New perspectives in the treatment of invasive candidiasis

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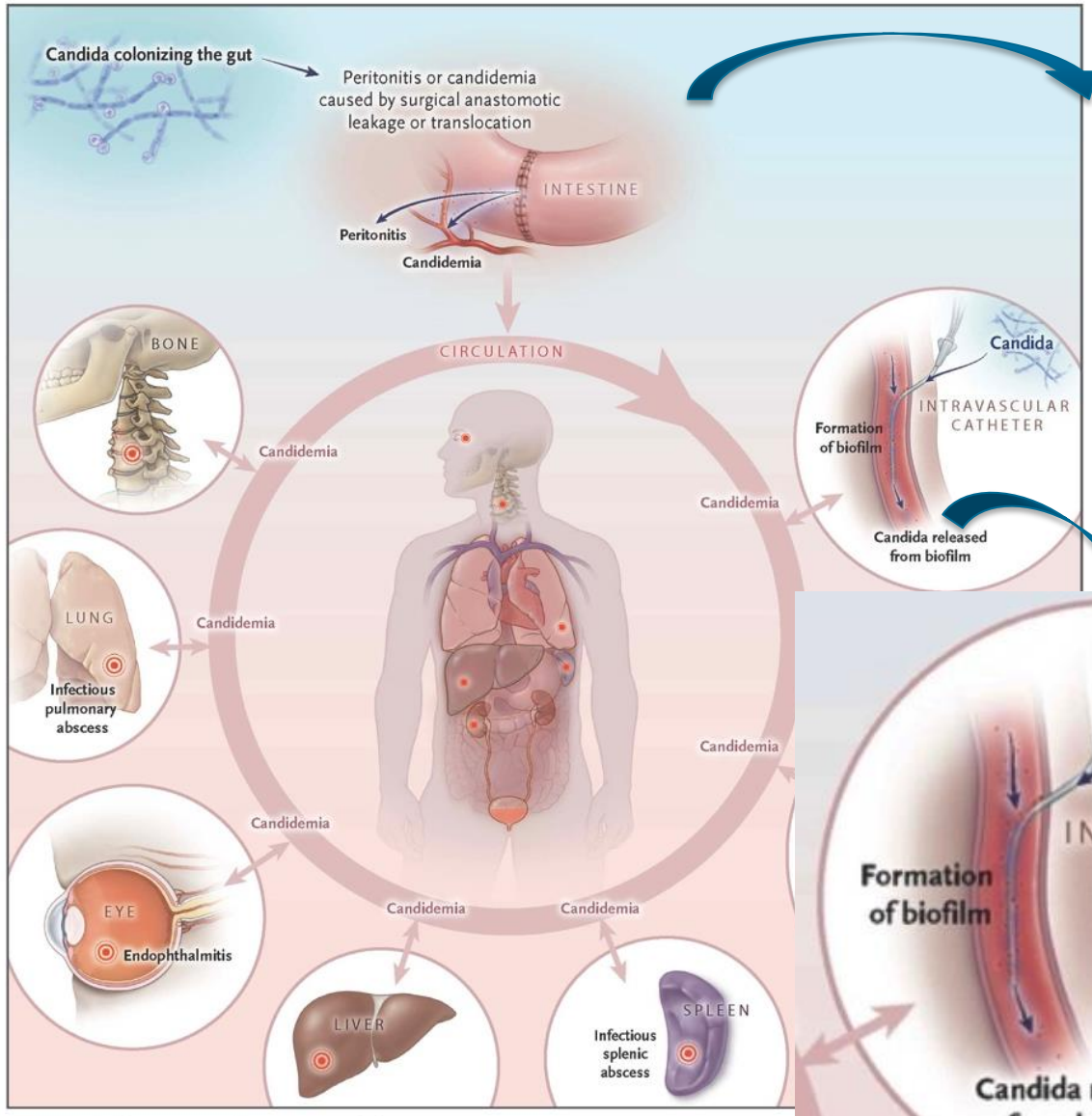
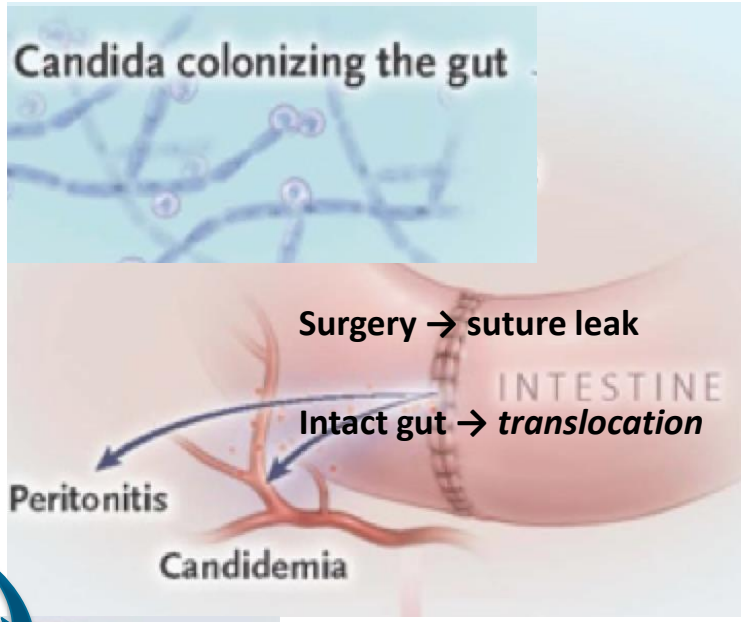
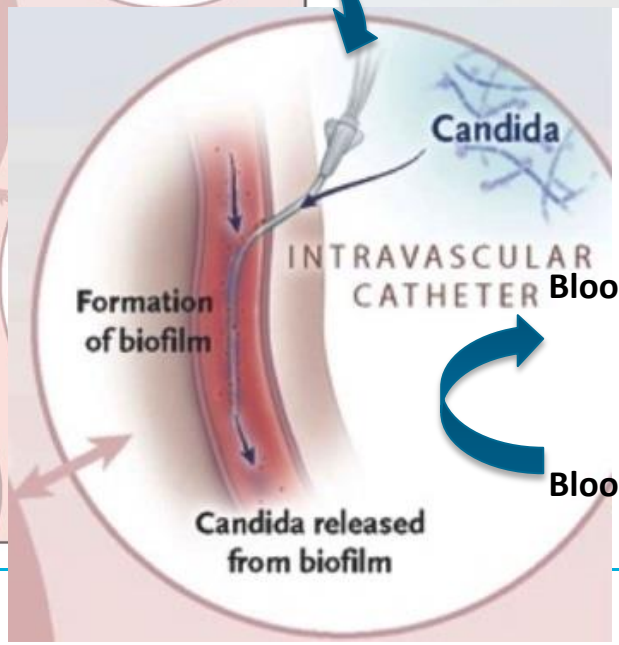
Pathogenesis of candidemia and invasive candidiasis







Bloodstream → catheter tip

Biofilm

Bloodstream ← catheter tip

Kullberg & Arendrup
New Engl J Med 2015

Invasive candidiasis

- ✓ Can we prevent invasive candidiasis in the ICU?

