6. Febril Nötropeni Mezuniyet Sonrası Eğitim Kursu
21-22 Nisan 2012 İstanbul

FUNGAL İNFEKSİYONLAR ve KILAVUZLAR :

ESCMID-EFISG Candida Kılavuzu

Prof. Dr. Sevtap Arıkan Akdağlı
Hacettepe Üniv. Tıp Fak. Tıbbi Mikrobiyoloji AD

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

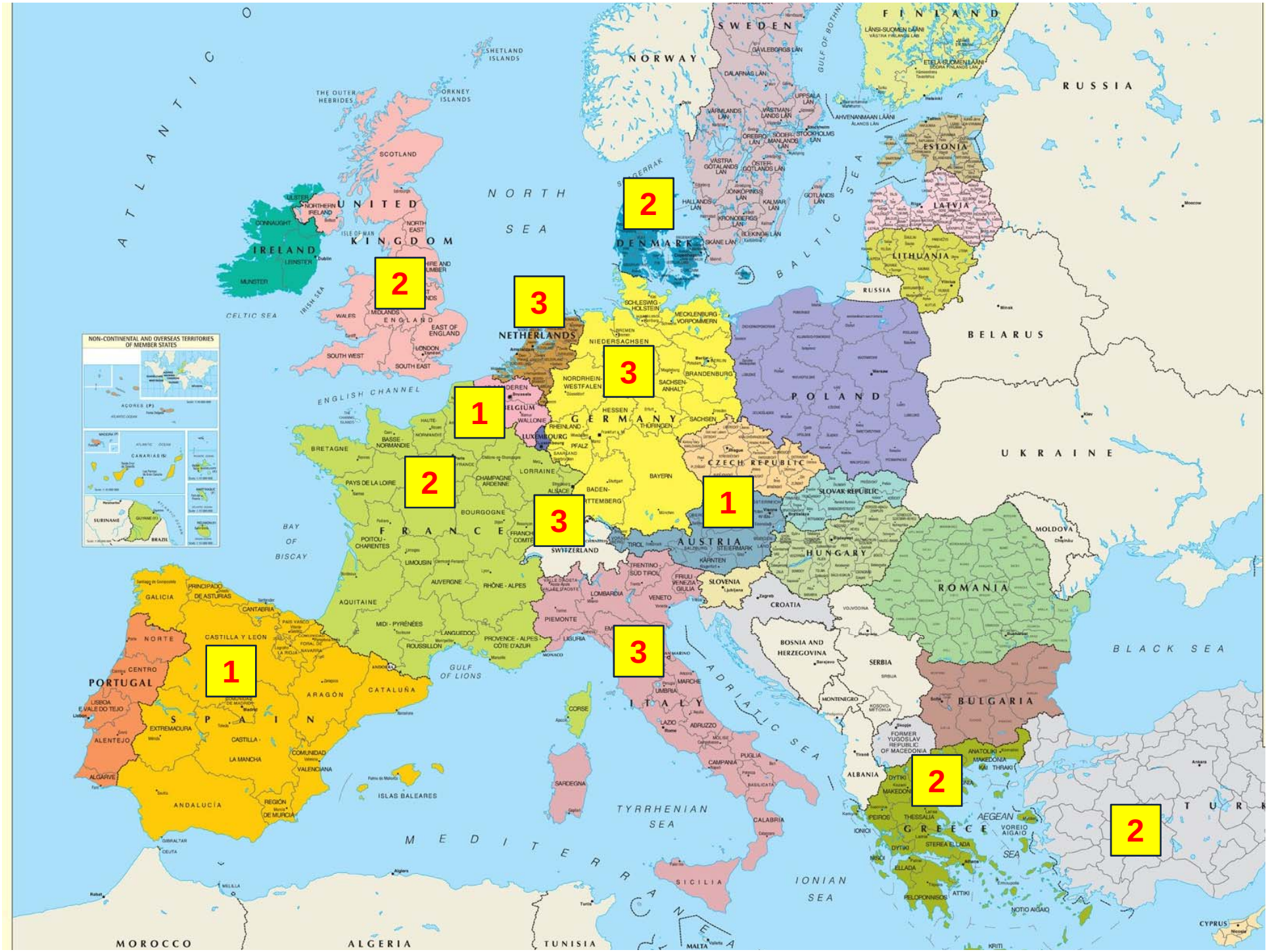
ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

Authors: Murat Akova, Maiken Arendrup, Sevtap Arikan-Akdagli, Matteo Bassetti, Jacque Bille, Thierry Calandra, Elio Castagnola, **Oliver A. Cornely**, **Manuel Cuenca-Estrella**, Peter Donnelly, Jorge Garbino , Andreas Groll, Raoul Herbrecht, **William Hope,** Henrik Elvang Jensen, Bart-Jan Kullberg, Cornelia Lass-Flörl, **Olivier Lortholary,** Wouter Meersseman, Georgios Petrikkos, Malcolm Richardson, Emmanuel Roilides, **Andrew J. Ullmann, Paul Verweij**, Claudio Viscoli

Main Coordinator: Andrew J. Ullmann

ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

Murat Akova, Hacettepe University, Ankara Turkey
Maiken Cavling Arendrup, Statens Serum Institut ,Copenhagen Denmark
Sevtap Arikan-Akdagli, Hacettepe University, AnkaraTurkey
Matteo Bassetti, San Martino University Hospital, Genoa, Genoa Italy
Jacque Bille, Centre Hospitalier Universitaire Vaudois, Lausanne Switzerland
Thierry Calandra, Centre Hospitalier Universitaire Vaudois, Lausanne Switzerland
Elio Castagnola, "G.Gaslini" Children's Hospital, Genova Italy
Oliver A. Cornely, Universität zu Köln, Cologne Germany
Manuel Cuenca-Estrella, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid Spain
Peter Donnelly, Radboud University Nimegen Medical Centre, Nijmegen, Netherlands
Jorge Garbino, University Hospitals Geneva, Geneva Switzerland
Andreas Groll, University Children's Hospital,Westfälische Wilhelms-Universität, Münster Germany
Raoul Herbrecht, Hôpital de Hautepierre, University of Strasbourg France
William Hope, The University of Manchester, Manchester United Kingdom
Henrik Elvang Jensen, University of Copenhagen, Frederiksberg Denmark
Bart-Jan Kullberg, Radboud University, Nijmegen, Netherlands
Cornelia Lass-Flörl, Division of Hygiene & Medical Microbiology, Innsbruck Medical University, Innsbruck Austria
Olivier Lortholary, Institut Pasteur, Université Paris Descartes, Hôpital Necker Enfants malades, **Paris France**
Wouter Meersseman, University Hospital Gasthuisberg, Leuven Belgium
Georgios Petrikkos, National and Kapodistrian University of Athens, Athens Greece
Malcolm Richardson, University Hospital of South Manchester, & The University of South Manchester, United Kingdom
Emmanuel Roilides, Aristotle University, Thessaloniki Greece
Andrew Ullmann, Johannes Gutenberg Universität, Mainz Germany
Paul Verweij, Radboud University, Nijmegen, Netherlands
Claudio Viscoli, University of Genoa, Genoa Italy


