Therapie der Candidämie system. Candidose bei Patienten mit Granulozytopenie

PEG – Frühjahrstagung
Sektion Antimykotische Chemotherapie
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Was ist besonders bei der Candidämie / inv. Candidose in der Granulozytopenie

- Faktoren, die mit einer hohen Letalität assoziiert sind, umfassen u.a.:
- die persistierende Candidämie,
- hoher APACHE-II Score,
- eine persistierende Granulozytopenie bzw. hämatologische Neoplasie
- ein verzögerter Beginn einer adäquaten systemischen antimykotischen Therapie

Risikofaktoren systemische Candidose/ Candidämie

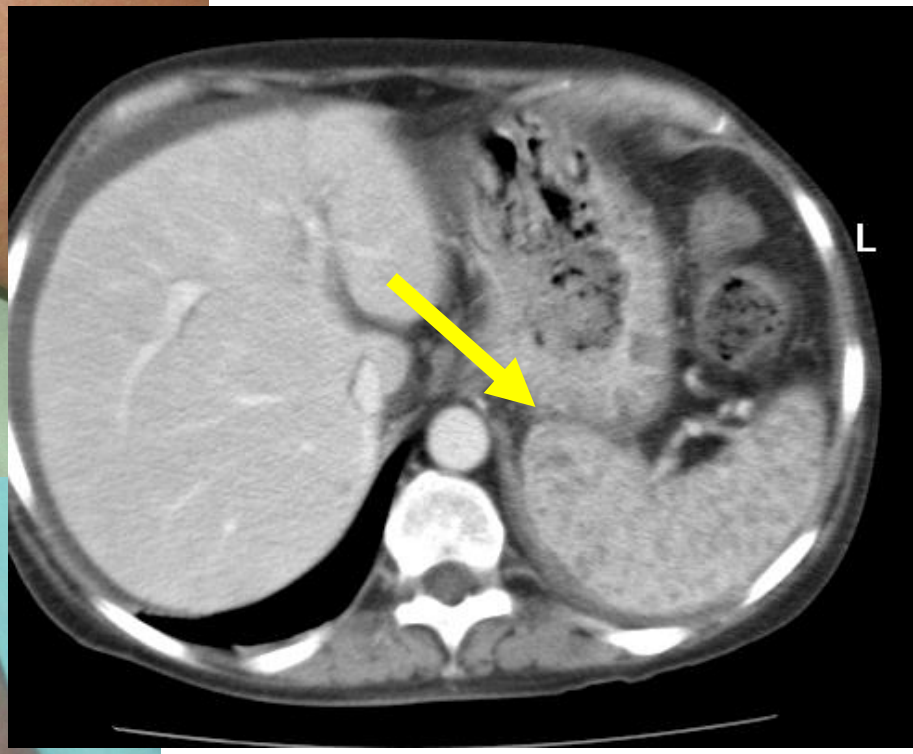
Population	Intention	Intervention	Reference	Comment
Candidemia in cancer patients	Predictor of inverse outcome in cancer patients (N=476)	Single-center retospective analysis (M.D. Anderson Cancer Center) 1988-1992	Anaissie E.J. (Am. J. Of Medicine 1998)	Poor prognosis: Neutropenia High APACHE II score Visceral dissemination 3-month follow-up: 52% died
Risk factors for fatal candidemia caused by *Candida albicans and* non-albicans *Candida species*	identification to help selecting patients who are more likely infected with *C. albicans versus* NAC.	Single-center retospective analysis (Taipeh, Taiwan) 1996 -1999	Cheng M.F. (BMC Infect. Dis 2015)	The significant risk factors for NAC: age < 65 years, cancer chemotherapy, neutropenia (WBC < 3000/mm3), severe thrombocytopenia count 20000 /mm3)