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MSG-01: Caspofungin prophylaxis[1] in high-risk ICU patients

Randomized, double-blind, multicenter study of Caspofungin vs. placebo

- Adult patients >48h in ICU
- Mechanical ventilation
- Central venous catheter
- Broad-spectrum antibiotics
- ≥1 of: TPN, dialysis, major surgery, pancreatitis, steroids/immunosuppressants

Ostrosky-Zeichner L, et al. *Clin Infect Dis* 2014; 58(9):1219–26

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MITT[2], N=186	Caspofungin	Placebo	Difference *P*
Invasive candidiasis proven/probable[3], after baseline	9.8%	16.7%	P=0.14
Proven invasive candidiasis	1.0%	4.8%	P=0.11
Mortality	16.7%	14.3%	P=0.35
Length of stay			n.s.

No support for antifungal prophylaxis among ICU patients

other than high-risk groups previously identified in the guidelines

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[1]Caspofungin has not been licenced for prophylactic use

[2]Modified intent to treat group: eligible patients without candidiasis at baseline, who received ≥1 dose of study drug

[2]Probable candidiasis (EORTC/MSG): 2x ß-glucan>80 AND clinical signs

Ostrosky-Zeichner L, et al. *Clin Infect Dis* 2014; 58(9):1219–26

Invasive candidiasis

- ✓ Can we detect & treat invasive candidiasis in the ICU earlier?

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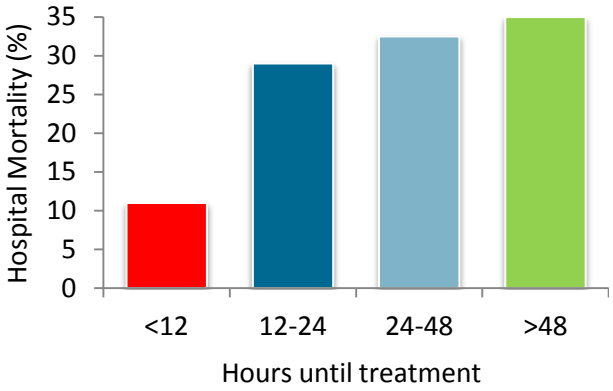
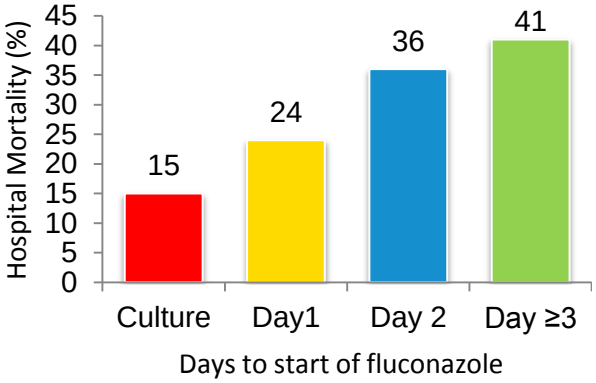
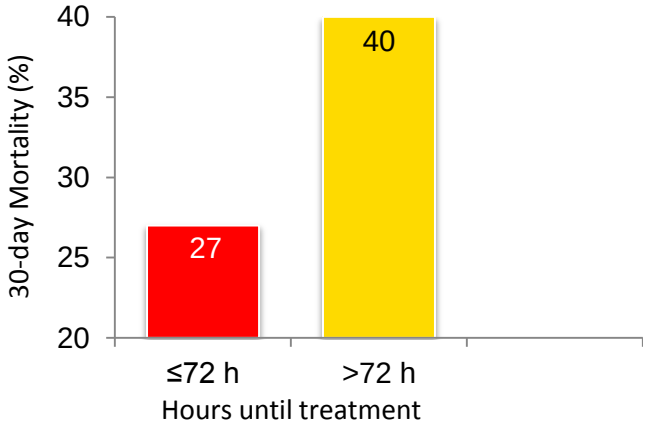
Candidemia: Importance of early appropriate treatment



157 patients – 2001–2004
Initiation of antifungal therapy <12 to >48 h after culture sample
Morrell M, et al. *AAC* 2005



230 patients – 4 centers – 2002–2005
Initiation of fluconazole 0 to ≥3 days
Garey KW, et al. *Clin Infect Dis* 2006



P=0.004

446 patients – 2001–2009
Intent to treat: 31.6–36.3% - N.S.
Shown: when Rx for <24 h classified as inappropriate
Grim SA, et al. *J Antimicrob Chemother* 2012

How to select patients for empirical therapy?

Patients admitted to ICU for >7 days (Spain)

Risk factors for developing invasive candidiasis

Develop *Candida score*

Multifocal colonization	1 point
Total Parenteral Nutrition	1 point
Surgery	1 point
Severe sepsis	2 points

- If ≥ 3 points → start treatment
- Sensitivity 60-80%, specificity 74-86%

Not universally applicable!

Local epidemiology (culture positivity) should guide local policy

León et al, Crit Care Med 2006

León et al, Crit Care Med 2009

Empirical Micafungin in ICU patients with Sepsis, Organ failure, and Candida colonization

Randomized, double-blind, multicenter study of Micafungin vs. placebo

- Nonneutropenic adult patients in ICU
- Mechanical ventilation≥ 5 days
- ≥1 Additonal organ dysfunction
- New ICU-acquired sepsis
- Broad-spectrum antibiotics ≥ 4 days
- ≥1 Site colonized with *Candida* species

MITT[1], N=251	Micafungin (14 days)	Placebo	Difference
28-day Survival free of proven fungal infection	68%	60%	HR 1.35 (0.87-2.08)
Survival (d28)	70%	70%	HR 1.04 (0.64-1.67)
Invasive fungal infections	9%	12%	Δ 2.8% (-5.0, 10.8)

No support for empirical antifungals among ICU patients
other than high-risk groups previously identified

