC 11	VCZ, POS: good in vitro-in vivo correlation

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

Treatment/*Scedosporium 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

Treatment/*Scedosporium species*

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 Borghi 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	

Treatment/*Scedosporium species*

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

Treatment/*Scedosporium prolificans*

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)

Treatment/*Scedosporium prolificans*

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 EJCMID 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

Treatment/*Scedosporium prolificans*

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

Treatment/*Scedosporium prolificans*

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Osteomyelitis/s epic arthritis	First line treatment	Voriconazole	B	III	Garcia-Vidal SpineJ09 Troke AAC 2008	Cases Good response
Osteomyelitis/s epic arthritis	Second line treatment	VOR + CAS + surgery	B	III	Steinbach JCM 2003	1 Case Good response
Osteomyelitis/s epic 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 epic arthritis	Adjunctive therapy	Surgery	A	III	Many reports	Increased recovery rates

Treatment/*Scedosporium prolificans*

Population	Intention	Intervention	SQR	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 ANZJO 1997	Recovery

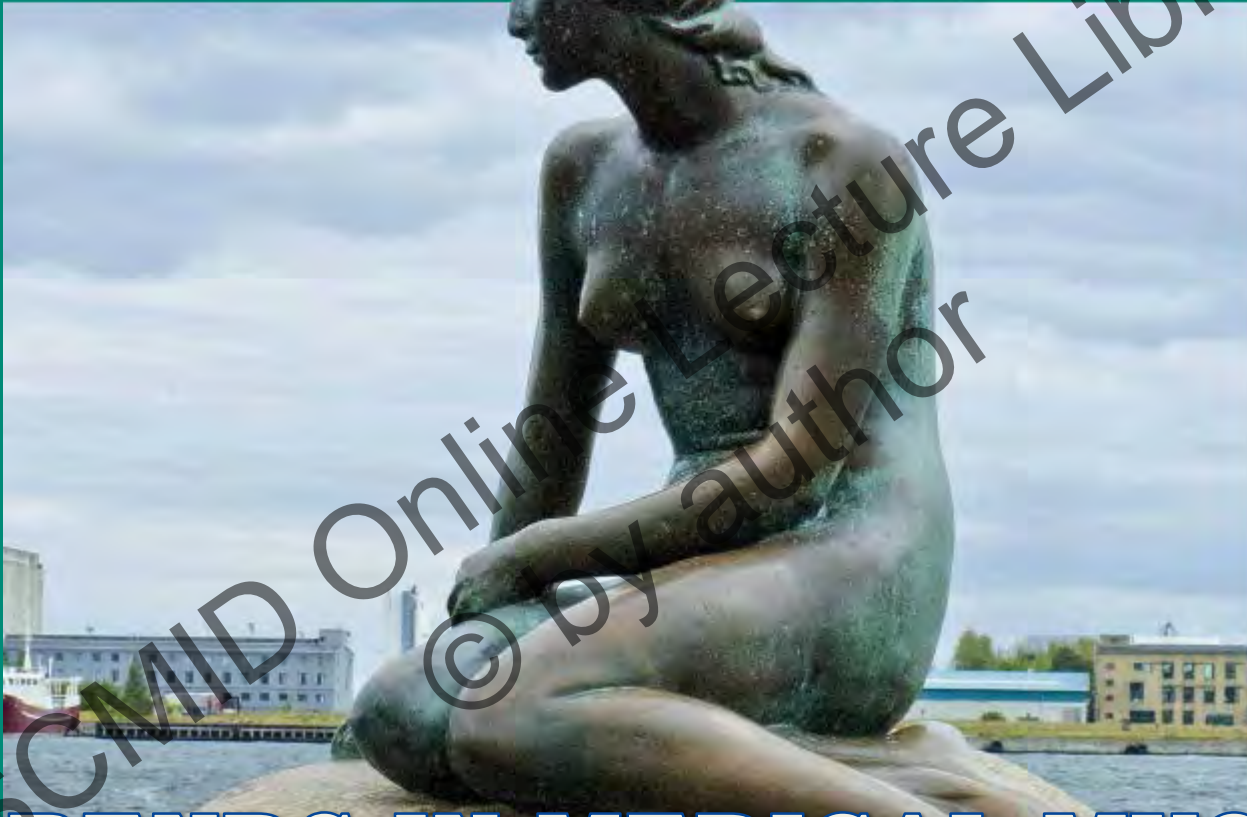
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Cytokine Treatment/*Scedosporium* species

Population	Intention	Intervention	SoR	QoE	Reference	Comment
HSCT recipients Neutropenic patients	To cure	GM-CSF (combined with antifungals)	B	III	Antachopoulo s Immunother 2012	Independent protective factor
Chronic granulomatous disease	To cure	GM-CSF (combined with antifungals)	A	II	Rodriguez Tudela Med Mycol 2009Bouza 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 recommendati on

Surgical debridement/*Scedosporium species*

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 HSTC, 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)



6th TRENDS IN MEDICAL MYCOLOGY

11-14 October 2013, Copenhagen, Denmark