1
2
3
1
2
3
1
3
2
2
NON-CONTINENTAL AND OVERSEAS TERRITORIES OF MEMBER STATES
ATLANTIC OCEAN
NORTH SEA
BALTIC SEA
IRISH SEA
CELTIC SEA
ENGLISH CHANNEL
BAY OF BISCAY
GULF OF LIONS
MEDITERRANEAN SEA
TYRRHENIAN SEA
ADRIATIC SEA
IONIAN SEA
AEGEAN SEA
BLACK SEA
GULF OF BOTHNIA
SWEDEN
NORWAY
FINLAND
RUSSIA
ESTONIA
LATVIA
LITHUANIA
BELARUS
POLAND
UKRAINE
DENMARK
IRELAND
UNITED KINGDOM
SCOTLAND
NETHERLANDS
BELGIUM
LUXEMBOURG
GERMANY
FRANCE
SWITZERLAND
AUSTRIA
CZECH REPUBLIC
SLOVAK REPUBLIC
HUNGARY
MOLDOVA
ROMANIA
BULGARIA
SLOVENIA
CROATIA
BOSNIA AND HERZEGOVINA
SERBIA
MONTENEGRO
ALBANIA
FORMER YUGOSLAV REPUBLIC OF MACEDONIA
GREECE
ITALY
PORTUGAL
SPAIN
MOROCCO
ALGERIA
TUNISIA
MALTA
CYPRUS
TURKEY
SICILIA
SARDEGNA
CORSE
ISLAS BALEARES
GIBRALTAR
CEUTA
MELILLA
IRELAND
NORTHERN IRELAND
SCOTLAND
WALES
ENGLAND
MIDLANDS
EAST OF ENGLAND
LONDON
SOUTH EAST
SOUTH WEST
NORTH EAST
THE OUTER HEBRIDES
ORKNEY ISLANDS
SHETLAND ISLANDS
ISLE OF MAN
CONNAUGHT
LEINSTER
MUNSTER
ULSTER
SCHLESWIG HOLSTEIN
MECKLENBURG-VORPOMMERN
NIEDERSACHSEN
BREMEN
HAMBURG
NORDRHEIN-WESTFALEN
BRANDENBURG
SACHSEN-ANHALT
SACHSEN
THÜRINGEN
HESSEN
RHEINLAND-PFALZ
SAARLAND
BADEN-WÜRTTEMBERG
BAYERN
WALLONIE
BRUXELLES
VLAANDEREN
LUXEMBOURG
BRETAGNE
BASSE-NORMANDIE
PAYS DE LA LOIRE
CHAMPAGNE-ARDENNE
LORRAINE
ALSACE
FRANCHE-COMTÉ
BOURGOGNE
POITOU-CHARENTES
LIMOUSIN
AUVERGNE
RHÔNE-ALPES
AQUITAINE
MIDI-PYRÉNÉES
LANGUEDOC-ROUSSILLON
PROVENCE-ALPES-CÔTE D'AZUR
MONACO
PIEMONTE
LIGURIA
LOMBARDIA
VENETO
TRENTINO-SÜD TIROL
FRIULI-VENEZIA GIULIA
EMILIA-ROMAGNA
TOSCANA
UMBRIA
MARCHE
LAZIO
ABRUZZO
MOLISE
CAMPANIA
PUGLIA
BASILICATA
CALABRIA
SICILIA
SARDEGNA
GALICIA
PRINCIPADO DE ASTURIAS
CANTABRIA
PAIS VASCO
NAVARRA
LA RIOJA
CASTILLA Y LEON
NORTE
CENTRO
LISBOA E VALE DO TEJO
ALENTEJO
ALGARVE
EXTREMADURA
CASTILLA-LA MANCHA
COMUNIDAD VALENCIANA
REGION DE MURCIA
ANDALUCÍA
ARAGÓN
CATALUÑA
ISLAS BALEARES
ANDORRA
SUOMEN LÄNNI
LÄNSI-SUOMEN LÄNNI
ETELÄ-SUOMEN LÄNNI
ÖSTRA MELLANSVERIGE
SMÅLAND MED ÖARNA
SYDSVERIGE
NORRA MELLANSVERIGE
MELLERSTA NORRLAND
ÖVRE NORRLAND
VÄSTSVERIGE
GÄVLEBORGS LÄN
DALARNAS LÄN
UPPSALA LÄN
VÄRMLANDS LÄN
VÄSTMANLANDS LÄN
ÖREBRO LÄN
SÖDERMANLANDS LÄN
STOCKHOLMS LÄN
VÄSTRA GÖTALANDS LÄN
ÖSTERGÖTLANDS LÄN
JÖNKÖPINGS LÄN
KRONOBERGS LÄN
KALMAR LÄN
GOTLANDS LÄN
HALLANDS LÄN
SKÅNE LÄN
BLEKINGE LÄN
ÅHVENANMAAN LÄÄNI
ÅLANDS LÄN
Moscow
Minsk
Kiev
Warsaw
Riga
Helsinki
Stockholm
Oslo
Copenhagen
Dublin
Belfast
Edinburgh
Cardiff
London
Amsterdam
Brussels
Luxembourg
Berlin
Frankfurt
Munich
Vienna
Prague
Bratislava
Budapest
Chisinau
Bucharest
Zagreb
Ljubljana
Sarajevo
Belgrade
Skopje
Tirana
Sofia
Athens
Ankara
Rome
Milan
Turin
Genoa
Venice
Florence
Naples
Palermo
Cagliari
Paris
Lyon
Marseille
Bordeaux
Toulouse
Nice
Strasbourg
Nantes
Lille
Madrid
Barcelona
Valencia
Sevilla
Zaragoza
Bilbao
Lisboa
Porto
Algiers
Tunis
Rabat
Valletta
Nicosia
Kriti
Peloponnisos
Attiki
Ionioi
Dytiki Ellada
Sterea Ellada
Thessalia
Peiros
Dytiki Makedonia
Anatoliki Makedonia kai Thraki
Notio Aigaio
Voreio Aigaio
Kriti
Azores (P)
Madeira (P)
Canarias (E)
Guyane (F)
Suriname
Brazil

Contact with other European Societies

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

- EORTC
- ESICM
- EBMT
- ECMM

Working Modules

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

- Diagnostic procedures
- ICU (medical & surgical), other non-immunocompromised (medical & surgical), other immunocompromised situations
- Paediatrics & PICU
- Haematology/Oncology
- HIV/AIDS

Working Modules

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

Diagnostic procedure	Maiken Arendrup, Sevtap Arikan-Akdagli, Jacques Bille, **Manuel Cuenca-Estrella**, Peter Donnelly, Henrik Elvang Jensen, Cornelia Lass-Flörl, Malcolm Richardson, **Paul Verweij**
ICU (medical & surgical)	Matteo Bassetti, Thierry Calandra, **Oliver Cornely**, Jorge Garbino, Bart-Jan Kullberg, Wouter Meersseman
Other non-immunocompromised (medical & surgical), other immunocompromised situations	
Paediatrics	Elio Castagnola, Andreas Groll, **William Hope,** Emmanuel Roilides
PICU	
Haematology/Oncology	Murat Akova, Raoul Herbrecht, **Andrew Ullmann,** Claudio Viscoli
HIV/AIDS	**Olivier Lortholary,** Georgios Petrikkos

bold: working module(s) coordinators

Working Module

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

Diagnostic procedures

Which diagnostic procedures to use and how to interpret the results?