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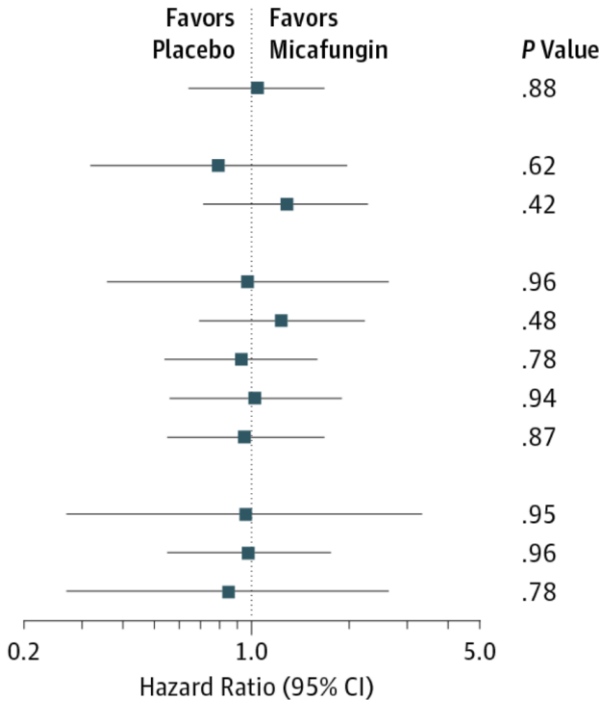
[1]Modified intent to treat group: patients who received ≥1 dose of study drug

Timsit JF, et al. *JAMA* 2016; 315(15):1555–64

Empirical Micafungin in ICU patients with Sepsis, Organ failure, and Candida colonization

28-Days' Survival

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	90	128	86	123	1.04 (0.64-1.67)	.88
SOFA score						
≤8	53	66	58	68	0.79 (0.32-1.96)	.62
>8	37	62	28	55	1.28 (0.71-2.27)	.42
Admission category						
Surgical	23	34	23	31	0.97 (0.36-2.63)	.96
Medical	67	94	63	92	1.23 (0.69-2.22)	.48
Colonization index ≥0.5[a]	70	101	70	99	0.93 (0.54-1.59)	.78
Corrected colonization index ≥0.4[b]	54	76	56	80	1.02 (0.56-1.89)	.94
Candida score ≥3	66	96	58	85	0.95 (0.55-1.67)	.87
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	17	25	0.96 (0.27-3.33)	.95
>80	61	91	58	84	0.98 (0.55-1.75)	.96
≤80	29	37	28	39	0.85 (0.27-2.63)	.78



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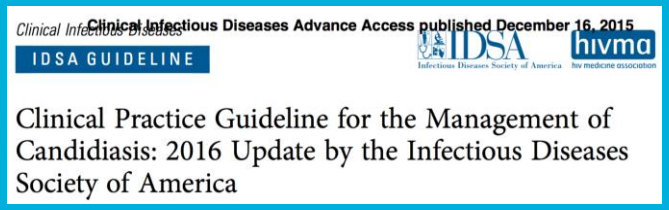
Invasive candidiasis

✓ What is the evidence behind the guidelines?



IDSA Clinical Practice Guideline for Management of Candidiasis 2016

ESCMID Diagnostic & Management Guidelines for *Candida* Diseases 2012

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IDSA 2016:
Treatment for candidemia

Compound	Comment	Recommendation	Evidence
Initial therapy			
Anidulafungin 200→100 mg		Strong	High
Caspofungin 70→50 mg		Strong	High
Micafungin 100 mg		Strong	High

Pappas PG et al. Clin Infect Dis 2016;62(4):409–17

IDSA 2016:
Treatment for candidemia

Compound	Comment	Recommendation	Evidence
Initial therapy			
Anidulafungin 200→100 mg		Strong	High
Caspofungin 70→50 mg		Strong	High
Micafungin 100 mg		Strong	High
Acceptable alternatives			
Fluconazole 800→400 mg	Selected patients – Not critically ill and unlikely to have FLU-resistant *Candida*	Strong	High
Voriconazole 6→3 mg/kg bid*	Little advantage over FLU as initial therapy	Strong	Moderate
L-Amphotericin B 3 mg/kg	Reasonable alternative if intolerance, limited availability, or resistance to other antifungal agents	Strong	High

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*Licensed dose: 6 mg/kg q12h for the first 24 hours, followed by 4 mg/kg BID. Voriconazole is indicated in the treatment of candidaemia in non-neutropenic patients (adults & children ≥2 yrs)

Pappas PG et al. Clin Infect Dis 2016;62(4):409–17

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European Society of Clinical Microbiology and Infectious Diseases

ESCMID: The paradigm shift
Directed therapy of candidemia

Compound	Recommendation	References	Comment
Anidulafungin 200→100 mg	A I	Reboli NEJM 2007 Kett Int J Antimicrob Agents 2008	
Caspofungin 70→50 mg	A I	Mora-Duarte NEJM 2002 Pappas Clin Infect Dis 2007	
Micafungin 100 mg	A I	Kuse Lancet 2007 Pappas Clin Infect Dis 2007	
L-Amphotericin B 3 mg/kg	B I	Kuse Lancet 2007 Dupont Crit Care 2009	
Voriconazole 6→3 mg/kg bid*	B I	Kullberg Lancet 2005 Ostrosky-Zeichner Eur J Clin Microbiol Infect Dis 2003 Perfect Clin Infect Dis 2003	
Fluconazole 800→400 mg	C I	Anaissie Clin Infect Dis 1996 Rex NEJM 1994 Rex Clin Infect Dis 2003 Philips Eur J Clin Microbiol Infect Dis 1997 Reboli NEJM 2007	
AmB lipid complex 5 mg/kg	C II	Anaissie ICAAC 1995 Ito Clin Infect Dis 2005	
AmB deoxycholate 0.7–1 mg/kg	D I	Bates Clin Infect Dis 2001 Anaissie Clin Infect Dis 1996 Rex NEJM 1994 Philips Eur J Clin Microbiol Infect Dis 1997 Mora-Duarte NEJM 2002	

*Licensed dose: 6 mg/kg q12h for the first 24 hours, followed by 4 mg/kg BID. Voriconazole is indicated in the treatment of candidaemia in non-neutropenic patients (adults & children ≥2 yrs)

Adapted from: Cornely OA, et al. *Clin Microbiol Infect* 2012; 18(Suppl 7):19–37.

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Directed therapy of candidemia
and invasive candidiasis in non-neutropenic adults

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Adapted from: Cornely OA, et al. *Clin Microbiol Infect* 2012; 18(Suppl 7):19–37.