Risikofaktoren systemische Candidose/ Candidämie

Population	Intention	Intervention	Reference	Comment
Candidemia in cancer patients	Predictor for mortality in candidemia w FLU-R Candida spp. HM = 138 ST = 150	population-based candidaemia survey (2001–2004)	Slavin M.A. (JAC 2010)	strongest predictors of mortality at onset of candidaemia invasive ventilation, elevated creatinine, intensive care unit (ICU) admission and receipt of systemic triazoles or corticosteroids in the previous 30 days
Candidemia haematological malignancies	population-based, prospective, multicentre study	nine tertiary care Greek hospitals (Jan 2009 - Feb 2012)	Gamaletsou M.N. (CMI 2013)	independent risk factors for the development of candidaemia: CVC, hypogammaglobulinaemia and a high APACHE II score; Candidaemia caused by C. parapsilosis also occurred more frequently in patients with haematological malignancies (20/40, 50%)

Akute disseminierte Candidose

- Der Begriff der akuten disseminierten Candidose hat sich bisher nicht allgemein etabliert.
- Per definitionem handelt es sich um eine Erkrankungsentität des onkologischen Patienten und wird vorwiegend bei schwerer und prolongierter Granulozytopenie beobachtet.
- Es besteht ein klinisches Krankheitsbild mit einem septischen Syndrom, persistierender Candidämie, hämodynamischer Instabilität und zahlreichen kutanen und viszeralen septische Metastasen das mit extrem hoher Letalität einhergeht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Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC)

- Surveillance study in patients with cancer from 30 EORTC centers (Nov 1992– Oct 1994)
- Fungemia episodes (n = 249) : n=90 solid tumor, n= 159 HM
- Neutropenia in tumor patients and acute leukemia and antifungal prophylaxis in hematology patients were significantly associated with non-albicans candidemia
- Overall 30-day mortality was 39% (97 of 249).
- In a univariate analysis, Candida glabrata was associated with the highest mortality rate

Viscoli et al. CID 1999

Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC)

Table 1. Species of *Candida* isolated in episodes of candidemia in the two populations of patients studied, one with solid tumors and the other with hematologic malignancies.

Pathogen	No. (%) of cases in which pathogen was isolated, per patient population		
	Solid tumors (n = 90)	Hematologic malignancies (n = 159)	Total (n = 249)
Candida albicans	63 (70)	58 (36)	121 (49)
Candida glabrata	4 (4)	20 (13)	24 (10)
Candida tropicalis	6 (7)	22 (14)	28 (11)
Candida parapsilosis	8 (9)	20 (13)	28 (11)
Candida krusei	2 (2)	20 (13)	22 (9)
Other non-*albicans Candida* species	7 (8)	19 (12)	26 (10)

