Fungal Infection in the ICU

Adel Mohamad Alansary, MD

Outline

- Magnitude of the problem
- Who are at risk?
- Diagnosis, another problem.
- Options for management.

- Approximately 10.4% of infections in an ICU are related to Candida species, with the majority being nosocomial.

Alberti C, Brun-Buisson C, Burchardi H et al. Intensive Care Med 2002;28:108–21

Most is acquired in ICU

Mean incidences of ICU-acquired candidemia in 24 Intensive Care Units (ICUs)		
Unit	**Number of admissions**	**ICU-acquired candidemia Per 1,000 admissions**
Medical ICU (N=12)	4,931	5.3
Surgical ICU (N=10)	2,745	7.3
Hematology Unit (N=1)	702	8.5
Burns Unit (N=1)	131	38.2
Total	**8,509**	**6.7**

Adapted from Bougnoux ME, et al. *Intensive Care Med.* 2008;34:292–299.

EPIC II

	All	Western Europe	Eastern Europe	South America	North America	Oceania	Africa	Asia
No. (%)	7087 (51.4)	3683 (49)	426 (56.4)	1290 (60.3)	607 (48.4)	285 (48.2)	89 (46.1)	707 (52.6)
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]
Microorganisms								
Positive isolates	4947 (69.8)	2678 (72.7)	357 (83.8)[b]	719 (55.7)[b]	457 (75.3)	204 (71.6)	54 (60.7)	478 (67.6)[b]
Gram-positive	2315 (46.8)	1311 (49.0)	185 (51.8)	273 (38.0)[b]	252 (55.1)	104 (51.0)	27 (50.0)	163 (34.1)[b]
Staphylococcus aureus	1012 (20.5)	525 (19.6)	77 (21.6)	138 (19.2)	123 (26.9)[b]	56 (27.5)[b]	16 (29.6)	77 (16.1)
MRSA	507 (10.2)	233 (8.7)	37 (10.4)	79 (11.0)	80 (17.5)[b]	19 (9.3)	11 (20.4)[b]	48 (10.0)

