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

Rare yeasts

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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 *mucilaginosa*
- ✓ *Saccharomyces*
  - *cerevisiae* and *boulardii*
- ✓ *Trichosporon*
  - *asahii, asteroides, dermatis, inkin, jirovecii , loubieri , mucoides* and *mycotoxinivorans*
- ✓ *Magnusiomyces capitatus*

Excluded species

- *Pneumocystis jirovecii* → Not rare
- *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*

Not shown to be relevant human pathogens

- Rare/emerging *Candida* spp. excluded (Covered in the *Candida* guideline)
  - as defined by the anamorphic name

Challenges/ limitations

- Taxonomy and ± correct species ID
  - Uncertainty particularly for older literature
  - Eg. *Trichosporon beigelii*
  - 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

Challenges/ limitations

- [illegible]
- [illegible]
- [illegible]
- [illegible]
  - Despite mycology experts, limited → no personal experience

≥ 239 references

+

Common sense and pragmatism

Translated knowledge & experience from other IFI

Added Caution:

Very few "A"s

Some "no recommendations"

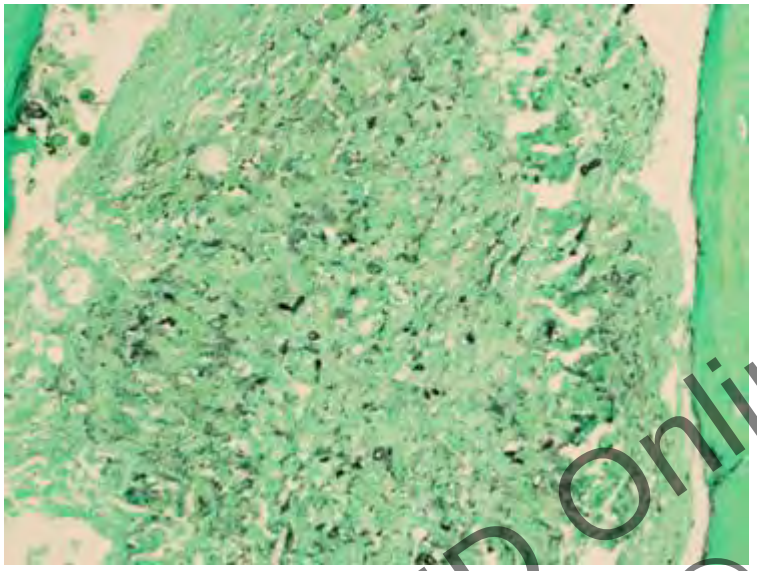
Diagnosis

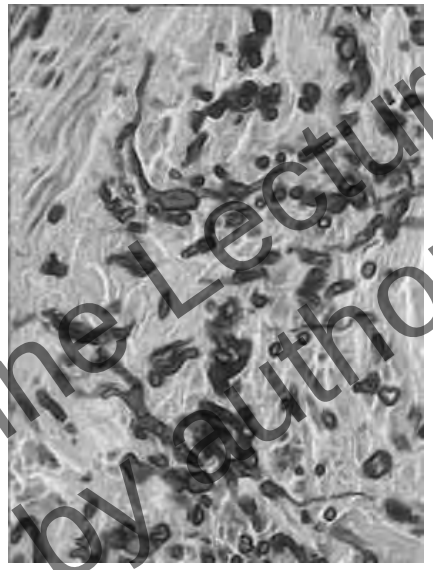
Direct Microscopy

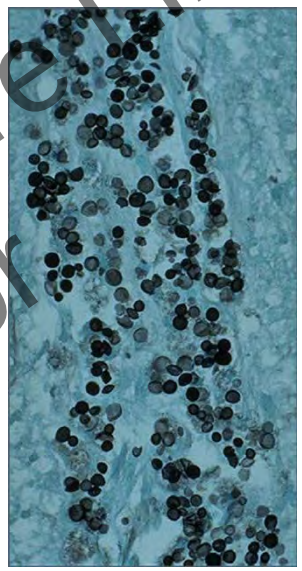
Population	Intention	Intervention	SoR	QoE	Reference	Comment
Any	To diagnose IFI	Direct microscopy preferably using optical brighteners	A	II^{ut}	Lass-Flörl CID 2007	Allows rapid (presumptive) diagnosis of fungal infection. Identification to genus and species level not possible.
Any	To diagnose cryptococcal 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

