An update on treatment of candidiasis - in a Nordic setting

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JAC

Adequacy of empirical antifungal therapy and effect on outcome among patients with invasive *Candida* species infections

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Calgary health region: 1.2 million inhabitants

From July 1999 until June 2004:

199 (207) patients with invasive *Candida* infection: *Candida* from blood and CSF:

C. albicans	103 (52 %)
C. glabrata	44 (22 %)

Empirical treatment with adequate therapy: mortality 14/51 **(27 %)**

vs

Inadequate treatment or no (empirical) treatment: mortality 68/148 **(46%)**

vs

No treatment at all: mortality 24/37 **(71 %)**

M.D. Parker, J Antimicrobial Chemother 2007;60:613-8

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Treatment strategies:

- targeted
- pre-emptive
- empirical
- prophylactic

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Our choice in treatment strategies depends on 2 parameters:

1. **The epidemiologic characteristics** (ICU, hospital, region, country)
2. **Host factors** (underlying illness, infection site, neutropenia, organ dysfunction, drugs, vascular lines….)

3. Pattern of resistance
4. Fungicidal or fungistatic?
5. Costs!

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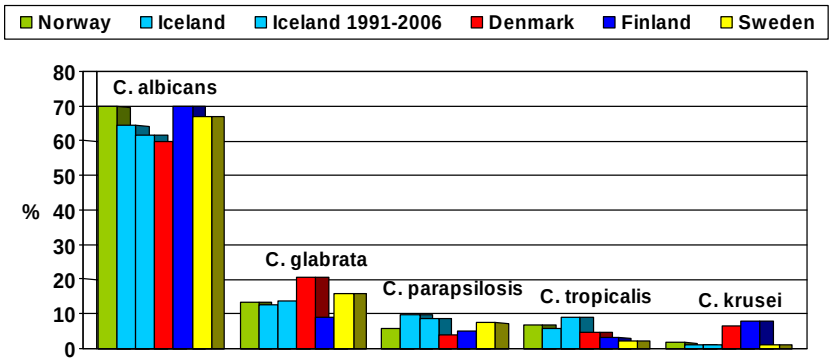
Candidemia in the Nordic countries:



Norway: 1991-2003: 1393 isolates from all laboratories. P. Sandven, J Clin Microbiol 2006;44:1977-81

Iceland: 1980-1999: 172 isolates from all laboratories. L.R.Ásmundsdottir, J Clin Microbiol 2002;40:3489-92
1991-2006: 219 isolates from all laboratories. L.R.Ámundsdóttir, Clin Infect Dis 2008:47:e17-24

Denmark: 2004-2006: 1089 isolates from parts of the country. M.C.Arendrup, Clin Microbiol Infect 2008;14:487-94

Finland: 1995-1999: 479 isolates from all laboratories. E. Poikonen, Emerg Infect Dis 2003;9:985-90

Sweden: 1998-1999: 191 isolates from parts of the country. L. Klingspor, Scand J Infect Dis 2004;36:52-55

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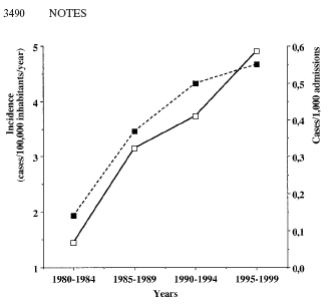
Incidence and species variation over time:

Finland: 1995-1999: stable incidence 1.3- 2.2/100 000 inhabitants
Stable *C. albicans* (70%).

