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European Society of Clinical Microbiology and Infectious Diseases

Diagnostic Working Module of ESCMID *Candida* Guidelines

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Conflict of interest disclosure

- In the past 5 years, M.C.E. has received grant support from **Astellas Pharma, bioMerieux, Gilead Sciences, Merck Sharp and Dohme, Pfizer, Schering Plough, Soria Melguizo SA**,
- He has been an advisor/consultant to the **Panamerican Health Organization, Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer, and Schering Plough**.
- He has been paid for talks on behalf of **Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough**.

Rationale of Recommendations by Quality of Evidence for Diagnostic Module. BIOMARKERS ONLY

Accuracy	
Highly recommended	Technique is accurate in >70% of cases (most)
Recommended	Technique accurate in 50 – 70% of cases (reasonable number)
Not Recommended	Technique accurate in <50% of cases (small number)
No recommendation	No data
Quality of evidence accepted	
Level I	Evidence from at least 1 properly designed prospective **multicentre** cross-sectional or cohort study
Level II	Evidence from (1) at least 1 well-designed prospective single-centre cross-sectional or cohort study or (2) a properly designed retrospective **multicentre** cross-sectional or cohort study or (3) from case-control studies
Level III	Opinions of respected authorities, clinical experience, descriptive case studies, or reports of expert committees

Rationale of Recommendations by Quality of Evidence for Diagnostic Module. BIOMARKERS ONLY

Accuracy	$\text{accuracy} = \frac{\text{number of true positives} + \text{number of true negatives}}{\text{numbers of true positives} + \text{false positives} + \text{false negatives} + \text{true negatives}}$
Highly recommended	Technique is accurate in >70% of cases (most)
Recommended	Technique accurate in 50 – 70% of cases (reasonable number)
Not Recommended	Technique accurate in <50% of cases (small number)
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Level I	Evidence from at least 1 properly designed prospective **multicentre** cross-sectional or cohort study
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Level III	Opinions of respected authorities, clinical experience, descriptive case studies, or reports of expert committees

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Diagnosis of candidaemia

What are the best tests for diagnosing candidaemia? 1

Specimen	Test	Considerations	Remarks/Recommendations
Blood	Blood culture	• Number of blood cultures: 3 (2 to 4) • Total volume: Children <2kg, 2 to 4 mL, between 2 and 12 kg, 6 mL, between 12 and 36, 20 mL. 40 to 60 mL for adults • Timing: Obtain blood cultures, one right after the other, from different sites following the clinical events that precipitated the blood culture • Site: Venipuncture remains the technique of choice. Blood obtained through an indwelling line is twice as likely to yield a contaminant than blood obtained through a properly prepared skin site • Frequency: Daily when candidaemia is suspected • Technique: Validated systems • Incubation time: At least five days • Performance: 50-75% S	• Essential investigation • Separate 20-ml blood samples obtained within a 30- min period, each divided equally between an aerobic and anaerobic blood culture vial in 10-ml aliquots, were considered to represent a single culture • A blood culture set compromising 60 mL blood obtained in a single session and divided in 10 mL aliquots among 3 aerobic and 3 anaerobic bottles • Lower sensitivity in neutropenic patients and under antifungal treatment • Sensitivity varies depending on the species and system (e.g. lower for BACTEC and *C. glabrata*) • ID is mandatory • Caution: Yeast in BC is not always *Candida* • Lysis-centrifugation showed efficacy when older systems of BC were used as comparators

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References:
1) Denning et al. Lancet Infect Dis 2003;3:230-40
2) Einsele et al. Clin Microbiol Infect 2008;14 Suppl 4:37-45
3) Gadea et al. Enf Infec Microbiol Clin 2007;25:336-40
4) Lass-Florl. Clin Microbiol Infect 2009;15 Suppl 5: 60-5
5) Richardson M. Hosp Med 2000;61:610-4
6) Baron et al. Cumitech 1C. Blood cultures IV

SUMMARY: Blood culture

Number: 3 (2 to 4)

Timing: Obtain blood cultures, one right after the other, from different sites

Site: direct puncture of the vein

Volume: Children <2kg, 2 to 4 mL, between 2 and 12 kg, 6 mL, between 12 and 36, 20 mL. At least 60 mL for adults

