MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

How do I interpret … *Candida* in respiratory secretions?

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Candida from respiratory tract cultures

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Why we shouldn't treat Candida from sputum/ETT/BAL

- Candida can be grown from mouths of healthy people/patients with/without pneumonia
- Autopsy studies: no correlation between pre-mortem Candida cultures and histopathologic evidence of Candida pneumonia
- Observational studies: no correlation between + Candida cultures from respiratory tract and outcomes
- RCT shows no benefit in treating a + respiratory tract culture for Candida

Candida – constituent of human microbiota

Found on skin, in GI tract, respiratory tract, vagina

- Contaminant? (artefact of sampling)
- Commensal? (native to human, benign, benefits from but does not harm host)
- Colonizer? (residing in/on body & multiplying, but not a member of the normal flora, and also not causing harm)
- Pathogen? (causing a disease)

Pendleton KM et al. Pathogens & Disease 2017;75: ftx 029

Casadevall A et al. Infect Immun 2000;68:6511

No culture-based or molecular test of respiratory specimens can distinguish between contamination, colonization and invasive disease.

Pendleton KM et al. Pathogens & Disease 2017;75: ftx 029

Table 1. Major risk factors for acquisition of *Candida* in the respiratory tract.

Host factors	Latrogenic causes	Immunosuppression	Extraneous
Genetic factors including (STAT1 and dectin-1 mutations)	Broad spectrum antibiotics	Neutropenia	Prolonged hospital stay
	Mechanical ventilation	Steroid use	ICU stay
		HIV	Burns
	Radiation therapy	Diabetes mellitus	
		Bone marrow or solid organ transplant	
		Use of systemic immunosuppression	

THE NEW ENGLAND JOURNAL OF MEDICINE July 14, 1960

THE SIGNIFICANCE OF *CANDIDA ALBICANS* IN HUMAN SPUTUM*

GERALD L. BAUM, M.D.†

TABLE 1. *Results of Cultures of Sputum for Fungi.*

GROUP	AGE RANGE	NUMBER CULTURED	CULTURES POSITIVE		
			ALL CANDIDA SPECIES	*C. albicans*	MOLD
	yr.				
Hospital patients	24-70	55	30	15	20
Hospital employees	20-47	34	12	5	18
Medical students	20-27	30	6	4	9

#

The differences in these three groups are not as important as the fact that candida exists at all.

#40 of 55 pts were on antibiotics; none of control groups on antibiotics

A rigorously conducted 21st century study

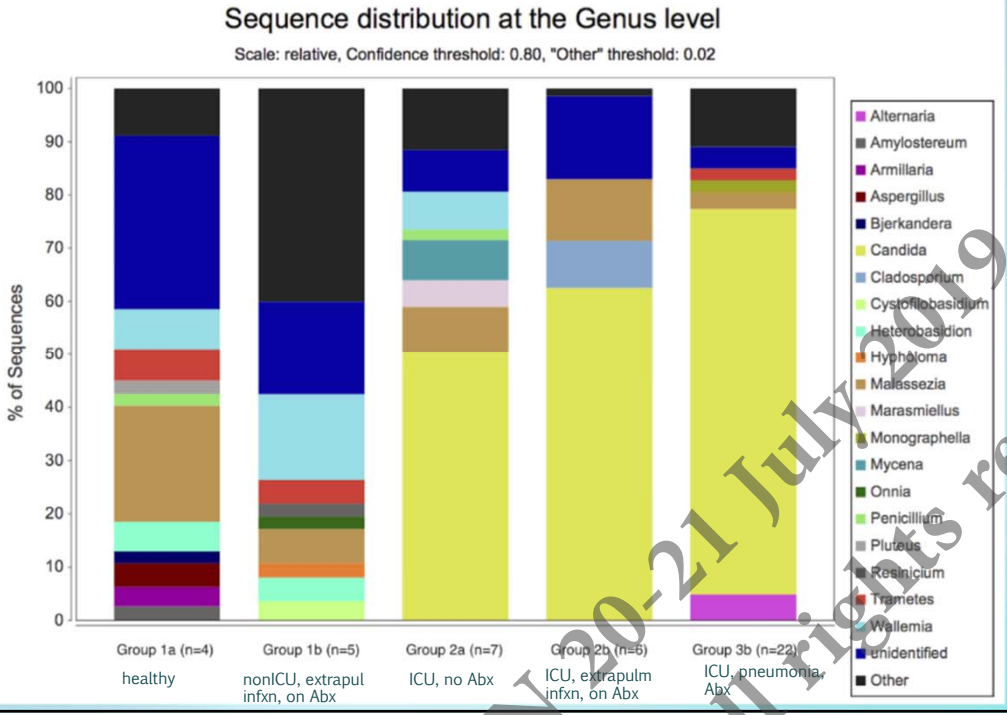
Table 2. *Candida* positive cultures from the oral cavity, lower respiratory tract (LRT), and the *Candida* colonization index.