Liposomal amphotericin B equal to echinocandin:
Micafungin invasive candidiasis trial

Randomised, double-blind multicentre study of micafungin vs liposomal amphotericin B

	Micafungin 100→200 mg	Liposomal amphotericin B 3→5 mg/kg	Estimated Difference (95% CI)
Success rate* (MITT; EOT) N=494	74%	70%	4.5% (-3.5, 12.4) *P*=NS
Success rate Neutropenic patients N=57	59%	56%	4.9% (-3.0, 12.8) *P*=NS
Mortality (12 weeks)	40%	40%	*P*=NS
Side Effects Creatinine rise (>ULN)	10%	30%	*P*<0.0001

*Treatment success defined as both clinical and mycological response at end of treatment
MITT, modified intent-to-treat population; EOT, end of treatment; ULN, upper limit of normal.

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Kuse E-R, et al. *Lancet* 2007; 369(9572):1519–27.

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Adapted from: Cornely OA, et al. *Clin Microbiol Infect* 2012; 18(Suppl 7):19–37.

Echinocandin superior to Fluconazole:
Anidulafungin invasive candidiasis trial

Randomized, double-blind, multicenter study of Anidulafungin vs. Fluconazole

	Anidulafungin 200→100mg	Fluconazole 800→400mg	Estimated difference % (95%CI; *P*)
Success Rate (MITT; EOivT) N=245	76%	60%	15.4% (3.9, 27.0; *P*<0.02)
Crude Mortality (8 wks)	23%	31%	*P*=0.13

Both arms allowed to switch to oral fluconazole after ≥10 days

MITT. modified intent-to-treat population; EOivT, End of intravenous Treatment

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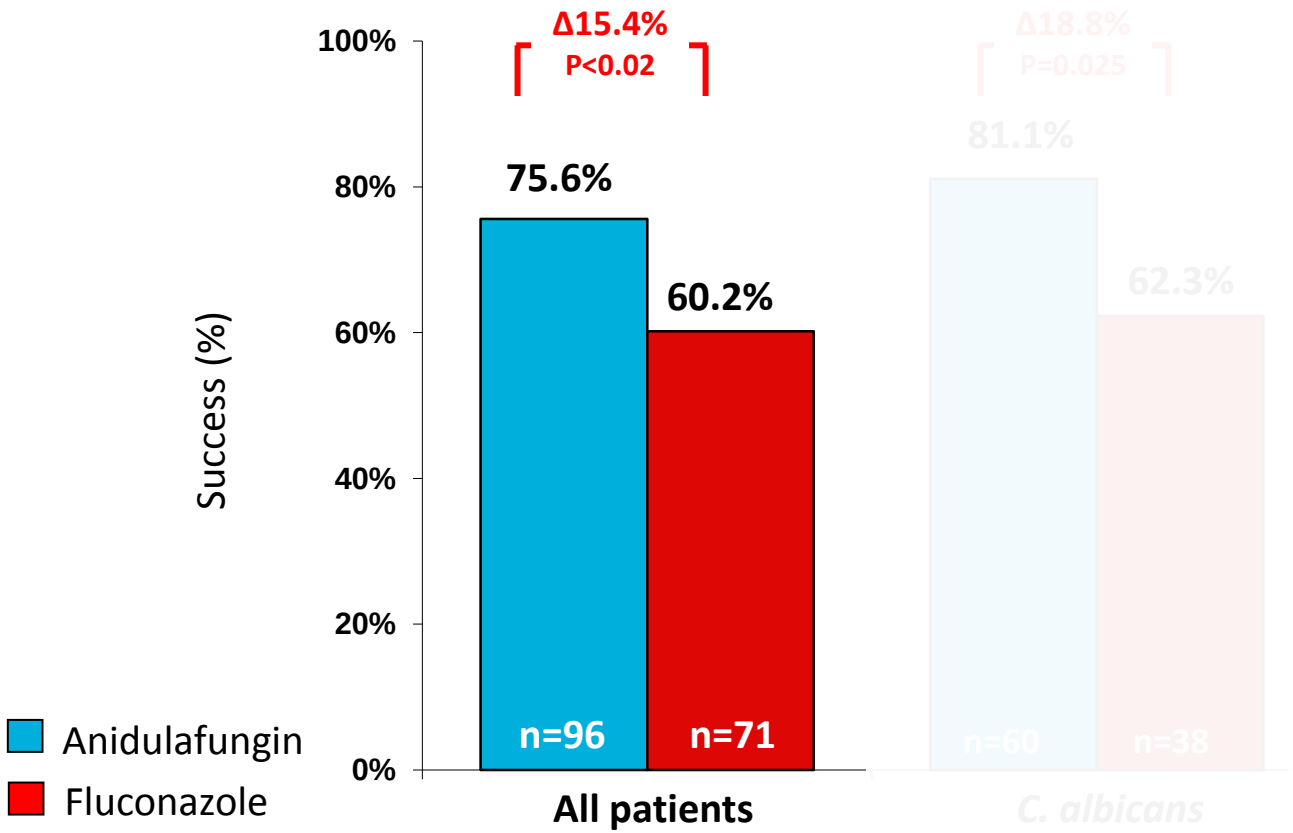
Reboli AC, et al. *N Engl J Med* 2007; 356(24):2472–82.

Anidulafungin candidemia study

*Success difference driven by C. albicans infections**



NS, no significant difference

*Patients with a single baseline pathogen

Reboli AC, et al. *N Engl J Med* 2007; 356(24):2472–82.