Frequency: Daily when candidaemia is suspected

Incubation time: At least five days

Performance: 50-75% S (neutropenic, species)

ID is mandatory (yeast in BC is not always *Candida*). Lysis-centrifugation (if older BC systems are used)

What are the best tests for diagnosing candidaemia? 2

Specimen	Test	Considerations	Remarks/Recommendations
Serum	**Mannan and Anti-Mannan**	• **Combined detection**	**RECOMMENDED Serial determinations may be necessary. High NPV**
	Other antibodies (such as Serion ELISA classic)	• Limited data for candidemia	No recommendation
	ß-D-Glucan	• Not specific for *Candida*	RECOMMENDED (for Fungitell) No recommendation for other tests. Serial determinations are recommended (twice a week). High NPV. Not validated in children
	Septifast	• Limited data for candidemia	No recommendation
	In house PCR	• No third party validation data available	No recommendation

Detection mannan and anti-mannan

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Mikulska *et al. Critical Care* 2010, 14:R222
http://ccforum.com/content/14/6/R222

CRITICAL CARE

RESEARCH Open Access

The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia

Malgorzata Mikulska[1*], Thierry Calandra[2], Maurizio Sanguinetti[3], Daniel Poulain[4], Claudio Viscoli[5], the Third European Conference on Infections in Leukemia Group

	14 studies, 453 patients and 767 controls		
	Platelia Ab	Ag	Both
Sensitivity	58 %	59 %	83 %
Specificity	93 %	83 %	86 %
+ prior culture	6 days in average		

What are the best tests for diagnosing candidaemia? 2

Specimen	Test	Considerations	Remarks/Recommendations
Serum	Mannan and Anti-Mannan	• Combined detection	RECOMMENDED Serial determinations may be necessary. High NPV
	Other antibodies (such as Serion ELISA classic)	• **Limited data for candidemia**	**No recommendation**
	ß-D-Glucan	• Not specific for *Candida*	RECOMMENDED (for Fungitell) No recommendation for other tests. Serial determinations are recommended (twice a week). High NPV. Not validated in children
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Diagnostic Performance of the (1→3)-β-D-Glucan Assay for Invasive Fungal Disease

Sophia Koo,[1,2,3] Julie M. Bryar,[1,4] John H. Page,[4] Lindsey R. Baden,[1,2,3] and Francisco M. Marty[1,2,3]

[1]Brigham and Women's Hospital, [2]Dana-Farber Cancer Institute, [3]Harvard Medical School, and [4]Harvard School of Public Health, Boston, Massachusetts

Clinical Infectious Diseases 2009; 49:1650–9

A total of 1308 BG assays were performed for 871 patients. 228 proven or probable IFD

Sensitivity 64%, specificity 84%. Positive likelihood ratio was 3.93 and the negative likelihood ratio was 0.43

FP: Albumin, intravenous immunoglobulin, and hemodialysis

Empirical systemic antifungal treatment did not reduce overall BG sensitivity.

Sensitivity was slightly lower among patients with hematologic malignancy or stem cell transplantation

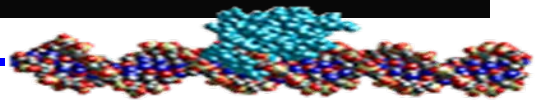
Koo et al. CID 2009

Fungal Infection	No. of proven infection	No. of probable infection
Candidiasis	83	3
Aspergillosis	26	38
Pneumocystis	0	28
Zygomycosis	7	1
Other yeasts	16	0
Other moulds	10	7

What are the best tests for diagnosing candidaemia? 2

Specimen	Test	Considerations	Remarks/Recommendations
Serum	Mannan and Anti-Mannan	•Combined detection	RECOMMENDED Serial determinations may be necessary. High NPV
	Other Ab (such as Serion ELISA classic)	•Limited data for candidemia	No recommendation
	ß-D-Glucan	•No specific for *Candida*	RECOMMENDED (for Fungitell) No recommendation for other tests. Serial determinations are recommended (twice a week). High NPV. Not validated in children
	Septifast	**•Limited data for candidemia**	**No recommendation**
	In house PCR	•No third party validation data available	No recommendation

