Candida infections in ICU

Gunda Jaya Hareesh

Epidemiology

- EPIC study – Point prevalence study on April 29, 1992

  1417 ICU – 10038 patients (32% post-surgical patients)

  63% mechanically ventilated, 78.9% intravenous catheter

  46.7% < 2days and 14% >21 days
- 44.8% had ≥1 infection (50.4% ICU acquired - 85% microbiological)
- 34.4% Enterobacteriaceae, 30.1% Staphylococcus, 28.7% Pseudomonas
- **17.1% Fungi** and 0.2% Viral

Vincent JL et al, JAMA. 1995 Aug 23-30;274(8):639-44

Epidemiology

- EPIC II study – Point prevalence study on May 8, 2007

  1265 ICU – 13796 patients across 75 countries (25 hospitals from India) - 56% ventilated

- 51% had one or more infections – of them 70% had positive cultures (47% gram +ve, 62% Gram –ve,**19% had fungal)**

- Most common staph (20%), pseudomonas (20%) and E.coli(16%)

- 71% receiving antibiotics (therapeutic/prophylactic)

- 16% of infected are on antifungals

Vincent J et al. *JAMA.* 2009;302(21):2323–2329

Characteristic	All Patients (n = 13 796)[a]	Not Infected (n = 6709)[b]	Infected (n = 7087)[c]
Reason for ICU admission			
Respiratory	3091 (22.4)	845 (12.6)	2246 (31.7)
Cardiovascular	3041 (22.0)	1541 (23.0)	1500 (21.2)
Surveillance/monitoring	2592 (18.8)	1968 (29.3)	624 (8.8)
Neurologic	2010 (14.6)	994 (14.8)	1016 (14.3)
Digestive/liver	1306 (9.5)	478 (7.1)	828 (11.7)
Trauma	1119 (8.1)	593 (8.8)	526 (7.4)
Renal	324 (2.3)	119 (1.8)	205 (2.9)
Other[e]	313 (2.3)	171 (2.5)	142 (2.0)

	No. (%)[a]							
	All	Western Europe	Eastern Europe	Central/ South America	North America	Oceania	Africa	Asia
Site of infection								
Respiratory tract	4503 (63.5)	2332 (63.3)	305 (71.6)[b]	851 (66)	345 (56.8)[b]	165 (57.9)	41 (46.1)[b]	464 (65.6)
Abdominal	1392 (19.6)	778 (21.1)	93 (21.8)	228 (17.7)[b]	101 (16.6)	50 (17.5)	16 (18)	126 (17.8)
Bloodstream	1071 (15.1)	546 (14.8)	53 (12.4)	139 (10.8)[b]	157 (25.9)[b]	49 (17.2)	16 (18)	111 (15.7)
Renal/urinary tract	1011 (14.3)	411 (11.2)	84 (19.7)[b]	222 (17.2)[b]	135 (22.2)[b]	33 (11.6)	15 (16.9)	111 (15.7)[b]
Skin	467 (6.6)	242 (6.6)	37 (8.7)	73 (5.7)	26 (4.3)	30 (10.5)	8 (9.0)	51 (7.2)
Catheter-related	332 (4.7)	171 (4.6)	21 (4.9)	73 (5.7)	16 (2.6)	15 (5.3)	4 (4.5)	32 (4.5)
CNS	208 (2.9)	100 (2.7)	20 (4.7)	40 (3.1)	14 (2.3)	11 (3.9)	4 (4.5)	19 (2.7)
Others	540 (7.6)	289 (7.8)	31 (7.3)	87 (6.7)	62 (10.2)	22 (7.7)	14 (15.7)[b]	35 (5.0)[b]
Fungi								
Candida	843 (17)	495 (18.5)	66 (18.5)	92 (12.8)[b]	83 (18.2)	26 (12.7)	6 (11.1)	75 (15.7)
Aspergillus	70 (1.4)	44 (1.6)	1 (0.3)	5 (0.7)	12 (2.6)	3 (1.5)	0	5 (1)
Other	50 (1)	22 (0.8)	5 (1.4)	7 (1)	10 (2.2)	2 (1)	0	4 (0.8)

Epidemiology

- Most common IFI in ICU is – Invasive Candidiasis (70%) followed by aspergillosis and mucormycosis
- Lab-based surveillance from 25 hospitals in 6 countries (4 from India)

Rank	Total (N=27,448)*	Urine (N=9,341)	Blood (N=1,910)	Other sterile fluid, tissue (N=889)	Intravascular catheter (N=393)	Intra-abdominal (N=392)
1	*Candida albicans* (17,916, 65.3%)	*C. albicans* (5,392, 57.7%)	*C. albicans* (790, 41.3%)	*C. albicans* (512, 57.6%)	*C. albicans* (234, 59.5%)	*C. albicans* (282, 71.9%)
2	*Candida tropicalis* (3,889, 14.2%)	*C. glabrata* (1,948, 20.8%)	*C. tropicalis* (486, 25.4%)	*C. tropicalis* (134, 15.1%)	*C. tropicalis* (60, 15.2%)	*C. tropicalis* (57, 14,5%)
3	*Candida glabrata* (3,682, 13.4%)	*C. tropicalis* (1561, 16.7%)	*C. glabrata* (266, 13.9%)	*C. glabrata* (123, 13.8%)	*C. parapsilosis* (58, 14.7%)	*C. glabrata* (36, 9.2%)
4	*Candida parapsilosis* (1,114, 4.0%)	*C. parapsilosis* (208, 2.2%)	*C. parapsilosis* (232, 12.1%)	*C. parapsilosis* (81, 9.1%)	*C. glabrata* (37, 9.4%)	*C. parapsilosis* (9, 2.2%)
5	*Candida krusei* (414, 1.5%)	*C. krusei* (118, 1.26%)	*C. guilliermondii* (37, 1.9%)	*C. guilliermondii* (12, 1.3%)	*C. guilliermondii* (3, 0.7%)	*C. krusei* (3, 0.7%)

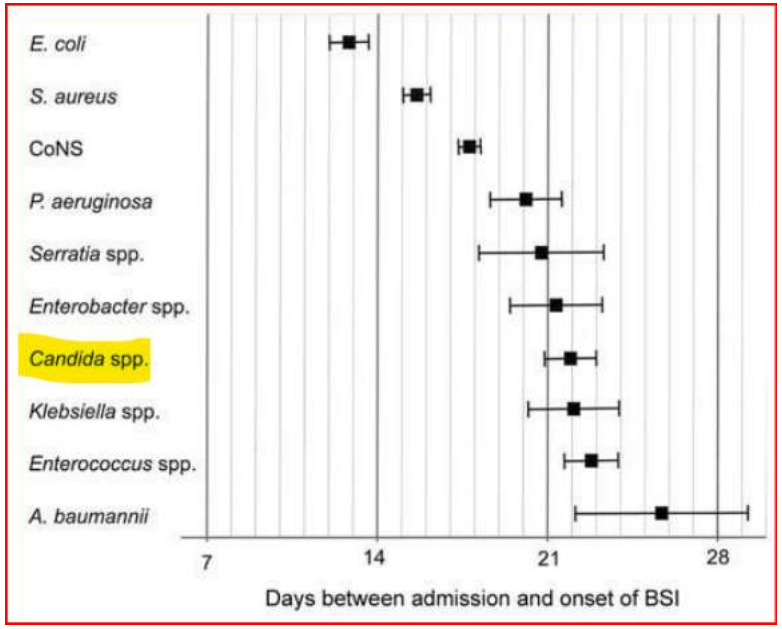
Cortegiani A etal. Arch Clin Infect Dis. 2017;12(4):e12414
Tan BH, Chakrabarti A et al Clinical Microbiology and Infection (2015)

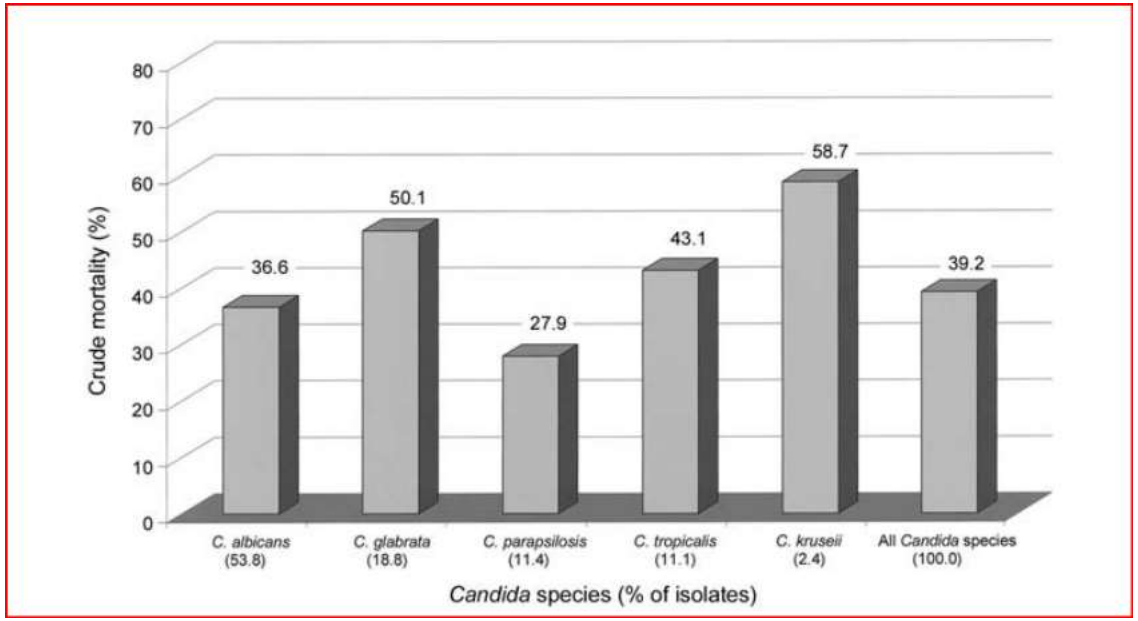
Epidemiology - Candidemia across world

	USA 1997	Latin America 1997	Europe 1997	India 1991-2000
albicans	56	41	53	14
parapsilosis	9	38	21	2
glabrata	19	2	12	3
tropicalis	7	12	6	38
guilliermondii	1	2	4	12
krusei	2		1	5
Others	6	5	3	26

Chakrabarti, A *et al Intensive Care Med* **41**, 285–295 (2015)

Epidemiology - Candidemia across world





Hilmar Wisplinghoff et al. *Clin Infect Diseases*,39,3,1 Aug 2004,309–317

Epidemiology of candidemia

- 27 ICUs from India – April 2011 – September 2012
- Of 215,112 patients – 1400 had candidemia (**6.51/1000 ICU admissions**)
- Median duration of candidemia was 8 days (4-15 days)
- Found our patients were younger and less serious patients when compared to other populations – due to prior broad-spectrum antibiotics and steroids in large numbers in our patients
- Crude mortality – 44.7%, Attributable 22.8%

82 % of healthcare providers were found to carry yeast on their hands
80 % were C. tropicalis

Species	**Prevalence**
C. tropicalis	41.6%
C. albicans	20.9%
C. parapsilosis	10.9%
C. glabrata	7.1%
C. auris	5.2%

Chakrabarti, A et al Intensive Care Med **41**, 285–295 (2015)
Chakrabarti A Scand J Infect Dis 41(4):275–284

Table 1 Antifungal susceptibility profile of highest burden *Candida* species circulating among adult candidemia intensive care patients from India, based on the CLSI M27-S4 (2012) guidelines

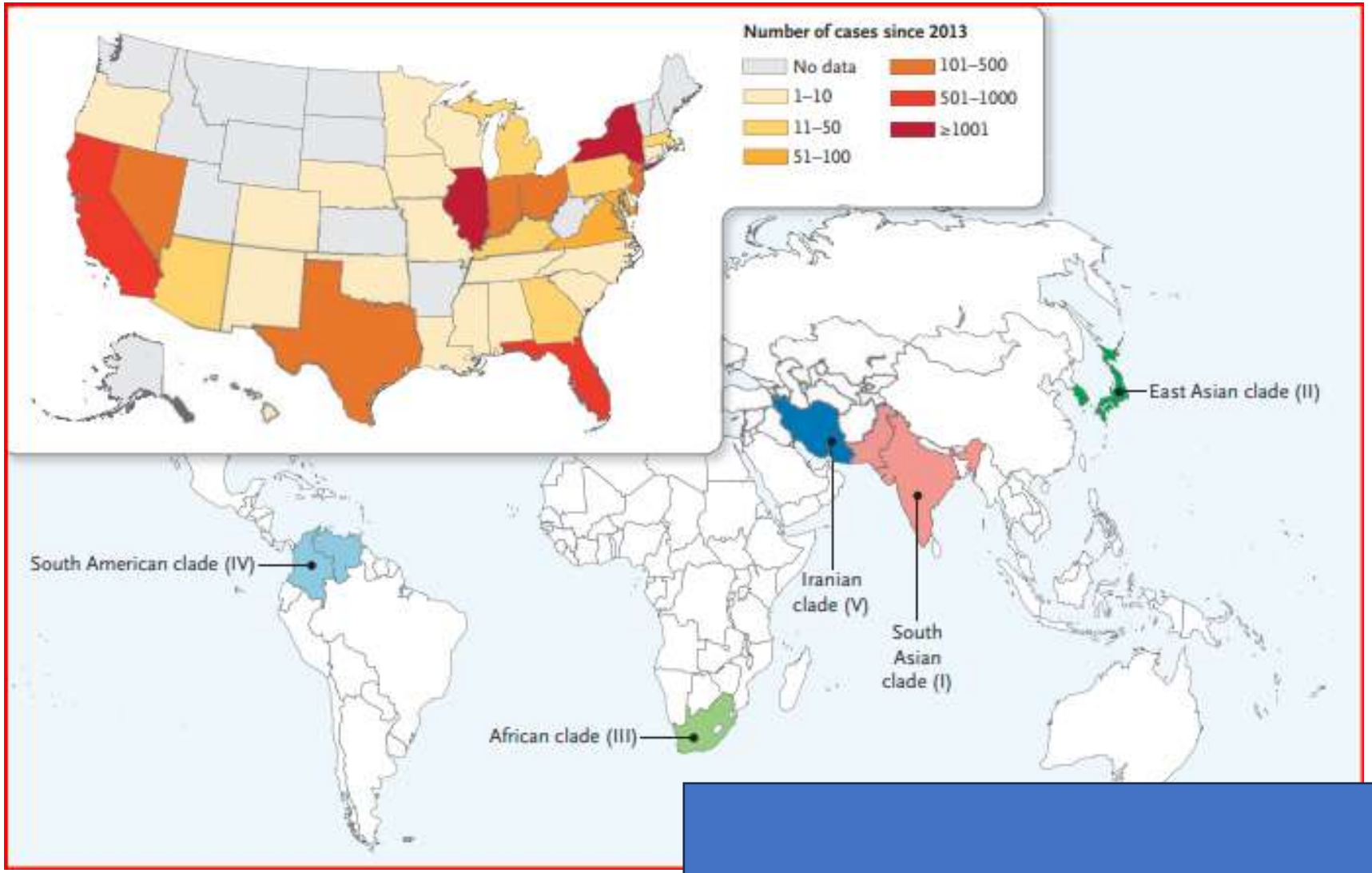
Antifungal	AFST	All species ($n = 918$)	*C. tropicalis* ($n = 382$)	*C. albicans* ($n = 192$)	*C. parapsilosis* ($n = 100$)	*C. auris* ($n = 52$)	*C. glabrata* ($n = 65$)	*C. rugosa* ($n = 29$)	*C. krusei* ($n = 16$)	*C. guilliermondii* ($n = 16$)
Amphotericin B	MIC_{50} (μg/ml)	–	0.50	0.25	0.50	1.00	0.25	0.25	0.50	0.25
	MIC_{90} (μg/ml)	–	1.00	1.00	1.00	2.00	1.00	1.00	1.00	1.00
	Resistant (%)	2.1 %	4 (1.0)	1 (0.5)	2 (2.0)	7 (13.5)	2 (3.1)	1 (3.4)	0 (0.0)	0 (0.0)
	MIC percentile (25–75)		0.25–1	0.12–1	0.25–1	0.25–1	0.12–0.5	0.12–0.5	0.25–0.7	0.22–1
Fluconazole	MIC_{50} (μg/ml)	–	0.50	0.50	1.00	8.00	0.50	0.50	6.00	0.50
	MIC_{90} (μg/ml)	–	2.00	2.00	4.00	64.00	2.00	8.00	8.00	4.00
	Resistant (%)	6.2 %	10 (2.6)	10 (5.2)	4 (4.0)	16 (30.8)	1 (1.5)	0 (0.0)	16 (100.0)	0 (0.0)
	SDD (%)	11.0 %	9 (2.4)	8 (4.2)	9 (9.0)	7 (13.5)	64 (98.5)	1 (3.4)	0 (0.0)	0 (0.0)
	MIC percentile (25–75)		0.25–1	0.12–1	0.25–1	1–64	0.25–1	0.5–2	3.25–8	0.5–1
Itraconazole	MIC_{50} (μg/ml)	–	0.06	0.06	0.06	0.03	0.03	0.03	0.12	0.12
	MIC_{90} (μg/ml)	–	0.12	0.25	0.12	0.50	0.12	0.12	0.50	1.00
	Resistant (%)	1.2 %	1 (0.3)	1 (0.5)	1 (1.0)	2 (3.8)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)
	SDD (%)	9.3 %	27 (7.1)	22 (11.5)	2 (2.0)	11 (21.2)	4 (6.2)	2 (6.9)	4 (25.0)	4 (25.0)
	MIC percentile (25–75)		0.03–0.12	0.03–0.12	0.03–0.06	0.03–0.18	0.03–0.06	0.03–0.06	0.05–0.25	0.03–0.25
Posaconazole	MIC_{50} (μg/ml)	–	0.03	0.03	0.03	0.06	0.03	0.03	0.12	0.06
	MIC_{90} (μg/ml)	–	0.25	0.25	0.12	0.50	0.12	0.25	0.50	0.25
	MIC percentile (25–75)		0.03–0.12	0.03–0.06	0.03–0.06	0.03–0.18	0.03–0.06	0.03–0.12	0.03–0.12	0.03–0.15
Voriconazole	MIC_{50} (μg/ml)	–	0.12	0.06	0.06	0.50	0.06	0.06	0.25	0.06
	MIC_{90} (μg/ml)	–	0.50	0.50	0.25	1.00	0.50	1.00	0.50	1.00
	Resistant (%)	5.6 %	31 (8.1)	15 (7.8)	3 (3.0)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	SDD (%)	22.9 %	128 (33.5)	58 (30.2)	18 (18.0)	1 (1.9)	1 (1.5)	2 (6.9)	0 (0.0)	0 (0.0)
	MIC percentile (25–75)		0.06–0.25	0.03–0.25	0.03–0.12	0.12–1	0.03–0.12	0.03–0.25	0.12–0.25	0.03–0.07
Anidulafungin	MIC_{50} (μg/ml)	–	0.03	0.03	0.25	0.12	0.03	0.12	0.06	0.12
	MIC_{90} (μg/ml)	–	0.25	0.25	1.00	1.00	0.25	2.00	0.50	2.00
	Resistant (%)	1.7 %	8 (2.1)	2 (1.0)	0 (0.0)	0 (0.0)	4 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Intermediate (%)	1.6 %	8 (2.1)	3 (1.6)	0 (0.0)	–	3 (4.6)	–	1 (6.3)	0 (0.0)
	MIC percentile (25–75)		0.03–0.06	0.03	0.06–1	0.06–0.04	0.03	0.03–0.5	0.03–0.09	0.03–0.62
Caspofungin	MIC_{50} (μg/ml)	–	0.25	0.25	0.50	0.50	0.25	0.50	0.50	0.50
	MIC_{90} (μg/ml)	–	0.50	0.50	1.00	2.00	0.50	2.00	1.00	1.00
	Resistant (%)	5.6 %	16 (4.2)	7 (3.6)	0 (0.0)	4 (7.7)	15 (23.1)	2 (6.9)	3 (18.8)	0 (0.0)
	Intermediate (%)	10.1 %	50 (13.1)	19 (9.9)	0 (0.0)	–	19 (29.2)	–	5 (31.3)	0 (0.0)
	MIC percentile (25–75)		0.12–0.25	0.12–0.25	0.25–0.5	0.25–1	0.12–0.25	0.5–1	0.25–0.5	0.25–0.62
Micafungin	MIC_{50} (μg/ml)	–	0.03	0.03	0.25	0.12	0.03	0.06	0.05	0.12
	MIC_{90} (μg/ml)	–	0.12	0.25	1.00	1.00	0.12	2.00	0.50	1.00
	Resistant (%)	1.7 %	5 (1.3)	2 (1.0)	0 (0.0)	0 (0.0)	4 (6.2)	1 (3.4)	0 (0.0)	0 (0.0)
	Intermediate (%)	2.2 %	11 (2.9)	4 (2.1)	1 (1.0)	–	3 (4.6)	–	1 (6.3)	0 (0.0)
	MIC percentile (25–75)		0.03	0.03	0.06–0.5	0.03–0.25	0.03	0.03–0.5	0.03–0.12	0.3