E. Poikonen, Emerg Infect Dis 2003;9:985-90

Iceland:



1980-84: 1.4/100 000
1995-99: 4.9/100 000
2003-06: 5.8/100 000

Stable *C. albicans* percentage (64%) throughout the period

L.R. Ásmundsdottir, J Clin Microbiol 2002;40:3489-92
L.R. Ásmundsdottir, Clin Infect Dis 2008:47:e17-24

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Sweden: 2 year survey of 6 centers serving 2,5-3 mill. inhabitants

191 episodes of candidemia: 0.32/1000 admissions

L. Klingspor, Scand J Infect Dis 2004;36:52-55

Norway: 13 year survey: 2,5- 3,0/ 100 000 inhabitants

Stable *C. albicans:* 69 %

P. Sandven, J Clin Microbiol 2006;44:1977-81

Denmark: **rate of fungemi: 98.1 % Candida sp.**

2004: 9.6/100 000 inhabitants, *C. albicans*: 66.1%
2005: ? /100 000 inhabitants, *C. albicans*: 60.7%
2006: 11.2/100 000 inhabitants, *C. albicans*: 53.8 %

} Tendency ↓

M.C. Arendrup, Clin Microbiol Infect 2008;14:487-94

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Norway: 1991-2003:

TABLE 3. Yeast species isolated from blood cultures in Norway from 1991 to 2003

Species	No. of isolates isolated in yr:													Total (%)
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	
C. albicans	76	52	58	65	67	59	72	81	78	88	92	100	99	987 (69.8)
C. glabrata	16	8	9	10	13	16	13	12	16	13	20	19	22	187 (13.2)
C. tropicalis	3	6	10	4	4	9	5	13	7	8	9	16	1	95 (6.7)
C. parapsilosis	10	11	6	5	6	6	5	1	2	10	5	6	9	82 (5.8)
C. krusei		1	2	1	5	2	2	1	1	1	1	4	1	22 (1.6)
C. dubliniensis								1		2	1		4	8 (0.6)
C. guilliermondii	1	2	1			2						1	1	8 (0.6)
C. norvegensis					1	1		1	1		1	2	1	8 (0.6)
C. kefyr					2	1	1	2				1		7 (0.5)
Other *Candida* spp.[a]	2		1	1	1							2		7 (0.5)
Yeast not identified		2		1			1							4 (0.3)
Total	108	82	87	87	99	96	102	113	106	122	130	151	138	1,415

[a] Other *Candida* spp. are as follows: *Candida blankii* (1 isolate), *Candida inconspicua* (1 isolate), *Candida lusitaniae* (2 isolates), *Candida sake* (2 isolates), *Candida sphaerica* (1 isolate).

C. albicans (%):	70%	63%	66%	75%	68%	61%	71%	72%	74%	72%	71%	66%	72%	69,8%

P. Sandven et al. J Clin Microbiol 2006;44:1977-81

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Specific age-groups and Candidemia:

Country	*C. parapsilosis* in the youngest	*C. glabrata* in the elderly
Norway	8 – 20 %	16 – 31 %
Sweden	20 %	24.3 %
Denmark	19 %	21 – 31 %*

*** > 41 years of age**

P. Sandven, J Clin Microbiol 2006;44:1977-81
L. Klingspor, Scand J Infect Dis 2004;36:52-55
M.C. Arendrup, Clin Microbiol Infect 2008;14:487-94

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Specific patient-groups and Candidemia:

From Sweden:

- Haematologic malignancies (n=18): 44 % *C. albicans*, 28 % *C. glabrata*
- Solid tumours (n=12): 41.7 % *C. glabrata*

L. Klingspor, Scand J Infect Dis 2004;36:52-55

From Finland: allogeneic HSCT patients: 1983-2002: 685 adult patients

- 60 patients w/ IFI:
  - 46: aspergillus – incidence of 6.7%
  - **9: candidiemia – incidence of 1.3 %**
  - 5: others: Fusarium (2), Absidia (1), Acremonium (1), Zygomycetes (1)
- Candida: *C. albicans* (8)
  C. krusei (2)
  C. glabrata (1)

E. Jantunen, Bone Marrow Transplant 2004;34:891-5

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From Finland: prophylaxis in patients with acute leukemia **1978-1999 and 1999-2004**