The PCR commercial systems



- **Light Cycler SeptiFast**
  - **Wallet et al. CMI 2009.**
    - **72 Sepsis. Three cases of candidaemia, SF detects 1/3**
  - **Von Lilienfeld-Toal M. JCM 2009**
    - **119 FN,**
      - **2 Candida, one by BC and one by SF**
      - **2 A. fumigatus, by SF only**
  - **Lamoth et al. JCM 2010**
    - **141 FN episodes. Detected 5 cases of candidaemia with BC negative**
  - **Lucignano et al. JCM 2011**
    - **32 cases of candidaemia in neonates and children. Septifast improved BC performance**

What are the best tests for diagnosing candidaemia? 2

Specimen	Test	Considerations	Remarks/Recommendations
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	Septifast	•Limited data for candidemia	No recommendation
	In house PCR	**•No third party validation data available**	**No recommendation**

Candida PCR in clinical samples

Journal of Medical Microbiology (2009), 58, 1106–1111 DOI 10.1099/jmm.0.007906-0

Rapid diagnosis of candidaemia by real-time PCR detection of *Candida* DNA in blood samples

Nele Wellinghausen,[1,2] Dunja Siegel,[1] Juliane Winter[1]† and Susanne Gebert[1]†

10.1111/j.1469-0691.2009.02762.x

Evaluation of nested and real-time PCR assays in the diagnosis of candidaemia

M. Khlif[1], C. Mary[2], H. Sellami[1], A. Sellami[1], H. Dumon[2], A. Ayadi[1] and S. Ranque[2]
1) *Laboratoire de Biologie Moléculaire Parasitaire et Fongique, Faculté de Médecine, University of Sfax, Sfax, Tunisia and* 2) *Laboratoire de Parasitologie-Mycologie, Hôpital de la Timone, Marseille, France*

A Prospective Clinical Trial of a Real-Time Polymerase Chain Reaction Assay for the Diagnosis of Candidemia in Nonneutropenic, Critically Ill Adults

Clinical Infectious Diseases 2008; 46:890–6

R. McMullan,[1] L. Metwally,[1] P. V. Coyle,[1] S. Hedderwick,[2] B. McCloskey,[3] H. J. O'Neill,[1] C. C. Patterson,[4] G. Thompson,[1,3] C. H. Webb,[1] and R. J. Hay[4]

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Candida PCR in clinical samples

Rapid diagnosis of candidaemia by real-time PCR detection of *Candida* DNA in blood samples

Nele Wellinghausen,[1,2] Dunja Siegel,[1] Juliane Winter[1]† and Susanne Gebert[1]†

Limited number of patients with proven infection

(Sn > 80 % and Sp > 90 %)

Many more studies with PCR from cultures

Evaluation of nest… candidaemia

M. Khlif[1], C. Mary[2], H. Sellami[1],
1) *Laboratoire de Biologie Moléculaire … cologie, Hôpital de la Timone, Marseille…*

A Prospe… Polymera… of Candidemia in Nonneutropenic, Critically Ill Adults

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JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2011, p. 665–670
0095-1137/11/$12.00 doi:10.1128/JCM.01602-10

Vol. 49, No. 2

PCR Diagnosis of Invasive Candidiasis: Systematic Review and Meta-Analysis▽†

Tomer Avni,[1]* Leonard Leibovici,[1] and Mical Paul[2]

54 studies with 4,694 patients, 963 of whom had proven/probable or possible IC.

The pooled sensitivity for the diagnosis of candidemia was 0.95 and the pooled specificity was 0.92 (0.88 to 0.95)

PCR positivity rates among patients with proven or probable IC were 85% (78 to 91%), while blood cultures were positive for 38% (29 to 46%)

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BUT… which one? Validation study is compulsory before recommendation

JOURNAL OF CLINICAL MICROBIOLOGY, Mar. 2010, p. 811–816
0095-1137/10/$12.00 doi:10.1128/JCM.01650-09

Vol. 48, No. 3

Comparison of Whole Blood, Serum, and Plasma for Early Detection of Candidemia by Multiplex-Tandem PCR[▽]

Anna Lau,[1,2] Catriona Halliday,[1,3] Sharon C.-A. Chen,[1,3] E. Geoffrey Playford,[4] Keith Stanley,[5] and Tania C. Sorrell[1,2]*

Sensitivity, specificity, positive predictive value, and negative predictive value of the assay with whole blood were 75%, 97%, 95%, and 85%, respectively.