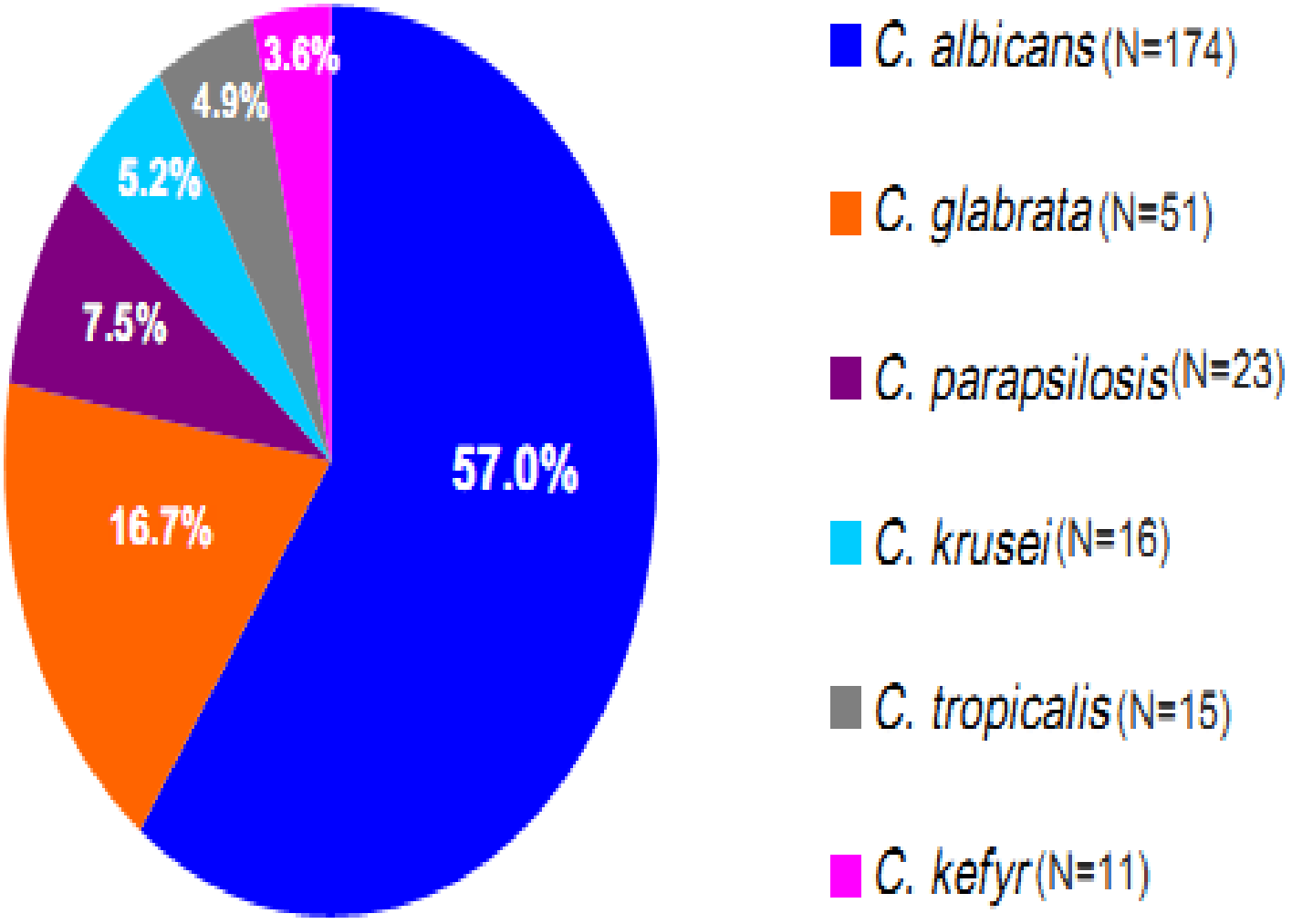
EPIC II

Fungi								
Candida	843 (17)	495 (18.5)	66 (18.5)	92 (12.8)[b]	83 (18.2)	28 (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)
Parasites	34 (0.7)	18 (0.7)	2 (0.6)	6 (0.8)	3 (0.7)	2 (1)	0	3 (0.6)
Other organisms	192 (3.9)	122 (4.6)	9 (2.5)	15 (2.1)[b]	22 (4.8)	8 (3.9)	2 (3.7)	14 (2.9)

EPIC II

Fungi	
Candida	843 (17)
Aspergillus	70 (1.4)
Other	50 (1)

Mycological analysis in 271 adult patients with 305 *Candida* species being identified *(Candida albicans* vs C. non-*albicans)*



Adapted from Leroy O, et al. *Crit Care Med.* 2009;37(5):1612-1618.

Alexandria 2008

- **Nosocomial infections in a medical-surgical intensive care unit.**
- Aly NY, Al-Mousa HH, Al Asar el SM.
- Of all nosocomial infections, 119 (85%) were culture-confirmed and 21 (15%) were clinically defined culture-negative infections. Of the culture-confirmed nosocomial infections, 81 (68%) were Gram-negative, 32 (27%) Gram-positive and 6 (5%) **fungal**.

Med Princ Pract. 2008;17(5):373-7

Increasing Incidence of Invasive Fungal Infections

- IV catheters.
- ICUs.
- Immunosuppressive agents.
- Organ transplantation.
- Hemodialysis.
- DM.

Underestimation

- Difficulty of diagnosis.
- ICU admission is an independent risk factor for fungal infection.
- We do not do postmortem examination.
- 4% of critically ill patients who die in an ICU present an unexpected fungal infection during postmortem examination.

Infect Control Hosp Epidemiol 2004;25:628–33.

Mortality rate of fungal infection in ICU

Invasive candidiasis in the intensive care unit

Luis Ostrosky-Zeichner, MD, FACP; Peter G. Pappas, MD, FACP

costly. With an attributable mortality of as much as 40% to 50%, invasive candidiasis has an estimated cost of $40,000 (U.S.) per episode (3–7). This review fo-

Crit Care Med 2006 Vol. 34, No. 3

Conclusion

- Fungal infection in ICU is 5-18% of all infections.
- 90 % is Candida with different susceptibility according to species.
- Attributable mortality reaches 50%.