- Azole and multi-drug resistance were seen in 11.8% and 1.9% isolates

Candida auris

- First reported in 2009 from ear discharge of a patient in Japan
- First documented bloodstream infection in 2011 from Korea
- Spread worldwide in a decade and is responsible for 25-40% of cases in South Africa and India
- Global warming may have enabled C.auris to break the human endothermy barrier
- 74 of 1400 cases were candida auris in a study conducted across 27 ICUs in India – Mortality was 50%
- Reported crude mortality is 30-60%

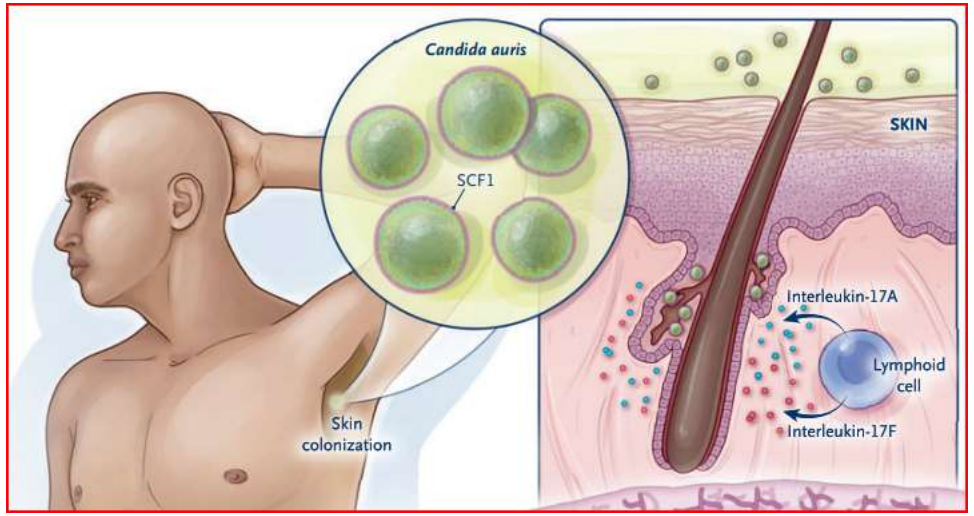
Anirima et al, Clinical epidemiological and Global Health, Volume 28,2024,101671
Chakrabarti, A et al Intensive Care Med **41**, 285–295 (2015)



Clade I, III, IV – multi-drug resistant invasive infections
Clade II – ear infections

Colonisation

- C.auris is distinct among yeast in that it readily spreads in healthcare settings
- Adapt to colonizing the human skin (nares, axilla and groin) – persist for many months, abiotic surfaces, including medical devices (for at least 7 days)



- IL-17 signalling combats mucocutaneous colonization
- Mannan structure different from the albicans group helps in evading phagocytosis/killing by neutrophils

Risk factors

Risk factors for candida species infections

+

Previous skin colonization by C. auris

(Candidemia in up to 25% of patients)

RISK FACTORS FOR INVASIVE CANDIDIASIS

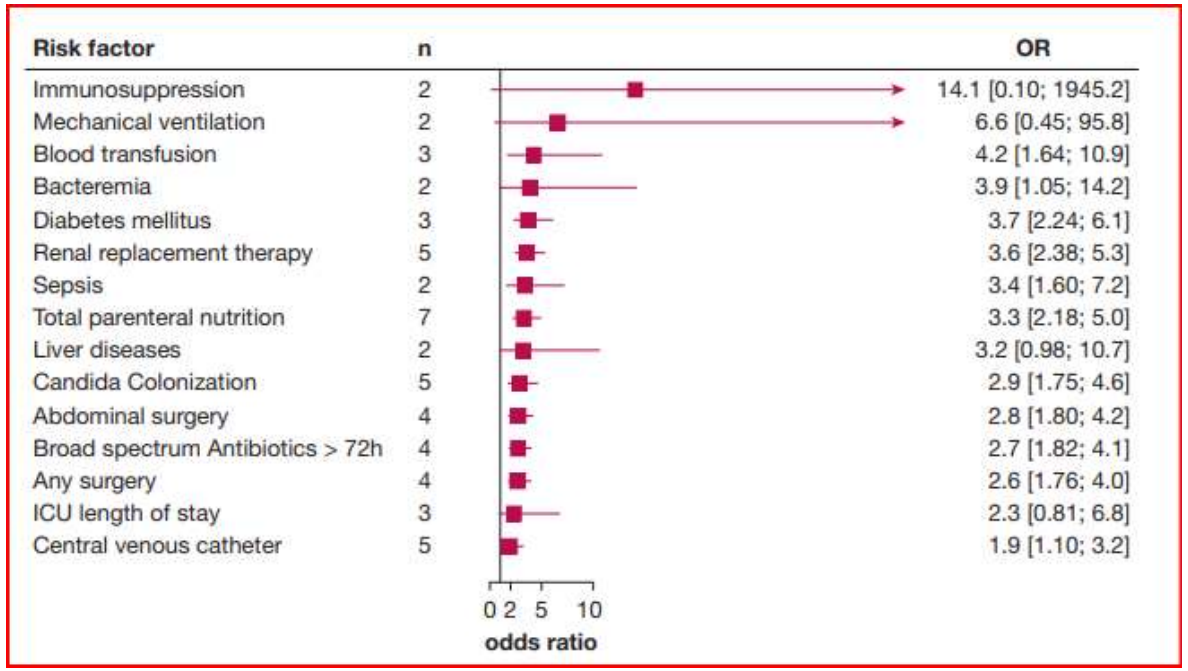
1. Critical illness – long-term ICU stay
2. Presence of central venous catheter or TPN
3. Hemodialysis
4. Abdominal surgery – anastomotic leak/laparotomies
5. Glucocorticoid use or chemotherapy for cancer
6. Acute necrotizing pancreatitis
7. Hematological malignancies, solid organ tumor
8. Solid organ transplantation
9. Use of broad-spectrum antibiotics
10. Candida colonization (colonization index >0.5 or corrected colonization index >0.4)

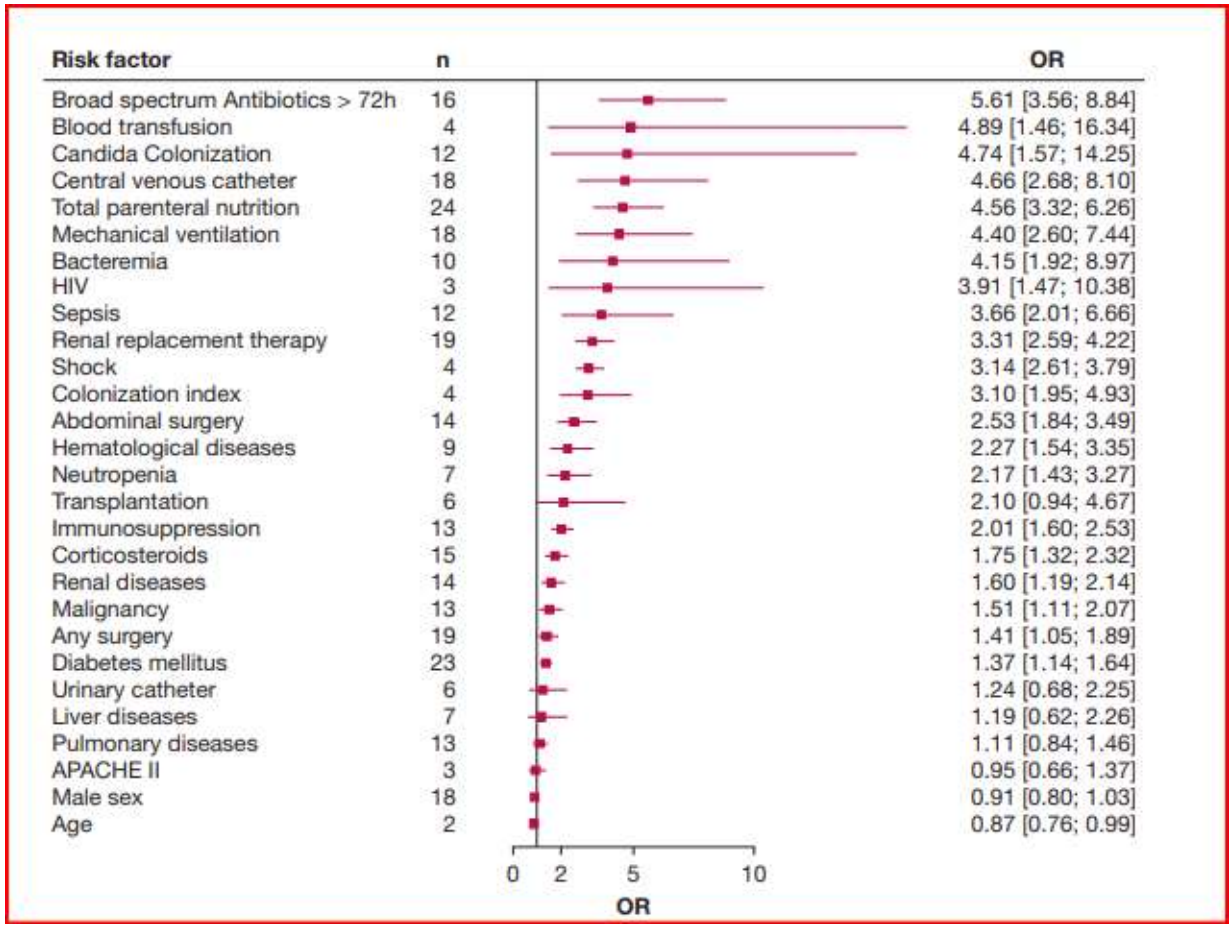
Risk Factors for Invasive *Candida* Infection in Critically Ill Patients

A Systematic Review and Meta-analysis

Daniel O. Thomas-Rüddel, MD; Peter Schlattmann, MD; Mathias Pletz, MD; Oliver Kurzai, MD; and Frank Bloos, MD, PhD

- 34 studies (4877 articles screened)
- ICU patients



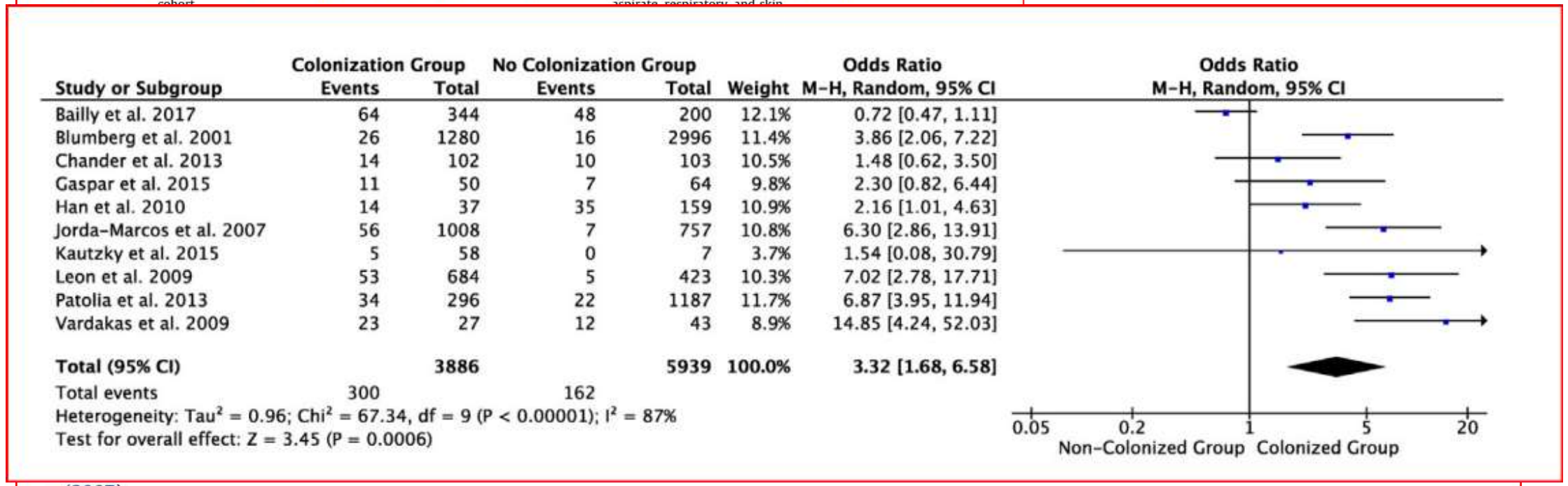


Colonisation as risk factor

Table 1
Study characteristics.