Anidulafungin study

Success vs APACHE II scores

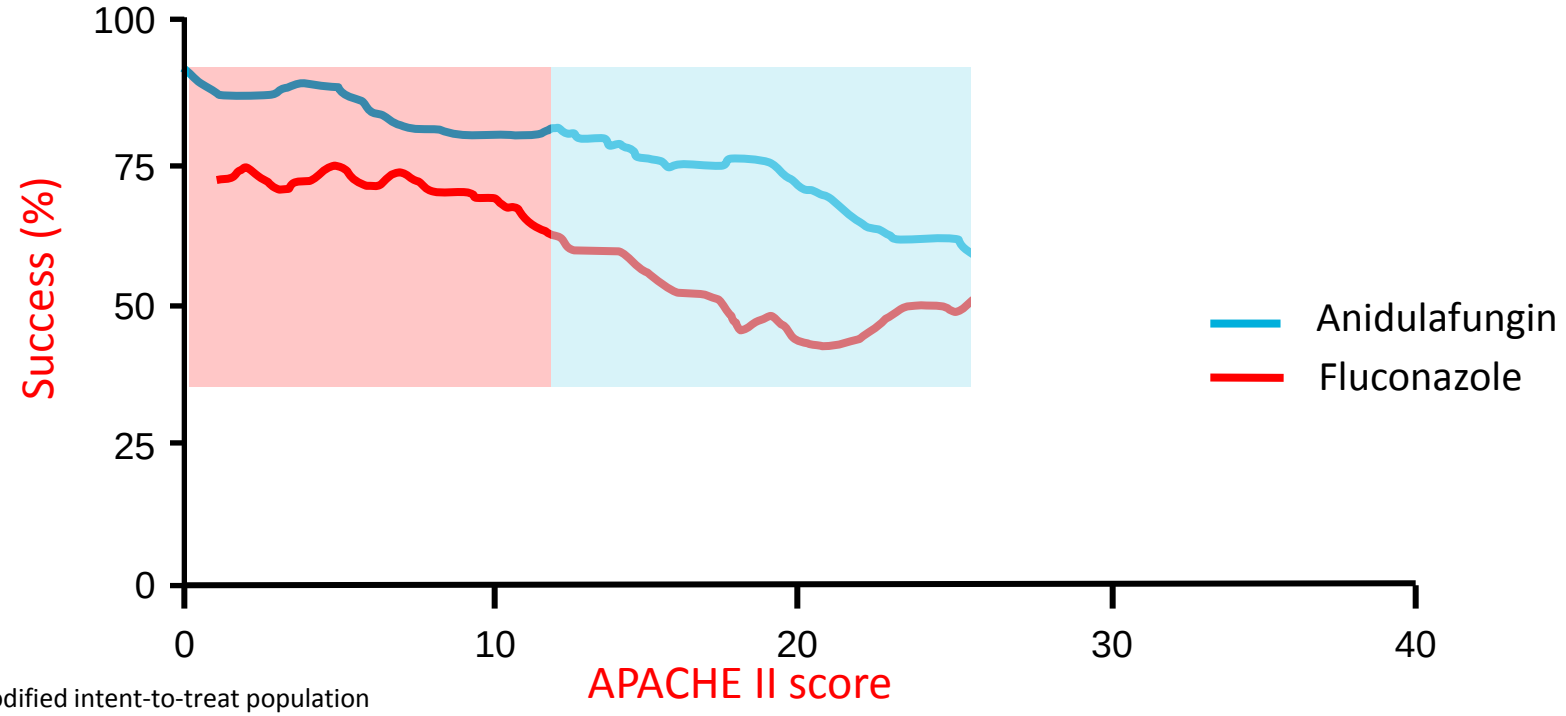
The IDSA (**2016**) favors an Echinocandin for all patients with candidemia/invasive candidiasis

Pappas et al., Clin Infect Dis 2016; 62: 409–17

The IDSA (**2009**) favors an Echinocandin

- for patients with moderately severe to severe illness
- or patients who have had recent azole exposure

Pappas et al., Clin Infect Dis 2009; 48: 503-535



MITT. modified intent-to-treat population

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Data on file. Pfizer Inc, New York, NY

New data 2009–2017?

Are echinocandins really superior to fluconazole?

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Mycoses Study Group MSG-02 Pooled Analysis

- 1915 patients - Individual patient-level pooled analysis
- Overall mortality 31.4%
- Treatment success (EOT) 67.4%

30-day mortality endpoint:

Increased mortality:	OR	P
Age	1.01	0.02
APACHE II score	1.11	0.0001

Decreased mortality:		
Echinocandin antifungal	0.65	0.02
CVC removal during therapy	0.50	0.0001

1. Treat early
2. Remove catheter
3. Start with echinocandin

Andes DR, et al. *Clin Infect Dis* 2012;54(8):1110–22.

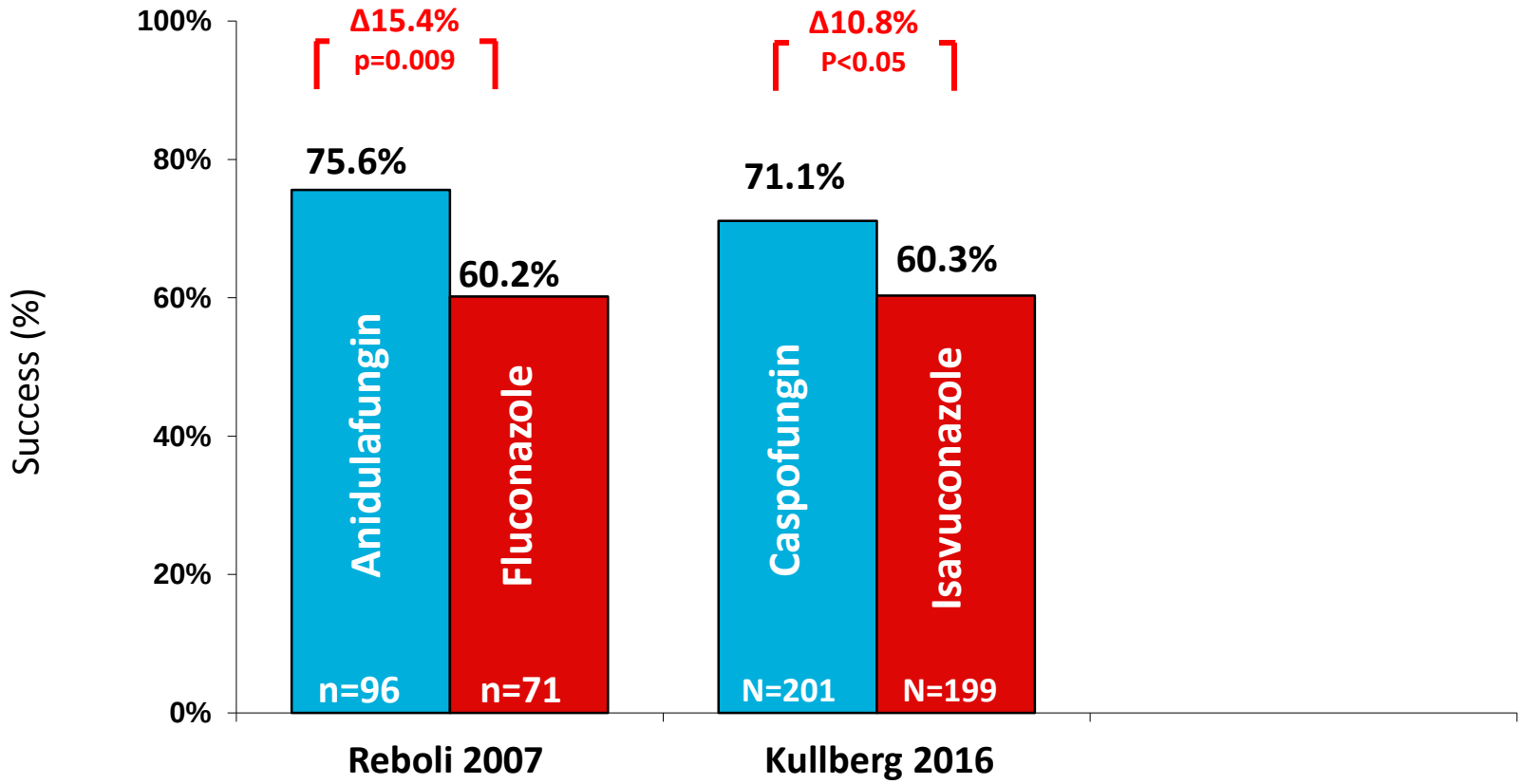
Second azole vs. echinocandin trial – similar difference