Histopathology



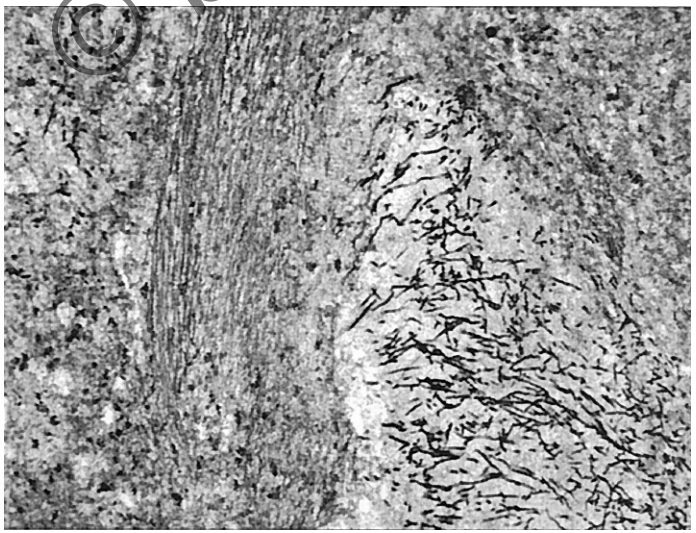


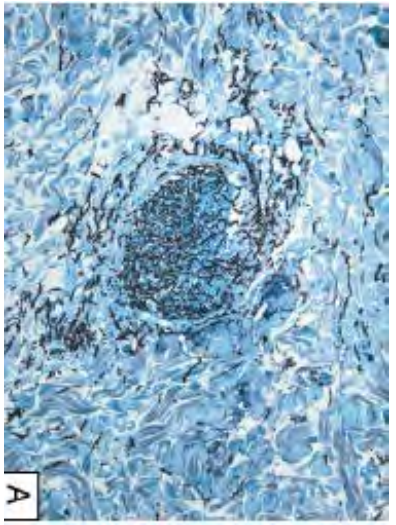


A-EI*

For tissue and sterile body fluids

Diagnose IFI; but no species ID provided





EI: Essential investigation

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 SJID 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.
		Blood culture incl. mycosis bottle	B	II^{t}	Arendrup JCM Jan 2011, Arendrup JCM Sep 2011, Horvath JCM 2004, Ericson DMID 2012, Cateau DMID 2012	Several studies have documented better yield for *Candida* and BACTEC and BacT/ALERT BC systems if a mycosis medium is included. Not shown specifically for rare yeasts.

EI: Essential investigation

Species specific culture procedures

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Immuno-compromised	Diagnose **other cryptococci** (non-neoformans; non-gattii	Culture: CSF, respiratory specimen, pleural fluid. Use SDA 30-35 °C.	A	III	McCurdy 2003 Comp. Ther. Dromer, 2012 265 /id	Growth better at lower tp; *C. albidus* associated w summer-type hypersensitivity pneumonitis
Neonates, children and adults with CVC and lipid supplementation suspected of *Malassezia* fungaemia	Diagnose ***Malassezia*** 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. Velegraki in Tragiannidis et al. 2010	Performance of modern automated blood culture systems is not investigated. *M. pachydermatis* is not lipid dependent.
	Diagnose inv ***Malassezia*** inf	Sterile specimens & pos BC: Use Sab overlaid with sterile olive oil, Dixon agar or other lipid containing agar for subculture	A	II	Gaitanis 2012, Clin. Microbiol. Rev. 25, 106, Arendrup 2009, CMI 2009, Kaneko JCM 2007	

Surrogate markers

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Immuno-compromised	Diagnose **other cryptococci** (non-neoformans; non-gattii	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	D	III	Dalle JCM 2005	Cross reaction demonstrated in a clin case and in vitro. However, sensitivity not examined.
		β-D-Glucan	D	II	Odabasi Med Mycol 2006	ß-D-glucan is not part of the cryptococcal cell wall.