Author, year	Study design	Country	Number of ICU sites (types of ICU)	Number of patients	Sites of Candida colonization	Active surveillance
Bailly et al. (2017)	Prospective cohort	France	Multicentre (medical, surgical and polyvalent ICUs)	544	N/A	N/A
Kautzky et al. (2015)	Prospective cohort	Austria	Single centre (medical ICU)	65	Urine, stool/rectal swabs, tracheal aspirates, oral swabs, and skin	Yes
Gaspar et al. (2015)	Prospective cohort	Brazil	Single centre (N/A)	114	Urine, stool, tracheal aspirate, and others	No
Chander et al. (2013)	Retrospective cohort	India	Single centre (medical/surgical ICU)	205	Urine	No
Patolia et al. (2013)	Retrospective cohort	USA	Single centre (medical ICU)	1483	Urine and endotracheal aspirate	No
Han et al. (2010)	Case-control	South Korea	Single centre (medical ICU)	196	Urine, stool, sputum	No
Vardakas et al. (2009)	Case-control	Greece	Single centre (medical/surgical ICU)	70	Stool, urine, and bronchioalveolar lavage	No
Leon et al. (2009)	Prospective cohort	Spain	Multicentre (medical/surgical ICUs)	1107	Stool/rectal swabs, urine, gastric/pharyngeal aspirate, respiratory, and skin	Yes

- 10 studies - 9825 patients
- 3886 - colonized by a Candida (40%)
- 462 - invasive candidiasis (4.7%)
- Colonization – 46.8% (29.9-61.8%)
- High NPV 96.9% (95% CI 92.0–98.9%)
- Low PPV 9.1% (95% CI 5.5–14.6%)

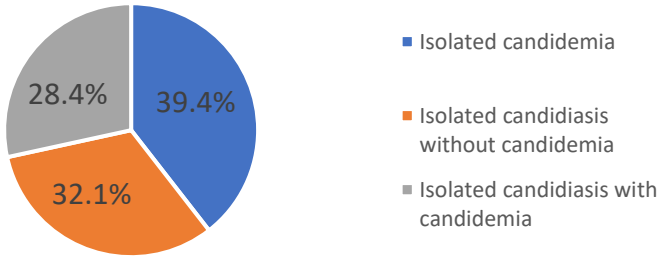


(2007)

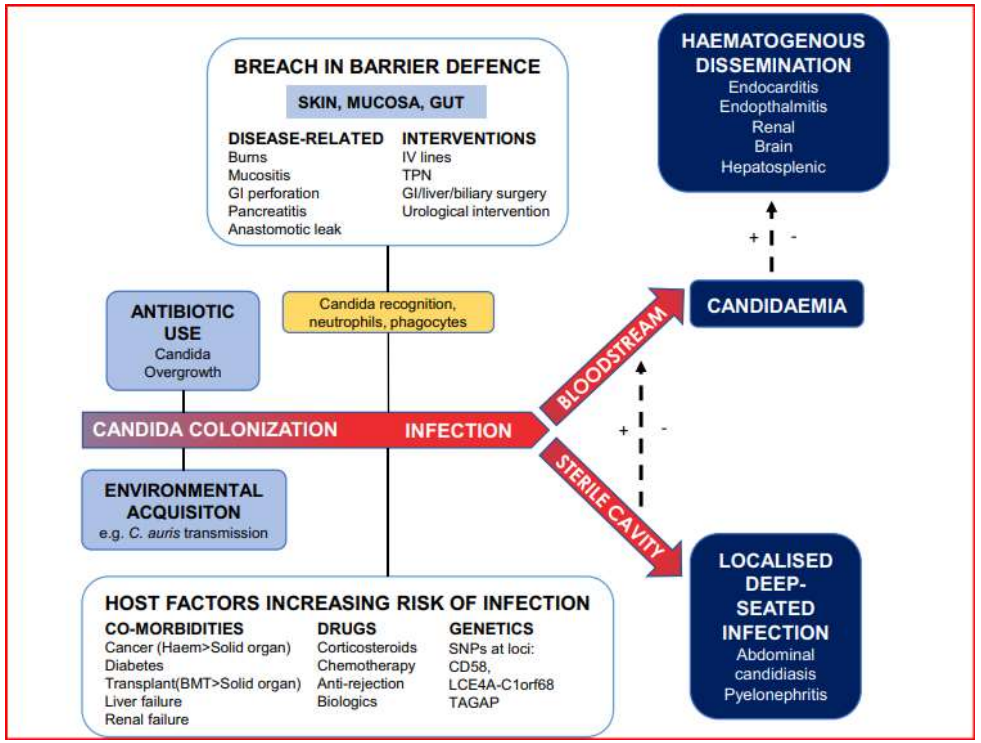
H. Alenazy et al. International Journal of Infectious Diseases 102 (2021) 357–362

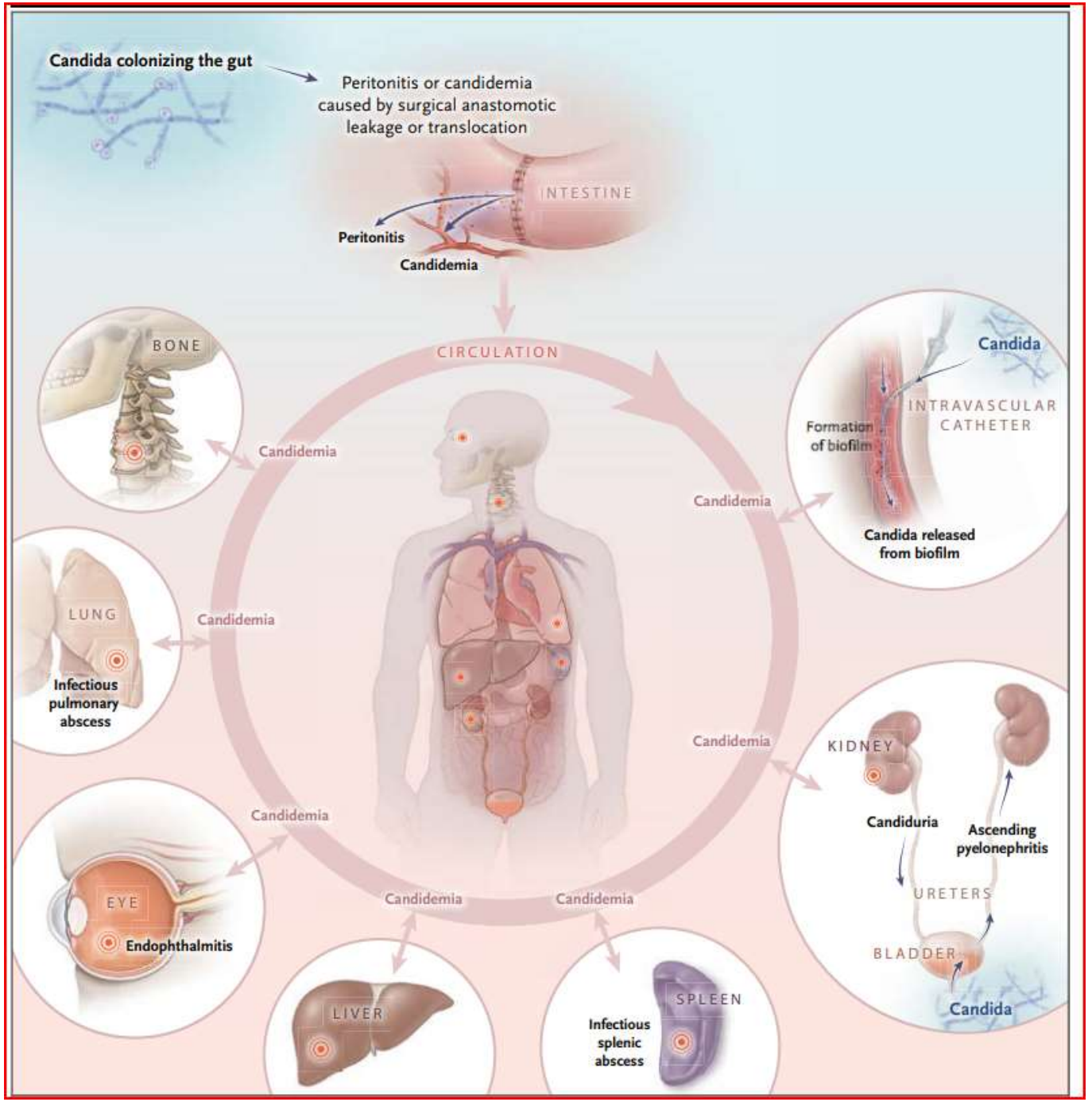
Definitions & Pathogenesis

- Invasive candidiasis comprises both candidemia and deep-seated tissue candidiasis
- Candidemia – Blood culture positive – most common form
  - Isolation of Candida species from at least 1 blood culture, is unequivocal
  - Candidemia can be due to CVC or non-CVC-related
    - CVC-related - Growth of ≥15 colonies of a Candida species from a removed catheter tip
      Identification of the same Candida species from the catheter tip and peripheral blood
      Differential time to positivity > 120 mins (81% sensitivity & 92% specificity – short-term catheter)
      (93% sensitivity & 75% specificity – long-term catheter)
- Deep-seated candidiasis arises from either hematogenous dissemination (candidemia) or direct inoculation of candida species to a sterile site, such as the peritoneal cavity (without candidemia)



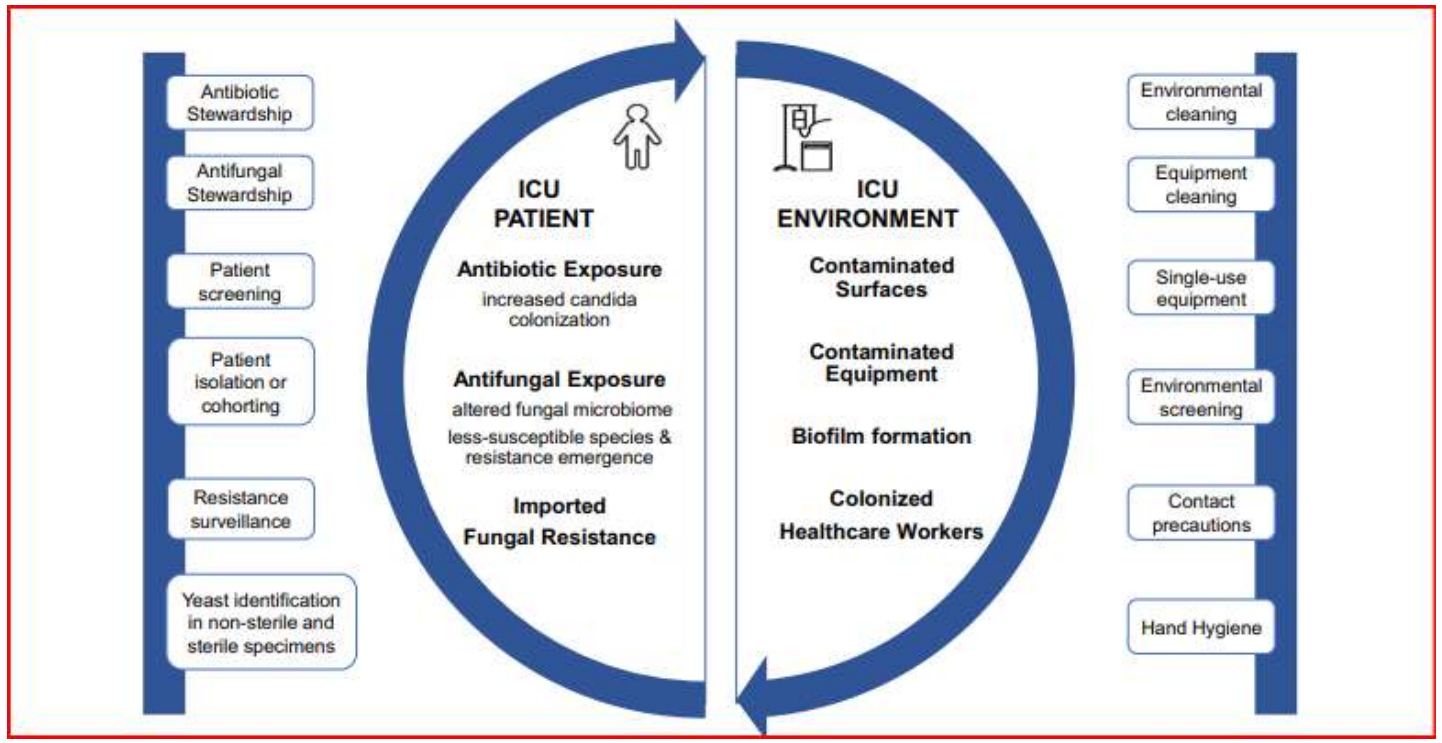
Ben-Ami R et al J Clin Microbiol. 2008 Jul;46(7):2222-6
Raad I, Hanna HA et al Ann Intern Med. 2004 Jan 6;140(1):18-25
Leroy et a. Crit Care Med 2009 Vol. 37, No. 5





Logan C et al, Intensive Care Med. 2020 Nov;46(11):2001-2014
Kullberg BJ et al, N Engl J Med. 2015 Oct 8;373(15):1445-56

Candida infections in ICU



Logan C et al, Intensive Care Med. 2020 Nov;46(11):2001-2014

EORTC MSGERC definition

- Proven IC - definitive evidence of the organism in a normally sterile site
  - Histopathologic, cytopathologic, or direct microscopic examination of material from a normally sterile site, obtained by needle aspiration or biopsy showing budding cells/pseudo hyphae/ hyphae consistent with Candida species but to be confirmed by culture or PCR
  - Recovery of candida by culture obtained by sterile procedure (<24 hrs from drain) from a normally sterile site showing a clinical or radiological abnormality consistent
  - Blood cultures yielding candida species
- Probable IC –
  1. 1 clinical criterion (fundus, hepatosplenic lesion on CT, clinical or radiological (non-pulmonary) abnormalities consistent and not explained otherwise)
  2. 1 mycological criterion (positive serum 1,3-β-d-glucan in 2 consecutive samples, candida in an intra-abdominal specimen obtained surgically or within 24 hrs of drainage)
  3. 1 host factors – Steroids ≥20 mg, ANC ≤500 or qualitative deficiency, Impaired gut wall integrity (surgery, chemotherapy, biliary tree abnormality, recurrent perforation, ascites, mucositis, severe pancreatitis, TPN), Impaired cutaneous barriers (candida colonisation - ≥2 cultures of respiratory secretions, stools, skin, wound, urine, drain >24 hrs), HSCT, Solid organ transplant

Bassetti M et al, Clin Infect Dis. 2021 Mar 12;72(Suppl 2):S121-S127

Time to Initiation of Fluconazole Therapy Impacts Mortality in Patients with Candidemia: A Multi-Institutional Study

Kevin W. Garey,[1] Milind Rege,[1] Manjunath P. Pai,[2] Dana E. Mingo,[3] Katie J. Suda,[4] Robin S. Turpin,[5] and David T. Bearden[6]

- Retrospective study, 230 patients
- Jan 2002-Jan 2005
- Hospitalized patients with candida BSI

Characteristic	Hospital discharge status: Alive	Dead	Relative risk (95% CI)	P
Underlying condition or risk factor				
Diabetes	44 (30)	12 (26)	0.83 (0.47–1.48)	.528
Cancer	35 (23)	12 (28)	1.18 (0.87–1.30)	.552
HIV infection	2 (1)	3 (6)	2.55 (1.19–5.46)	.061
Hemodialysis	12 (8)	6 (13)	1.41 (0.70–2.87)	.360
Surgical admission	42 (29)	15 (32)	1.11 (0.65–1.89)	.701
Variables assessed on date of blood culture				
APACHE II score	15.3 ± 5.9	20.8 ± 8.0	…	<.001
WBC count, mean 10^9 cells/L ± SD	13.1 ± 10.5	16.0 ± 13.1	…	.154
Hospitalized in ICU	41 (28)	33 (70)	3.76 (2.16–6.54)	<.001
Central venous catheter	116 (80)	43 (91)	2.23 (0.86–5.79)	.069
Corticosteroid treatment	14 (10)	10 (21)	1.89 (1.09–5.79)	.036
Total parenteral nutrition	32 (22)	15 (33)	1.50 (0.89–2.53)	.139
Mechanical ventilation	20 (14)	20 (43)	2.82 (1.77–4.47)	<.001

Table 1. Yeast isolates from patients with candidemia.

Fungal isolate	No. (%) of patients: Total	Hospital mortality	Mean no. of days ± SD to initiation of fluconazole
Candida albicans	129 (56)	33 (26)	0.7 ± 1.26
Candida glabrata	38 (17)	17 (45)	0.58 ± 1.41
Candida parapsilosis	25 (11)	0 (0)	0.76 ± 1.16
Candida tropicalis	15 (7)	4 (27)	0.6 ± 1.24
Candida krusei	8 (3)	3 (38)	0.5 ± 1.31
Mixed *Candida* culture	8 (3)	5 (63)	0.5 ± 1.51
Candida lusitaniae	4 (2)	1 (25)	0.25 ± 0.5
Candida rugosa	1 (<1)	0 (0)	0

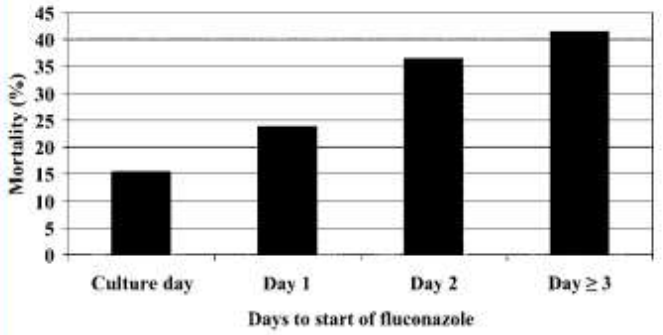


Figure 2. Relationship between hospital mortality and the number of days to initiation of fluconazole therapy. We calculated the days to the start of fluconazole therapy by subtracting the start date of fluconazole therapy from the culture date of the first blood sample positive for y ($P = .0009$ for trend, using the Mantel-Haenszel χ^2 test).

Table 3. Multivariate model of independent risk factors for hospital mortality.

Variable	Adjusted OR (95% CI)	P
Time from culture date to start of fluconazole therapy, days	1.50 (1.09–2.09)	.0138
APACHE II score, 1-point increments	1.13 (1.08–1.18)	<.001

HIGHER SUSPICION

- In non-neutropenic patients with candidemia – distant sites of infection are uncommon
- 15% of patients have ocular manifestations
- 1-2% develop endophthalmitis

- DILATED FUNDUS EXAMINATION IS A MUST WITHIN A WEEK AFTER INITIATION OF TREATMENT
- FUNDUS TO BE DONE AFTER RECOVERING OF NEUTROPHILS IN NEUTROPENIC PATIENT

- Endocarditis – uncommon – routine echo is not recommended if no RF for IE is present (intravenous drug abuse, pre-existing valvular disease, or the presence of a prosthetic cardiac valve)

Pappas, P et al, Nat Rev Dis Primers 4, 18026 (2018)

WHAT HAS TO BE DONE?

- Prophylactic antifungal?
- Biomarker-based pre-emptive therapy?
- Risk-based empirical therapy?
- Targeted therapy?

Definitions

- Prophylactic - critically ill patients with risk factors (such as immunosuppression) and/or risk factors linked to the reason for their admission (septic shock, abdominal surgery, long ICU stay, broad-spectrum antibiotic therapy, etc.)
- Pre-emptive therapies –
  - diagnosis based on fungal biomarkers (β d-glucan (BDG), Candida antibody, and mannan antigen assay)
  - therapy triggered by microbiological evidence without proof of invasive infection (radiology)
- Empirical therapy - Signs and symptoms with specific risk factors for IC, **irrespective of biomarkers**
- Directed/targeted therapies - Microbiological confirmation of invasive infection due to Candida species (e.g. a positive blood culture for Candida species)

RISK PREDICTION?

