The Rationale for Empiric Antifungal Therapy in the Non-Neutropenic Patient

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Different Forms of Invasive Candidiasis (IC)

- Candidemia in the absence of deep-seated candidiasis
  - 39.5% of IC
- Candidemia with associated deep-seated candidasis
  - 28.4% of IC
- Deep-seated candidasis without detectable candidemia
  - 32.1% of IC. Missed by blood cultures

Leroy et al Crit Care Med 2009;37:1612-18
Clancy and Nguyen CID 2013;56:1284-92.

Candidemia and Invasive Candidiasis (IC)

What we know

- Common (2nd in rank order in NAM and EU ICUs) [JAMA 2009;302:2323-9]
- Deadly (attributable mortality 49%) [CID 2003;37:1172-7]
- Expensive [CMR 2007;20:133-63]
- Management involves time-critical decision making [CID 2012; 54:1739-46]

RD1

Slide 3

RD1 Gagne paper highlights costs of $130K for these patients

Rahul Dhanda, 5/3/2013

Invasive Candidiasis: Incidence in the US

- Zaoutis et al *CID 2005; 41: 1232-9:*
  - Children 47/100,000 adm (U.S.)
  - Adults 30/100,000 adm (U.S.)
  - Meningococcal dz in U.S. 0.5-5/100,000 adm
- Forrest et al *J Infect 2008; 56:126-9:*
  - Incidence of candidemia 0.7-0.95/ 1000 pt-d
  - Incidence of MRSA BSI 0.3-0.4/ 1000 pt-d

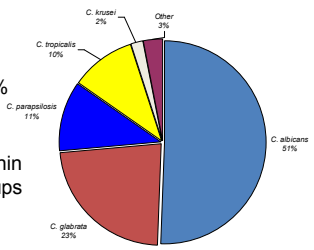
Candida Bloodstream Infection
A common device-associated pathogen

Pathogen	% of all CLABSI	Rank
Coag-negative staph	34.1	1
Enterococcus species	16.0	2
Candida species	11.8	3
Staphylococcus aureus	9.9	4
Klebsiella pneumoniae	4.9	5

Hidron, et al. *Infect Control Hosp Epidemiol* 2008;29:996–1011.

Candidiasis: Mycology

- Genus *Candida* contains over 200 species
- Five account for ~97% of human infections
- New species being described that fall within older phenotypic groups
  - *C. orthopsilosis*
  - *C. metapsilosis*
  - *C. nivariensis*
  - *C. bracarensis*



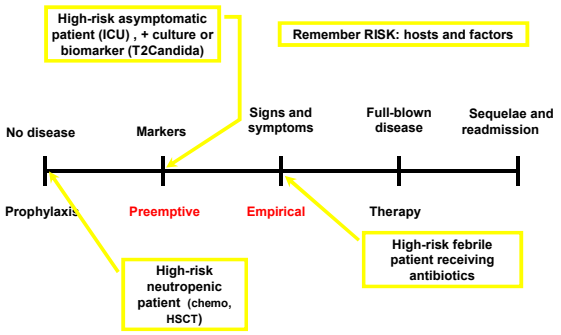
Distribution of species for *Candida* bloodstream infection, US hospitals

IC Related Excess Mortality, Length of Stay (LOS), and Associated Costs

- Burden of disease >400,000 cases/yr worldwide
- Excess mortality rates: 10%-49%
- Excess LOS in hospital: 3.4-30 days
- Excess costs: $6,200-$92,000
- Average total cost of candidemia: $38,758 (85% due to excess LOS)

Pfaller & Diekema CMR 2007;20:133-63
Brown et al Sci Transl Med 2012;4:165rv13

Candidemia Management: Who and When to Treat?



Populations At Risk / Risk Factors

Immunocompromised	Nonimmunocompromised	Neonates
In addition to →	Broad-spectrum antibiotics	←In addition to
Granulocytopenia	Hemodialysis	Gestational age
SCT	Central venous catheter	Low APGAR
Mucositis	IV drug use	Length of NICU stay
GVHD	Severity of illness	H_2 blockers
Type of chemotherapy	Total parenteral nutrition	Shock
Organ transplants	GI perforation or surgery	Intubation
	Colonization	GI disease
	Diabetes	Congenital malformations
	LOS in ICU	
	Pancreatitis	
	Sepsis	

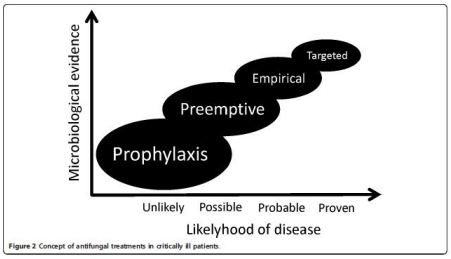


Figure 2 Concept of antifungal treatments in critically ill patients.