Surrogate markers

Population	Intention	Intervention	SoR	QoE	Reference	Comment
FUO without response to AB	Diagnose Inv. ***M. capitatus***	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.
		β-D-Glucan	C	III	Odabasi Med Mycol 2006	Culture supernatant positive but no clinical data.
FUO without response to AB	Diagnose Inv. ***Rhodotorula***	β-D-Glucan	C	III	Odabasi Med Mycol 2006	*R. mucilaginosa* culture supernatant positive but no clinical data.

Surrogate markers

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

Microbiology Susceptibility Testing 2

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Invasive ***Cryptococcus*** infection (other than *C. neoformans* & *C. gattii*)	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 2009; 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.
	For **epidemio-logical** purposes	EUCAST/CLSI ref testing	B	II		

Susceptibility Testing 1

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Trichosporon Inv infection	To **guide** treatment	EUCAST/CLSI ref testing	C	II	Rodriquez-Tudela AAC 2005, Araujo Ribeiro Rev Ibero Micol 2008, Zaragosa AAC 2011	Spp. specific susceptibility patterns, ID difficult by conventional methods. But no breakpoints for these spp.
	For **epidemiological** purposes	EUCAST/CLSI ref testing	B	II	Rodriquez-Tudela AAC 2005, Araujo Ribeiro Rev Ibero Micol 2008, Zaragosa AAC 2011	Limited data suggest species specific differences in susceptibility. More data necessary and might help future treatment choice before susceptibility testing is available
Malassezia 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 *M. pachydermatis* also published by Nijima et al. 2011, Vet. Microb. 149, 288-290.

Conventional Species Identification

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Trichosporon Inv infection	To guide treatment	Phenotypic species ID (incl commercial systems)	D	II	Rodriquez-Tudela AAC 2005	Only valid to the genus level. Species specific differences in susceptibility
Malassezia 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-glucosidae activity and catalase activity;	C	II	Gaiatanis 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)
Malassezia	Identification *M. pachydermatis*	Growth on SDA	B	II	Gaiatanis et al. 2012. Clin. Microbiol. Rev. 25: 106	*M. pachydermatis* may be less susceptible to azoles

Molecular-based Identification

Intention	Intervention	SoR	QoE	Reference	Comment
Identify ***Cryptococcus*** 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 ***Trichosporon*** 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 ***Malassezia*** isolates	ITS rDNA sequencing; IIS and restriction analysis; D1D2 sequencing; D1D2 and restriction analysis; or Luminex platform using rDNA sequences	B	II	Gaiatanis 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 ***Geotrichum & Magnusiomyces***	D1D2 domains and/or ITS 1+2 regions of rDNA	B	II		MALDI-TOF is promising, but performance depend on the database

Treatment

Prophylaxis

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Primary prophylaxis: Rare yeasts are rare – thus no indication for specific primary prophylaxis. Most rare yeasts are covered by standard *Aspergillus* prophylaxis (exception: *Rhodotorula*).						
Immunosuppressed, prior diagnosis of invasive rare yeast infaction	Secondary prophylaxis (To prevent recurrence)	Last drug effective in the same patient			No data	Sound recommen-dation, but coverage of other organisms may also be indicated.
Immunosuppressed	To prevent *S. boulardii* infection	Avoid probiotics containing *S. boulardii*	A	II	Thygesen BMJ Case Reports 2012; Stefanatou Mycoses 2011; Basseti Am J Med 1998; de Llanos International Journal of Food Microbiology 2006; Herbrecht CID 2005; Munoz CID 2005	
	To prevent *Malassezia*, *Rhodotorula, Kodamaea ohmeri*	Scrupulous adherence to standard hygienic measure-ments	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); Perniola 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