Primary objective	Compare the efficacy of isavuconazole vs caspofungin in patients with candidemia or other invasive *Candida* infections
Study design	Multinational, double-blind, randomized, non-inferiority study of iv isavuconazole versus iv caspofungin; switch to oral treatment >Day 10
Study population	450 adult patients with candidemia/invasive candidiasis; >85% power to demonstrate non-inferiority of isavuconazole to caspofungin at a non-inferiority margin of 15%

1. Reboli AC, et al. *N Engl J Med* 2007; 356(24):2472–82
2. Kullberg et al. ECCMID 2016,Abstr. 1239; 11 April 2016

Are echinocandins superior to azoles?

Second azole vs. echinocandin trial – similar difference



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Cornely et al. Clin Microbiol Infect 2012: 18 (suppl 7) 19-37

Special populations
ICU patients

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Invasive candidiasis in the ICU

Registrational trials, ICU patient subgroups	Global success, n / %	Reference source
Fluconazole	13/28 46%	Kett J, Cubillos GF. *Antimicrob Agents* 2008; 32(Suppl 2):S99–S102.
d-Amphotericin B	32/57 56%	DiNubile MJ, et al. *J Crit Care* 2007;22(3):237–44.
Micafungin	75/120 63%	Dupont BF, et al. *Crit Care* 2009;13(5):R159.
L-Amphotericin B	73/110 66%	Dupont BF, et al. *Crit Care* 2009;13(5):R159;
Caspofungin	27/40 68%	DiNubile MJ, et al. *J Crit Care* 2007;22(3):237–44.
Anidulafungin	24/35 69%	Kett J, Cubillos GF. *Antimicrob Agents* 2008; 32(Suppl 2):S99–S102.

Invasive candidiasis in the ICU in Europe (ICE) trial

- Phase IIIb, prospective, open-label, non-comparative multicentre trial
- Anidulafungin in high-risk ICU patients with additional risk factors:
  - post-abdominal surgery
  - solid tumor
  - renal insufficiency
  - hepatic insufficiency
  - solid organ transplant
  - Neutropenia
  - Age ≥65 years

Ruhnke M, et al. *Clin Microbiol Infect* 2012; 18(7):680–7.

Invasive candidiasis in the ICU

Registrational trials, ICU patient subgroups	Global success, n / %	Reference source
Fluconazole[3]	13/28 46%	Kett J, Cubillos GF. *Antimicrob Agents* 2008; 32(Suppl 2):S99–S102.
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Anidulafungin[3]	24/35 69%	Kett J, Cubillos GF. *Antimicrob Agents* 2008; 32(Suppl 2):S99–S102.

ICE study subgroups – Anidulafungin	Global success, n / % (EOT)
Post-abdominal surgery	54/79 68%
Elderly (≥65 years)	49/72 68%
Renal failure	44/58 76%
Solid tumor	31/41 76%
Hepatic insufficiency	18/25 72%
Neutropenia	6/12 50%
Solid organ transplant	3/8 38%

Ruhnke M, et al. *Clin Microbiol Infect* 2012; 18(7):680–7.

Septic shock due to candidemia

Retrospective cohort study – 224 patients – single center – 2002-2011

Variable	Survived	Died	*P*
N (224)	69	155 (69%)	
Multivariate analysis:			
Antifungal treatment <24h of shock	99% (68)	72% (112)	<0.001
Inadequate source control <24h (e.g., catheter removal)	1% (1)	39% (61)	<0.001
Echinocandin	77% (53)	49% (76)	<0.001
Fluconazole/voriconazole Ampho B None	19% (13) 4% (3) 0% (0)	16% (25) 8% (13) 27% (41)	

1. Treat early
2. Remove catheter
3. Start with echinocandin

Kollef et al. Clin Infect Dis 2012; 54: 1739

Special populations
Abdominal candidiasis

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Abdominal candidiasis – The missing 50%

2-year retrospective cohort, U Pittsburg Medical Center

Patients	N
Candidemia	161
Intraabdominal candidiasis	163
Intraabdominal candidiasis	163
▪ Primary peritonitis	8
▪ GI tract source	103
▪ Hepatobiliary/pancreatic source	52
Mortality (100 days)	28%
Bacterial co-infection	67%
Candidemia	6%

Vergidis P, Clancy CJ et al, PLoS ONE 2016:11(4);e015247

Abdominal candidiasis – The missing 50%

2-year retrospective cohort, U Pittsburg Medical Center

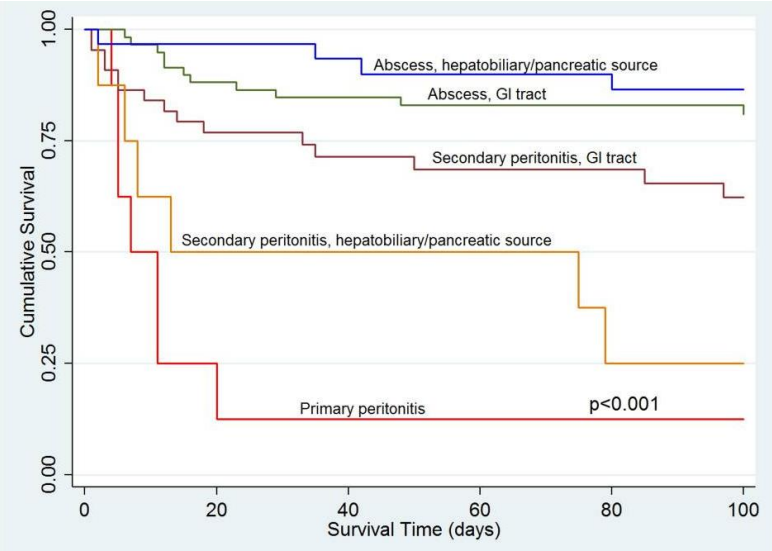
Patients	N
Candidemia Intraabdominal candidiasis	161 163
Intraabdominal candidiasis ▪ Primary peritonitis ▪ GI tract source ▪ Hepatobiliary/pancreatic source	163 8 103 52
Mortality (100 days)	28%
Bacterial co-infection Candidemia	67% 6%