Eggimann P, Bille J, Marchetti O. Ann Intensive Care. 2011; 1:37

The evidence for prophylaxis

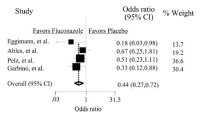


Figure 1. Impact of fluconazole prophylaxis on candidal infections. *CI*, confidence interval.

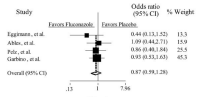
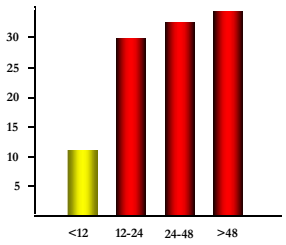


Figure 2. Effect of fluconazole prophylaxis on mortality. *CI*, confidence interval.

Shorr, et al. Crit Care Med, 2005.

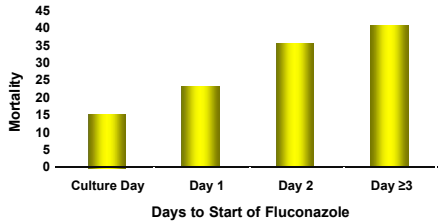
Time-Dependent Mortality: The Justification for Empiric Therapy

- Delay in treatment is an independent determinant of hospital mortality
- All patients (N=157)
- Delay, 33.1%
- No delay, 11.1%



Morrell et al. *Antimicrob Agents Chemother.* 2005;49:3640-3645.

Timing: The Foundation for Empiric Therapy



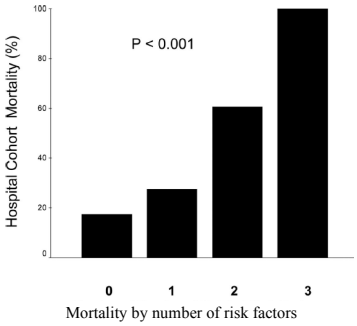
Garey et al. *Clin Infect Dis*. 2006;43:25-31.

Adequacy of Initial Empirical AF Therapy: Relationship to Outcome in Candidemic Pts

- Parkins et al JAC 2007;60:613-18
- Only 30% of 199 pts received empirical therapy
- Empirical therapy was adequate in only 26% of pts
- Adequate empirical therapy associated with reduction in mortality from 46% to 27%
- Empirical therapy with fluconazole most likely to be inadequate
  - wrong dose (23%)
  - resistant organism (77%)
- Accurate and timely ID and AST is important

Parkins et al JAC 2007;60:613-18

Treatment related risk factors for hospital mortality in patients with candidemia



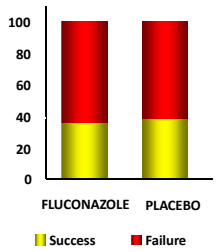
Mortality by number of risk factors

[retained CVC, inadequate initial FLU dose, treatment delayed >48 h]

Labelle et al. Crit Care Med 2008;36:2967.

Empiric Therapy: A Failed Attempt

- 270 ICU patients
- Fluconazole 800 mg vs placebo
- Composite end point for success
  - No fever
  - No invasive fungal infection
  - No discontinuation due to toxicity
  - No need for other antifungals



Schuster et al. *Ann Intern Med*. 2008;149:83-90.

Importance of Empiric AF Therapy and Source Control in Sepsis due to IC

224 pt with sepsis attributed to IC
- delayed (>24h) antifungal treatment
- failure to achieve timely source control
- independently associated with a greater risk of hospital mortality (AOR, 33.75 and 77.40, respectively).