Table 1 The numbers on invasive candida infections in the two groups

	Period I[1] n = 847	Period II[2] n = 242	P
Candidaemia	**21** (2.5%)	**3** (1.2%)	0.325
C. albicans	7 (0.8%)	1 (0.4%)	0.693
Non-*albicans* spp.	9 (1.1%)[3]	2 (0.8%)	1.000
Unspecified yeast	5 (0.6%)	0	
Disseminated candidiasis	**53** (6.2%)	**1** (0.4%)	<0.001
Culture positive	20	0	
C. albicans	10		
Non-*albicans* spp.[4]	7		
Unspecified yeast	3		
Histology positive	32	0	
Probable candidiasis	1	1	
Total	**74** (8.7%)	**4** (1.6%)	<0.001

[1]Period I: patients treated in 1978–1999, no fluconazole prophylaxis.
[2]Period II: patients treated in 1999–2004, fluconazole prophylaxis used.
[3]Non-*albicans* spp. = *C. krusei* (5), *C. tropicalis* (3) and *C. glabrata* (1).
[4]Non-*albicans* spp. = *C. krusei* (2), *C. tropicalis* (2), *C. parapsilosis* (2) and *C. glabrata* (1).

A. Nihitinen. Eur J Haemotol 2008;80:391-6

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Specific problems of susceptibility to antifungal drugs in the Nordic countries?

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Norway:

1991-2003: 1393 isolates: 95.3 % tested

- Fluconazole: 1991-1996: 10.7% MIC ≥ 16 mg/l
  1997-2003: 11.7% MIC ≥ 16 mg/l

C. albicans: 100 % (N=934): S
C. parapsilosis: 1.3 % (N=1): MIC ≥ 16 mg/l
C. tropicalis: 3.2 % (N=3): MIC ≥ 16 mg/l

P. Sandven et al. J Clin Microbiol 2006;44:1977-81

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Denmark: 2004 - 2007

1025 Candida isolates (90.5%):

- Fluconazole: 25 isolates **(2.2%)** with MIC ≥ 4 mg/l
- Voriconazole: 951 isolates (83.9%)

  C. albicans: all susceptible (MIC ≤ 1 mg/l)

  C. glabrata: 19 of 232 isolates MIC ≥ 1 mg/l: **2004: 3 %**
  2005: 8 %
  2006: 14 %

M.C. Arendrup et al. Clin Microbiol Infect 2008;14:487-94

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Iceland: 99 isolates from 1991-1999

TABLE 2. In vitro susceptibility of 99 fungal BSIs to amphotericin B, itraconazole, and fluconazole

Antifungal agent	Species	No. of isolates	MIC (μg/ml)			MIC_{50}[c]	MIC_{90}[d]
			Mean	Median	Range		
Amphotericin B	*C. albicans*	67	0.08	0.064	0.016–0.25	0.064	0.125
	C. glabrata	12	0.23	0.22	0.125–0.38	0.19	0.25
	C. parapsilosis	11	0.15	0.125	0.125–0.25	0.125	0.190
	C. tropicalis	5	0.21	0.25	0.125–0.25	0.25	0.25
	C. dubliniensis	4	0.03	0.275	0.023–0.047	0.023	0.047
Itraconazole	*C. albicans*	67	0.04	0.023	0.008–0.75	0.023	0.094
	C. glabrata[a]	12	0.46	0.315	0.125–2	0.25	0.50
	C. parapsilosis	11	0.08	0.064	0.008–0.19	0.064	0.125
	C. tropicalis	5	0.03	0.016	0.006–0.064	0.016	0.064
	C. dubliniensis	4	0.08	0.0945	0.008–0.125	0.064	0.125
Fluconazole	*C. albicans*	67	0.36	0.19	0.094–8	0.190	0.380
	C. glabrata[b]	12	12.67	8	4–48	8.0	24
	C. parapsilosis	11	1.60	1	0.19–8	1.0	2.0
	C. tropicalis	5	1.13	0.38	0.125–4	0.380	4.0
	C. dubliniensis	4	2.14	0.22	0.125–8	0.190	8.0