109 patients with candidaemia

Blood, serum and plasma

JOURNAL OF CLINICAL MICROBIOLOGY, Mar. 2010, p. 811–816
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Anna Lau,[1,2] Catriona Halliday,[1,3] Sharon C.-A. Chen,[1,3] E. Geoffrey Playford,[4] Keith Stanley,[5] and Tania C. Sorrell[1,2]*

EARLY DIAGNOSIS OF CANDIDEMIA

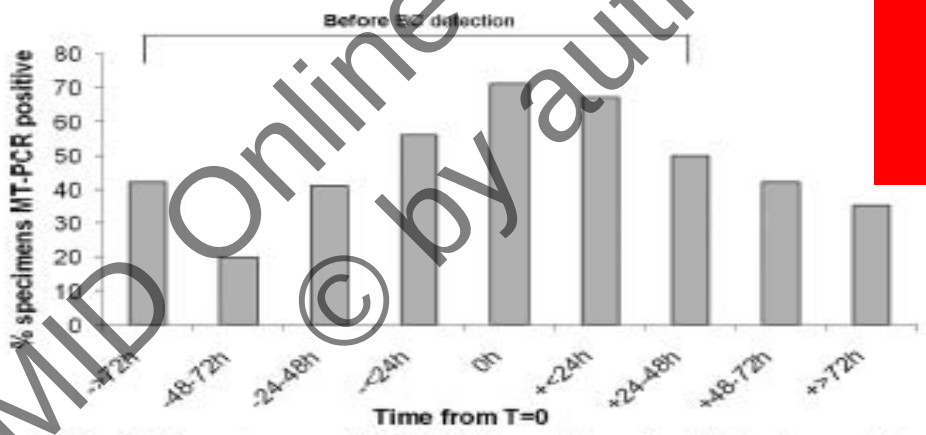

FIG. 2. Percentage of MT-PCR-positive whole-blood samples stratified by collection times relative to the time that the first positive blood culture (BC) sample was drawn ($T = 0$) for 255 specimens collected from 109 candidemic patients.

Mean 2.2 days (0.5 to 8 days)

109 patients with candidaemia

Blood, serum and plasma

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Diagnosis of invasive candidiasis

What are the best tests for diagnosing invasive candidiasis? 1

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Specimen	Test	Considerations	Remarks/Recommendations
Tissue sample / body fluids from normally sterile sites	Direct microscopy and histopathology	• Obtained and collected aseptically • Transport to the lab promptly • Tissue for histopathology should be placed in fixative as rapid as possible (caution: sample can dry up) • Special stains should be use including optical brighteners, silver stains and PAS • Morphology cannot be used for definitive ID	• Small samples are prone to sampling error • Samples for culture must not be placed in chemical fixing fluids • Sample must be kept moist • Expertise needed for interpretation
	Culture	Include fungal selective media	• Yeast isolation from normally sterile tissues or fluids is usually indicative of deep seated infection • Negative culture results do not exclude Candida infection. Blood cultures have low diagnostic yield • Process promptly to avoid multiplication of organisms. If not possible, store at 4-5 degrees • Identification is mandatory

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	Culture	Include fungal selective media	• Yeast isolation from normally sterile tissues or fluids is usually

References:

1) Lass-Florl. Clin Microbiol Infect 2009;15 Suppl 5: 60-5
2) Richardson M. Hosp Med 2000;61:610-4
3) Kaufmann. Eur Epidemiol 1992;8:377-382
4) Jensen et al. J Pathol 1997;181:100-105
5) Jensen et al. Acta Pathol Microbiol Immunol Scand, 1996;104:241-258
6) Marklein G et al. J Clin Microbiol 2009;47:2912-17

What are the best tests for diagnosing invasive candidiasis?