RISK FACTORS

Risk factors

- Prolonged length of stay
- High acuity
- Diabetes
- Renal failure
- Hemodialysis
- Broad-spectrum antimicrobials
- Central venous catheter

Risk factors

- Parenteral nutrition
- Immunosuppressive drugs
- Cancer and chemotherapy
- Severe acute pancreatitis
- Candida colonization at multiple sites
- Surgery
- Transplantation

For Aspergillus

- Hospital construction works.
- HIV.
- Prolonged use of IV steroids.
- Malnutrition.
- Liver cirrhosis.
- COPD.

Determinants of mortality in non-neutropenic ICU patients with candidaemia

Deborah JE Marriott[1,2*], E Geoffrey Playford[3,4*], Sharon Chen[4,5], Monica Slavin[6], Quoc Nguyen[1]
David Ellis[7], Tania C Sorrell[4,5] for the Australian Candidaemia Study

Variable	Dying patients*	Surviving patients*	Univariate analysis**		Multivariate analysis†	
			Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)††	*P*
Male sex	55/97 (57%)	45/76 (59%)	1.00 (0.67 to 1.49)	0.99		
Age	63.3 ± 16.7 years	51.1 ± 19.2 years	1.03 (1.01 to 1.04)	<0.001	1.03 (1.01 to 1.4)	<0.001
Antifungal agents prior to diagnosis	10/96 (10%)	6/76 (8%)	1.03 (0.53 to 1.98)	0.93		
Non-receipt of antifungal agents after diagnosis	20/97 (21%)	5/76 (7%)	5.17 (3.08 to 8.68)	<0.001	7.90 (3.73 to 16.71)	<0.001
Candida albicans	43/97 (44%)	26/76 (34%)	0.73 (0.49 to 1.10)	0.13		
Vascular access device removed or not in place	55/80 (69%)	64/79 (84%)	0.41 (0.26 to 0.67)	<0.001		
TPN receipt	53/96 (55%)	26/76 (34%)	1.52 (1.02 to 2.28)	0.04		
Haemodialysis	23/97 (24%)	8/76 (11%)	1.66 (1.04 to 2.66)	0.03		
Corticosteroid receipt	33/97 (34%)	20/76 (26%)	1.36 (0.89 to 2.07)	0.17		
Non-multitrauma patient	93/97 (96%)	60/76 (79%)	3.25 (1.19 to 8.87)	0.02	6.97 (1.64 to 29.67)	0.009
Recent surgery	71/97 (73%)	47/76 (62%)	1.24 (0.79 to 1.94)	0.35		
Other healthcare related infections	73/97 (75%)	55/76 (72%)	0.85 (0.53 to 1.35)	0.49		
Ventilation at day 1	82/96 (85%)	55/76 (72%)	1.51 (0.86 to 2.67)	0.15	4.03 (1.93 to 8.41)	<0.001

Factors associated with increased mortality

- Age.
- Mechanical ventilation.
- failure to receive anti-fungal therapy.
- ICU admission diagnosis.