97 %

[a] Ten strains of *C. glabrata* were classified as susceptible-dose dependent to itraconazole (MIC, 0.25 to 0.5 μg/ml), and one strain was resistant (MIC, ≥1 μg/ml).
[b] Three strains of *C. glabrata* were classified as susceptible-dose dependent to fluconazole (MIC, 16 to 32 μg/ml).
[c] MIC at which 50% of the isolates tested are inhibited.
[d] MIC at which 90% of the isolates tested are inhibited.

L.R.Ásmundsdottir, J Clin Microbiol 2002;40:3489-92

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Patient populations :

1. In non-neutropenic patients
2. In neutropenic patients
3. Neonatal candidiasis

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The design of the studies on antifungal therapy:

1) populations: small, not calculated sample size, possible/ probable/certain, subgroups, risk profiles

2) endpoints: clinical improvement, microbiological improvement, defervescence, lack of breakthrough IFI, toxicity, adverse events, mortality – at day 7, at 2 w, at 6 w?

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Table 1. Infectious Diseases Society of America–US Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from Canadian Task Force on the Periodic Health Examination [15].

IDSA GUIDELINES

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David Andes,[4] Daniel K. Benjamin, Jr.,[5] Thierry F. Calandra,[11] John E. Edwards, Jr.,[6] Scott G. Filler,[6] John F. Fisher,[7] Bart-Jan Kullberg,[12] Luis Ostrosky-Zeichner,[8] Annette C. Reboli,[9] John H. Rex,[13] Thomas J. Walsh,[10] and Jack D. Sobel[3]

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EJC SUPPLEMENTS 5 (2007) 49–59

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journal homepage: www.ejconline.com

Treatment of invasive *Candida* and invasive *Aspergillus* infections in adult haematological patients ☆

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[d]*Hôpital Saint Louis, Paris, France*
[e]*Hôpital Edouard Herriot, Lyon, France*
[f]*Hôpital Henri Mondor, Créteil, France*

*** ECIL-1: European conference on infections in leukemia**

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journal homepage: www.ejconline.com

Empirical antifungal therapy in neutropaenic cancer patients with persistent fever ☆

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*** ECIL-1: European conference on infections in leukemia**

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EJC SUPPLEMENTS 5 (2007) 43–48

available at www.sciencedirect.com

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journal homepage: www.ejconline.com

Primary antifungal prophylaxis in leukaemia patients ☆

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THERAPY IN PRACTICE

Drugs 2008; 68 (14): 1941-1962
0012-6667/08/0014-1941/$53.45/0

Patients at High Risk of Invasive Fungal Infections

When and How to Treat

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The Nonneutropenic Patient

Targeted therapy:

IDSA

Initial therapy:
Fluconazole (AI) →

- **Less critically ill or**
- **No azole exposure or (AIII)**
- ***C. parapsilosis***

or

Caspofungin/Micafungin/Anidulafungin – may be switched to Fluconazole (AI)

- **Moderately severe to severe illness or**
- **Recent azole exposure or (AIII)**
- **high risk of *C. glabrata* or *C. krusei***

Alternative:
Amfotericin B deoxycholate (AmB)/Lipid formulated AmB (LFAmB) (AI) or (Voriconazole AI)

When intolerance or limited availability

Köln, Germany

Initial therapy:
Caspofungin/Micafungin/Anidulafungin – may be switched to Fluconazole

Alternative:
LFAmB

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IDSA:

Step-down therapy:

- from EC to fluconazole when (likely) susceptible isolates and clinically stable condition
- from AmB to fluconazole when (likely) susceptible isolates and clinically stable condition
- from EC to voriconazole p.o. when *C. krusei* or *C. glabrata*

For all patients: reconsider response to treatment already started!