Candida cultures	1a, healthy adults, (n = 87)	1b, non-ICU, extrapulmonary infection, AB therapy (n = 18)	2a, ICU, no AB therapy (n = 8)	2b, ICU, extrapulmonary infection, AB therapy (n = 23)	3b, ICU, pneumonia, AB therapy (n = 34)
Oral cavity positive	25 (29%)*	14 (74%)*	4 (50%)	12 (52%)	20 (59%)*
LRT positive	1 (1%)**	2 (11%)	2 (25%)**	6 (26%)**	14 (41%)**
Candida colonization index (median)	n.d.	n.d.	0.25	0.25	0.25

*stat sig, 1a vs 1b, 1a vs 3b
** stat sig 1a vs 2a, 1a vs 2b, 1a vs 3b

Healthy adults were undergoing elective plastic surgery, specimens obtained while intubated under GA (long list of exclusions incl no antifungals in prev 8 wk)
All "AB therapy" had to have been there for ≥2 days
2a also no pulm disease, no CAP, ASP, HAP, VAP (+ long list of exclusions)

Krause R et al. PLoS One 2016;11:e0155033



By sequencing, no Candida in LRT of healthy subjects

- No pt in 2a, 2b or 3b developed candidemia or IFI

No assn btw Candida-dominated LRT flora and 30-day mortality

Krause R et al. PLoS One 2016;11:e0155033

Candida pneumonia? An immediate post-mortem study

- 25 patients dying in ICU after >72hrs' stay
- Excluded: anyone under immunosuppression, with hematologic malignancy, with ANC <1000
- Upon death, set FiO2 100%, then:
  - ETT aspirate via mucus trap/collector
  - Bronchoscopy through each lung (different scope for each lung) with PSB sampling
  - As above, with BAL
  - Lung biopsies through thoracotomy, guided by light of bronchoscope
  - Lung biopsies through above incisions, unguided

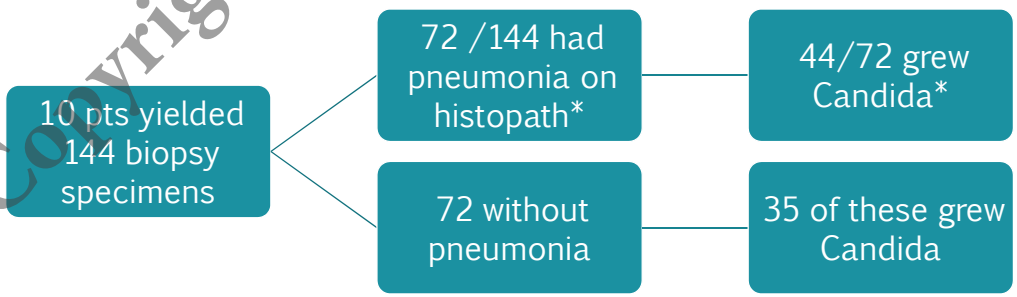
El-Ebiary M et al. Am J Resp Crit Care Med 1997;156:583

Candida pneumonia? ICU immediate pm results

- Out of 25 patients, 10 (40%) grew Candida from a **lung biopsy** specimen
- 3/10 had grown a Candida from pre-mortem sample (ETT/BAL)

El-Ebiary M et al. Am J Resp Crit Care Med 1997;156:583

A lung biopsy with Candida – also not Candida pneumonia!