DIAGNOSIS

Diagnosis

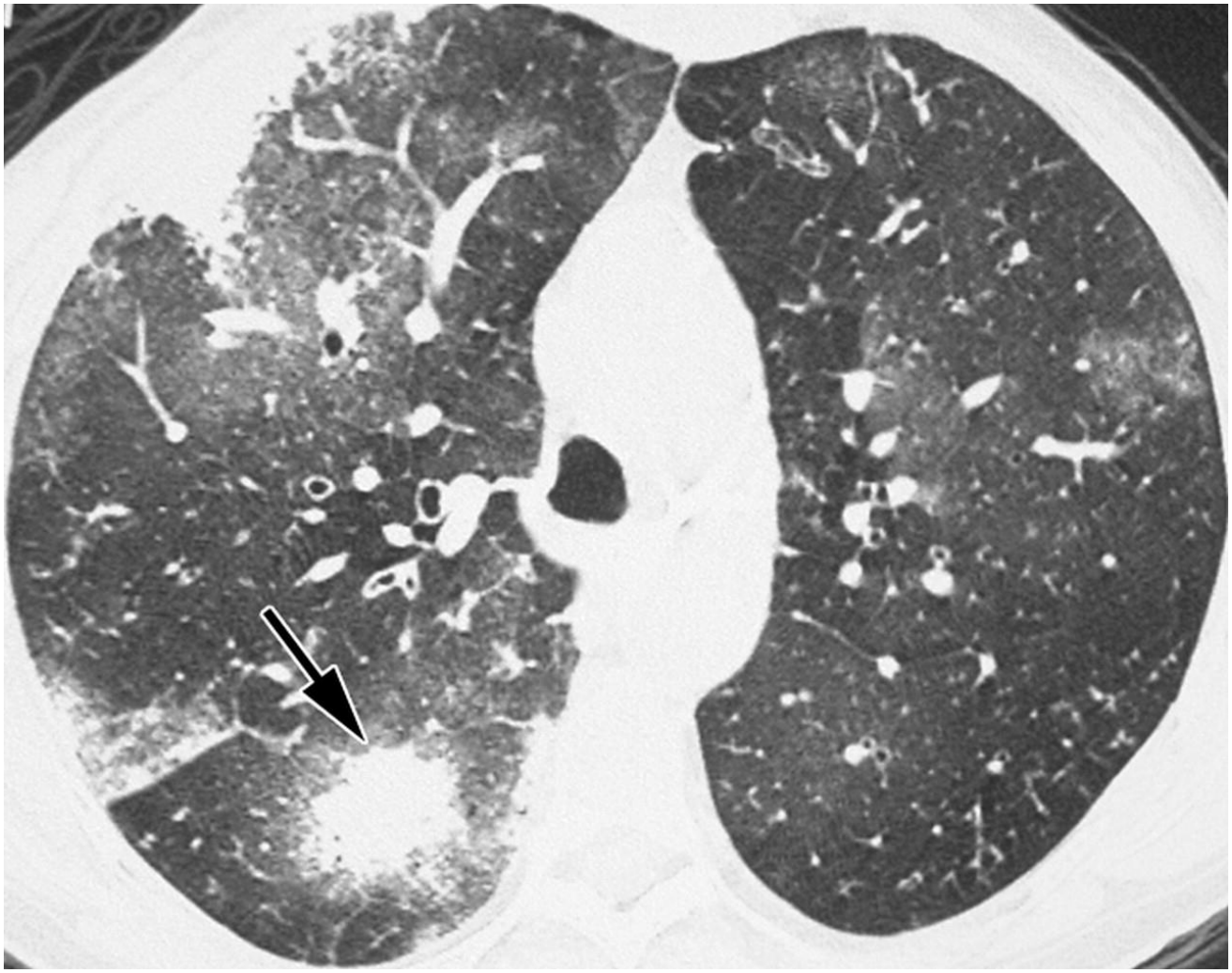
- Traditional methods:
  - Microscopic examination.
  - Cultures: Blood cultures yield 50% sensitivity, takes days for candidiasis, weeks for molds.

Radiology

Infection site	Imaging finding
Lower Respiratory Tract Infection	Dense well-circumscribed lesions halo sign
	Air-crescent sign
	Cavity
Sinonasal infection	Sinusitis on imaging, with clinical signs
CNS infection	Focal lesions on imaging
	Meningeal enhancement on CT or MRI
Disseminated candidiasis	Small target like abscesses ('bulls-eye' lesions) in liver or spleen

Clin Infect Dis 2008;46(12):1813e21.

Candida albicans infection



Franquet T et al. Radiology 2005;236:332-337

Radiology

Newer Methods

- ***Serology:***
- *Galactomanann test*: specific for Aspergillus. False positive results with Tazobactam/pipracillin.
- *B D-Glucan (BDG)*: non specific, requires serial testing. False positive with HD, Bacteremia, Drugs. Negative test rules out fungal infection. (NPV).

Bronchoscopy

- Yield of BAL culture is 30%.
- GM testing of BAL improves utility.

Utility of Galactomannan (GM) Detection in Bronchoalveolar Lavage (BAL) Samples

Number of patients: 160	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Serum	47	93	73	82
BAL	85	100	100	88

GM detection in CT-based BAL fluid has a high positive predictive value (PPV) for diagnosing invasive pulmonary aspergillosis (IPA) early in untreated patients