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The Nonneutropenic Patient

Empirical therapy:

IDSA (BIII)

Initial therapy:

Fluconazole

or

Caspofungin/Micafungin/Anidulafungin – may be switched to Fluconazole

Alternatives:

AmB-d/LFAmB

(or Voriconazole)

Köln, Germany

Initial therapy:

No well designed trials exist to make recommendations

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The Neutropenic Patient

Targeted therapy:

IDSA

Initial therapy:

Caspofungin (AII)/Micafungin (AII)/Anidulafungin (AIII) – may be switched to Fluconazole,
or
LFAmB (AII)

Recommended for most patients

Alternative:

Fluconazole (BII) → **Less critically ill, no azole exposure or *C. parapsilosis***

or

Voriconazole (BIII) → **Where mould coverage is also desired**

Köln, Germany

Initial therapy:

Caspofungin or Micafungin
– may be switched to Fluconazole

Alternative:

LFAmB

ECIL-1

Initial therapy:

Caspofungin (BII)
or
LFAmB (BII)
or
Vorconazole (BII)

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The Neutropenic Patient

Empirical therapy:

IDSA

Initial therapy:
Caspofungin (AI)
or
LFAmB (AI)
or
Voriconazole (BI)

Alternatives:
Fluconazole (BI) or
Itraconazole (BI) or
AmB (AI)

Köln, Germany

Initial therapy:
Caspofungin
or
LFAmB

ECIL-1

Initial therapy:
Caspofungin (AI)
or
LFAmB (AI)

Alternatives:
Voriconazole (BI)
or
AmB (BI or DI)

Not recommended if azole prophylaxis

NB! toxicity

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Pre-emptive therapy

IDSA

Do no mention this category

Köln, Germany

No well designed prospective trials exist to make recommendations

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The Neonatal patient with Candidiasis

IDSA

Initial therapy:
AmB (AII)
or
Fluconazole (BII)

Alternative:
LFAmB – if not UTI (BII)
or
Echinocandins?

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Prophylactic therapy

Clinical condition	IDSA	Köln, Germany	ECIL-1
Solid-organ Tx: Liver (AI) Pancreas (BII) Small-bowel (BIII)	Fluconazole or LFAmB		
ICU patients:	Fluconazole (BI)	Fluconazole	
The neutropenic host:			
Chemotherapy-induced neutropenia:	Fluconazole (AI) or Posaconazole (AI) or Caspofungin (BII) Alternative: Itraconazole (AI)	**Acute leukemia/AML or MDS:** Posaconazole	**Acute leukemia/AML or MDS**: Posaconazole (AI)
HSCTx recipient with neutropenia	Fluconazole (AI) or Posaconazole (AI) or Micafungin (AI)	Posaconazole	Fluconazole (CI)
Prior allogeneic HSCTx (GvHD)		Posaconazole	Fluconazole (AI) Posaconazole (AI)
Neonates < 1000 g:	Fluconazole (AI)		

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How to bring the epidemiologic data together with therapeutic recommendations?

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To conclude I:

In the Nordic countries:

- the incidence of candidiasis is still, mostly, low
- *C. albicans* is the most common *Candida* sp. observed
- age-related incidence of specific *Candida* sp. do not differ from many other countries
- drug resistance is of no large concern

- knowledge of the epidemiology of specific patient populations is scarce
- knowledge of our treatment practice and outcome of such is lacking

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To conclude II:

- treatment according to IDSA guidelines of 2009 seems sensible in a Nordic setting

- prophylaxis may not be warranted due to low incidence of candidemia in a Nordic patient population

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Chronic Disseminated Candidiasis

IDSA

Initial therapy:
Fluconazole (AIII) → For clinically stable patients
or
LFAmB/AmB (AIII)

Alternative:
Caspofungin/Micafungin/Anidulafungin (BIII)

Step-down therapy:

LFAmB/AmB to fluconazole if susceptible and clinically stable

EC to fluconazole if susceptible and clinically stable

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