- a) Importance of physical examination including imaging
- b) Sampling issues
  - a. Conventional
  - b. Non-conventional diagnostic procedures:
    - i.Serology (antigen assay)
    - ii.Molecular- based analysis
- c) Interpretation of results
  - a. Role of susceptibility testing for treatment decisions
  - b. Need for species identification & susceptibility: when?
- d) Imaging/bioimaging
- e) Defining disease/failure/success (also a question for the other groups)

Working Modules

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

Hematology/Oncology	Pediatrics	PICU
ICU (medical & surgical), "normal host"	HIV/AIDS	Other immunocompromised situations

- When is prophylaxis indicated? Which agents?
- When is empiric or pre-emptive therapy indicated? Which agents?
- Which antifungal agent(s) is(are) needed for targeted treatment (treatment duration and various host factors will need special attention)?
    a) Candidaemia
    b) Invasive candidiasis
        - Special attention is required on the location of disease
    c) Chronic disseminated candidiasis (if applicable)
    d) Mucosal candidiasis
- Consider miscellaneous issues (not exclusive):
    a) Biofilm formation issues on CVC and other hardware
    b) Granulocyte transfusions, cytokine treatment
    c) How to treat during renal failure

    d) How to treat during hepatic failure

Strength of the EFISG Recommendation by Quality of Evidence

Two Parts:

- Strength of recommendation
- Quality of Evidence

Strength of recommendation

Grade A	ESCMID (fungal infection study group) **strongly** supports a recommendation for use
Grade B	ESCMID (fungal infection study group) **moderately** supports a recommendation for use
Grade C	ESCMID (fungal infection study group) **marginally** supports a recommendation for use
Grade D	ESCMID (fungal infection study group) **supports** a recommendation against use

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

Strength of the EFISG Recommendation by Quality of Evidence

Quality of evidence

Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II*	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

*: added index:

$_r$:	meta-analysis (or systematic review of RCT);
$_t$:	transferred evidence i.e. results from different patients‘ cohorts, or similar immune-status situation;
$_h$:	comparator group: historical control;
$_u$:	uncontrolled trials
$_a$:	for published abstract (presented at an international symposium or meeting)

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

Consensus

- Meetings in
  - Vienna April 2010 (ECCMID)
  - Mainz December 2010
  - Frankfurt January 2011

- Electronic communication
- FTP-Server
- Telephone Conferences

EFISG ESCMID FUNGAL INFECTION STUDY GROUP

European Society of Clinical Microbiology and Infectious Diseases

Diagnostic Working Module of ESCMID *Candida* Guidelines

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)
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

EFISG ESCMID FUNGAL INFECTION STUDY GROUP

European Society of Clinical Microbiology and Infectious Diseases

Diagnosis of candidaemia

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

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

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

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

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

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

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

Małgorzata 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		

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

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

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

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	**•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

EFISG ESCMID FUNGAL INFECTION STUDY GROUP

European Society of Clinical Microbiology and Infectious Diseases

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

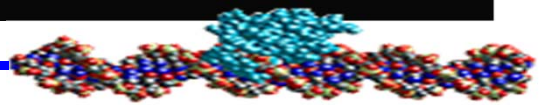
EFISG ESCMID FUNGAL INFECTION STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

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

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

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**

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

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**

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

JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2011, p. 665–670 Vol. 49, No. 2
0095-1137/11/$12.00 doi:10.1128/JCM.01602-10
Copyright © 2011, American Society for Microbiology. All Rights Reserved.

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%)

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

JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2011, p. 665–670 Vol. 49, No. 2
0095-1137/11/$12.00 doi:10.1128/JCM.01602-10
Copyright © 2011, American Society for Microbiology. All Rights Reserved.

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%)

BUT... which one? Validation study is compulsory before recommendation

EFISG ESCMID FUNGAL INFECTION STUDY GROUP

European Society of Clinical Microbiology and Infectious Diseases

Diagnosis of invasive candidiasis

What are the best tests for diagnosing invasive candidiasis? 1

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

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 used 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

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? 2

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

Specimen	Test	Considerations	Remarks/Recommendations
Tissue sample / body fluids from normally sterile sites (cont.)	Immunohistoche-mistry	• 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
		r *Candida*	• RECOMMENDED. If available (twice a week). Not validated in children
		data	• No recommendation

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. 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.

EFISG ESCMID FUNGAL INFECTION STUDY GROUP

European Society of Clinical Microbiology and Infectious Diseases

Diagnosis of chronic disseminated candidiasis

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

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

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

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

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

Małgorzata 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 %

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

pre_culture

EFISG ESCMID FUNGAL INFECTION STUDY GROUP

European Society of Clinical Microbiology and Infectious Diseases

Diagnosis of oropharyngeal candidiasis and oesophagitis

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

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

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

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.

EFISG ESCMID FUNGAL INFECTION STUDY GROUP

European Society of Clinical Microbiology and Infectious Diseases

Diagnosis of *Candida* vaginitis

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

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

EFISG ESCMID FUNGAL INFECTION STUDY GROUP

European Society of Clinical Microbiology and Infectious Diseases

AST Recommendations

AST: Antifungal Susceptibility Testing

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

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

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

EFISG ESCMID FUNGAL INFECTION STUDY GROUP

European Society of Clinical Microbiology and Infectious Diseases

TDM Recommendations

TDM: therapeutic drug monitoring

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

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 and in patients on extracorporeal membrane oxygenation)

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

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

ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

Authors: Oliver A. Cornely, Matteo Bassetti, Thierry Calandra, Jorge Garbino, Bart-Jan Kullberg, Wouter Meersseman and ESCMID Candida Guidelines Committee

ICU (medical & surgical)

Other non-immunocompromised, other immunocompromised situations

Prophylaxis: Which Agents?

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

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages	To prevent intraabdominal candida infection	Fluconazole 400mg/d	B	I	Eggimann CCM 1999	Placebo, N=43
	As above	Caspofungin 70/50mg/d	C	II_u	Senn ICM 2009	Single arm, N=19
Critically ill surgical patients with an expected length of ICU stay ≥ 3d	To delay the time to fungal infection	Fluconazole 400mg/d	C	I	Pelz Ann Surg 2001	Placebo, N=260
Ventilated for 48h and expected to be ventilated for another ≥72h	To prevent invasive candidiasis / candidaemia	Fluconazole 100mg/d (in the context of SDD)	C	I	Garbino ICM 2002	Placebo, N=204

Prophylaxis: Which Agents?