Viscoli et al. CID 1999

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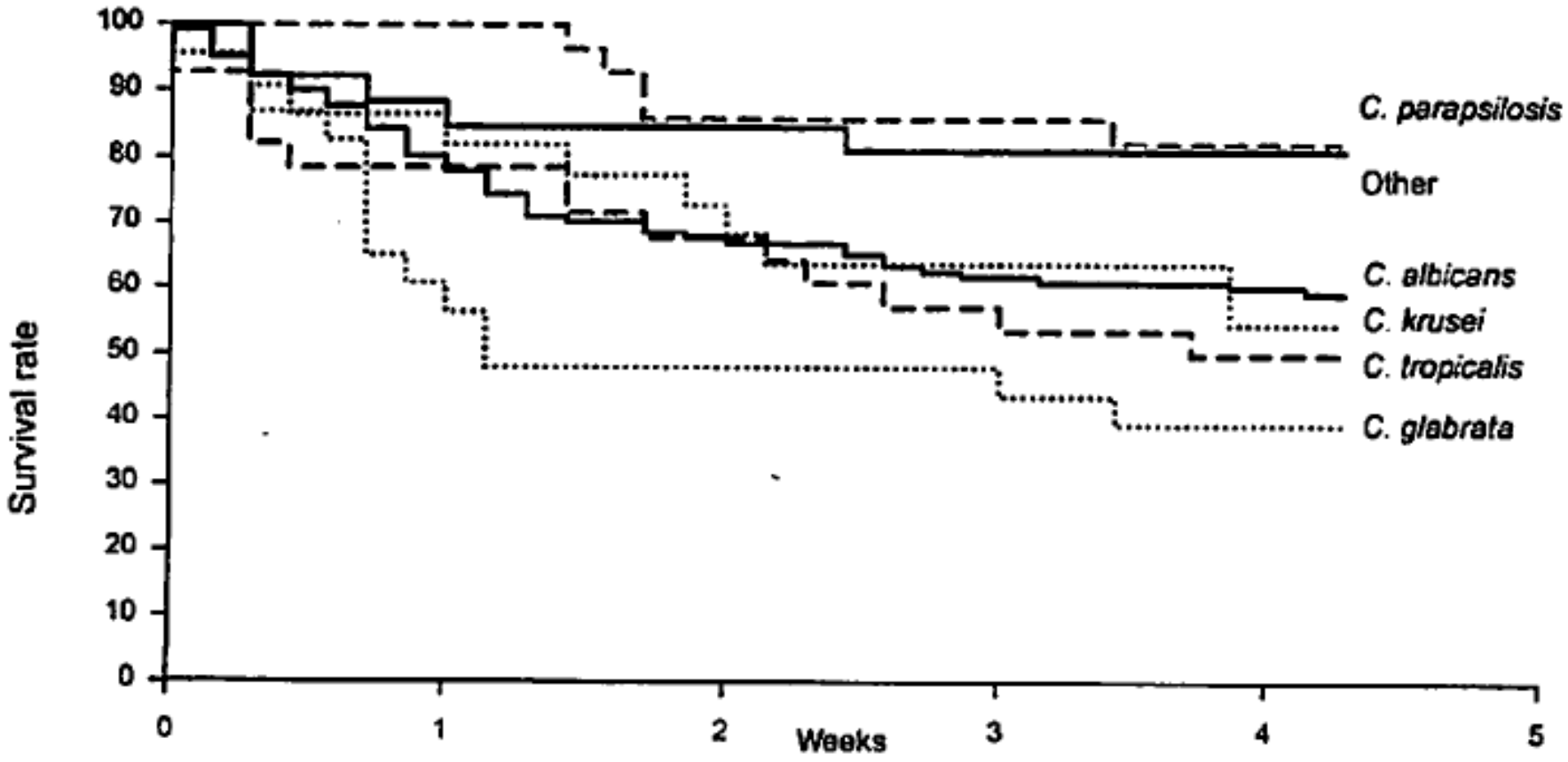

Viscoli et al. CID 1999

Epidemiology and Outcome of Fungemia in a Cancer Cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031)

Oliver A. Cornely,[1,2,3] Bertrand Gachot,[4,5] Hamdi Akan,[6] Matteo Bassetti,[7] Omrun Uzun,[8] Christopher Kibbler,[9] Oscar Marchetti,[10] Peter de Burghgraeve,[11] Safaa Ramadan,[11] Liisa Pylkkanen,[11] Lieveke Ameye,[12] Marianne Paesmans,[12] and Peter J. Donnelly[13]; on behalf of the EORTC Infectious Diseases Group

- prospective cohort study including 145.030 admissions of patients with cancer from 13 EORTC centers (Jan 2005 – Nov 2009)
- Fungemia in 297patients: 56% solid tumor, 47% HM, 17% HSCT
- Age ranged from 17 to 88 years (median 56 years)
- C. albicans (48%, n=128)
- After 4 weeks, the survival rate was 64%
- poor prognostic factors: septic shock, tachypnoea
- good prognostic factors: antifungal prophylaxis, remission of underlying cancer