Kollef et al Clin Infect Dis 2012;54:1739-46

Correlation Between 30-Day Crude Mortality and Timing in IM Wards

Timing	Treatment (%) (N=133)	Mortality (%) (N=133)
< 48 h	10 (7.5)	2/10 (20.0)
48-72 h	15 (11.3)	5/15 (33.3)
72-96 h	38 (28.6)	20/38 (52.6)
> 96 h	53 (39.8)	30/53 (56.6)
No therapy	17 (12.8)	12/17 (70.6)

Diagnosing *Candida* Infections: The Dilemma

Early diagnosis is difficult

- Non-specific clinical signs and symptoms
- Invasive diagnostic procedures risky
- Lack of sensitive, minimally invasive assays

Blood Cultures in the Diagnosis of IC

- Presently the "Gold Standard" for diagnosis
  - Insensitive
  - Slow
  - Highly variable performance across systems

Determinants of Blood Culture Positivity for *Candida*

- Inoculum concentration (and volume of blood)
- Species
- Growth rate (CA, CT, CP > CG, CK)
- Antifungal exposure
- Blood culture system and medium
  - Bactec
  - BacT/ALERT
- Duration of incubation
- Aerobic vs anaerobic atmosphere

Sensitivity of Blood Cultures in the Diagnosis of Autopsy-Confirmed Invasive Candidiasis

Study	Patient population	No. episodes	Sensitivity %	Sensitivity n/N
Berenguer, 1993	Autopsy	229	39	90/229
Ness 1989	Heme	7	71	5/7
Singer, 1977	Heme	16	31	5/16
Van Burik, 1998	HSCT	62	52	32/62
Kami, 2002	Heme	91	21	19/91
Thorn, 2010	Mixed	10	50	5/10
Total	Mixed, autopsy	415	38	156/415

Clancy and Ngyuen CID 2013;56:1284-92

Blood Cultures for Detection of IC: Summary

- Sensitivity in diagnosis of IC is poor
- Time to positivity is an issue
- Early empiric/preemptive therapy is key to minimize mortality
- BCs remain at the heart of IC care guidelines, but emerging alternative technologies aimed at complementing the deficiencies of BC, particularly related to improving time-critical diagnostics are essential in limiting mortality and the emergence of antifungal resistance

Rapid Methods for the Identification of *Candida* spp Post-culture

- PNA FISH
- MALDI-TOF MS
- Application to blood cultures and agar-based cultures
- Results within ~1h (or at least same day)

Clinical Prediction Rules: León Rule

- Multicenter retrospective study in Spain
- *Candida* score (rounded)
  - Multifocal colonization: +1
  - Surgery: +1
  - Severe sepsis: +2
  - Total parenteral nutrition: +1
- Performance
  - Score >2.5
    - Relative risk = 7.75
    - Sensitivity = 0.81
- Created and validated with same database

The MSG rule

Specific time frames

LEAST ONE OF THE FOLLOWING:
- ❑Use of antibiotics
- ❑ Presence of a central venous catheter

AND AT LEAST TWO OF THE FOLLOWING:
- ❑ Use of total parenteral nutrition
- ❑ Any type dialysis
- ❑ Any major surgery
- ❑ Pancreatitis
- ❑ Systemic steroids
- ❑ Other systemic immunosuppressive agents

Performance:
Incidence of IC 9.9%, RR 4.4

Ostrosky-Zeichner, et al. EJCMID 2007.

Length of stay as a key risk factor

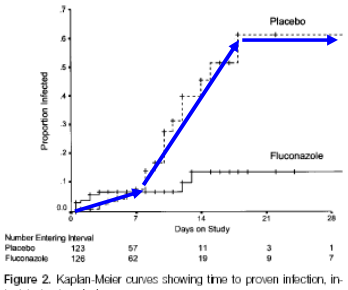


Figure 2. Kaplan-Meier curves showing time to proven infection, intent-to-treat analysis.

Pelz, Ann Surg 2001.

Modified MSG rule

Three key criteria for inclusion (all 3 are necessary):

- **Mechanical ventilation** during days 1-3 of ICU admission.
- **Central venous catheter** during days 1-3 of ICU admission.
- **Broad spectrum antibiotics** (antibiotics with activity against ≥ 2 bacterial classes) on days 1-3 of ICU admission.

AND at least *one* of the following risk factors:

- **Parenteral nutrition** on days 1-3 of ICU admission
- **Any type of dialysis** on days 1-3 of ICU admission.
- **Major surgery** (performed under general anesthesia) within 7 days prior to ICU admission
- **Pancreatitis** (by CT or lipase > 1000u) within 7 days prior to ICU admission.
- **Systemic steroids** (> 1 dose of prednisone equivalent to ≥ 20 mg/day) within 7 days prior to ICU admission.
- **Other immunosuppressive agents** (> 1 dose) within 7 days prior to ICU admission.