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

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Surgical ICU patients	To prevent invasive candidiasis / candidaemia	Ketoconazole 200mg/d	**D**	**I**	Slotman Arch Surg 1987	Placebo, N=57
Critically ill patients with risk factors for invasive candidiasis / candidaemia	As above	Itraconazole 400mg/d	**D**	**I**	Havlicek Int Surg 2008	Open, N=147
SICU with catabolism	As above	Nystatin 4 Mio IU/d	**D**	**I**	Cerra Arch Surg 1992	Placebo, N=46

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

Empiric Therapy: When is it Indicated?

Population	Intention	Intervention	SoR	QoE	Reference
At risk + persistent FUO	Reduce overall mortality	Antifungal treatment (unspecified)	C	III	Garey CID 2004 Morrell AAC 2005 Parkins JAC 2007 Kumar Chest 2009
Adult ICU patients with fever despite broad-spectrum antibiotics, APACHE II >16	Resolution of fever	Fluconazole 400mg/d	D	I	Schuster Ann Int Med 2008

Definitions:

- Empiric = persistent FUO / **Fever driven approach**
- Pre-emptive = treatment based on a validated marker / **Diagnosis driven approach**

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

Pre-emptive Therapy: ß-D-Glucan

Popu-lation	Intention	Inter-vention	SoR	QoE	Reference	Comments
ICU	Early treatment of invasive candidiasis / candidaemia	To treat when ß-D-glucan test is positive	C	II_u	Desmet JCM 2009 Digby Clin Diagn Lab Immunol 2003 Koo CID 2009 Mohr JCM 2011 Presterl Int JID 2009 Takesue WJSurg 2004 Pickering JCM 2005	•Low specificity •Low sensitivity •High NPV •False positives with •Haemodialysis •Other fungal or •Bacterial infection •Wound gauze •May be useful in PCP

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

Pre-emptive Therapy: Candida sp. isolated from respiratory secretions

Popula-tion	Intention	Intervention	SoR	QoE	Reference	Comment
Any	Cure	Any antifungal	D	II_u	Meersseman Int Care Med 2009	• No data from ICU populations • Case series with haematological malignancy

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

Targeted Treatment: Yeast in Blood Cultures

Population	Intention	Intervention	SoR	QoE	Reference
Candida isolated from **one** (peripheral blood or central line) blood culture defines candidaemia	Cure	Antifungal treatment	A	II	De Pauw CID 2008 Lecciones CID 1992 Kullberg Lancet 2006
Candidaemia	Cure	Antifungal treatment	A	III	Bodey EJCMID 1992 Edwards ICAAC 1982 Groll J Infect 1996 Kume Pathol Int 2003

Comment:

- Previous definitions described **asymptomatic patients** with a blood culture positive for Candida. It has been debated whether such patients need antifungal treatment.
- This is a very rare clinical situation, since usually a blood culture would be triggered by a clinical sign (e.g. fever)
- Even surveillance blood cultures positive for Candida should prompt immediate treatment.

Targeted Treatment of Candidaemia
Polyenes

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

Compound	SoR	QoE	Reference	Comment
Amphotericin B, deoxycholate, any dose	D	I	Ullmann CID 2006 Bates CID 2001 Anaissie CID 1996 Rex NEJM 1994 Philips EJCMID 1995 Mora-Duarte NEJM 2002	
Amphotericin B, liposomal	B	I	Kuse Lancet 2007 Dupont Crit Care 2009	•Similar efficacy as micafungin •Higher toxicity than micafungin
Amphotericin B, lipid complex	C	II_a	Anaissie ICAAC 1995 Ito CID 2005	
Amphotericin B, colloidal dispersion	D	II_u	Noskin CID 1998	•Mostly immunocompromised patients (HCT, haematology/oncology or SOT) rather than ICU patients

HCT, haematopoietic stem cell transplantation; SOT, solid organ transplantation.

Targeted Treatment of Candidaemia
Echinocandins

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

Compound	SoR	QoE	Reference	Comment
Anidulafungin 200/100	A	I	Reboli NEJM 2007	• Broad spectrum • Resistance rare • Fungicidal • Local epidemiology • *C. parapsilosis, C. krusei* • Safety profile • Less drug-drug interactions than caspofungin
Caspofungin 70/50	A	I	Mora-Duarte NEJM 2002 Pappas CID 2007	• Largely as above
Micafungin 100	A	I	Kuse Lancet 2007 Pappas CID 2007	• Largely as above • Consider EMA warning label

Targeted Treatment of Candidaemia
Azoles

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

Compound	SoR	QoE	Reference	Comment
Fluconazole	C	I	Anaissie CID 1996 Rex NEJM 1994 Rex CID 2003 Philips EJCMID 1995 Reboli NEJM 2007 Tuil CCM 2003 Abele-Horn Infect 1996 Leroy CCM 2009 Gafter-Gvili Mayo Clin Proc 2008	• Limited spectrum • Inferiority to anidulafungin (<u>especially</u> in the subgroup with high APACHE scores), • *C. parapsilosis*
Itraconazole	D	II_a	Tuil CCM 2003 (abstract)	
Posaconazole	D	III	No reference found	• PO only
Voriconazole	B	I	Kullberg Lancet 2005 Ostrosky EJCMID 2003 Perfect CID 2003	• Limited spectrum compared to echinocandins • Drug-drug interactions • IV in renal impairment • Need for TDM

TDM, Therapeutic drug monitoring.

Targeted Treatment of Candidaemia Combinations

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

Compound	SoR	QoE	Reference	Comment
Efungumab + Lipid-associated amphotericin B	D	II	Pachl CID 2006	
Amphotericin B deoxycholate + Fluconazole	D	I	Rex CID 2003	Efficacious, but • Increased risk of toxicity in ICU patients • No survival benefit
Amphotericin B deoxycholate + 5-fluorocytosine	D	II	Abele-Horn Infect 1996	
other two-drug combinations	D	III	Leroy CCM 2009	

Targeted Treatment of Candidaemia: Duration & Diagnostics

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

Population	Intention	Intervention	SoR	QoE	Reference
No organ involvement	Avoid organ involvement	Treat for 14 days after the end of candidaemia	B	II	Oude-Lashof CID 2011
		Take 1 blood culture per day until negative	B	III	No reference found
	Detect organ involvement	Transoesophageal echocardiography	B	II_a	Fernández-Cruz ICAAC 2010
		Fundoscopy	B	II	Oude-Lashof CID 2011 Rodriguez Med 2003 Brooks Arch Int Med 1989 Parke Ophthalmol 1982
		If CVC, PICC, or intravascular devices, search for thrombus	B	III	No reference found
Any	To simplify treatment	Step down to flucona-zole after 10 days of IV, if • Species is susceptible • Patient tolerates PO • Patient is stable	B	II	Reboli NEJM 2007 Mora-Duarte NEJM 2002 Pappas CID 2007

CVC, Central venous catheter; PICC, Peripherally inserted central catheter.