* Only 1 with histopath evidence of Candida pneumonia – see next slide

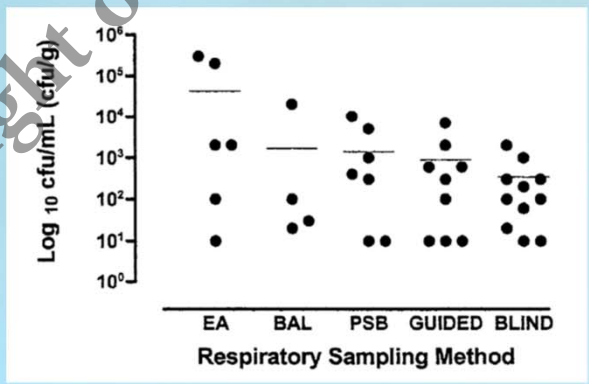
El-Ebiary M et al. Am J Resp Crit Care Med 1997;156:583

Candida from 10 post-mortem lung biopsies, but …

- Lung biopsy from only 1 person had histopath evidence of Candida pneumonia – specimen also grew *C. krusei*
- This person also had pre-mortem ETT asp and blood c/s with *C. krusei*

El-Ebiary M et al. Am J Resp Crit Care Med 1997;156:583

Candida pneumonia? ICU immediate post-mortem results



- ✓ Candida is uniformly distributed through the lungs in mechanically ventilated patients
- ✓ Candida colonization is extensive throughout the lungs

El-Ebiary M et al. Am J Resp Crit Care Med 1997;156:583

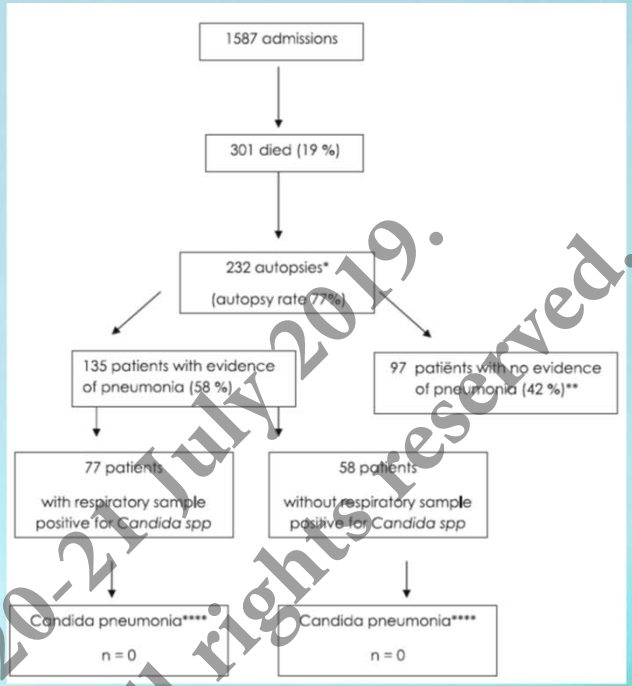
Significance of the isolation of *Candida* species from airway samples in critically ill patients: a prospective, autopsy study

Definition of Candida pneumonia

Yeast invasion on a background of alveolar and interstitial inflammation

Of pts dying of/with pneumonia, 57% had grown Candida from a resp sample before death

Resp sample + for Candida had to be + in the 2 weeks prior to death



Meersemann W et al. Intensive Care Med 2009;35:1526

Limiting the reporting of Candida from resp samples

1 Mar 01 – 4 Nov 01

- all fungi from resp specimens reported to genus or species level if fungal culture requested
- if only bacterial culture requested and yeast grown – rapid identification then reported as "presumptive *C. albicans*"

5 Nov 01 – 1 Mar 02

- if yeast grown, do urease test tro Cryptococcus, then reported as "yeasts, not Cryptococcus"

Barenfanger J et al. J Clin Micro 2003;41:5645

Results of limiting yeast reporting from resp samples

	LOS (days)	
Full ident grp	12/1 (10.9 – 13.2)	p=0.02
Limited ident grp	10.1 (8.1 – 10.1)	