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SUMMARY of tissue samples and body fluids

Microscopic Examination:

- Obtained and collected aseptically
- Transport to the lab promptly
- Tissue for histopathology should be placed in fixative rapidly
- Special stains should be use including optical brighteners, silver stains and PAS
- Morphology cannot be used for definitive ID. Expertise needed for interpretation

Culture:

- Use selective media
- Yeast isolation from normally sterile tissues or fluids is usually indicative of deep seated infection
- Negative culture results do not exclude *Candida* infection. Blood cultures have low diagnostic yield
- Identification is mandatory

What are the best tests for diagnosing invasive candidiasis? 2

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Specimen	Test	Considerations	Remarks/Recommendations
Tissue sample/body fluids from normally sterile sites (cont.)	Immunohistochemistry	• Not generally available. If yeast seen in tissue but BC negative then use immunohistochemistry	• Genus specific antibody commercially available only (e.g. Rabbit anti *C. albicans*, type A:Biotin, Serotec, No.1750-5557) • Only positive results reliable
	Tissue PCR	• Use free DNA materials • Not generally available • No third party validation data available	• Not commercially available • These techniques might be carried out following Laser microdissection
	In situ hybridization	• Not generally available	
Serum	Mannan and Anti-Mannan	• Combined detection • Not enough data available	• No recommendation. It can be more useful for chronic disseminated candidosis
	ß-D-Glucan	• Not specific for *Candida*	• RECOMMENDED. If available (twice a week). Not validated in children
	Septifast and in-house PCR	• No published data available	• No recommendation

What are the best tests for diagnosing invasive candidiasis? 2

Specimen	Test	Considerations	Remarks/Recommendations
Tissue sample/body fluids from normally sterile sites (cont.)	Immunohistochemistry	• Not generally available. If yeast seen in tissue but BC negative then use immunohistochemistry	• Genus specific antibody commercially available only (e.g. Rabbit anti *C. albicans*, type A:Biotin, Serotec, No.1750-5557) • Only positive results reliable
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4. Jensen et al. J Pathol 1997;181:100-105
5. Jensen et al. Acta Pathol Microbiol Immunol Scand, 1996;104:241-258
6. Mikulska et al. Critical Care 2010;14:R222
7. Koo et al. Clin Infec Dis 2009;49:1650-9
8. Lischewski et al. 1996. Microbiology, 142, 2731-2740.

What are the best tests for diagnosing invasive candidiasis?

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SUMMARY of other techniques

Immunohistochemistry

Not generally available, use specific antibody commercially available

Tissue PCR

Not commercially available. No third party validation

In situ hybridization

Not commercially available. No third party validation

Mannan and Anti-Mannan in serum

No data

ß-D-Glucan in serum

RECOMMENDED, same than those in candidaemia

Septifast and in-house PCR in serum

No data

8. Lischewski et al. 1996. Microbiology, 142, 2731-2740.

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Diagnosis of chronic disseminated candidiasis

What are the best tests for diagnosing chronic disseminated candidiasis? 1

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Specimen	Test	Considerations	Remarks/Recommendations
Tissue sample	Direct microscopy/Histopathology	• **A tissue biopsy is highly recommended** • Same as invasive candidiasis	• Same as invasive candidiasis
	Culture Immunohistochemistry Tissue PCR In situ hybridization	Same as invasive candidiasis	
Blood	Blood culture	Same as invasive candidiasis	
Serum	**Mannan and Anti-Mannan**	• **Combined detection**	• **RECOMMENDED**
	ß-D-Glucan	• Not specific for *Candida*	• RECOMMENDED (as supplementary test). Not validated in children
	Septifast and in-house PCR	No published data available	• No recommendation

References: identical as candidaemia

Detection mannan and anti-mannan

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Mikulska *et al. Critical Care* 2010, 14:R222
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CRITICAL CARE

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14 studies, 453 patients and 767 controls

	Platelia Ab	Ag	Both
Sensitivity	53 %	59 %	82 %
+ pre_culture	6 days in average		

Chronic disseminated candidiasis:
21 cases, 86 % S
16 days prior culture

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Diagnosis of oropharyngeal candidiasis and oesophagitis

What are the best tests for oropharyngeal candidiasis and oesophagitis? 1

Specimen	Test	Considerations	Remarks/Recommendations
Swab	Culture	• **Include fungal selective media**	• To avoid overgrowth by colonizing bacteria • **Species identification and susceptibility testing is recommended in recurrent/complicated cases in patients with prior azole exposure**
	In house PCR	• **Not validated**	
Biopsy	Microscopy/histopathology	• Same as invasive candidosis	• **Biopsy is not mandatory, might discriminate between infection and colonization**
	Culture	• As above	
	In-house PCR	• Not validated	• As above

What are the best tests for oropharyngeal candidiasis and oesophagitis? 1

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Specimen	Test	Considerations	Remarks/Recommendations
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	In-house PCR	• Not validated	• As above

References:
1) Thompson et al. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:488-95
2) Gadea et al. Enfermedades Infecciosas y Microbiologia Clinica 2007;25:336-40
3) Powderly et al. AIDS Res Hum Retroviruses 1999;15:1405-12.