Catheter-Related Candidemia

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

Population	Intention	Intervention	SoR	QoE	Reference
Any patient with central venous catheter	To improve survival	Remove indwelling lines (not over a guidewire)	A	II	Andes CID 2012*
Any patient in whom a central venous catheter cannot be removed	To clear candidaemia	Treat with echinocandin, liposomal amphotericin B, or amphotericin B lipid complex	B	II	Kucharikova AAC 2010 Kuhn AAC 2002 Mukherjee IJAA 2009 Nucci CID 2010 Rex CID 1995
		Treat with azole, or amphotericin B deoxycholate	D	II	Almirante JCM 2005 Leroy CCM 2009 Liu J Infect 2009 Rodriguez CMI 2007 Weinberger JHI 2005

*Andes et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis : A patient level **quantitative review of randomized trials**. CID 2012 March 12. Data from 1915 pat.s from 7 trials.

Conclusion: Two treatment-related factors were associated with *improved survival* and greater clinical success: *use of an echinocandin and removal of the CVC*.

Chorioretinitis/Endophthalmitis
Polyenes & Echinocandins

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

Population	Intervention	SoR	QoE	Reference
Chorioretinitis/ Endophthalmitis	Amphotericin B deoxycholate	C	II	Oude-Lashof CID 2011
	Amphotericin B deoxycholate + 5-fluorocytosine	C	III	Edwards Medicine 1974 Parke Ophth 1982 McQuillen CID 1992 Essman Ophth Surg Lasers 1997
	Liposomal amphotericin B	B	III	Oude-Lashof CID 2011 Goldblum Ophth Res 2004 Neppert Klin Mbl Augheilk 1992
	Liposomal amphotericin B + 5-fluorocytosine	B	III	No reference found
	Amphotericin B deoxycholate	C	III	Virata CID 1999
	Amphotericin B lipid complex + 5-fluorocytosine	B	III	Darling J Infect 2000
	Caspofungin	D	II_u	Gauthier CID 2005 Cornely JAC 2007 Sarria CID 2005 Hakki AAC 2006 Spriet JAC 2009

Chorioretinitis/Endophthalmitis
Azoles & Surgery

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

Population	Intervention	SoR	QoE	Reference
Chorioretinitis/ Endophthalmitis, susceptible species	Fluconazole	A	II_u	Essman Ophth Surg Lasers 1997 Luttrull AmJOphth 1995 Laatikainen AmJ Ophth 1992 Akler CID 1995 Riddell CID 2011
	Voriconazole	A	II_u	Thiel AAC 2007 Oude-Lashof CID 2011 Breit Am J Ophth 2005 Hakki AAC 2006 Riddell CID 2011
Endophthalmitis, i.e. vitreal involvement	Amphotericin B deoxycholate intraocular injection	B	II_u	Essman Ophth Surg Lasers 1997 Grueb Cornea 2006 Payne Arch Ophthalmol 2010
	Vitrectomy	B	II_u	Essman Ophth Surg Lasers 1997

Central Nervous System

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

Population	Intervention	SoR	QoE	Reference
Meningitis	Liposomal amphotericin B +/- 5-fluorocytosine	B	III	Houmeau Arch Fr Pediatr 1993 Ng Arch Int Med 1995 Jarlov ScandJID 1995
	Amphotericin B deoxycholate +/- 5-fluorocytosine	D	II_u	Casado CID 1997 Chen ScandJID 2004 Smego Rev Inf Dis 1984 Chen ScandJID 2004
	Amphotericin B deoxycholate +/- 5-fluorocytosine	D	III	Perfect JAC 1994 (animal model)
	Fluconazole	C	III	Aleixo J Infect 2000 Chen ScandJID 2004 Cruciani EJCMID 1992
	Voriconazole	C	III	Schwartz Blood 2005 Weiler AAC 2011 Kullberg Lancet 2005
	Caspofungin	D	III	Liu JCM 2004 (case) van Hal EIC 2008 (case)

Endocarditis

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

Population	Intention	Intervention	SoR	QoE	Reference
Native valve	Decrease mortality	Surgery within 1 week	A	II_u	Falcone Medicine 2009 Ellis CID 2001 Lefort ICAAC 2009
		Liposomal Ampho B +/- 5-fluorocytosine	B	II_a	Lefort ICAAC 2009
		Caspofungin +/- 5-fluorocytosine	C	II_a	Lefort ICAAC 2009
Prosthetic valve	Decrease mortality	Early surgery	A	III	Falcone Medicine 2009 Boland Mycoses 2010
Prosthetic valve, if surgery contra-indicated	Suppression of infection	Fluconazole	C	III	Boland Mycoses 2010
	Cure	Liposomal Ampho B	B	III	Boland Mycoses 2010
	Cure	Caspofungin	B	III	Boland Mycoses 2010
Pacemaker, ICD, VAD	Cure	Removal	A	III	Baddley EJCMID 2008 Aslam CID 2010

ICD = implantable cardioverter defibrillator, VAD = ventricular assist device

Joint Infection

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

Population	Intention	Intervention	SoR	QoE	Reference
Arthritis	Cure	Fluconazole 400, ≥6 wks	A	II_u	Pérez-Gómez Sem Arth Rheum 1998 Hansen Scand JID 1995
		Liposomal Ampho B / ABLC 2 wks, followed by Fluconazole 400, total ≥6 wks	A	II_u	Hansen Scand JID 1995
		Echinocandin ≈2 weeks followed by Fluconazole 400, total ≥6 wks	B	III	Cornely JAC 2007 Sim Hon Kon Med J 2005
		Voriconazole 2x3 mg/kg ≥6 wks	B	III	Sili CID 2007
Prosthetic joint infection	Cure	Prosthesis removal	A	III	Tunkel AJM 1993
Prosthetic joint infection with prosthesis retention	Chronic suppres-sion	Fluconazole life long	A	III	Merrer J Infect 2001 Kelesdis Scand JID 2010 Levine Clin Orthop Relat Res 1986

Urinary Tract Infection

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

Population	Intention	Intervention	SoR	QoE	Reference
Asympto-matic	Eliminate candiduria	None	A	III	Revankar 2010 Kauffman CID 2000
		Fluconazole 200mg d1-14*	C	I	Sobel CID 2000 Kauffman CID 2000
		Removal of urinary catheter	B	I	Sobel CID 2000
		Ampho B bladder irrigation	C	II_r	Tuon IJID 2009 Kauffman CID 2000
Pyelo-nephritis	Cure	Caspofungin 70/50mg for 9-28d	C	III	Sobel CID 2007
		Fluconazole +/- 5-FC**	A	III	No reference
		Ampho B deoxycholate +/- 5-FC	A	III	No reference
Cystitis	Cure	Fluconazole	A	III	Sobel CID 2000 Kauffman CID 2000
		Amphotericin B +/- 5-fluorocytosine	B	III	Sobel CID 2000 Kauffman CID 2000
Fungus balls	Cure	Surgical intervention	A	III	Bartone J Urol 1988 Shih Urol 2005

*In pre-operative patients treatment is indicated to suppress candiduria; **if species is susceptible.