Vergidis P, Clancy CJ et al, PLoS ONE 2016:11(4);e015247

Abdominal candidiasis

2-year retrospective cohort, U Pittsburg Medical Center

Predictors of mortality multivariate analysis	Odds Ratio (95% CI)
Age	1.06 (1.03, 1.09)
Antifungal Rx started ≤5d	0.36 (0.13, 0.96)
Abscess	0.25 (0.11, 0.57)
Source control intervention ≤5d	0.23 (0.11, 0.57)



1. Treat early
2. Control source
3. Start with echinocandin

Vergidis P, Clancy CJ et al, PLoS ONE 2016:11(4);e015247

Empiric echinocandin therapy in ICU patients following surgery for intraabdominal infection (INTENSE)

Randomized, double-blind, multicenter study of micafungin vs. placebo

- Adult patients ≥48h in ICU
- Intraabdominal infection (community- or hospital-acquired)
- Requiring surgery and ICU stay
- Exclusion: e.g., acute pancreatitis, CAPD, organ transplant, *documented* invasive candidiasis

Randomized, N=252	Micafungin	Placebo	Difference (CI)
Baseline invasive candidiasis	5	2	
Full analysis cohort No baseline candidiasis, ≥1 dose	124	117	
Proven invasive candidiasis (IDRB)	11.1%	8.9%	2.24 (-5.52, 10.20)
Mortality	4.3%	0.8%	*P* = NS
Per protocol cohort Proven invasive. candidiasis (IDRB) + no protocol violations, ≥3 days Rx	6.3%	5.7%	0.65 (-7.17, 8.95)

No support for empiric/preemptive treatment if no baseline candidiasis at surgery

Radboudumc [1] IDRB, independent data review board

Knitsch W et al. Clin Infect Dis 2015; 61: 1671-8

Special populations
C. glabrata and *C. parapsilosis*

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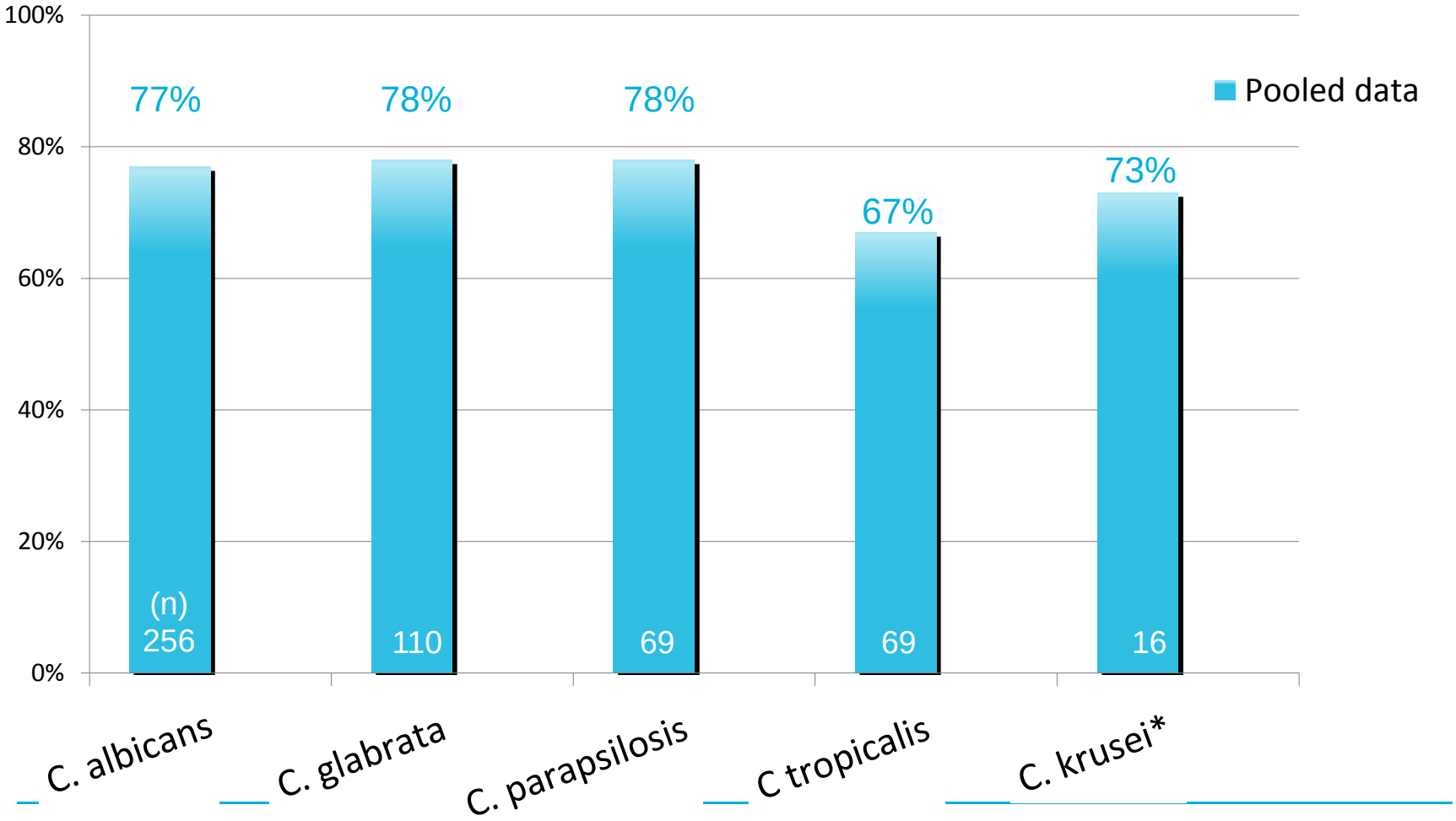
Echinocandins for *non-albicans* candidemia

Efficacy of anidulafungin in 504 Patients with Invasive Candidiasis

Pooled database of 4 prospective open-label trials



**C. krusei* infections were excluded from the anidulafungin vs. fluconazole trial*

Kullberg BJ, et al. J Antimicrob Ther 2017, in press

Special populations
Neutropenic patients

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Efficacy in neutropenic patients with invasive candidiasis

Published Trials, Neutropenic subgroups	Global success, n/N, %	Source
d-Amphotericin B	4/10 40%	Mora-Duarte J et al. N Engl J Med 2002; 347: 2020–2029
L-Amphotericin B	12/15 80%	Kuse ER et al. Lancet 2007; 369: 1519–1527
Anidulafungin	26/46 57%	Herbrecht et al. EHA 2014;P1187
Caspofungin	20/38 53%	Mora-Duarte J et al. N Engl J Med 2002; 347: 2020–2029 Pappas PG et al. Clin Infect Dis 2007; 45: 883–893 Betts RF et al. Clin Infect Dis 2009; 48:1676–84
Micafungin	45/63 71%	Pappas PG et al. Clin Infect Dis 2007; 45: 883–893 Kuse ER et al. Lancet 2007; 369: 1519–1527

When can I step down to fluconazole?