- Models based on microbiological parameters only
- Models based on clinical parameters (clinical prediction rules)
- Models based on both microbiological and clinical parameters

MICROBIOLOGY

CI	>0.5
CCI	>0.4

	Design	Centre /Population	N	Cases	Score developed	PPV	NPV	Sen	Spe
Pittet et al (1994)	Prospective	Single Surgical ICU and neonates	29	11 (38%)	COLONISATION INDEX CORRECTED COLONISATION INDEX	66 100	100 100	100 100	100 100

	Infected	Non Infected	p-value
CI	0.7	0.47	<0.01
CCI	0.56	0.16	<0.01

COLONISATION - Isolation of Candida ≥3 samples from the same or different sites ≥ 2 consecutive screening days
INFECTION – Requiring anti-fungal treatment

Colonisation index = number sites colonized by candida/total number of sites tested
Corrected colonisation index = Number of sites with heavy growth of candida/ total number of sites positive for candida

PROBLEM

- Almost 50% of patients are colonised with candida and only 10-20% of them develop invasive candidiasis
- Leads to over-treatment
- Progression to Invasive candidiasis is reduced but no mortality benefit was observed
- Change in ICU microbiome

Logan C et al. Intensive Care Med. 2020 Nov;46(11):2001-2014

CLINICAL PARAMETERS?

	Design	Centre /Population	N	Cases	Score developed	PPV	NPV	Sen	Spe
Ostrosky et al (2007)	Retro	Multiple Surgical and medical ICUs	2890	88 (3%)	Ostrosky - Zeichner Clinical Prediction Rule	9	97	34	94
Ostrosky et al (2009)	Retro	Multiple Surgical and medical ICUs	597	22 (3.7%)	Revised Ostrosky - Zeichner Clinical Prediction Rule	10	97	50	83

1. **<u>Mechanical ventilation for least 48 h</u>**
2. Antibiotic use and CVC (D1-D3 of admission)

At least one of the following additional risk factors:

a. Any surgery (within last 7 days),
b. Steroids and immunosuppressive use (within last 7 days)
c. Pancreatitis (within last 7 days)
d. TPN (D1-D3 of admission)
e. Any dialysis (D1-D3 of admission)

Microbiological + Clinical

	Design	Centre /Population	N	Cases	Score developed	Sen	Spe
Leon et al. 2006	Prospective	Multicentre Surgical/medical	1699	97 (5.8%)	Candida score	81	74

- 73 medical/surgical ICU (n=1699)
- >18 yrs admitted for at least 7 days
- Screening at admission and once a week (tracheal & gastric aspirates, pharyngeal exudates, and urine)

Patient group	Nonsurvivors		Odds Ratio (95% Confidence Interval)[a]	
	No.	Mortality Rate[b]	Crude	Adjusted[c]
Neither colonized nor infected, $n = 719$	239	33.2%	1	1
Candida species colonization, $n = 883$				
Unifocal, $n = 388$	103	26.5%	1.02 (0.8–1.4)	1.04 (0.8–1.4)
Multifocal, $n = 495$	252	50.9%	1.55 (1.3–2)	1.54 (1.2–1.9)
Candidal infection, $n = 97$	56	57.7%	2.74 (1.8–4.2)	3.2 (2.0–5.0)

Variable	Unifocal or Multifocal *Candida* Species Colonization n = 883	Proven Candidal Infection n = 97	p Value
Age, yrs, mean (SD)	58.9 (17.0)	58.5 (16.9)	.825
Male/female	577/306	68/29	.337
APACHE II score on admission, median (range)	19 (1–67)	17 (6–45)	.203
Length of ICU stay, days, median (range)	20 (7–166)	28 (7–138)	<.001
APACHE II score, no. (%)			
<15	302 (34.2)	37 (38.5)	.137
15–25	408 (46.3)	48 (50.5)	
>25	173 (19.5)	12 (11.0)	
Diagnosis on ICU admission, no. (%)			
Medical	449 (50.8)	34 (35.1)	<.001
Surgical	258 (29.2)	51 (52.6)	
Trauma	176 (19.9)	12 (12.4)	
Underlying disease, no. (%)			
Chronic bronchitis	197 (22.3)	14 (14.4)	.073
Diabetes mellitus	136 (15.4)	14 (14.4)	.801
Chronic liver disease	40 (4.5)	2 (2.1)	.255
Chronic renal failure	44 (5.5)	4 (4.1)	.710
Heart failure	40 (4.5)	2 (2.1)	.255
Risk factors, no (%)			
Broad spectrum antibiotics	866 (98.0)	97 (100)	.380
Central venous catheter	873 (98.9)	97 (100)	.292
Urinary catheter	870 (98.5)	93 (95.9)	.078
Mechanical ventilation	837 (94.8)	92 (94.8)	.982
Enteral nutrition	695 (78.7)	68 (70.1)	.053
Arterial catheter	666 (75.4)	68 (70.1)	.251
Total parenteral nutrition	462 (52.3)	85 (87.6)	<.001
Corticosteroids	214 (24.2)	22 (22.7)	.734
Hemodialysis or continuous hemofiltration	106 (12.0)	29 (29.9)	<.001
Severe sepsis, no. (%)	156 (17.7)	63 (64.9)	<.001
Candida species colonization, no. (%)			<.001
Unifocal	390 (44.1)	17 (17.5)[a]	
Multifocal	493 (55.8)	69 (71.1)[a]	

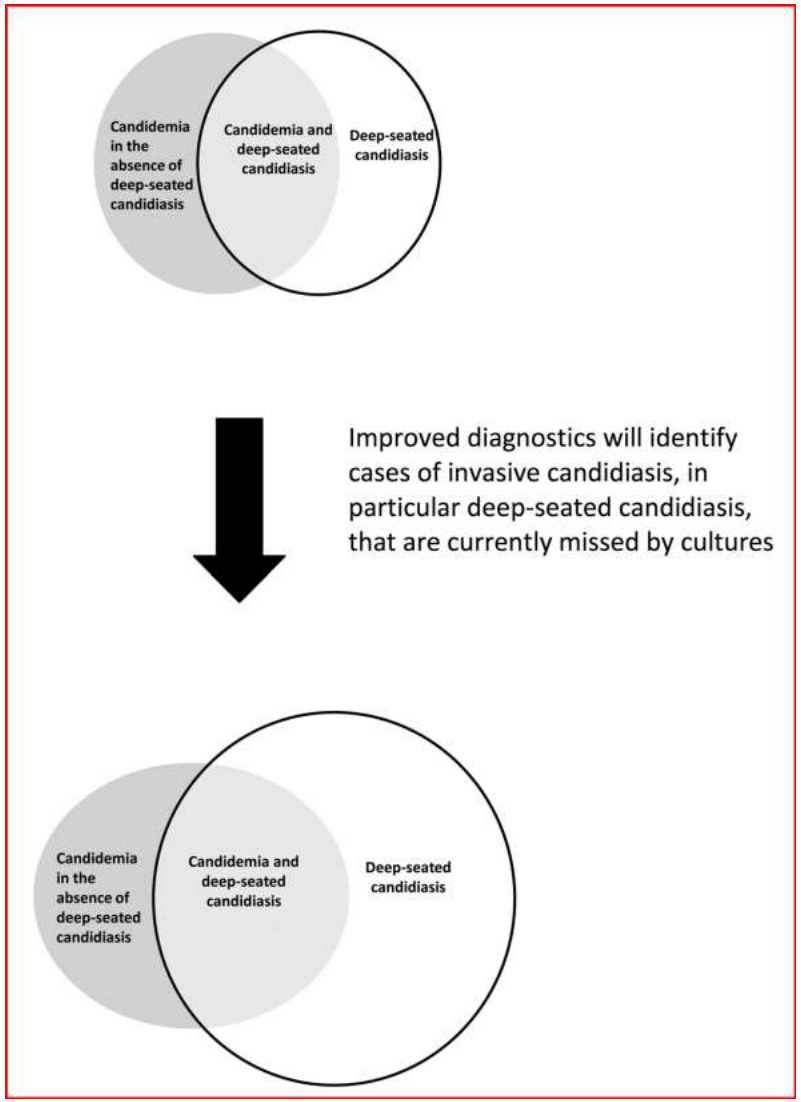
- Candida score = 1X(total parenteral nutrition) + 1X(surgery) + 1X(multifocal Candida species colonization) + 2X(severe sepsis)
- A cut-off value of 2.5 - sensitivity of 81% and a specificity of 74%
- score of 2.5 are 7.75 times as likely to have proven infection (risk ratio 7.75; 95% CI, 4.74–12.66) than patients with a Candida score up to 2.5

When to use

- Risk prediction models, because of their simplicity and high negative predictive values, should be used for identifying high-risk patients

DIAGNOSIS

- Culture-based tests
- Non culture-based tests



Blood culture

- Only diagnostic approach that allows subsequent susceptibility testing
- Sensitivity is 21%-71% in invasive candidiasis without candidemia
- Overall, 38% (156/415 patients)

- By inclusion of candidemia blood culture sensitivity in invasive candidiasis is 63%-83%

Table 2. Performance of Blood Cultures in Autopsy Studies of Invasive Candidiasis

Reference	Year	No. of Patients	Underlying Disease	Sensitivity
Louria (from [13])	1962	19	Hematologic malignancies, solid tumors, medical and surgical conditions	42%
Bodey (from [13])	1966	61	Acute leukemia	25%
Taschdjian (from [13])	1969	17	Malignancies and other medical conditions	47%
Hart (from [13])	1969	16	Hematologic malignancies, solid tumors, transplant, medical and surgical conditions	44%
Bernhardt (from [13])	1972	14	Transplant and surgical conditions	36%
Gaines (from [13])	1973	26	Hematologic malignancies, solid tumors, medical and surgical conditions	54%
Myerowitz (from [13])	1977	39	Hematologic malignancies, solid tumors, medical and surgical conditions	44%
Ness [9]	1989	7	Hematologic malignancies and bone marrow transplant recipients	71%
Singer [37]	1977	16	Hematologic malignancies	31%
Berenguer [13]	1993	37	Mostly hematologic malignancies and solid tumors	43%
Van Burik [38]	1998	62	Bone marrow transplant recipients	52%
Kami [39]	2002	91	Hematologic malignancies	21%
Thorn [40]	2010	10	Hematologic malignancies, gastrointestinal disease, transplant, prematurity	50%

- For almost 75% of patients in Group 1 and Group 2, overall sensitivity is approximately 50% across all groups
- 95% blood cultures - positive within 96 hours
- But TTP is species dependent (glabrate grows slower than albicans)

Clancy et al CID 2013:56 (1 May)

Blood culture

- Requires viable candida in blood
- 10 ml (0.2% of circulation) is captured during sampling
- Increase in yield with serial blood cultures and culture during febrile episodes
- Negative blood cultures may be due to intermittent or transient release of viable cells into the bloodstream and rapid elimination from circulation
- Pathogenesis may also affect sensitivity – catheter-related candidemia has a higher burden and gut-related has less load as it enters the liver which is efficient in clearing fungi
- Conventional blood culture may delay the diagnosis and delay anti-fungal treatment

Blood culture

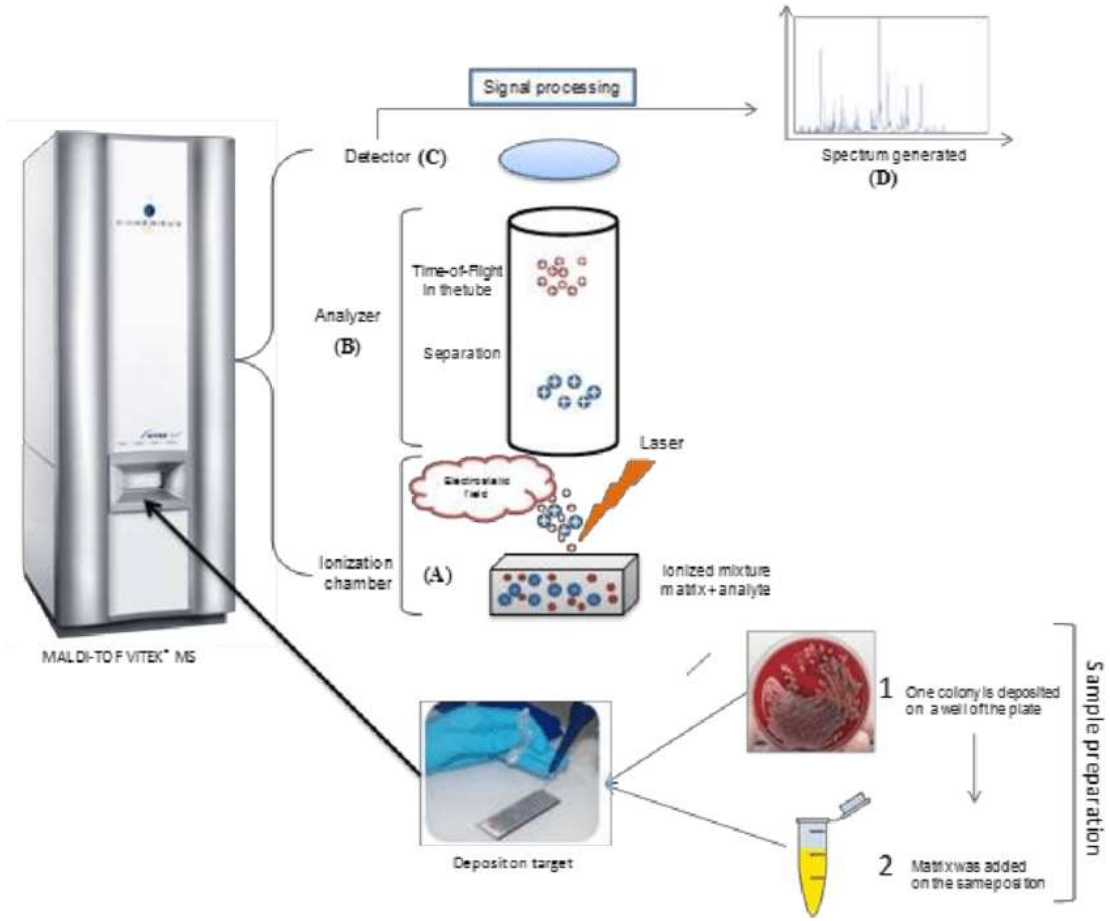
- Standard automated blood cultures are not inferior for detecting yeast when compared to fungal-specific culture bottles BACTEC Myco/F Lytic or Mycosis IC/F bottles, BACT/ALERT FAN aerobic bottles
- Cultures of tissues or fluid recovered from infected sites during deep-seated candidiasis also exhibit poor sensitivity (often <50%) and slow turnaround times, and require invasive sampling procedures that may be dangerous or contraindicated due to underlying medical conditions
- Drawbacks –
  - Requires live cells in the blood
  - Higher turnaround time
  - Not suitable for invasive candidiasis (deep-seated)

Non conventional culture based tests

- Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF)
- Peptide nucleic acid fluorescent in situ hybridization (PNA-FISH)
- β-D glucan (Fungitell) assay
- T2 Candida assay – PCR based assays
- BioFire Film Array blood culture identification (BCID) panel
- Antigen & Antibody detection
- Candida species germ tube antibody

MALDI TOF MS

- Post-culture technique that uses mass spectroscopy
- Requires **pure growth of an organism** on artificial media
- No influence on the time to diagnosis of candidemia
- **Accurate species identification** is done in almost 90-95% of samples in 10-15 mins
- 1-1.5 days less than conventional techniques with reduced cost



Tan KE J Clin Microbiol 50
Marklein G et al, J Clin Microbiol 47

Peptide nucleic acid fluorescent in situ hybridization (PNA-FISH)

- Performed **directly on a positive blood culture result** rather than waiting for the growth of pure colonies
- A positive result narrowing the identification to a paired result (C albicans/C parapsilosis vs C glabrata/C krusei vs C tropicalis), not to the level of single-species specificity

Mc Carty et al. Infect Dis Clin N Am 35 (2021) 389–413

T2 candida assay – FDA approved

- Magnetic resonance detection to identify Candida organisms in **whole-blood**
- It groups results into C. albicans/C. tropicalis, C. krusei/C. glabrata, or C. parapsilosis.
- Results are available within 3 to 4 hours after specimen processing
- Sensitivity 88.9% PPV 91.7% NPV 99.6%
- Prior antifungal treatment was associated with persistently positive T2Candida results even after blood cultures cleared

Mc Carty et al. Infect Dis Clin N Am 35 (2021) 389–413

PCR-based assays – No FDA approval

- A major limitation of PCR studies is the lack of standardized methodologies and multicenter validation of assay performance

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

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

Medicine E[1] and Unit of Infectious Diseases,[2] Rabin Medical Center, Beilinson Hospital and Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel

Received 9 August 2010/Returned for modification 15 September 2010/Accepted 17 November 2010

Invasive candidiasis (IC) is a significant cause of morbidity and mortality. Diagnosis relies on culture-based methods, which lack sensitivity and delay diagnosis. We conducted a systematic review assessing the diagnostic accuracy of PCR-based methods to detect *Candida* spp. directly in blood samples. We searched electronic databases for prospective or retrospective cohort and case-control studies. Two reviewers abstracted data independently. Meta-analysis was performed using a hierarchical logistic regression model. Random-effects metaregression was performed to assess the effects of study methods and infection characteristics on sensitivity or specificity values. We included 54 studies with 4,694 patients, 963 of whom had proven/probable or possible IC. Perfect (100%) sensitivity and specificity for PCR in whole-blood samples was observed when patients with cases had candidemia and controls were healthy people. When PCR was performed to evaluate patients with suspected invasive candidiasis, the pooled sensitivity for the diagnosis of candidemia was 0.95 (confidence interval, 0.88 to 0.98) and the pooled specificity was 0.92 (0.88 to 0.95). A specificity of >90% was maintained in several analyses considering different control groups. The use of whole-blood samples, rRNA, or P450 gene targets and a PCR detection limit of ≤10 CFU/ml were associated with improved test performance. 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%). We conclude that direct PCR using blood samples had good sensitivity and specificity for the diagnosis of IC and offers an attractive method for early diagnosis of specific *Candida* spp. Its effects on clinical outcomes should be investigated.