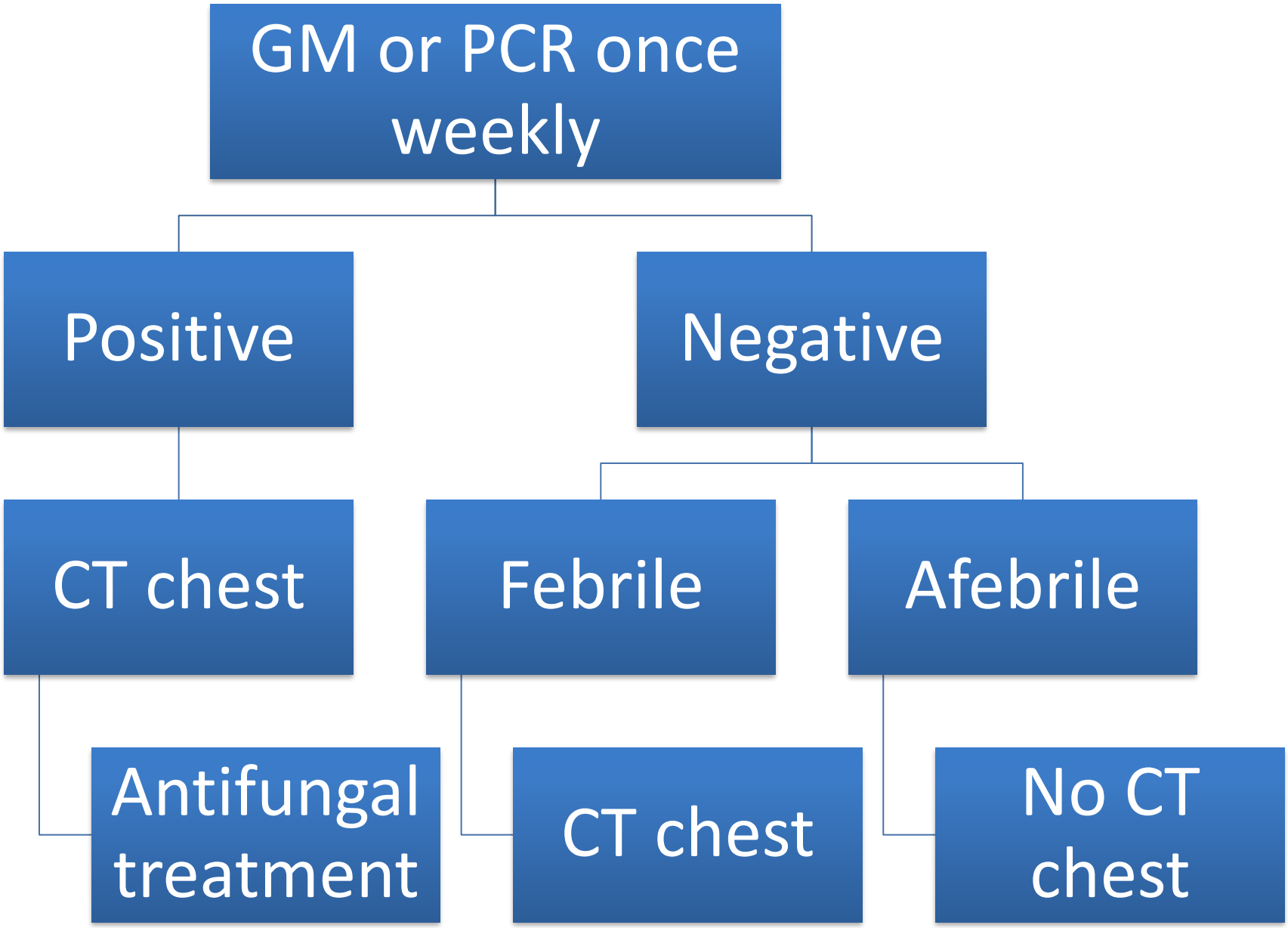
GM index <0.5 in BAL virtually excludes diagnosis

Becker MJ, et al. *Br J Haematol.* 2003;121:448-57.
D'Haese J, et al. *J Clin Microbiol.* 2012;50:1258-63.

- PCR: false positive due to environmental contamination, clinical colonization. False negative due to rigid cell wall of Fungi.
- Combinations:
  - PCR and GM.
  - Use clinical judgment.