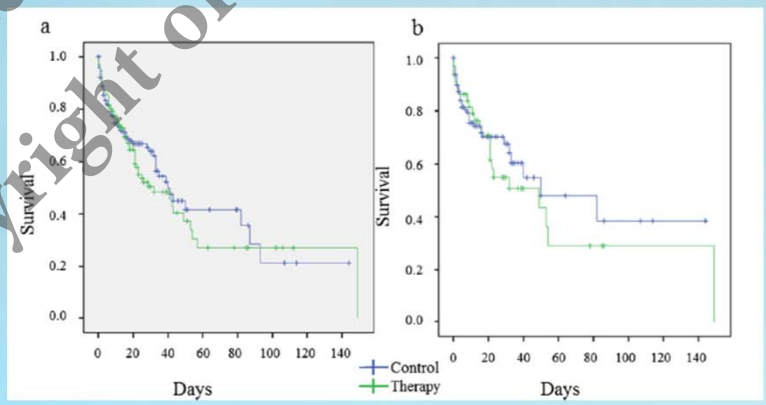
	Mean actual variable cost ($)	
Full ident grp	9407 (7870 – 10945)	*p*=0.003
Limited ident grp	6973 (5042 - 8905)	

	No. (%) of pts receiving antifungals	
Full ident grp	103 (38.6)	*p*=0.004
Limited ident grp	16 (20/8)	

No difference in mortality

Barenfanger J et al. J Clin Micro 2003;41:5645

Retrospective ICU study – 322 pts with Candida pulm colonization, multi-site colonized pts excl



a: all in cohort, incl those with pneumonia before Candida isolated
(99% on abx before Candida isolated, 38%of them were already on anti-fungals, rest had it added)

b: no pre-existing pneumonia

Survival also not different for both groups (anti-fungals *vs* none) in both cohorts (p>0.05 in both cohorts)

Lindau S et al. J Intensive Care 2015;3:31

Impact of *Candida* spp. isolation in the respiratory tract in patients with intensive care unit-acquired pneumonia

- Prospective study in 6 ICUs of a teaching hospital (Barcelona)
- Recruited pts with ICU-acquired pneumonia. (Those who did not grow Candida from a resp tract sample were excluded.)
- 385 patients followed for outcomes
- 82 of these (21%) had Candida from a resp tract sample – they tended to
  - be sicker (SOFA score worse)
  - diabetic
  - trend towards more frequent previous surgery, worse renal func, lower T^0C at onset of pneumonia

Terraneo S et al. Clin Microbiol Infect 2016;22:94ei

Impact of *Candida* spp. isolation in the respiratory tract in patients with intensive care unit-acquired pneumonia

	Candida spp. (*n* = 82)	No *Candida* spp. (*n* = 303)	p
Patients with NV-ICUAP that needed subsequent intubation, *n* (%)	27 (79)	71 (57)	0.018
ICU stay, days	21±16	22±20	0.79
Hospital stay, days	44±28	43±36	0.99
Inappropriate empiric treatment, *n* (%)	10 (26)	38 (18)	0.24
Non-response to treatment, *n* (%)	48 (59)	167 (55)	0.58
Ventilator-free days at day 28[a]	12 (0–24)	7 (0–23)	0.50

Terraneo S et al. Clin Microbiol Infect 2016;22:94ei

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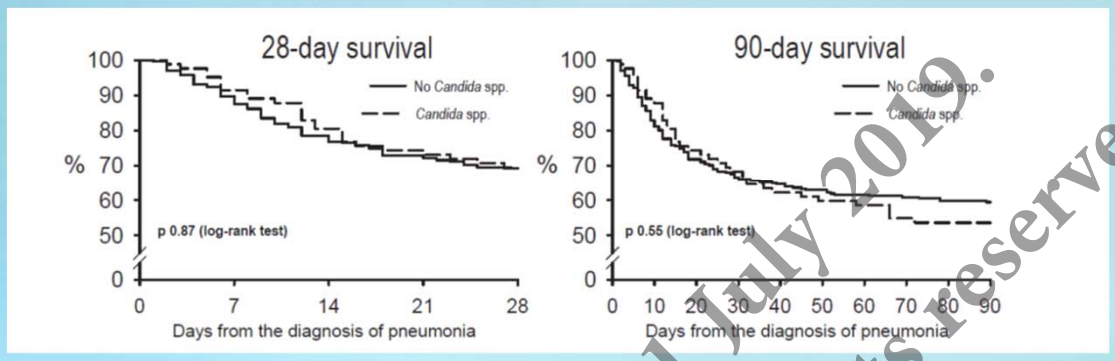