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Diagnosis of *Candida* vaginitis

What are the best tests for *Candida* vaginitis? 1

Specimen	Test	Considerations	Remarks/Recommendations
Swab/ vaginal secretions	**Direct microscopy**	• A swab is less useful for microscopy, vaginal secrete spread directly onto a microscopy slide and left to dry is recommended	• Not all *Candida* spp. form hyphae during infection (e.g. *C. glabrata*), microscopy in such cases will reveal yeast cells only
	Culture	• Semiquantitative technique using fungal selective agar	• **Species identification and susceptibility testing is recommended in recurrent/complicated cases in patients with prior azole exposure**
	Commercial tests	• Use validated tests only	
	In-house PCR	• Not validated	

What are the best tests for *Candida* vaginitis? 1

Specimen	Test	Considerations	Remarks/Recommendations
Swab / vaginal secretions	Direct microscopy	• A swab is less useful for microscopy, vaginal secrete spread directly onto a microscopy slide and left to dry is recommended	• Not all *Candida* spp. form hyphae during infection (e.g. *C. glabrata*), microscopy in such cases will reveal yeast cells only
	Culture	• Semiquantitative technique using fungal selective agar	• Species identification and susceptibility testing is recommended in recurrent/complicated cases in patients with prior azole exposure
	Commercial tests	• Use validated tests only	
	In-house PCR	• Not validated	

References:
1) Quan. Postgrad Med 2010;122:117-27
2) Dan et al. Diagn Microbiol Infect Dis 2010;67:52-5
3) Marot-Leblond et al. J Clin Microbiol 2009;47:3821-5
4) Weissenbacher et al. Arch Gynecol Obstet 2009;279:125-9

AST Recommendations

When are AST recommended for patient management and when for epidemiological reasons? 1

Isolated from	FOR patient management	FOR Epidemiology
Blood and other deep sites	**All isolates** and particularly: 1. Strains from patients exposed to antifungal agents 2. Clinical failures 3. Rare and emerging species 4. Species that are known to be resistant or less susceptible to antifungal drug(s) in clinical use	• All isolates should be tested using a **reference method or a validated commercial method**
Superficial sites	• Failed to respond or relapsing infection • Surveillance cultures from patients exposed to antifungal agents	• Periodical epidemiological studies should be done

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References:
1) CLSI M27-A3, M27-S3, M44-A2
2) EUCAST Discussion Document E.Dis 7.1
3) Pfaller et al. J Clin Microbiol 1995;33:1104-7
4) EUCAST-AFST. Clin Microbiol Infect 2008;14:193-95
5) EUCAST-AFST. Clin Microbiol Infect 2008; 14:985-987
6) Alexander et al. J Clin Microbiol 2007;45: 698-706
7) Dannaoui et al. Clin Microbiol Infect 2010;16: 863-9
8) Cuenca-Estrella et al. J Clin Microbiol 2010;48:1782-6
9) Arendrup MC et al. Antimicrob Agents Chemother 2010;54:426-39

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TDM Recommendations

TDM: therapeutic drug monitoring

Are therapeutic drug monitoring (TDM) indicated for patient management? 1

- TDM must be used for patients treated with 5-fluorocytosine
- **TDM is not normally required for drugs used in the treatment of *Candida* infections** (ECMO (extra-corporeal membrane oxygenation) can reduce echinocandin concentration)
- TDM is recommended if voriconazole is prescribed (voriconazole TDM is highly recommended in unsatisfactory response to therapy, suspicion of toxicity or drug interaction(s), impaired liver or renal function an in patients on extracorporeal membrane oxygenation)

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References:
1) Trifilio et al. Cancer 2007;109:1532-5
2) Pascual et al. Clin Infect Dis 2008;46:201-11
3) Buchkowsky et al. Ther Dr Monit 2005; 27:322-33
4) CLSI M27-S3 (itraconazole)
5) Andes et al. Antimicrob Agents Chemother 2009;53:24-34