Problem with PCR based technique

- Low CFU?
- The estimated burden of yeasts required for reliable DNA-based PCR detection is 5 to 10 CFU/ml

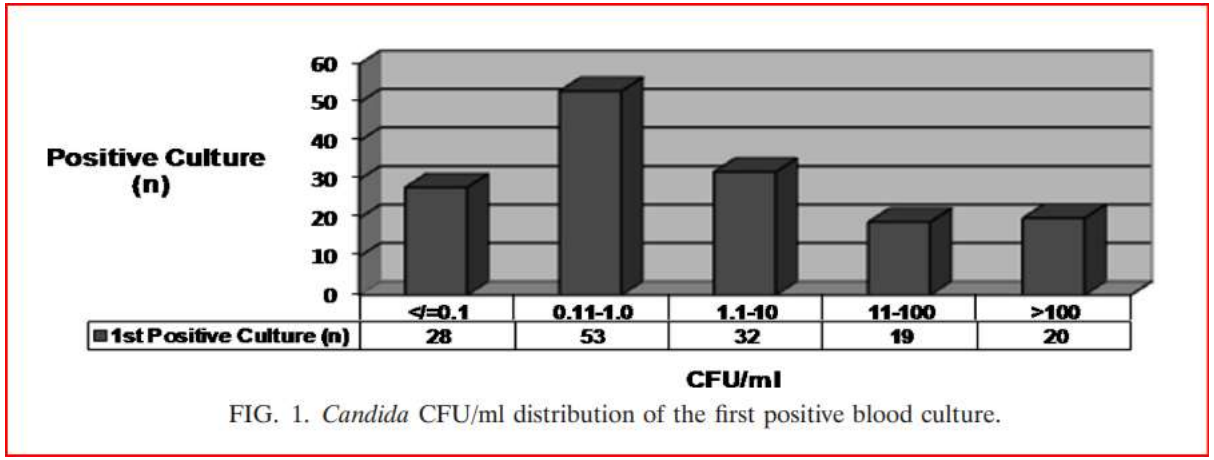


FIG. 1. *Candida* CFU/ml distribution of the first positive blood culture.

Pfeiffer CD et al, J Clin Microbiol. 2011 Aug;49(8):2879-83

STRUCTURE OF CELL WALL

- Cell wall – necessary for survival - dynamic structure – continuous remodeling during the life of the organism
- Exoskeletal structure - chitin, **glucan**, **mannan**, and glycoproteins
- BG component = mainly of glucose polymers linked via β-1,3-glycosidic bonds, forming the BG backbone of the fungal cell wall
- As the fungus grows and divides, this cell wall is continuously remodeled and some BG is released as soluble forms, most of which are multiple strands intermingled as triple helices and the rest as single strands or random coils

Antigen and Antibody detection

- Antigen detection - limited by rapid clearance from the bloodstream
- Antibody testing – performed well even in immunocompromised hosts
- Serum IgG responses against specific antigens have typically performed better than IgM

- Well studied test - combined mannan/anti mannan antibody assay, which is currently approved for use in Europe but not the United States (Platelia Candida Ag and Ab; BioRad)

Results: Overall, 14 studies that comprised 453 patients and 767 controls were reviewed. The patient populations included in the studies were mainly haematological and cancer cases in seven studies and mainly intensive care unit and surgery cases in the other seven studies. All studies but one were retrospective in design. Mn sensitivity was 58% (95% confidence interval [CI], 53-62); specificity, 93% (95% CI, 91-94) and DOR, 18 (95% CI 12-28). A-Mn sensitivity was 59% (95% CI, 54-65); specificity, 83% (95% CI, 79-97) and DOR, 12 (95% CI 7-21). Combined Mn/A-Mn sensitivity was 83% (95% CI, 79-87); specificity, 86% (95% CI, 82-90) and DOR, 58 (95% CI 27-122). Significant heterogeneity of the studies was detected. The sensitivity of both Mn and A-Mn varied for different *Candida* species, and it was the highest for *C. albicans*, followed by *C. glabrata* and *C. tropicalis*. In 73% of 45 patients with candidemia, at least one of the serological tests was positive before the culture results, with mean time advantage being 6 days for Mn and 7 days for A-Mn. In 21 patients with hepatosplenic IC, 18 (86%) had Mn or A-Mn positive test results at a median of 16 days before radiological detection of liver or spleen lesions.

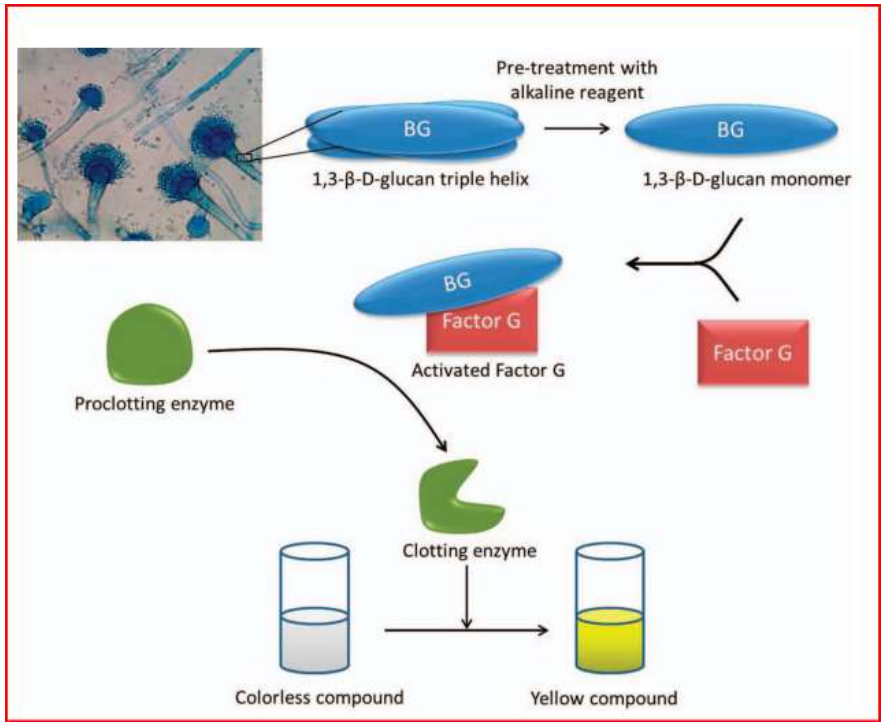
Mikulska M et al. Crit Care. 2010;14(6):R222

Peter G. Pappas et al. Clinical Infectious Diseases, Volume 62, Issue 4, 15 February 2016

β-D-glucan

- Cell wall constituent of Candida, Aspergillus, Pneumocystis jiroveci, and several other fungi
- Approved by US FDA in 2004
- True-positive results are not specific for invasive candidiasis but rather suggest the possibility of an invasive fungal infection
- β-D-glucan detection can identify cases of invasive candidiasis days to weeks prior to positive blood cultures, and shorten the time to initiation of antifungal therapy

<60 pg/ml= Negative
60-80 pg/ml = Indeterminate
>80 pg/ml = Positive



FUNGITELL ASSAY
activate the Limulus amebocyte lysate clotting cascade in the blood of Limulus polyphemus, the North American horseshoe crab.

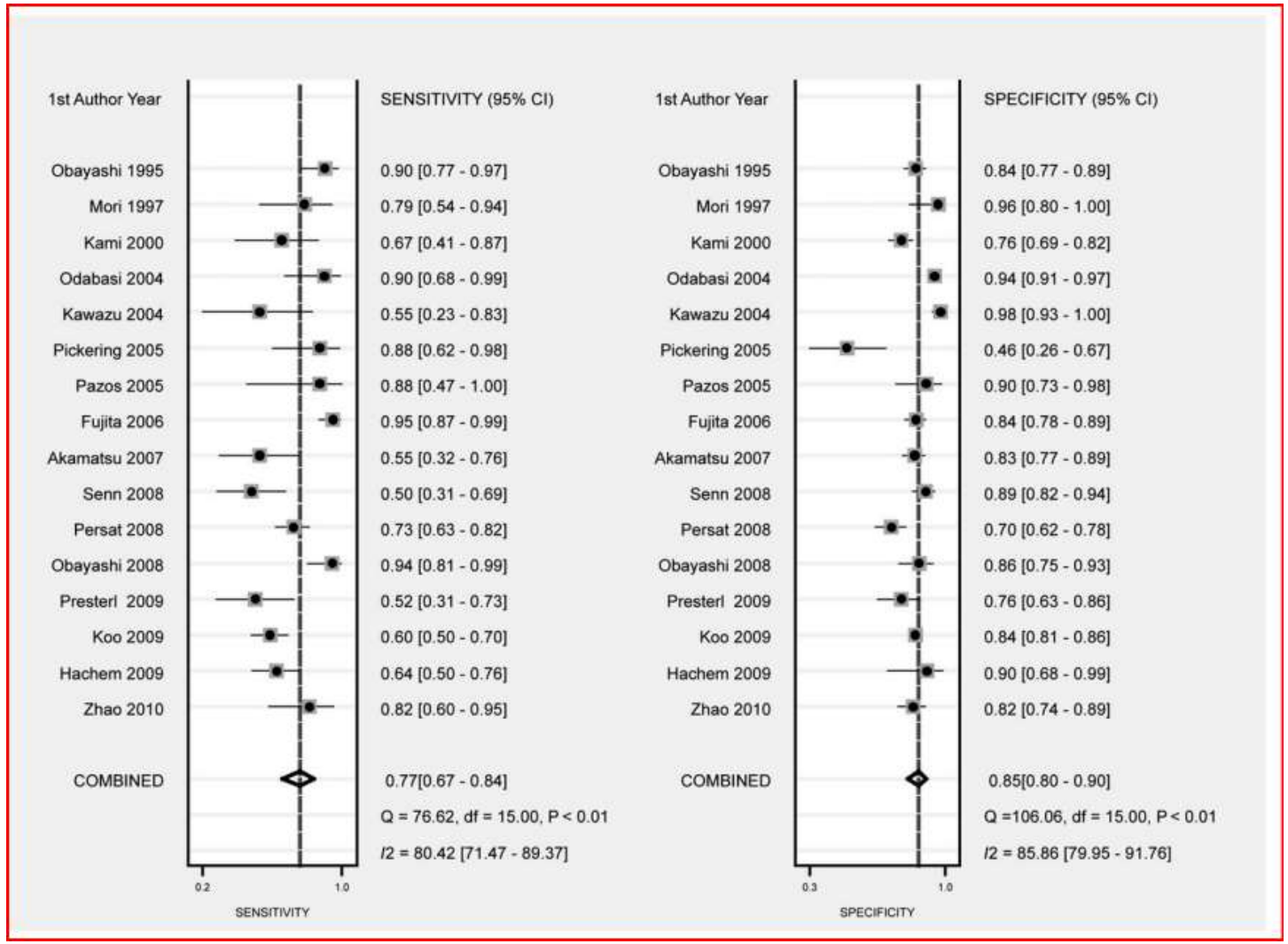
Limulus amebocyte lysate clotting cascade can also be activated via another zymogen (factor C) by bacterial endotoxin = False positive

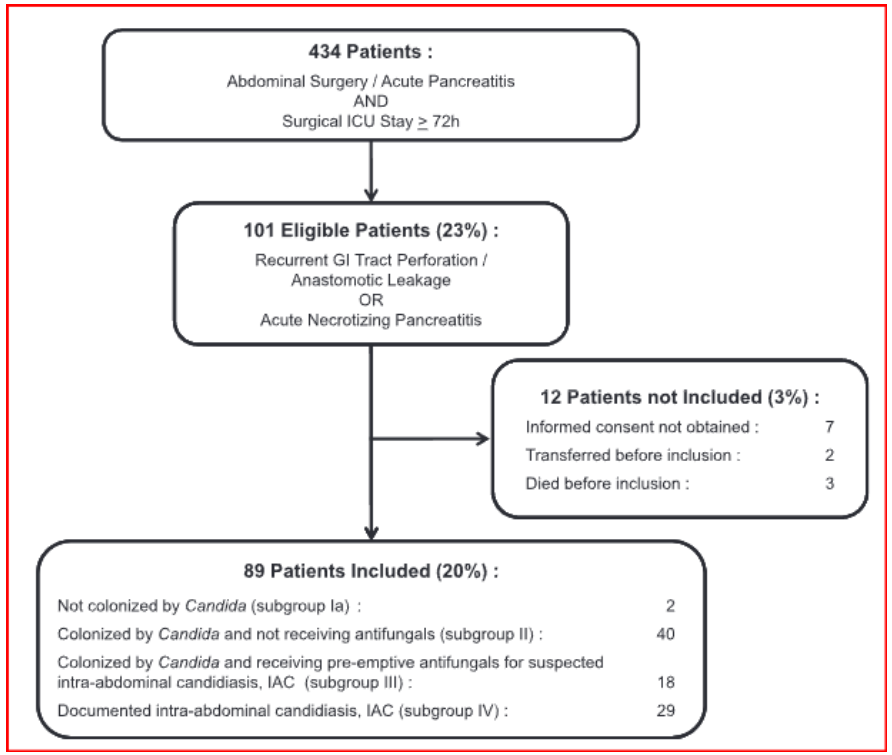
Tran et al Arch Pathol Lab Med—Vol 140, February 2016

β-D-glucan

Problem
LOW SENSITIIVITY

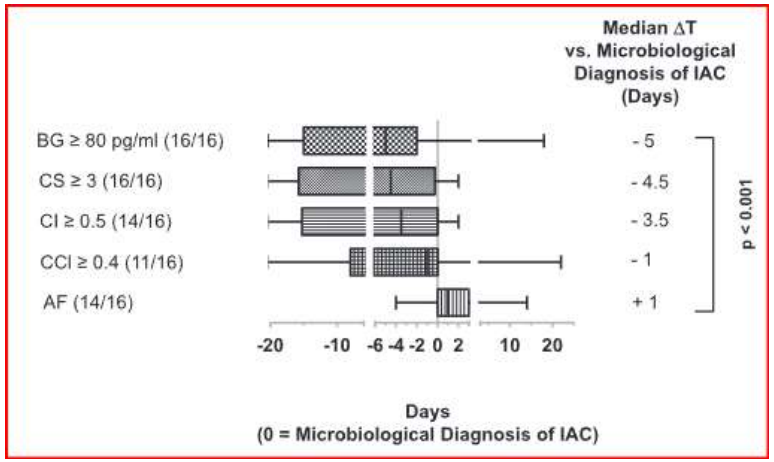
Study	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Notes
Obayasi 2008 Study of 456 Autopsy Cases	78.0	98.4	86.7	97.1	Blood culture testing sensitivity was **8.3%.** Used 80 pg/mL positivity cutoff.
Obayashi et al 15 candidemia patients BG Results Comparison Study	93.3	77.2	51.9	97.8	Lower specificity and PPV due **to false positives in bacteremia patients**.
Ostrosky et al 2005 163 proven/Probable IFI vs 170 subjects Multicenter Prospective Study	64.4 (80) 69.9 (60)	92.4 (80) 87.1 (60)	89 (80) 83.8 (60)	73 (80) 75.1 (60)	Sensitivity lower in probable group. Cryptococcus sp, Mucor sp, and Rhizopus sp not detectable.
Meta-Analysis by Karageorgopoulos et al	76.8 (95% CI: 67.1–84.3)	85.3 (95% CI: 79.6–89.7)	-	-	**Specificity increases with at least 2 sequential positive results.**