A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization*

Variable	Proven Candidal Infection %	*p* Value	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)
Surgery on ICU admission				
No	6.9			
Yes	16.5	<.001	2.69 (1.76–4.10)	2.71 (1.45–5.06)
Total parenteral nutrition				
No	2.8			
Yes	15.5	<.001	6.46 (3.48–11.98)	2.48 (1.16–5.31)
Severe sepsis				
No	4.5			
Yes	28.8	<.001	8.63 (5.49–13.56)	7.68 (4.14–14.22)
Candida species colonization				
No	4.2			
Yes	12.3	<.001	3.20 (1.85–5.53)	3.04 (1.45–6.39)


GM or PCR once weekly
Positive
Negative
CT chest
Febrile
Afebrile
Antifungal treatment
CT chest
No CT chest

So

- Setting: risk factors.
- Send cultures.
- Use GM or BDG.
- Determine type using: Chrome Agar culture, or chemical reactive testing (API).
- Always remember radiological signs.

So

- Frontiers:
  - Antifungal susceptibility.
  - PCR.
  - Proteomic methods: mass spectrometry.

MANAGEMENT

Polyenes: Amphotericin B

- Activity
  - Candida except Candida lusitaniae
  - Aspergillus Except Aspergillus terreus
  - Zygomycosis (Mucor).
  - Dimorphic fungi (Blastomyces, Parracoccidioides, Histoplasma and Coccidioides
- Toxicity

Azoles

- Fluconazole, Itraconazole, Posaconazole and Voriconazole.
- Activity: Candida species.
- C. glabrata and C. kruzei are resistant to Fluconazole.
- Molds and Cryptococcus neoformans are sensitive to Posaconazole and Voriconazole.

Resistance

- Develops if duration >14 days, with possible cross resistance.

Echinocandins

- Inhibit glucan synthetase.
- Active against all Candida including Candida parapspilosis with raised MIC.
- Active also against Aspergillus.
- All are well tolerated and given by IV infusion.

		Common Susceptibility Patterns				
Species	Frequency (%)	Amphotericin B	5-FC	Fluconazole and Itraconazole	Voriconazole and Posaconazole[a]	Echinocandins[b]
C. albicans	40–60	S	S	S	S	S
C. glabrata	20–30	S to I	S	S-DD to R	S to S-DD?	S
C. krusei	5–10	S to I	I to R	R	S to S-DD?	S
C. lusitaniae	0–5	R	S	S	S	S
C. parapsilosis	10–20	S	S	S	S	S to I?
C. tropicalis	20–30	S	S	S	S	S

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

Condition or treatment group	Therapy		
	Primary	Alternative	Comments
Candidemia			
Nonneutropenic adults	Fluconazole 800-mg (12-mg/kg) loading dose, then 400 mg (6 mg/kg) daily or an echinocandin[a] (A-I). For species-specific recommendations, see text.	LFAmB 3–5 mg/kg daily; or AmB-d 0.5–1 mg/kg daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses, then 200 mg (3 mg/kg) bid (A-I)	Choose an echinocandin for moderately severe to severe illness and for patients with recent azole exposure. Transition to fluconazole after initial echinocandin is appropriate in many cases. Remove all intravascular catheters, if possible. Treat 14 days after first negative blood culture result and resolution of signs and symptoms associated with candidemia. Ophthalmological examination recommended for all patients.

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

Suspected candidiasis treated with empiric antifungal therapy			
Nonneutropenic patients	Treat as above for candidemia. An echinocandin or fluconazole is preferred (B-III).	LFAmB 3–5 mg/kg daily or AmB-d 0.5–1 mg/kg daily (B-III)	For patients with moderately severe to severe illness and/or recent azole exposure, an echinocandin is preferred. The selection of appropriate patients should be based on clinical risk factors, serologic tests, and culture data. Duration of therapy is uncertain, but should be discontinued if cultures and/or serodiagnostic tests have negative results.

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

7. Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia (A-III).

8. Intravenous catheter removal is strongly recommended for nonneutropenic patients with candidemia (A-II).

What about combination therapy?

- Echinocandin with Voriconazole or AmB.
- Aspergillosis only.
- No clear evidence to support.

All in All

- Awareness about fungal infection in non-neutropenic critically ill patients is increasing.
- Diagnosis is difficult, but tests are improving.
- Clinical risk factors, radiology are mainstay of suspicion.
- GM, BDG, PCR and culture lead to definitive diagnosis.

All in All

- Array of therapy is increasing allowing tailored treatment.
- Antifungal susceptibility, TDM allow delivering the right drug with a therapeutic level.

THANK YOU