Cornely et al. CID 2015

Pathogen Isolated by Treating Center	Total n = 297 (%)	Solid Tumor[b] n = 165 (%)	Hematological Malignancy[b] n = 140 (%)	Allogeneic HSCT n = 28 (%)	Autologous HSCT n = 22 (%)	No Transplant n = 247 (%)
Single pathogen	**288 (97.0%)**	**159 (97%)**	**137 (98%)**	**27 (96.4%)**	**22 (100%)**	**239 (96.8%)**
Candida albicans	120 (40.4%)	92 (56%)	31 (22%)	2 (7.1%)	7 (31.8%)	111 (44.9%)
Non-albicans candida	138 (46.5%)	59 (36%)	82 (59%)	21 (75.0%)	12 (54.6%)	105 (42.5%)
C. glabrata	29 (9.8%)	25 (15.2%)	6 (4.3%)	1 (3.6%)	1 (4.5%)	27 (10.9%)
C. tropicalis	39 (13.1%)	11 (6.7%)	30 (21.4%)	2 (7.1%)	4 (18.2%)	33 (13.3%)
C. parapsilosis	28 (9.4%)	16 (9.7%)	11 (7.9%)	5 (17.9%)	2 (9.1%)	21 (8.5%)
C. krusei	25 (8.4%)	5 (3.0%)	20 (14.3%)	6 (21.4%)	4 (18.2%)	15 (6.1%)

- median time from BC to initiation of AFT 2d (0-21d)
- 242 (81%) patients received AFT:
  - 79 (35%) fluconazole, 51 (22%) echinocandin, 32 (14%) intravenous amphotericin B,
- CVC was removed in 167(67%)
- Breakthrough fungemia in 69 (23%) patients

Cornely et al. CID 2015

Candidemia in Cancer Patients: A Prospective, Multicenter Surveillance Study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC)

Epidemiology and Outcome of Fungemia in a Cancer Cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031)

Mortality did not change over years and remained high (30-day mortality about 39%)

30-day crude mortality was 40% in haema patients and 45% in oncology patients

Viscoli et al. CID 1999

Cornely et al. CID 2015

Slavin et al. JAC 2010

Therapie der Candidose in der Granulozytopenie - ZVK

- The role of catheter removal in granulocytopenic patients is particularly controversial as the gastrointestinal mucosa, damaged by cytotoxic chemotherapy, is thought to be the main port of entry for yeasts to the bloodstream.
- However, as the central venous line might be colonised, it is recommended to remove them in these patients as well as in non-granulocytopenic patients (AII; u.a. Slavin et al. JAC 2010).

ABLC zur Therapie der Candidämie

Response rate among patients infected with *Candida albicans as a function of neutrophil status at start and end of therapy* with amphotericin B lipid complex (ABLC).

Type of infection	Unknown → unknown	Neutropenia → neutropenia	Neutropenia → normal	Normal → neutropenia
C. albicans (n = 364)	7/8 (88%)	5/25 (20%)	24/35 (67%)	1/5 (20%)
Non-albicans Candida spp. (n = 375)	4/6 (67%)	11/40 (28%)	29/46 (63%)	2/7 (29%)
C. albicans +non-albicans Candida spp. (n = 90)	3/3 (100%)	1/5 (20%)	3/5 (60%)	--
Multiple non-albicans Candida spp. (n =25)	14/17 (82%)	17/71 (24%)	58/89 (65%)	3/14 (21%)

Ito et al. CID 2005 (Suppl. 6

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Ito et al. CID 2005 (Suppl. 6

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ORIGINAL ARTICLE

WILEY mycoses

Efficacy of micafungin for the treatment of invasive candidiasis and candidaemia in patients with neutropenia

Pranatharthi Chandrasekar[1] | Bhawna Sirohi[2] | Nita L. Seibel[3] | Jack W. Hsu[4] | Nkechi Azie[5] | Chunzhang Wu[5] | Markus Ruhnke[6]

- pooled, post hoc analysis of 2 Phase 3 trials with micafungin
- of 685 patients, 77 had neutropenia
- most common: C. tropicalis (31*/77**), C. albicans (295*/608**)
- overall success: 63.6% with vs 72.9% without neutropenia
- clinical and mycological response was similar
- neutropenia duration or Candida spp. did not impact micafungin's overall success

* Mit Granulozytopenie; ** ohne Granulozytopenie

Overall, clinical and mycological success at end of treatment by neutropenia resolution