Targeted Treatment – Antifungals- first line 1

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

Targeted Treatment – Antifungals- first line 2

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Geotrichum candidum	cure	Ampho-tericin B ± 5-FC	B	III	Henrich Transpl Infect Dis 2009 Sfakianakis Med Mycol 2007 Andre Pediatr Infect Dis J 2004 Ng Med J Malaysia 1994	Preferred agent is amphotericin B (w/wo 5-FC), but as data is scarce and several cases are non-successful, hence a B recommendation
		Vori-conazole	-	-	Henrich Transpl Infect Dis 2009 Wildfeuer Mycoses 1998	Low MIC values. One breakthrough failure case (while on micafungin), but voriconazole TDM levels not reported.
		Fluco-nazole	D	III	Henrich Transpl Infect Dis 2009 Cordoba Rev Argent Microbiol. 2011	No clinical data . MICs elevated (≥8 mg/L)
		Echino-candins	D	II	Henrich Transpl Infect Dis 2009	Level of evidence based on in vitro susceptibility testing demonstrating intrinsic resistance, 1 breakthrough case on micafungin

Targeted Treatment – Antifungals- first line 3

Population	Intention	Intervention	SoR	QoE	Reference	Comment
K. ohmeri inv inf	cure	Ampho-tericin 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;
		Fluco-nazole	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].
		Echino-candins	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)
		Vori-conazole	-	-		No data

Targeted Treatment – Antifungals- first line 4

Population	Intention	Intervention	SoR	QoE	Reference	Comment
M. capitatus inv inf	cure	Ampho-tericin 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.
		Vori-conazole	B	III	Gadea JCM 2004	Less data available, but promising in vitro susceptibility
		Fluco-nazole	-	-	Serena Int J Antimicrob Agents 2007	In vitro resistant - but animal model data suggest activity
		Echino-candins	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.

Targeted Treatment – Antifungals- first line 5

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Rhodotorula inv infection	To cure	Ampho-tericin ± 5FC	A	III	Nunes AAC 2013, Diekema JCM 2005, Garcia-Suarez Mycoses 2010	In vitro susceptible, Amphotericin associated with good outcome in clinical practice.
		Echino-candin	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.
		Azoles	D	II	Nunos 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.

Targeted Treatment – Antifungals- first line 6

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Saccharo-myces inv infection	To cure	Ampho-tericin B	B	III	Enache-Angoulvant CID 2005	Most clinical experience; toxicity risk higher than for echinocandins
		Echino-candin	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 litterature (+&-neutropenic), no emergence of *S. cervisiae* after intro of echinocandins as first line agents for candidaemia, two recent failure cases neutropenic (unpublished data)
		Fluco-nazole	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 *C. glabrata*)
Saccharo-myces inv infection, **severe/penetration issue**	To cure	Ampho-tericin B + 5-FC	B	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.

Targeted Treatment – Antifungals- first line 7

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Trichosporon inv inf	cure	Vorico-nazole	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.
		Fluco-nazole	C	III	Suzuki Eur J Haem 2010; Girmenia JCM 2005; Ruan CID 2009;	Most experience and data is with fluconazole
		Echino-candin	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.
		Ampho-tericin	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

Targeted Treatment – Antifungals- first line 8

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Malassezia inv inf in **unstable** pt	Cure	Ampho-tericin	B	III	Tragiannidis Mycoses 2009; Gaitanis Clin Microbiol Rev 2012	
Malassezia inv infection	Cure	Fluco-nazole	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
		Vorico-nazole	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.
		Echino-candins	D	III	Tragiannidis Mycoses 2009; Gaitanis Clin Microbiol Rev 2012	Intrinsically resistant

Targeted Treatment – Antifungals- first line 9

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
		Voriconazole	-	-	Serena AAC 2004; Espinel-Ingroff JCM 1998	Insufficient data, scarce in vitro testing suggests susceptibility but no clinical data in the literature
		Fluconazole	D	II	Serena AAC 2004; Espinel-Ingroff JCM 1998	Level of evidence based on in vitro susceptibility testing demonstrating intrinsic resistance
		Echinocandins	D	II	Serena AAC 2004; Espinel-Ingroff JCM 1998	Level of evidence based on in vitro susceptibility testing demonstrating intrinsic resistance

“non-drug-related interventions”

Population	Intention	Intervention	SoR	QoE	Reference	Comment
CVC related rare yeast	Clear the infection	CVC removal	B	II	Gaitanis et al. 2012; Tragiannidis et al. 2009, Mycoses 53, 187-195 (Malassezia)	Rare yeast inf have been strongly associated with CVC in place

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