Bone Infection

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

Population	Inten-tion	Intervention	SoR	QoE	Reference
Osteomyelitis / spondylodiscitis	Cure	Surgical debridement*	C	III	Hendricks CID 2001 Miller CID 2001
	Cure	Fluconazole 400 mg 6-12 months	A	II_u	Hennequin CID 1996 Sugar DMID 1990 Miller CID 2001
	Cure	Liposomal Ampho B / ABLC 2-6 wks followed by Fluco-nazole 400 mg, total 6-12 months	A	II_u	Hennequin CID 1996 Miller CID 2001
	Cure	Echinocandin 2-6 wks follow-ed by Fluconazole 400 mg total 6-12 months	B	III	Cornely JAC 2007 Legout Scand JID 2006
	Cure	Voriconazole 2x3 mg/kg ≥6 weeks	B	III	Schilling Med Mycol 2008

*Indications for surgery are instability, or e.g. large abscess.

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

ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

HIV and AIDS

Olivier Lortholary on behalf of George Petrikkos and ESCMID Candida Guidelines Committee

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

Introduction

- Mucosal candidiasis is mostly caused by *C. albicans*
- After long term fluconazole exposure, fluconazole or even multiply azole resistant *C. albicans* may occur
- Intrinsically less azole susceptible species may occur such as *C. glabrata*
- Oropharyngeal but not vaginal candidiasis is a marker of immune deficiency

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

Primary prophylaxis of mucosal candidiasis (OPC/Oesophagitis)

Recommendation		Reference
There is no indication of primary antifungal prophylaxis of OPC in Europe although effective [interactions/acute therapy effective/induction of resistance/no mortality related to OPC/cost)	DIII	Powderly NEJM 1995 Schuman Ann Intern Med 97 Havlir CID 1998 Goldman CID 2005
The best prophylaxis is the appropriate compliance to HAART	AI	

Treatments of oropharyngeal candidiasis (OPC) Summary

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

Proposal	Rec	References
Local treatments with AmB or nystatin should be discouraged (HIV+)	DIII	
Clotrimazole not available in several European countries		
Fluconazole (100mg/d, 7-14d) 1st line therapy	AI	Pons 1993,1997 Koletar 1990, Sangeorzan
Miconazole mucoadhesive tablet	BII	Van Roey JAIDS 2004, Not approved in all European countries
Alternatives (other azoles/echinocandins) should not be used as 1st line therapy	DIII	
Ampho B i.v. should never be used	DIII	
Chronic suppressive therapy unnecessary	DIII	
HAART should be initiated (HIV+)	AI	

Other systemic azoles than fluconazole during OPC

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

Recommendation	Reco	Reference
Itraconazole oral solution (200 mg/d): **should not be used as first line therapy** (GI tract disturb/erratic absorption/drugs interaction);	CI	
only in refractory OPC and in case of fluconazole resistance	AII	
Itraconazole capsules (poor absorption)	DIII	Cartledge JAC 1997
Voriconazole (200 mg bid): **should not be used as first line therapy** (it as effective as fluconazole and higher side effects rate)	CII	Ruhnke AAC 1997
Position of posaconazole (400 mg/ twice daily): **should not be used as first line therapy;**	BI	Vasquez CID 2006 Vasquez HIV CT 2007
recommended in refractory OPC in case of fluconazole resistance	AII	Skiest CID 2007

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

Treatments of oesophageal candidiasis Summary

Proposal	Rec	References
Start treatment without endoscopy	AIII	
No local treatments; only systemic agents	DIII	
Oral fluconazole (200-400 mg/d for 14-21d): 1st line therapy	AI	De Wit 1989
Deoxycholate amphotericin i.v.(0.3-0.7 mg/kg/d) should no longer be used	CIII	
Echinocandins can be used in patients who cannot swallow but not better than fluconazole (or favour micafungin 150 mg/d as it is the only EMEA approved echinocandin? But higher relapse rate than fluconazole also true for anidulafungin	BI	De Wet CID 2004 Krause CID 2004
Itraconazole oral solution as an alternative	BI	
Posaconazole (400 mg bid) or voriconazole (200 mg bid) or any echinocandin **not considered 1st line therapy but considered in refractory or fluconazole resistant cases**	AII(posa)/ CII(echino)/ CIII (vori)	Ally CID 2001
Suppressive therapy (Fluconazole 100-200 mg 3x/w) if recurrent infections	BI	

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

Secondary prophylaxis of mucosal candidiasis

Proposal	Rec	Reference
Not recommended	DIII	
Fluconazole maintenance therapy (7 randomized studies) should be **reserved to patients failing HAART therapy with relapsing OPC after HAART optimization & susceptible isolate** [doses ranging : 50-200 mg/d, and from 150 mg-400 mg**/week**	BI	Leen J Infect 1990 Stevens Arch Int Med 1991 Just Nubling EJCMID 1991 Mariott Med J Aust 1993 Schuman Ann Int Med 97 Havlir CID 1998 Pagani JAC 2002
Favour daily administration of fluconazole **if esophagitis**	BI	
Oral posaconazole b.i.d. **if esophagitis**	BII	

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

Vulvovaginal candidiasis

- Topical azoles if uncomplicated. AII
- Oral fluconazole (150 mg/wk) **for recurrences**. AIII

Interaction between azoles and HAART

- Azoles are Cyp3A inhibitors and thus ARV concentrations may increase
- Itraconazole concentrations may increase with protease inhibitors
- Non-nucleoside inhibitors decrease azole concentrations (itraconazole and voriconazole)
- Azoles increase maraviroc but not raltegravir concentrations

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

ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

Authors: Andrew J. Ullmann, Murat Akova, Raoul Herbrecht,Claudio Viscoli and ESCMID Candida Guidelines Committee

Haematology and Oncology

Treatment (Dose) of invasive disease/candidaemia in Neutropenia/HCT

Intervention: success including survival

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

Agent	Rec	Duration	References
Fluconazole	BII_t		Rex NEJM 1994, Anaissie CID 1996, Anaissie Am J Med 1996 (Caution regarding resistance) Because of old data, FLUC should rather be considered as a step-down treatment option.
Itraconazole	DIII		Only one abstract in non-neutropenics published 2003 in CCM (O. Tuil & Y. Cohen)
Posaconazole	DIII		One case report in non neutropenic (Anstead GM
Voriconazole	CII_t		
Anidulafungin	BII_t		
Micafungin	AII_t		
Caspofungin	AII_t		
Liposomal Amphotericin B	BII_t		
AmB lipid complex	CII_a		
AmB colloid dispersion	CIII		Noskin CID 1998
Deoxycholate Amphotericin B	DII_t		Anaissie CID 1996, Muarte Duarte NEJM 2002, Walsh NEJM 1999, Ullmann CID 2006

Individuals with negative blood cultures for > 14 days but remain neutropenic at day 28 [or not expected to recover from neutropenia] should be evaluated for the resolution of clinical signs and symptoms including exclusion of endocarditis and endophthalmitis by appropriate examination (Rex NEJM 1994) BII_t

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

Treatment (Combinations) of invasive disease/candidaemia in Neutropenia

Intervention: success including survival

Agent	Rec	Duration	References
Deoxycholate amphotericin B & 5-fluorocytosine	DIII	N/A	Too toxic and erratic PK
Deoxycholate amphotericin B & fluconazole (sequential therapy only)	CII_t	N/A	Rex CID 2003 (study regarding non-antagonism, **value in comparison to safer echinocandins unclear, therefore only an option**), Kullberg et al (Lancet 2005) studied voriconazole vs. sequential D-AmB and fluconazole **No difference in main endpoints**; more toxicity in the AmB arm, despite only 3 days AmB median.
Efungumab & lipid formulation of amphotericin B	DIII	N/A	Pachl J et al. 2006, flaws in the design of study

Other combinations not studied;

Expert opinion say combination might be useful in severe deep-seated infections (abdominal inf., CNS inf., endocarditis) CIII

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

Prophylaxis in Neutropenia
WHEN? Dose?