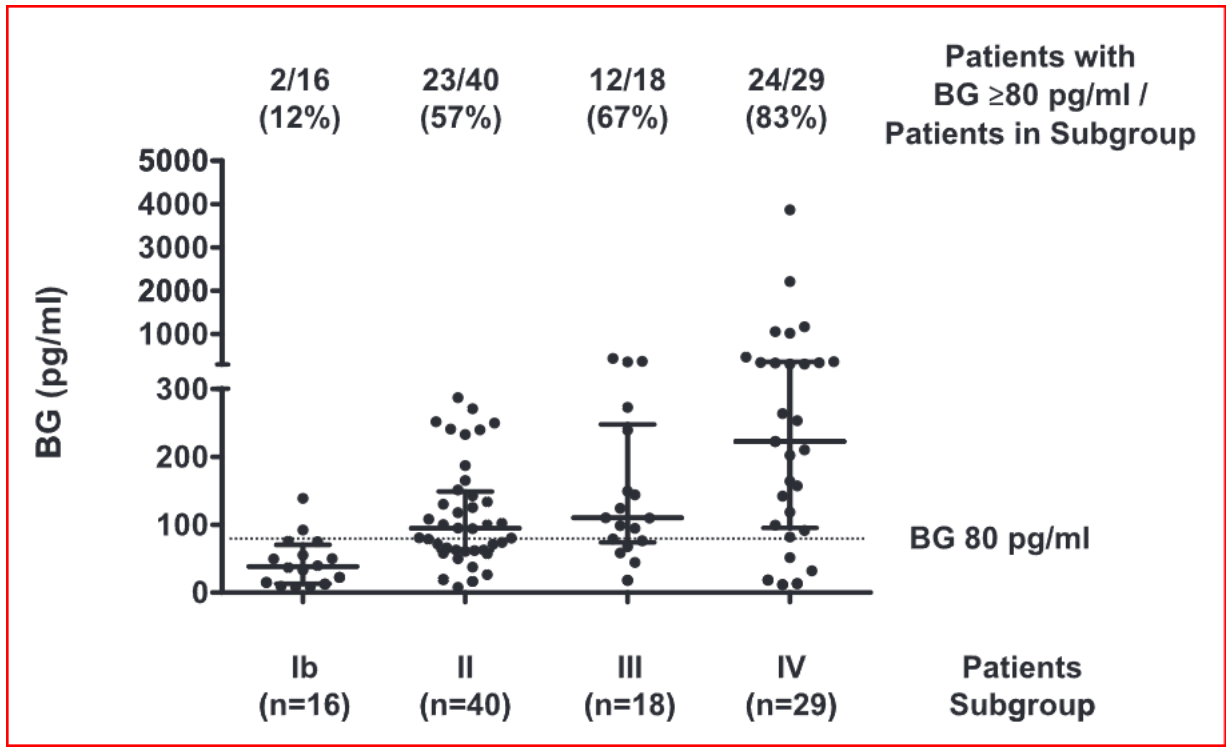

1st Author Year
SENSITIVITY (95% CI)
Obayashi 1995 0.90 [0.77 - 0.97]
Mori 1997 0.79 [0.54 - 0.94]
Kami 2000 0.67 [0.41 - 0.87]
Odabasi 2004 0.90 [0.68 - 0.99]
Kawazu 2004 0.55 [0.23 - 0.83]
Pickering 2005 0.88 [0.62 - 0.98]
Pazos 2005 0.88 [0.47 - 1.00]
Fujita 2006 0.95 [0.87 - 0.99]
Akamatsu 2007 0.55 [0.32 - 0.76]
Senn 2008 0.50 [0.31 - 0.69]
Persat 2008 0.73 [0.63 - 0.82]
Obayashi 2008 0.94 [0.81 - 0.99]
Presterl 2009 0.52 [0.31 - 0.73]
Koo 2009 0.60 [0.50 - 0.70]
Hachem 2009 0.64 [0.50 - 0.76]
Zhao 2010 0.82 [0.60 - 0.95]
COMBINED 0.77[0.67 - 0.84]
Q = 76.62, df = 15.00, P < 0.01
I2 = 80.42 [71.47 - 89.37]
0.2
1.0
SENSITIVITY
1st Author Year
SPECIFICITY (95% CI)
Obayashi 1995 0.84 [0.77 - 0.89]
Mori 1997 0.96 [0.80 - 1.00]
Kami 2000 0.76 [0.69 - 0.82]
Odabasi 2004 0.94 [0.91 - 0.97]
Kawazu 2004 0.98 [0.93 - 1.00]
Pickering 2005 0.46 [0.26 - 0.67]
Pazos 2005 0.90 [0.73 - 0.98]
Fujita 2006 0.84 [0.78 - 0.89]
Akamatsu 2007 0.83 [0.77 - 0.89]
Senn 2008 0.89 [0.82 - 0.94]
Persat 2008 0.70 [0.62 - 0.78]
Obayashi 2008 0.86 [0.75 - 0.93]
Presterl 2009 0.76 [0.63 - 0.86]
Koo 2009 0.84 [0.81 - 0.86]
Hachem 2009 0.90 [0.68 - 0.99]
Zhao 2010 0.82 [0.74 - 0.89]
COMBINED 0.85[0.80 - 0.90]
Q =106.06, df = 15.00, P < 0.01
I2 = 85.86 [79.95 - 91.76]
0.3
1.0
SPECIFICITY



55 of 89 were colonised
29 had invasive abdominal candidiasis
27 had negative blood cultures

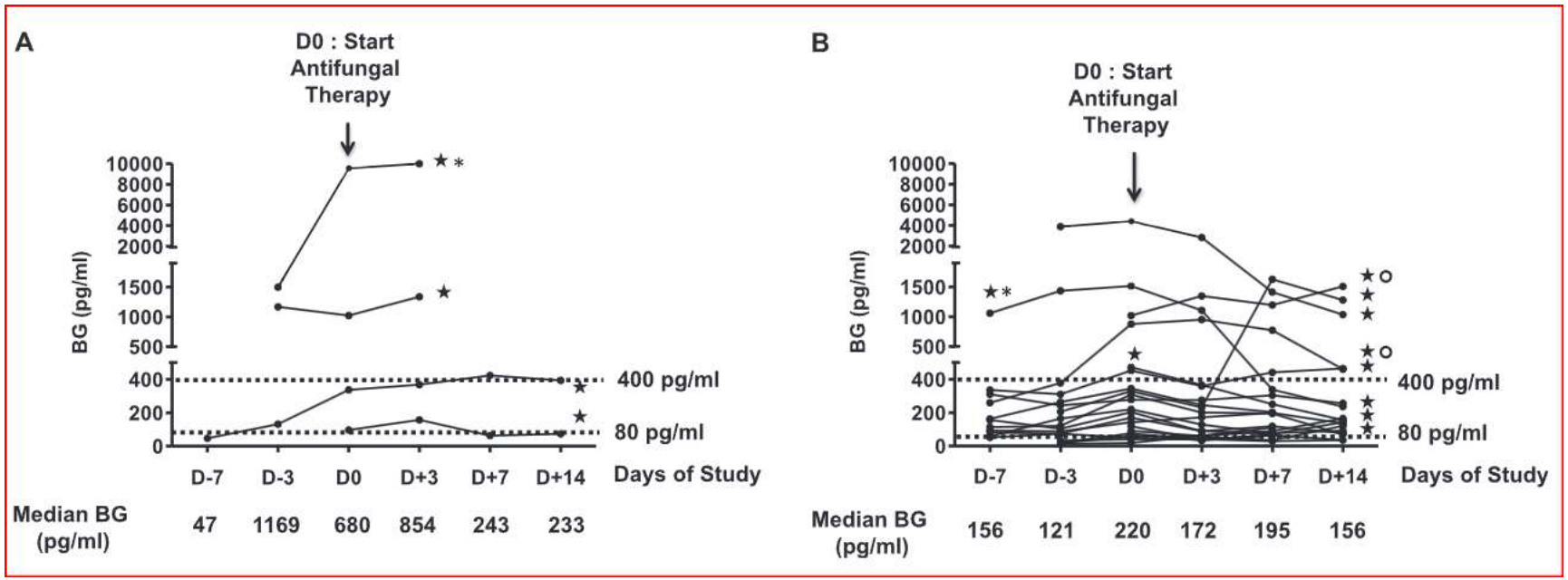
Median Beta-d-glucan – 253 vs 99 (IAC vs Colonisation)





Tissot et al. Am J Respir Crit Care Med. 2013 Nov 1;188(9):1100-9

If BDG > 400
Severe sepsis (91% versus 28%)
Mortality (36% versus 6%)



FALSE POSITIVE

Table 1. Potential Causes of False Fungitell Results[a]

Organisms known to contain little or no 1,3-β-D-glucan
- *Cryptococcus*
- Zygomycetes (*Mucor* spp, *Rhizopus* spp, *Lichtheimia corymbifera*)

Substances thought to cause false-positive Fungitell results
- Cellulose membranes used in hemodialysis
- Exposure to glucan-containing gauze
- Products (such as blood or albumin, among others) filtered through glucan-containing filters
- High triglycerides, hemoglobin
- Some antibiotics, such as intravenous amoxicillin-clavulanic acid

[a] Although most fungi produce 1,3-β-D-glucan as part of cell wall synthesis, some organisms, such as *Cryptococcus* and the Zygomycetes species, produce little or none of this substance and, therefore, Fungitell results would likely be negative in these patients. Likewise, some substances are known to cause false-positive results.

Dimorphic fungi: Coccidioides immitis, Histoplasma capsulatum, Sporothrix schenckii
Pneumocystis jiroveci
Systemic bacterial infections
Severe mucositis

BioFire Film Array BCID assay

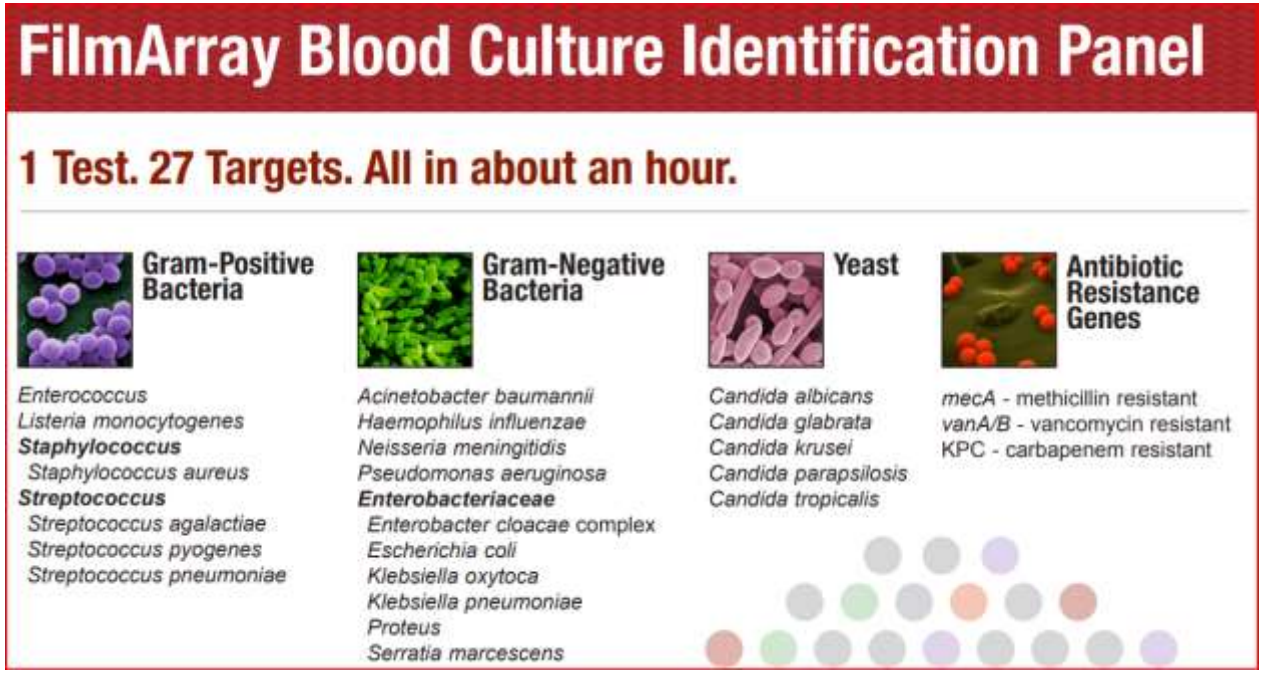


TABLE 4 Performance summary of the FilmArray BCID panel versus culture for *Candida* spp. in positive blood cultures (Table view)

Organism	Isolates detected: BCID/comparator		No. of results: BCID/comparator				Sensitivity or PPA[a]: TP/(TP + FN) (%)	95% CI	Specificity or NPA[a]: TN/(TN + FP) (%)	95% CI
	Clinical arm	Seeded arm	TP +/+	FP +/−	FN −/+	TN −/−				
Candida albicans	20/16	48/48	64	4	0	2,139	64/64 (100)	94.4–100	2,139/2,143 (99.8)	99.5–99.9
Candida glabrata	14/12	37/37	49	2	0	2,156	49/49 (100)	92.7–100	2,156/2,158 (99.9)	99.7–100
Candida krusei	4/4	33/33	37	0	0	2,170	37/37 (100)	90.5–100	2,170/2,170 (100)	99.8–100
Candida parapsilosis	9/7	52/54	59	2	2	2,144	59/61 (96.7)	88.7–99.6	2,144/2,146 (99.9)	99.7–100
Candida tropicalis	3/3	36/36	39	0	0	2,168	39/39 (100)	91.0–100	2,168/2,168 (100)	99.8–100
All yeast isolates	49/42	207/208	248	8	2	10,777	248/250 (99.2)	97.1–99.9	10,777/10,785 (99.9)	99.9–100

Salimnia H J Clin Microbiol. 2016 Mar;54(3):687-98

Diagnosis of candida auris

Diagnostic Approach	Description
Culture-based testing	Isolation of C. auris in culture is important for reporting antifungal susceptibility patterns
Morphological features	Unlike most other Candida species, C. auris grows well at 40-42°C
Chromogenic media	CHROMagar- Colonies appear white or pink with a blue halo within 48 hours
Conventional identification systems (VITEK-2 YST, API 20C, BD Phoenix, and MicroScan)	Misidentify C. auris as other Candida species
MALDI-TOF mass spectrometry	Accurate identification of C. auris can be achieved using MALDI-TOF mass spectrometry
Molecular methods	- Sequencing of the D1-D2 region of the 28S rDNA or internal transcribed spacer regions can reliably identify C. auris. - Real-time PCR assays are sensitive and specific for direct detection

FUND ICU DEFINITIONS - 2024

Table 1 Research definition for proven invasive candidiasis in non-neutropenic, adult patients in ICU

Type of proven invasive candidiasis	Definition
Candidemia Consensus reached after two rounds of remote voting and one round of live meeting voting (100% agreement)	Proven candidemia is defined by the isolation of *Candida* spp. from at least one blood culture obtained from venipuncture (not from a catheter)
Deep-seated candidiasis Consensus reached after three rounds of remote voting and one round of live meeting voting (100% agreement)	Proven deep-seated candidiasis is defined by the identification of *Candida* spp. on specimens obtained through surgery or US-guided or CT-guided puncture from normally sterile deep sites[a] other than blood, in a patient without a suspected mucosal perforation or recent gastrointestinal or urogenital surgery that could result in contamination of the body cavity. Identification can be achieved by means of direct microscopy, culture, or histology[b] Identification of *Candida* spp. by histology defines proven disease also in presence of alterations possibly leading to contamination of the site The histological evidence of budding cells consistent with *Candida* spp. defines proven invasive candidiasis Species identification through PCR or culture is necessary for hyphae or pseudohyphae, which may be observed also for other yeasts

Table 2 Research definition for probable deep-seated candidiasis in non-neutropenic, adult patients in ICU

Definition of probable deep-seated candidiasis
Consensus reached after three rounds of remote voting and one round of live meeting voting (95% agreement)
Probable deep-seated candidiasis is defined by the presence of at least one clinical criterion plus at least one mycological criterion
Clinical criteria
Funduscopic lesions compatible with invasive candidiasis or radiological abnormalities consistent with an infectious disease process that remain unexplained after investigations for other infectious/non-infectious processes; such abnormalities should be evident in deep sites where invasive candidiasis may develop either because of direct inoculation or because of previous, undetected hematogenous spread (e.g., IAC, endocarditis, osteomyelitis, arthritis, mediastinitis, meningitis[a]); the investigations carried out for excluding alternative diagnoses should be reported in detail
Mycological criteria
Recovery of *Candida* spp. from an intra-abdominal specimen, the mediastinum, or pleuritis/pleural empyema after alteration of the gastrointestinal or urogenital wall integrity (perforation/surgery). Specimens should be obtained during surgery, puncture, or obtained from a newly inserted drain as soon as possible (no later than 24 h after placement). This mycological criterion does not apply to the isolation of *Candida* spp. from peritoneal fluid after gastrointestinal/urogenital perforation if complete source control is rapidly obtained (within 24 h from perforation and after peritoneal fluid collection). This may reflect contamination before development of invasive disease and does not define a mycological criterion for probable deep-seated candidiasis. In case of source control performed > 24 h after perforation or in case of recurrent peritonitis (e.g., anastomosis leakage), isolation of *Candida* spp. from the peritoneum (from an intra-abdominal specimen during surgery or obtained from an external drainage inserted from < 24 h) does define a mycological criterion for probable deep-seated candidiasis. The same concepts apply to Candida mediastinitis and pleuritis/pleural empyema after esophageal perforation
For other deep sites (and for the mediastinum and the abdomen in the absence of perforation), the presence of concomitant proven candidemia can be considered as a mycological criterion for probable deep-seated candidiasis, although the disease should be classified as proven IC in research studies (proven candidemia plus probable deep-seated candidiasis)

No role of BDG as per definition

MANAGEMENT

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, *Candida* Colonization, and Multiple Organ Failure

The EMPIRICUS Randomized Clinical Trial

- Population - Critically ill adult patients (1)mechanically ventilated ≥ 5 days (2) ≥ 1 colonization site (other than rectal swab or stool) positive for Candida species using traditional culture methods; (3) ≥ 1 additional organ dysfunction; (4) previous treatment for more than 4 days using broad-spectrum antibacterial agents within the last 7 days; (5) 1 arterial or central vein catheter, and (6) 1 new finding of ICU-acquired sepsis of unknown origin
- Intervention & Control - Empirical micafungin 100 mg OD X 14days (n = 131) vs placebo (n = 129)
- Outcome –
  - primary - was survival without proven IFI 28 days after randomization
  - secondary - new proven fungal infections,

    survival at day 28 and day 90

    organ failure

    serum (1-3)-β-D-glucan level evolution

    incidence of ventilator-associated bacterial pneumonia

Figure 3. Comparison of Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	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

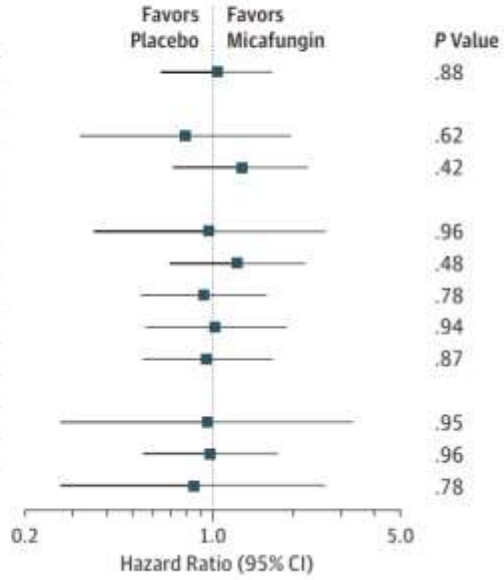


Table 2. Proven Invasive Fungal Infection at Inclusion and 28-Day Follow-up[a]