	Neutropenia resolved[a] (n = 38)	Neutropenia unresolved (n = 39)
Overall treatment success	35 (92.1)	14 (35.9)
Clinical success	37 (97.4)	19 (48.7)
Mycological success	35 (92.1)	24 (61.5)

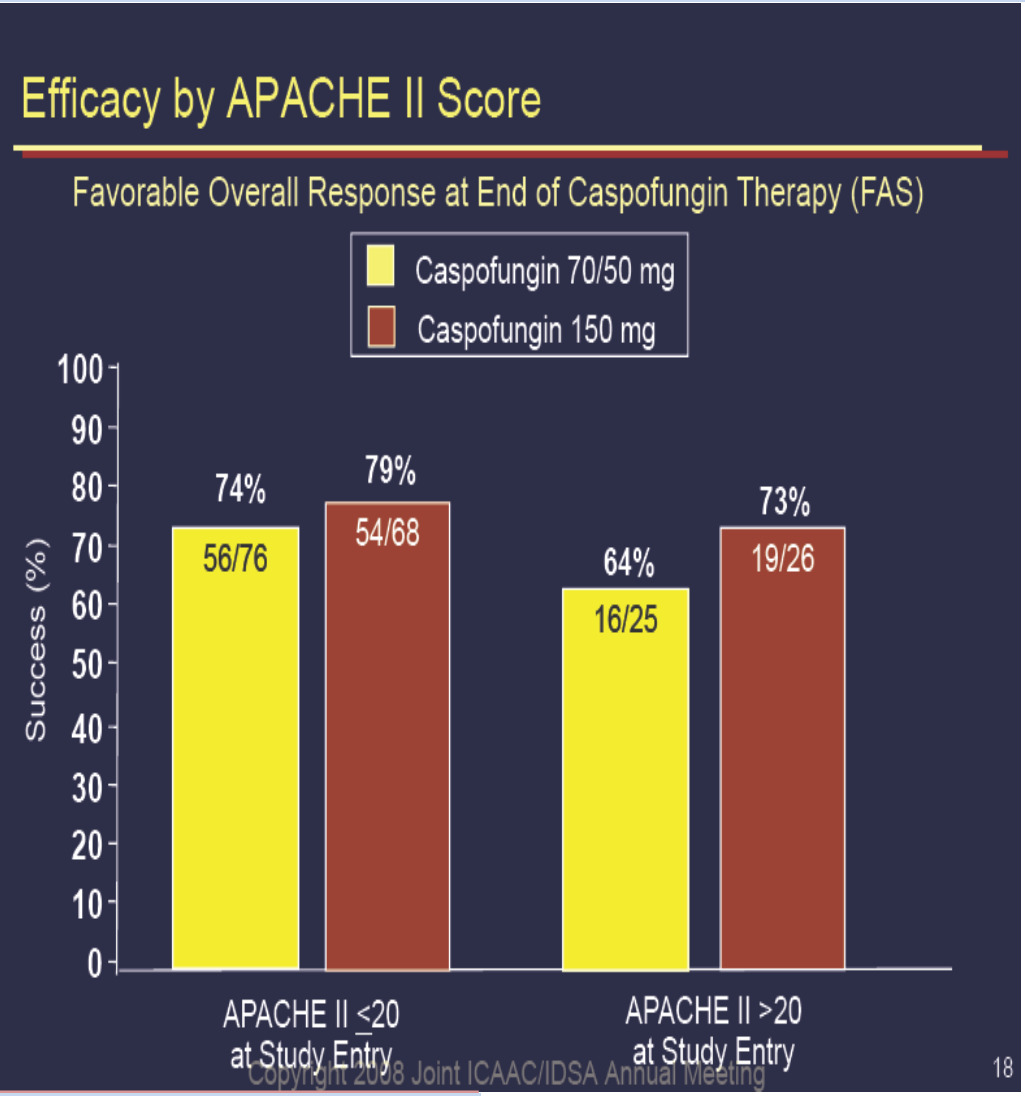
Chandrasekar et al. Mycoses 2018

Mortality in patients with baseline neutropenia versus those without neutropenia at baseline