Intention: morbidity reduction including survival advantage

Situation	Recommendation	References
Early neutropenic phase	Fluconazole (CI), Itraconazole (CI), Voriconazole (ND), Posaconazole (CII_t), Caspofungin (ND), Micafungin (CI), Anidulafungin (ND), L-Amphotericin B (DI)	1) Glasmacher , 2006;JAC;57:317 2) Menichetti ,CID 1999;28:250 3) Gøtzche , BMJ 1997;314:1238 4) Harousseau AAC 2000;44:1887 5) Boogaerts, JAC 2001 6) Oren, BMT, 2006;38:127 7) Penack, Ann Oncol 2006;17:1306 8) Cornely, NEJM 2007;356:335 9) Hirata, Leuk Lymphoma 2010;51:853
Duration of prophylaxis	No prophylaxis recommended (BII)	Gøtzche , BMJ 1997;314:1238
Different decision in antibody treatment?	No evidence for prophylaxis (BIII)	ND

ND: no data

Explanation/Issues: A study showed no diff. between flu and itra (1). But, it was open-label and no placebo. Another randomized,placebo controlled study showed superiority for itra for preventing Candida (2), but no overall mortality advantage (less mortality due to Candida, n.s.). In the Penack trial (7) low dose L-AmB was ineffective for Candida disease.

Prophylaxis in autologous HCT
WHEN? Dose?

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

Intention: morbidity reduction including survival advantage

Situation	Recommendation	References
Early neutropenic phase	Fluconazole (ND), Itraconazole (CII), Voriconazole (ND), Posaconazole (CII_t), Caspofungin (ND), Micafungin (ND), Anidulafungin (ND), any amphotericin B formulation (ND)	1) Jathavedam A, et al. Biol Blood Marrow Transplant. 2008 May;14(5):595-600 2) Nucci M, et al. CID 2000;30:300 3) Cornely NEJM 2007
Duration of prophylaxis	No prophylaxis recommended (BIII)	
Different decision in antibody treatment?	No evidence for prophylaxis (BIII)	

ND: no data

Explanation/Reason/Issues:

Indirect evidence for survival advantage in prophylaxis for invasive Candida inf.s is only available from Cornely et al. NEJM article. None was studied for other drugs for candidiasis.

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

Prophylaxis in allogeneic HCT

Intention : morbidity & survival advantage

Commentary:

The group recognizes that other fungal infections possibly play a more important role on the **outcome and mortality** in this patient population (e.g. **filamentous fungi**).

Various antifungal agents had similar outcomes as fluconazole and have received strength of recommendation due to this finding.

The strength of recommendation when including all possible fungal infections would be most likely different by EFISG and a prescribing physician must be aware of this.

Prophylaxis in allogeneic HCT

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

*Intention: **1.** morbidity reduction (Candida)*

Situation	Recommendation	References
During early neutropenic phase	Fluconazole (AI), Voriconazole (AI) Posaconazole (AII_t), Micafungin (AI), Itraconazole (BI) Liposomal AmB (BII), Caspofungin (CII_u), Anidulafungin (ND)	Goodman JL NEJM 1992; Morgenstern G Brit J Haema 1999; Marr KA Blood 2004 (180 days); Cornely OA NEJM 2007; Wingard JR (100-180 days) Blood 2010; van Burik CID 2004; Chou LS Pharmacotherapy 2007; Kelsey SM BMT 1999; Penack O Ann Onco 2006
During later phase within first 100 days	Fluconazole (AI), Voriconazole (AI), Itraconazole (BI), Caspofungin (CII_u) , Posaconazole (CIII), Micafungin (CIII), Liposomal AmB (CIII), Anidulafungin (ND)	Slavin M JID 1995, Winston DJ Ann Intern Med 2003 (180 days); Marr KA Blood 2004 (180 days); Cornely OA NEJM 2007; Wingard JR Blood 2010; van Burik CID 2004; Chou LS (up to 100 days) Pharmacotherapy 2007
During GVHD (moderate to severe)	Fluconazole (AI); Posaconazole (AI), Voriconazole (BI) Itraconazole (CI); others (ND)	Ullmann NEJM 2007; Wingard JR Blood 2010; Chou LS Pharmacotherapy 2007

Explanation/Reason/Issues/Comments:
Due to **safety issues** with **itraconazole and amphotericin B**, those drugs received a **weaker strength of recommendation** (Marr Blood 2004; Chou LS Pharmacotherapy 2007; Ullmann CID 2006)

Prophylaxis in allogeneic HCT

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

*Intention : **2.** survival advantage (Candida)*

Situation	Recommendation	References
During early neutropenic phase	Fluconazole (AI); Itraconazole (CI); Posaconazole (BII_t)*, Voriconazole (CI); Micafungin (CI), Caspofungin (CIII), Anidulafungin (ND), Liposomal AmB (CIII) *: identical outcome regarding Candida infection compared to flu/itra but the **overall** mortality rate in the Cornely trial was lower with posaconazole.	Goodmann JL NEJM 1992; Morgenstern G Brit J Haema 1999; Marr KA Blood 2004 (180 days); Cornely OA NEJM 2007; Wingard JR (100-180 days) Blood 2010; van Burik CID 2004; Kelsey SM BMT 1999; Penack O Ann Onco 2006
During later phase within first 100 days	Fluconazole (AI); Itraconazole (CI); Posaconazole (CIII), Voriconazole (CI); Micafungin (CIII), Caspofungin (CII_u), Anidulafungin (ND), Liposomal AmB (CIII)	Slavin M JID 1995 (day 110); Winston DJ Ann Intern Med 2003 (180 days); Marr KA Blood 2004 (180 days); Cornely OA NEJM 2007; Wingard JR Blood 2010; van Burik CID 2004;
During GVHD (moderate to severe)	Fluconazole (CI); Itraconazole (CI); Posaconazole (BI)*, Voriconazole (CI)*, others (ND) *: identical outcome regarding Candida infection compared to fluconazole but the rate of **fungal related** mortality in the Ullmann trial was lower with posaconazole.	Ullmann NEJM 2007; Wingard JR Blood 2010