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Echinocandin to azole transition in candidemia patients

- Phase IV open-label non-comparative anidulafungin candidemia/invasive candidiasis study

- Anidulafungin iv → oral fluconazole/voriconazole transition after ≥5 days if:
  - tolerate oral Rx
  - afebrile for >24 h
  - hemodynamically stable
  - not neutropenic
  - documented *Candida* clearance from bloodstream

*MITT, modified intent-to-treat population

Vazquez J, et al. *BMC Infect Dis* 2014:14;97.

Echinocandin to azole transition in candidemia patients

	All patients	Early switch population
	% (N) [95% CI]	% (N) [95% CI]
MITT population (N)	250	102
Global success at EOT	68% (170/250) [62.2–73.8]	79% (81/102) [71.6–87.3]
Mortality (ITT population)	23% (65/282)	14% (14/102)
Success at End of iv Therapy	83% (208/250) [78.6–87.8]	95% (97/102) [90.3–99.3]

- ✓ A paradigm shift:
- ✓ Start all patients on echinocandin
- ✓ Continue echinocandin until stabilization
- ✓ DO switch early after stabilization and negative follow-up blood culture

1. Treat early
2. Remove catheter
3. Start with echinocandin
4. Step down to azole once stabilized*

* Azole susceptible, non-neutropenic, no intravascular devices, tolerate oral Rx, hemodynamically stable, *documented clearance from bloodstream*

Vazquez J, et al. *BMC Infect Dis* 2014:14;97.

EOT, end of therapy; MITT analysis: missing/unknown values set as failures

Summary thoughts

- Candidemia / invasive candidiasis emerge from intestinal colonization
- Early and accurate diagnosis of abdominal candidiasis is crucial
- Prophylaxis and empirical therapy in the ICU are not supported by trials
- Supporting data on superiority of echinocandins in the ICU setting has been emerging[1,2]
- IDSA 2016 and ESCMID 2012 prioritized echinocandins as the first choice for treatment of candidemia/invasive candidiasis [3,5]
- Echinocandin success rates for *C. parapsilosis* and other non-albicans species are comparable to *C. albicans* outcomes for initial therapy.[4]
- Rapid (Day 5) step down to azoles in stabilized patients is feasible, *not based on species or susceptibility report only* but after clinical stabilization[8]

1. DiNubile MJ, et al. *J Crit Care* 2007;22(3):237–44; 2. Kett DH, Cubillos GF. *Int J Antimicrob Agents* 2008; 32(Suppl 2):S99–S102; 3. Cornely OA, et al. *Clin Microbiol Infect* 2012; 18(Suppl 7):19–37; 4. Colombo AL, et al. *Antimicrob Agents Chemother* 2010; 54(5):1864–71; 5. Pappas PG, et al. *Clin Infect Dis* 2016; 62:409-17; 6. Herbrecht R, et al. Presented at EHA 2014 [#P1187]; 7. Kullberg B, et al. Presented at ICAAC, Sep 11, 2012 ; 8. Vazquez J, et al. *BMC Infect Dis* 2014:14;97.

Thank you

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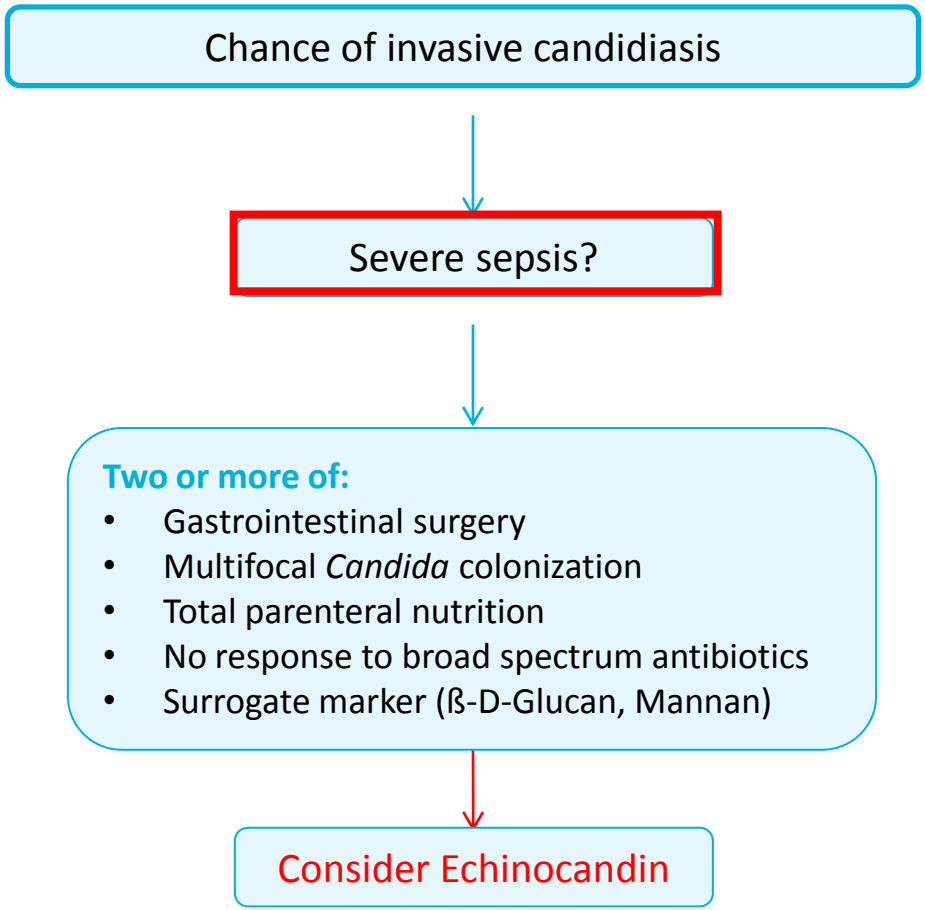
How to select patients for presumptive therapy? An expert-based view



discussed in:
Kullberg & Arendrup New Engl J Med 2015