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Impact of *Candida* spp. isolation in the respiratory tract in patients with intensive care unit-acquired pneumonia

Among patients with Candida isolated from resp tract, antifungal treatment was not a/w different LOS or mortality

Terraneo S et al. Clin Microbiol Infect 2016;22:94ei

RCT: antifungal for VAP with Candida in ETT

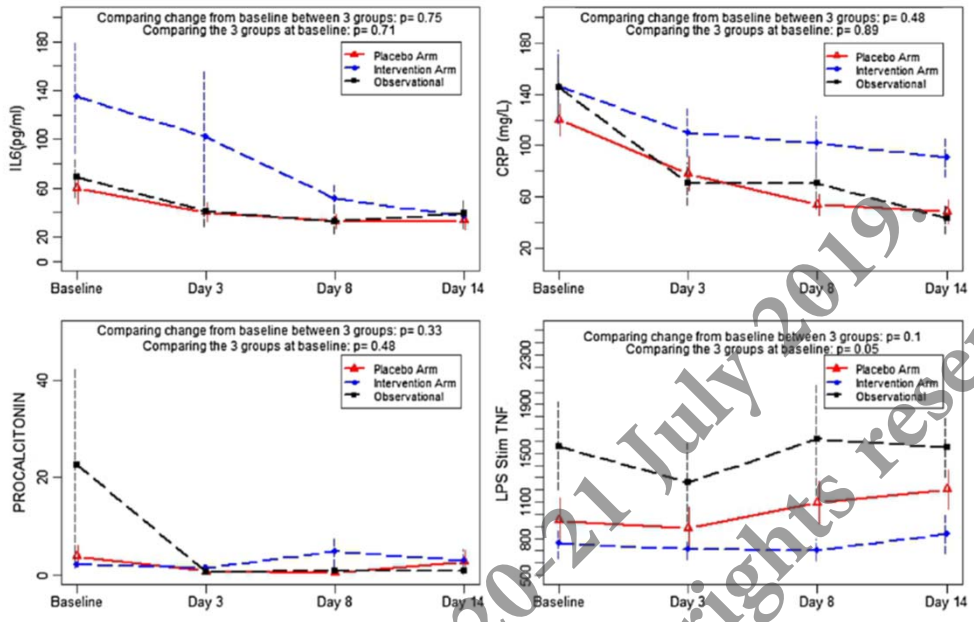
- Prospective, multicentre, placebo-controlled RCT (Canada)
- "clinically-suspected" VAP, Candida from ETT/BAL, no Candida from other sites
- Non-immunocompromised, in iCU at least 96hr, "VAP" developing after at least 48hr
- Randomized to anidulafungin vs matching placebo (auto-switch to fluconazole or matching placebo if *C. albicans*)
- Also included an observational group without candida from resp tract but in their ICU
- Multiple outcomes assessed, incl levels of BDG, procalcitonin, IL-6, and survival

Albert M et al. Intensive Care Med 2014;40:1313

RCT: antifungal for VAP with Candida in ETT

	Placebo	Antifungal	p	Observational
n	29	31		29
APACHE	23	22		20.9
Baseline SOFA	38	38		38
ICU LOS	11.5	13	0.35	11
Hospital LOS	29	28	0.9	29.5
28-day mortality	6 (20.7%)	7 (22.6%)	0.86	5 (17.2%)
90-day mortality	7 (24.1%)	10 (32.3%)	0.49	6 (20.7%)

Albert M et al. Intensive Care Med 2014;40:1313



Albert M et al. Intensive Care Med 2014;40:1313

Summary

- Candida can be cultured from the oral cavity of healthy persons
- Sequencing studies show that even when Candida is dominant in the lower resp tract, there is no association with outcomes
- Observational studies show that there is no association between treatment for resp tract Candida and outcomes in ICU patients
- Autopsy studies show that it is very rare to find a case of Candida pneumonia in patients who had Candida cultured from their ETT aspirate/BAL
- One RCT shows no benefit in treating Candida cultured from resp tract with anti-fungals