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

Secondary Prophylaxis

- Secondary prophylaxis is **not indicated in case of prior candidaemia without any sign of deep seated infection** – including situations in which the patient is exposed to a new immunosuppressive condition such as prolonged neutropenia induced by chemotherapy, autologous or allogeneic HCT **(CIII)**

Empiric treatment in Neutropenia incl HCT

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

WHEN: 3 to 4 days of persistent fever in all major trials (All), not defined for relapsing fever

Issues: Recommendations **only apply to patients with expected prolonged duration of neutropenia (>10 days)** e.g.:

- induction/consolidation chemotherapy of AML-MDS, autologous or allogeneic HCT;
- extensive diagnosis work-up is required to exclude a clinically or mycologically documented infection which might require specific therapy

Empiric treatment in Neutropenia incl. HCT

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

Dosage & *Intention: morbidity reduction*

Agents // Situation (trial included allo HCT)	Rec	References
Liposomal amphotericin B (3mg/kg/d) (Allo= yes)	AI	Walsh NEJM 1999; Prentice Br J Haematol 1997; Wingard CID 2000; Walsh NEJM 2002; Walsh NEJM 2004; Maertens Pediatr Inf Dis J 2010
Caspofungin (70 mg on D1 then 50 mg) (Allo=yes)	AI	Walsh NEJM 2004; Maertens Pediatr Inf Dis J 2010
Amphotericin B colloidal dispersion (4 mg/kg/d) (Allo=yes)	BI	White CID 1998
Amphotericin B lipid complex (5 mg/kg/d) (Allo=yes)	BI	Wingard CID 2000
Itraconazole (200 mg iv Q12h on D1 & D2 then 200 mg iv/d) (Allo=not reported)	BI	Boogaerts Ann Intern Med 2001; Ehninger Onkologie 2007
Voriconazole (2 x 6 mg/kg on D1 then 2x3 mg/kg/d) (Allo=yes)	BI	Walsh NEJM 2002
Micafungin (100 mg) (Allo = yes)	BII	Tamura Leuk Lymphoma 2009; Kubiak Clin Ther 2010
Amphotericin B deoxycholate (0.5 – 1.0 mg/kg/d) (Allo=yes)	CI	White CID 1998; Walsh NEJM 1999; Boogaerts Ann Intern Med 2001; Ehninger Onkologie 2007
Anidulafungin	No Recomm.	No data

Explanation/Issues:
*__Limitation for fluconazole due to lack of anti mould activity: need to rule out a mould infection with Aspergillus,__ GM test and chest and sinus CT scan.
Only BI for amphotericin B colloidal dispersion due to safety issue with this agent; amphotericin B lipid complex more toxicity in a direct comparison to liposomal AmB.
For micafungin: Tamura = non comparative trial (dose 50-150 mg) ; Kubiak = 323 pts, retrospective, observational, sequential cohort (dose 100 mg)

Pre-emptive treatment:

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

No real data on Candida diseases

No recommendation

- Candida colonization does not play a role in this patient population
- **Criteria defining pre-emptive treatment of fungal infection in cancer patients are poorly defined and associated more to filamentous fungal infections**

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

Autologous/allogeneic HCT/Neutropenia

How to treat if intolerant or not responding

Recommendation	Reference
If receiving fluconazole or L-Amp B switch to echinocandin (BII_t)	Mora-Duarte NEJM 2007, Kuse ER Lancet 2007, Reboli NEJM 2007, Pappas CID 2007

Explanation/Issues:

No adequately powered, randomized trials for candidaemia in either neutropenics or HCT recipients….

Identification of *Candida* species may be helpful (e.g. *C. krusei*).

Mucosal Candidiasis

Sites

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

Diseases	Agents/Recommendation
Oropharyngeal	flu (AI), itra solution (AII), posa (AII), Nystatin susp (non-neutropenic, mild) (BII), buccal miconazole (BII_t), vori (BII) echinocandin (BII), Amp B (BII) [i.v. echinocandins and lipid AmB possible in very severe and refractory cases (BII)]
Oesophageal	Flu (AI), posa (AI) itra (AIII), vori (AIII), echinocandin (BII), [i.v. echinocandins and lipid AmB possible in very severe and refractory cases (BII)]

References:
Reminder: Identify species
Wilcox JID 1997, Ally R CID 2001, Gligorov 2010

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

Chronic Disseminated Candidiasis

Intention: Diagnosis

Recommendation	Recommendation	Reference
Ultrasound-abdomen	BIII	Pagano L et al. Haematologica 2002
CT- abdomen	BIII	If ultrasound is negative, Pagano L et al. Haematologica 2002
MRI abdomen	BII	MRI: high accuracy: Semelka et al. Am J Roentgenl 1997 Sallah et al. Acta Haematol 1998

Treatment in Chronic Disseminated Candidiasis

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

Intention: Success (incl. survival)

Recommendation	Duration	Reference
Lipid formulations of AmB (AIII)	8 weeks	Better exposure, duration recommendation: Queiroz-Telles F, et al. Pediatr Infect Dis J 2008 Sep; 27 (9): 820-6, Kuse ER et al Lancet 2007
Fluconazole (BIII)	Reported duration: minimum 3 months	L.-M. Poon, H.-Y. Chia, L.-K. Tan, T.-C. Liu,-P. Koh Successful intensive chemotherapy followed by autologous hematopoietic cell transplantation in a patient with acute myeloid leukemia and hepatosplenic candidiasis: *case report* and review of literature. Transpl Infect Dis 2009: 11: 160–166 Pagano L et al. Haematologica 2002
Other azoles effective (BIII)		Lacking Data
Steroid therapy (CIII)	Until defervesced	Legrand F,Lecuit M, Dupont B, Bellaton E, Huerre R, Rohrlich PS, Lortholary O.Adjuvant Corticosteroid Therapy for Chronic Disseminated Candidiasis. Clinical Infectious Diseases 2008; 46:696–702
AmB Deoxycholate (DIII)		**Toxicity** issues

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

Cytokines, Colony-stimulating Factors, Granulocyte Infusions

Recommendation	Reference
For secondary prophylaxis no recommendation, G-CSF **Granulocyte-Infusions with antifungal agents (Data from paed.s)** (CIII)	Grigull L, Support Care Cancer 2006, **very weak recommendation. Might be an option for desperate cases.**
Immunomodulation for (*primary or other)* refractory cases, **G-CSF** (CIII)	Ofran Y, Vox Sanguinis 2007; Safdar A, Cancer 2006 (IFNγ1b); Sachs UJ Transfusion 2006; Dignani MC, Cancer 2005; Lee JJ, Leukemia 2001; Di Mario A, Haematologica 1997; Dignani MC Leukemia 1997

Explanation/Issues:
No controlled trials, only anecdotal data with small numbers of patients exist.

Since persistent neutropenia is related with treatment failure, recovery from neutropenia substantiates the efficacy of antifungals (Annaise AJM 1998). Therefore, the use of CSFs appears to be an option (CIII)

A recent Cochrane review indicates **no mortality difference for all infections in neutropenics** (Massey E, Cochrane Database Syst Rev 2009; Jan 21).