	No. (%)			
	All Patients (N = 251)	Micafungin (n = 128)	Placebo (n = 123)	Absolute Difference (95% CI)
No. of invasive fungal infections from inclusion to day 28[b]				
≥1	27 (11)	12 (9)	15 (12)	2.82 (−5.0 to 10.8)
2	3 (1)	0	3 (2)	2.44 (−0.9 to 6.9)
Invasive fungal infections by species at inclusion	12 (5)	8 (6)	4 (3)	3.00 (−2.7 to 8.9)
Candida albicans	7 (50)	4 (44)	3 (60)	15.6 (−31.3 to 53.7)
Candida glabrata	5 (36)	4 (44)	1 (20)	24.4 (−25.1 to 57.7)
Candida tropicalis	1 (7)	0	1 (20)	20.0 (−14.1 to 62.5)
Aspergillus fumigatus	1 (7)	1 (11)	0	11.0 (−36.2 to 82.4)
No. of invasive fungal infections at follow-up (day 28)[b]				
≥1[c]	19 (8)	4 (3)	15 (12)	9.1 (2.5 to 16.3)
2	2 (1)	0	2 (2)	1.6 (−1.5 to 5.7)
Invasive fungal infections by species				
Candida albicans	13 (59)	3 (75)	10 (55)	19.4 (−29.7 to 49.4)
Candida glabrata	2 (9)	0	2 (9)	11.1 (−38.5 to 32.8)
Candida parapsilosis	3 (14)	0	3 (14)	16.7 (−33.5 to 39.2)
Candida inconspicua	1 (4)	1 (25)	0	25.0 (−2.0 to 69.9)
Trichosporon[d]	2 (9)	0	2 (11)	11.1 (−38.5 to 32.8)
Aspergillus fumigatus	1 (4.5)	0	1 (6)	5.6 (−43.7 to 25.8)

Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients (Review)

Cortegiani A, Russotto V, Maggiore A, Attanasio M, Naro AR, Raineri SM, Giarratano A

Cochrane Library

Cochrane Database of Systematic Reviews

- 22 studies 2761 patients
- All cause mortality - RR 0.93, 95% CI 0.79 to 1.09, P value = 0.36
- Outcome of proven invasive fungal infection - reduced the risk - RR 0.57, 95% CI 0.39 to 0.83, P value = 0.0001
- Risk of fungal colonization - RR 0.71, 95% CI 0.52 to 0.97, P value = 0.03
- Risk of developing superficial fungal infection - RR 0.69, 95% CI 0.37 to 1.29, P value = 0.24
- Adverse events requiring cessation of treatment RR 0.89, 95% CI 0.62 to 1.27, P value = 0.51

EMPIRICAL TREATMENT

- In another study, the use of empirical fluconazole in critically ill patients ventilated for 5 days did not decrease mortality risk or occurrence of invasive candidiasis

Bailly S et al. Am J Respir Crit Care Med. 2015 May 15;191(10):1139-46

Prophylaxis and empirical treatment in ICU

- Prophylaxis
  - High-risk patients if the local incidence of invasive candidiasis >5%
  - Daily scrub with chlorhexidine decreased the incidence of candidemia
- Empirical
  - Critically ill patients with risk factors and NO OTHER KNOWN CAUSE OF FEVER and culture data from non sterile sites (if any) [clinical + microbiological]
  - Start treatment as soon as possible – if fungal sepsis causing shock – mortality is 100% without treatment and 50% with treatment
  - Markers – BDG – variable results in studies – 70-90% sensitivity but low PPV
    ?Role of serial testing

Peter G. et al. 2016 Update by the Clinical Infectious Diseases, Volume 62, Issue 4, 15 February 2016

DEFINITIVE TREATMENT

Comparative efficacy and safety of systemic antifungal agents for candidemia: a systematic review with network meta-analysis and multicriteria acceptability analyses

Eric L. Domingos[a], Raquel O. Vilhena[a], Josiane M.M.F. Santos[a], Mariana M. Fachi[a], Beatriz Böger[a], Livia M. Adam[a], Fernanda S. Tonin[a,b,*], Roberto Pontarolo[c]

- 13 trials (n=3632) published 2022
- Caspofungin and micafungin have a higher clinical and mycological response
- Higher discontinuation with conventional ampho B

	Overall response	Microbiol. response	Recurrence	Discontinuat	Abnor. liver function
AMB	49%	-	52%	88%	87%
ANI 50 mg	31%	-	-	-	-
ANI 75 mg	45%	-	-	-	-
ANI 100 mg	41%	-	-	45%	37%
CAS 50 mg	64%	47%	71%	43%	46%
CAS 150 mg	72%	77%	17%	44%	12%
FLU 400 mg	18%	-	-	60%	68%
ISA 200 mg	48%	8%	28%	42%	-
L-AMB	53%	51%	-	55%	-
MIC 100 mg	66%	75%	74%	35%	-
MIC 150 mg	63%	43%	58%	45%	-

ORIGINAL ARTICLE

mycoses WILEY

Comparative effectiveness of amphotericin B, azoles and echinocandins in the treatment of candidemia and invasive candidiasis: A systematic review and network meta-analysis

Koray K. Demir[1] | Guillaume Butler-Laporte[1,2,3] | Olivier Del Corpo[1] | Taline Ekmekjian[4] | Donald C. Sheppard[1,2,3,5] | Todd C. Lee[1,2,5,6] | Matthew P. Cheng[1,2,3,5]

- 13 RCTs = 3528 patients
- Echinocandins are preferred

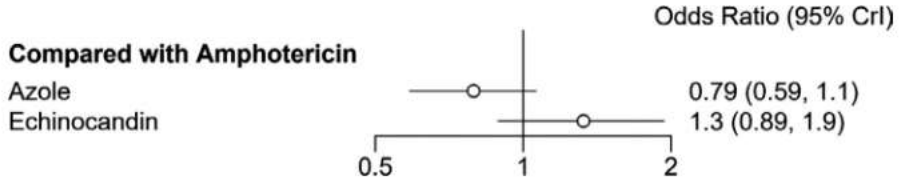
FIGURE 3 Odds ratios for the primary outcome for antifungal classes, in comparison with amphotericin B

TABLE 3 Comparison matrix of medication classes across studies

	Amphotericin	Azole	Echinocandin
Amphotericin		0.78 (0.60, 0.99)	1.41 (1.04, 1.92)
Azole	1.29 (1.02, 1.66)		1.82 (1.35, 2.5)
Echinocandin	0.71 (0.52, 0.96)	0.55 (0.40, 0.74)	

Note: The drug in a given column is compared to the corresponding drug in the associated row. The numerical values correspond to odds ratios for the primary outcome (treatment success) with 95% confidence intervals. An odds ratio greater than one represents a favourable comparison.

FIGURE 4 Odds ratios for the primary outcome for antifungal classes, in patients with bloodstream infection specifically



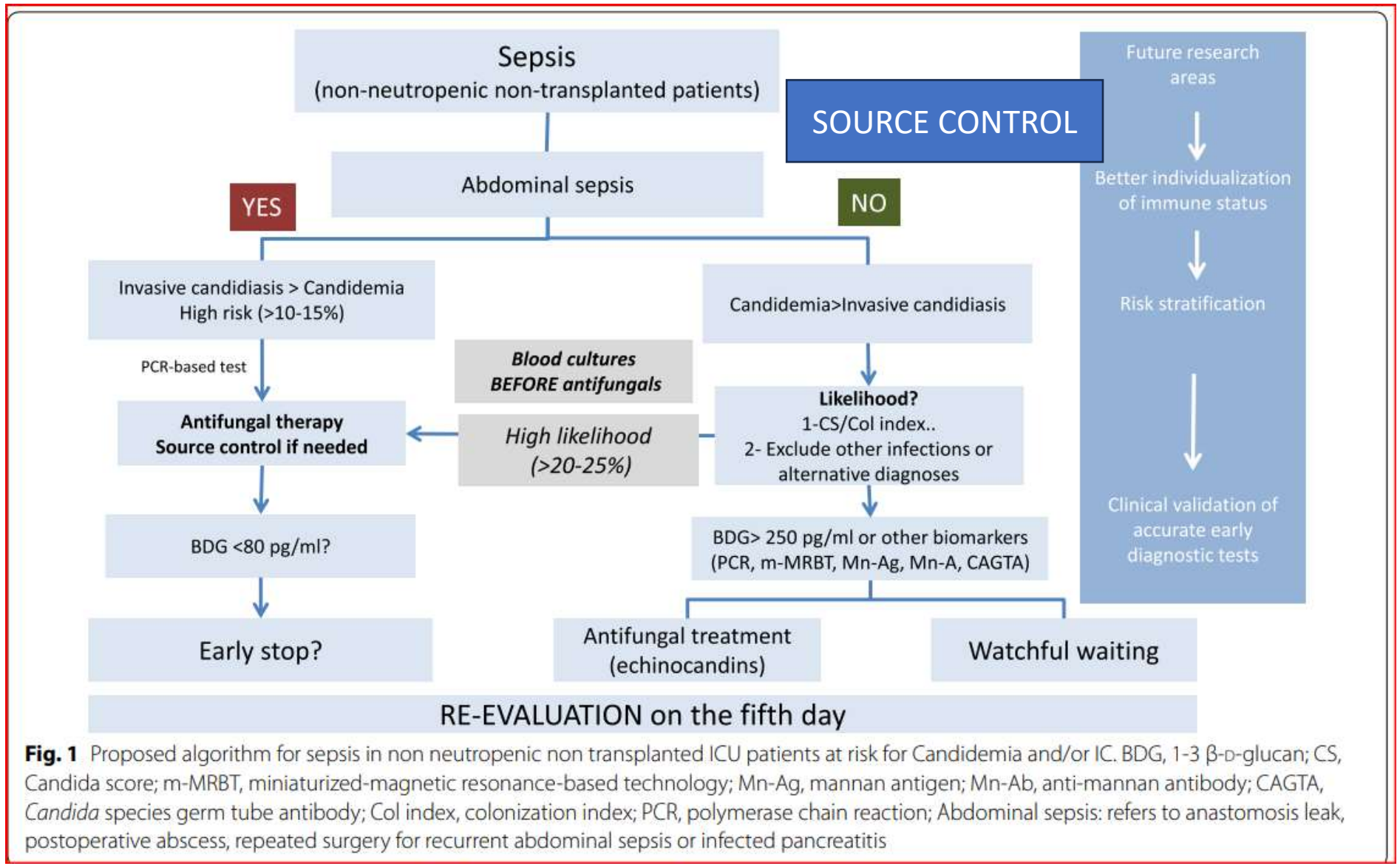


Fig. 1 Proposed algorithm for sepsis in non neutropenic non transplanted ICU patients at risk for Candidemia and/or IC. BDG, 1-3 β-D-glucan; CS, Candida score; m-MRBT, miniaturized-magnetic resonance-based technology; Mn-Ag, mannan antigen; Mn-Ab, anti-mannan antibody; CAGTA, *Candida* species germ tube antibody; Col index, colonization index; PCR, polymerase chain reaction; Abdominal sepsis: refers to anastomosis leak, postoperative abscess, repeated surgery for recurrent abdominal sepsis or infected pancreatitis

Clinical evaluation of antifungal de-escalation in *Candida* infections: A systematic review and meta-analysis

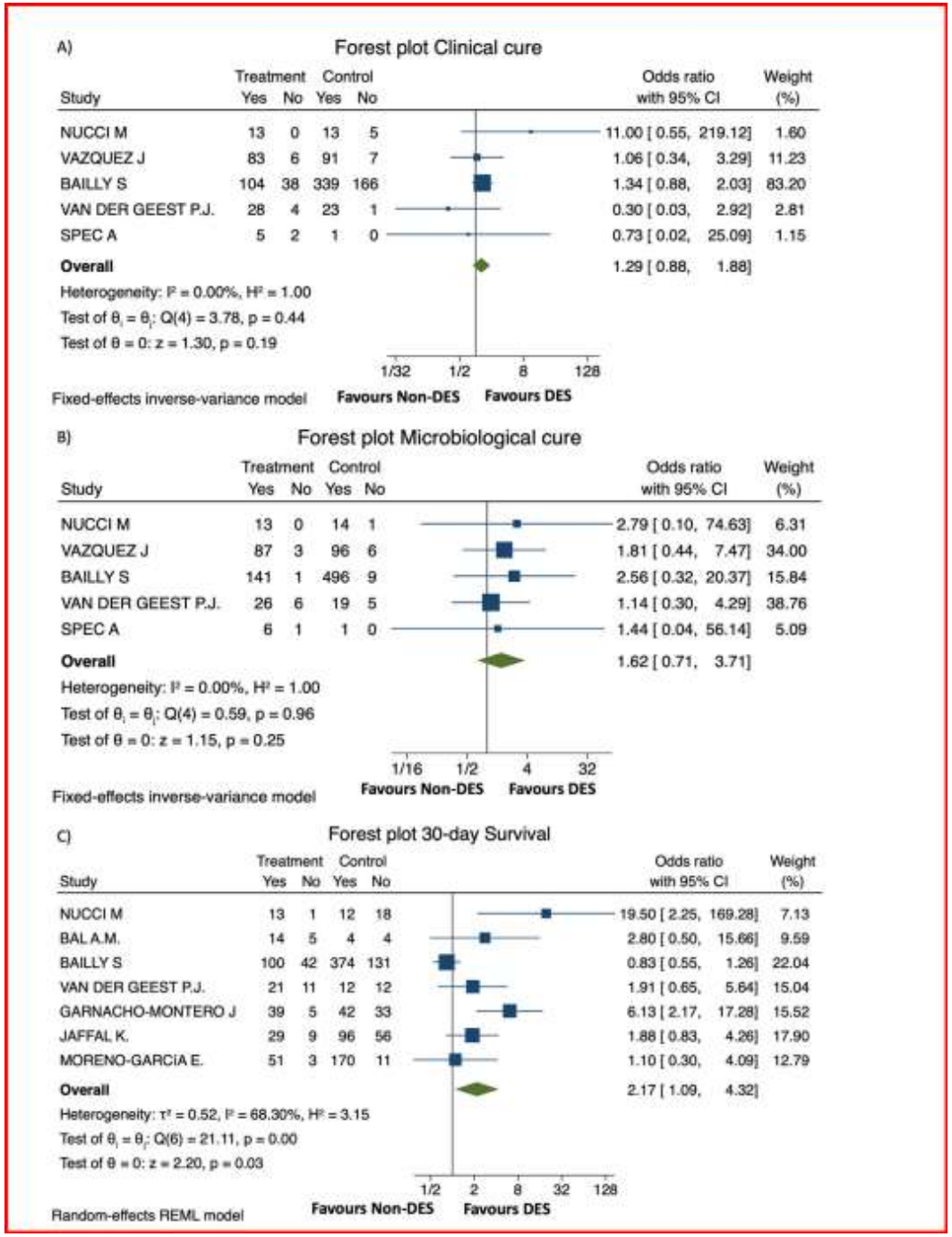
Marta Albanell-Fernández[1,*], Fernando Salazar González[2], Olalla Montero Pérez[3], Victoria Aniyar[4], Francisco-Javier Carrera Hueso[5], Alex Soriano[6,7], Carolina García-Vidal[6,7], Pedro Puerta-Alcalde[6,7], José Antonio Martínez[6,7], Pedro Vázquez Ferreiro[8]

Table 1
Characteristics of selected studies included in the meta-analysis.