	Neutropenic (n = 77)	**Non-neutropenic (n = 608)**
Overall mortality, n/n (%)	36/77 (46.8)	218/608 (35.9)
Day 28 mortality, n/n (%)	30/74 (40.5)	142/574 (24.7)
Day 84 mortality, n/n (%)	35/49 (71.4)	206/340 (60.6)

Chandrasekar et al. Mycoses 2018

Caspofungin gegen Candidämie / Candidose
Höhere Dosis bei Granulozytopenie?



Factor	Caspofungin 70/50-mg group (*n* = 102)	Caspofungin 150-mg group (*n* = 95)
Single site of *Candida* infection		
Blood (candidemia)	67/91 (73.6)	62/79 (78.5)
Abscess	…	3/3 (100)
Peritoneal fluid	3/4 (75.0)	5/5 (100)
Pleural fluid	1/1 (100)	…
Chronic disseminated (hepatosplenic)	0/1 (0)	…
Urine (pyelonephritis)	…	1/1 (100)
Multiple sites of *Candida* infection		
Blood and eye (endophthalmitis)	0/2 (0)	3/5 (60.0)
Blood and peritoneal fluid	2/2 (100)	0/2 (0)
Blood and pleural fluid	0/1 (0)	…
APACHE II score at entry		
≤20	56/76 (73.7)	54/68 (79.4)
>20	16/25 (64.0)	19/26 (73.1)
Neutropenia status at entry		
Nonneutropenic		
Neutropenic	2/3 (66.7)	1/1 (100)
Baseline *Candida* species isolate		
C. albicans	27/39 (69.2)	32/39 (82.1)
C. glabrata	8/9 (88.9)	7/9 (77.8)
C. guilliermondii	2/3 (66.7)	1/1 (100)
C. krusei	…	1/2 (50.0)
C. lusitaniae	1/1 (100)	1/1 (100)
C. parapsilosis	11/18 (61.1)	17/21 (81.0)

33%

57%

Betts et al. CID 2009

ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients

by Frederic Tissot, Samir Agrawal, Livio Pagano, Georgios Petrikkos, Andreas H. Groll, Anna Skiada, Cornelia Lass-Flörl, Thierry Calandra, Claudio Viscoli, and Raoul Herbrecht

Haematologica 2016 [Epub ahead of print]

Table 5: ECIL-6 recommendations for first-line treatment of candidemia after species identification

Candida species	Overall population		Hematological patients	
C. albicans	Echinocandins [a]	A I	Echinocandins	A II
	Fluconazole [b]	A I	Fluconazole	C III
	Liposomal amphotericin B	A I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	A II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	A II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. glabrata	Echinocandins [a]	A I	Echinocandins	A II
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. krusei	Echinocandins [a]	A II	Echinocandins [a]	A III
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
Oral stepdown	Voriconazole	B I	Voriconazole	C III
C. parapsilosis	Fluconazole	A II	Fluconazole	A III
	Echinocandins [c]	B II	Echinocandins	B III

[a] same grading for anidulafungin, caspofungin, micafungin ; [b] not in severely ill patients; [c] if echinocandin-based regimen introduced befo
identification and patient responding clinically and microbiologically (sterile blood cultures at 72h), continuing use of echinocandin migh

Therapie der invasiven Candidose

- Therapie der Wahl für die Candidämie
  - Patienten in der Granulozytopenie
    - Echinocandin: AI
    - liposomal AmB: AI (BI)
    - Isacuconazol (keine Zulassung): ?
  - Andere hämato-onkologische Patienten:
    - Echinocandine: AI
    - Liposomal Amb: AI
    - Voriconazol: CI
    - Fluconazol: CI
    - Isacuconazol (keine Zulassung): ?
  - Stabiler Zustand und + S-C*andida spp*: Fluconazol 400mg oder Voriconazol “step-down” bei Respondern auf ein Echinocandin: BII