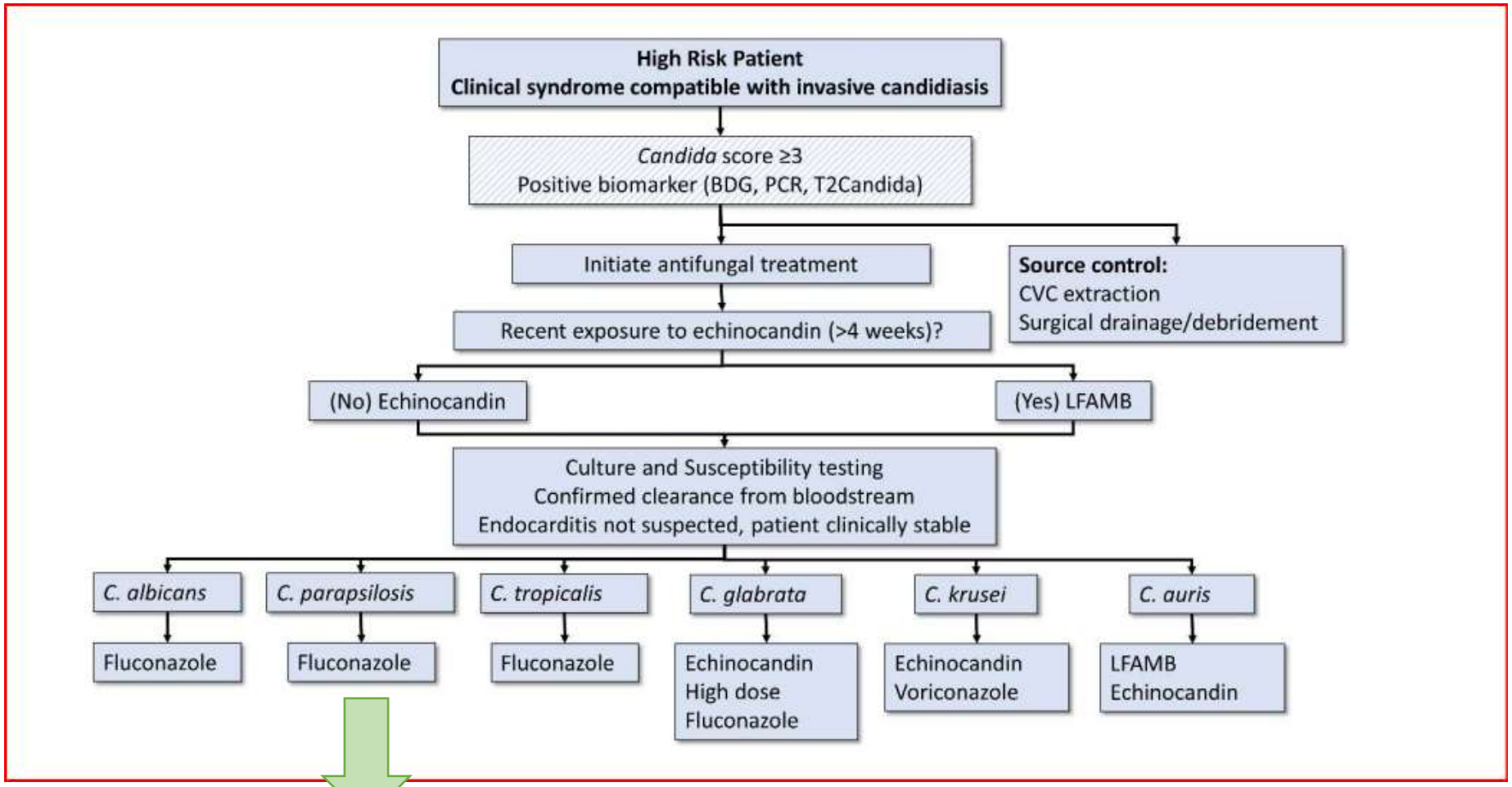
Author [ref]	Inclusion period	Study design	Type of population	Echinocandin used	Dose of echinocandin	Azole used	Dose of azole	n DES group	n Non-DES group	N total	Day of de-escalation
Bailly et al. [6]	2012-2013	Cohort study	Critically ill patients	ND	ND	Fluconazole	800-400 mg/24 h	142	505	647	5
Bal et al. [2]	2011-2013	Cohort study	Critically and non-critically ill patients	Caspofungin Micafungin	(C) LD: 70 mg MD:35-70 mg/24 h (M) 100 mg/24 h	Fluconazole Voriconazole	(F) 800-200 mg/24 h (V I.V) LD: 6 mg/kg/12 h MD:4 mg/kg/12h (V P.O) LD: 400 mg/12 h MD:200 mg/12h	19	7	26	4.6
Garnacho-Montero et al. [17]	2011-2016	Case-controls study	Critically ill patients	Anidulafungin Caspofungin Micafungin	(A) LD: 200 mg MD:100 mg/24 h (C) LD: 70 mg MD: 35-70 mg/24 h (M) 100 mg/24 h	Fluconazole	(F) LD:800 mg MD:400 mg/24 h	44	75	119	5
Jaffal et al. [12]	2012-2013	Case-controls study	Critically ill patients	Caspofungin	ND	Fluconazole Voriconazole	ND	38	152	190	5
Moreno-García et al. [3]	2007-2016	Case-controls study	Critically and non-critically ill patients	ND	ND	Fluconazole	ND	54	181	235	5
Nucci et al. [16]	2008-2009	Clinical trial	Critically ill patients	Anidulafungin	(A) LD: 200 mg MD:100 mg/24h	Voriconazole	(V) LD: 400 mg/12 h MD:100-200 mg/12h	14	30	44	6
Spec et al. [24]	2015-2016	Clinical trial	Critically ill patients	Micafungin	100 mg/24 h	Fluconazole	LD: 800 mg MD:400 mg/24 h	7	1	8	6.5
Van Der Geest et al. [15]	2010-2014	Case-controls study	Critically ill patients	Anidulafungin	(A) LD: 200 mg MD:100 mg/24 h	Fluconazole	LD: 800 mg MD:400 mg/24 h	32	24	56	5
Vazquez et al. [14]	2007-2010	Clinical trial	Critically ill patients	Anidulafungin	(A) LD: 200 mg MD:100 mg/24 h	Fluconazole Voriconazole	(F) 400 mg/24 h (V) 200 mg/12 h	102	148	250	5

A, anidulafungin; C, caspofungin; DES, de-escalation group; F, fluconazole; LD, loading dose; M, micafungin; MD, maintenance dose; ND, no data; non-DES, non-de-escalation group; V, voriconazole.

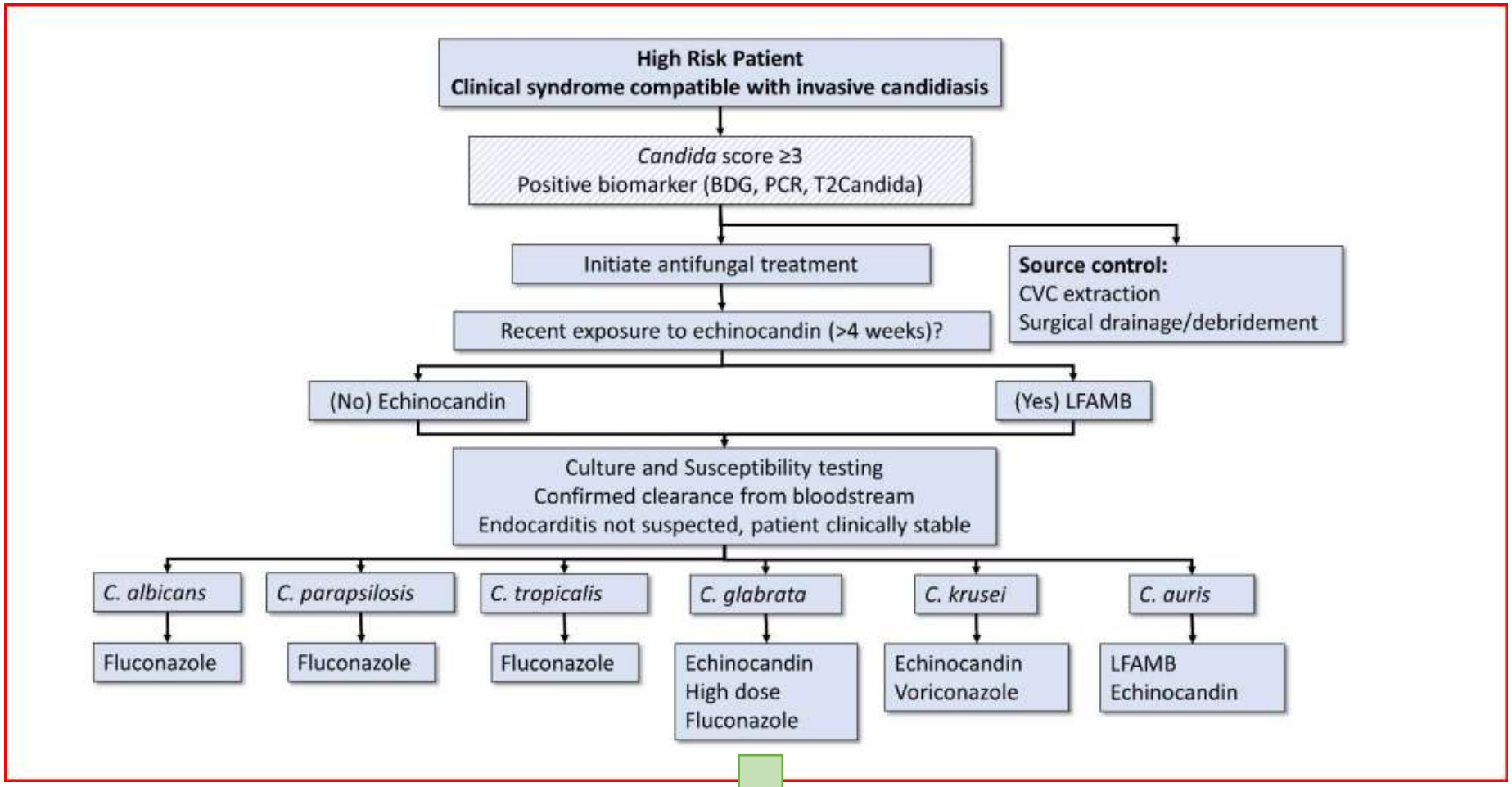
- 9 studies = 1853 patients
- Mean days of de-escalation was 5.2 days



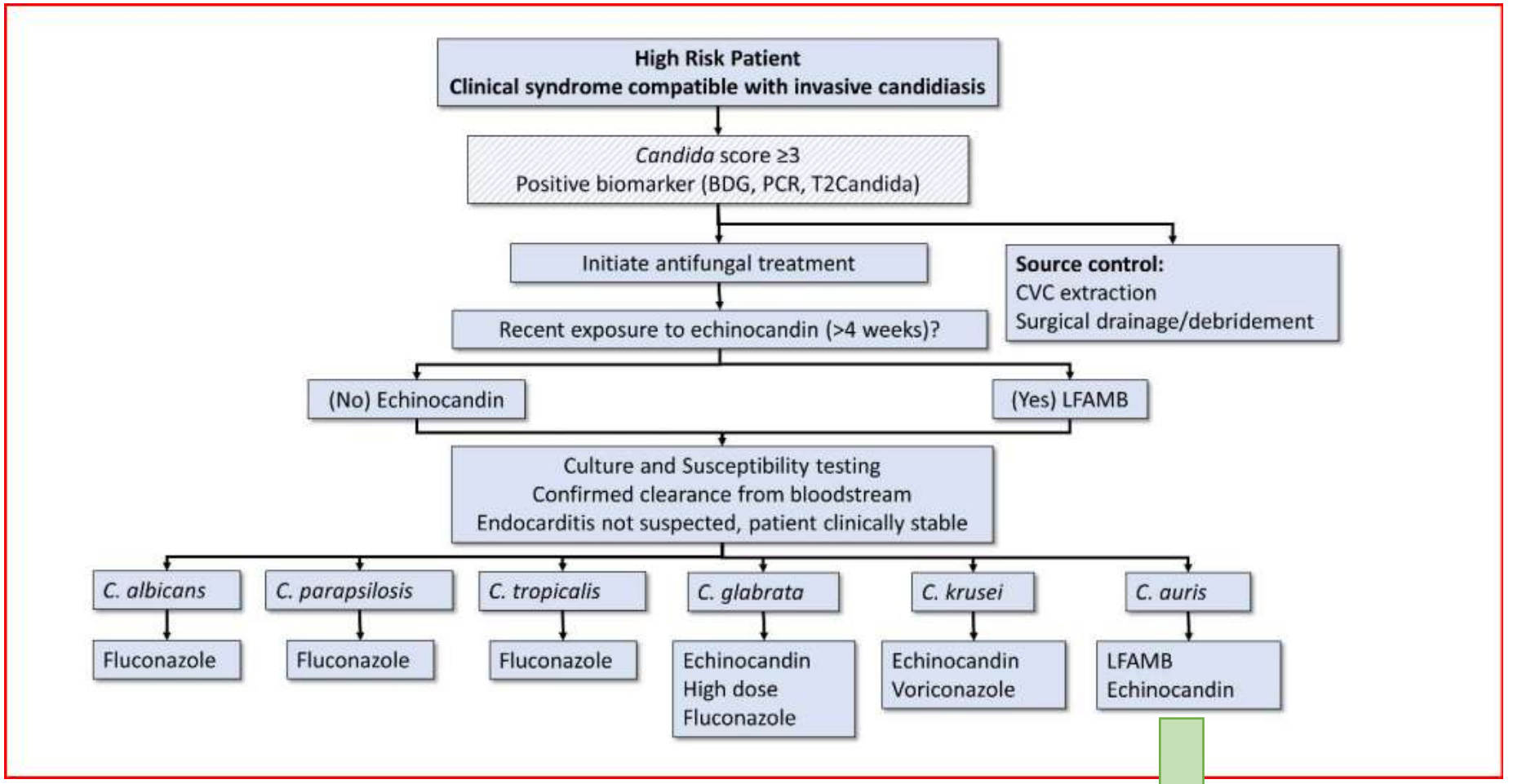
- Clinical cure 1.29 (0.88-1.88)
- Microbiological cure 1.62 (0.71-3.71)
- 30-day survival 2.17 (1.09-4.32)



Less susceptible to echinocandin
Numerically more treatment failures
but not statistically significant
But can be given

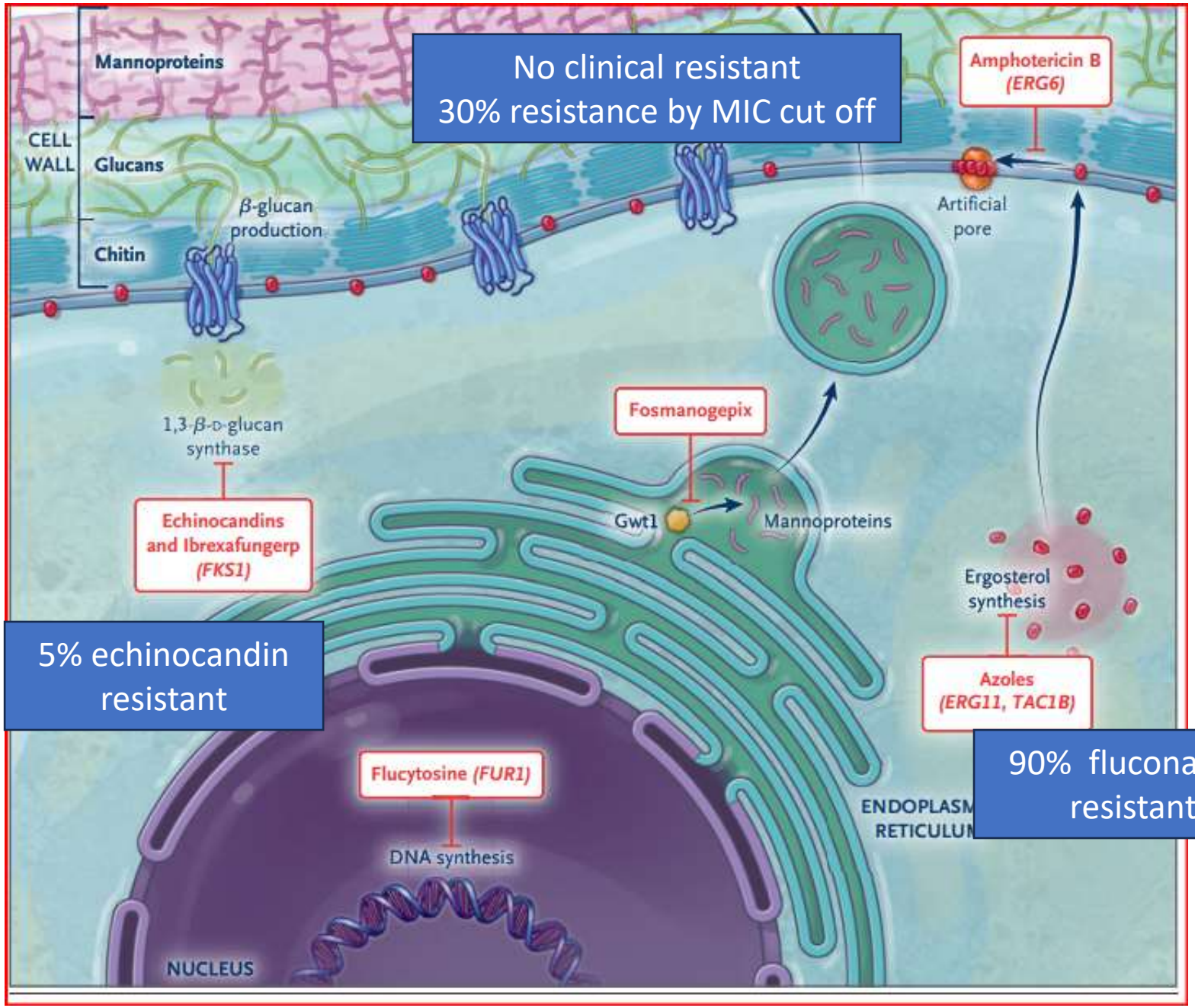


Fluconazole – uncertain
Failure and resistance increasing
Given as de escalating agent



Optimal treatment – not defined
RECOMMENDED – Echinocandins
Resistance strain are emerging

Resistance in C.auris



Resistance

	2011-2012 (74 isolates India)	2017 (54 isolates India, Pak, S.Africa)
Fluconazole	58.1%	93%
Amphotericin B	13.5%	35%
Echinocandins	9.5%	7%

Treatment –No proper consensus

- Echinocandins are preferred first line (caspofungin, micafungin, and anidulafungin) – Poor CNS penetration
  - Caspofungin inactive against C.auris biofilms
- At least 2 weeks after the blood culture is sterile
- Flucytosine – for UTI
- If clinical worsening or 5th day blood culture positive – resistance suspected -> amphotericin B
- If azoles are sensitive – they can be used as a step–down treatment

	First line	Alternatives	Duration	
Non neutropenic candidemia	Echinocandins	Flucytosine Amp B	14 days after last sterile blood culture and symptom resolution	Source control Daily cultures De-escalation at 5 days Fundus within week Echo for IE +/-
Neutropenic candidemia	Echinocandins	Liposomal Amp B Voriconazole	14 days after last sterile blood culture and symptom resolution With resolved neutropenia	?Catheter removal - As presumed GI is cause De-escalation Fundus after neutrophils recover
Disseminated candidiasis	Liposomal AmpB or Echinocandins	Flucytosine	3–6 mo and resolution or calcification of radiologic lesions	?Dual therapy with Flucytosine De-escalation to oral after stabilisation
Endocarditis	Ampho B or Echinocandins		Atleast 6 wks after valve replacement	Replacement is almost always necessary (large veg)
Cystitis	Fluconazole	Ampho B	1-2 wks	Echinocandins – minimal role Liposomal – no role cUTI – treat as candidemia

THANK YOU