MSG Rule Performance

- 20% of ICU patients, 10% incidence of invasive candidiasis, RR > 4
- Incidence increases to almost 20% if traditional and serologic methods are used for diagnosis
- Has been incorporated into a RCT of caspofungin vs placebo (MSG 01) for primary prophylaxis in high risk ICU pts

Candida Colonization

- Colonization index: N sites colonized/N sites tested (positive >0.5; corrected >0.4)
- Leon rule: multifocal *Candida* colonization, TPN, surgery, sepsis

Table 2 Comparison of invasive candidiasis prediction rules

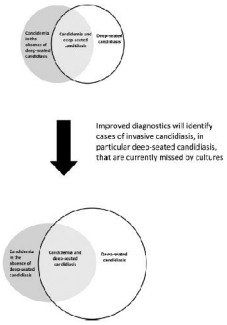
Score, year	Patients (*n*) type of study	ICUs	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)	Threshold
Colonization index, 1994 [46]	29 prospective	1	100	66.6 (43–83)	64.7 (41–83)	100	≥0.5
Dupont score, 2003 [54][a]	57 prospective	1	84	50	67	72	≥3
Candida score, 2006 [39]	1,699 retrospective	73	81 (69–89)	74 (70–77)	24.6 (19–31)	97.4 (95–98)	≥ 3
Candida score, 2009 [55]	1,107 prospective	36	77.6 (65–86)	66.2 (63–69)	13.8 (10–17)	97.7 (96–98)	≥3
Ostrosky rule, 2011 [56]	597 retrospective	6	90 (72–97)	48 (44–52)	6 (4–9)	99 (97–99)	MV + BSA + CVC + other

ICU intensive care unit, *MV* mechanical ventilation, *BSA* broad-spectrum antibiotics, *CVC* central venous catheter
[a] Grade C

Leon C, Ostrosky-Zeichner L, Schuster M. Intensive Care Med 2014; 40:808-19

Non-Culture Based Diagnosis of IC

Figure 1. Impact of nonculture diagnostics on identifying different types of invasive candidiasis. The 3 entities that must be considered when diagnosing invasive candidiasis are shown from left to right in the Venn diagrams. At present, data suggest that the 3 groups are roughly similar in size (top Venn diagram). A reasonable estimate from the literature is that blood cultures are approximately 50% sensitive in diagnosing invasive candidiasis, missing roughly half of the deep-seated candidiasis in the second group and all cases in the third group. Moving from left to right across the groups, the relative impact of nonculture diagnostics on identifying previously unrecognized invasive candidiasis is increased. Nonculture diagnostics, for the most part, will identify new cases of deep-seated candidiasis (bottom Venn diagram), primarily by detecting *Candida* nucleic acid and cellular components that persist in the blood or that are released from deep tissue sites. By identifying previously unrecognized infections, nonculture diagnostics will improve our understanding of the clinical spectrum of invasive candidiasis.



Clancey NJ, Nguyen MH.Clin Infect Dis 2013; 56: 1284-92

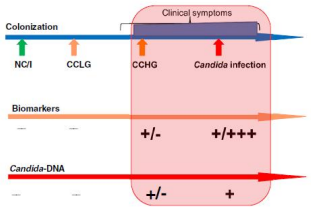


Fig. 2 Interrelation between microbiology, clinical, biomarkers, and *Candida* DNA. *NC/I* no colonized/infected, *CCLG Candida* colonization low grade, *CCHG Candida* colonization high grade

Leon C, Ostrosky-Zeichner L, Schuster M. Intensive Care Med 2014; 40:808-19

Use of *Beta-D-Glucan* Assay to Diagnose Candidemia

Author	Population	Sampling	Sensitivity, %	Specificity, %	PPV,%	NPV, %
Obayashi[a]	Febrile patients	Single	90	100	59	97
Odabasi[b]	AML / MDS	Multiple, 2+	65	96	57	97
Ostrosky-Zeichner[c]	Hospitalized patients	Single	64	92	89	73
Mohr[d]	ICU patients, surveillance	Multiple, 2+	100	63	–	–

PPV, positive predictive value; NPV, negative predictive value.

a. Obayashi et al. *Lancet*. 1995;345:17-20.
b. Odabasi et al. *Clin Infect Dis*. 2004;39:199-205.
c. Ostrosky-Zeichner et al. *Clin Infect Dis*. 2005;41:654-659.
d. Mohr et al. Presented at: 45th ICAAC; Washington, DC. 2005. Abstract M-168.

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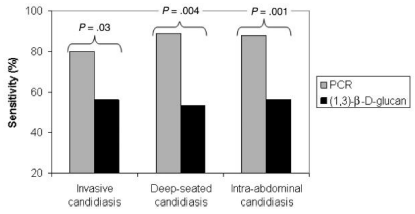


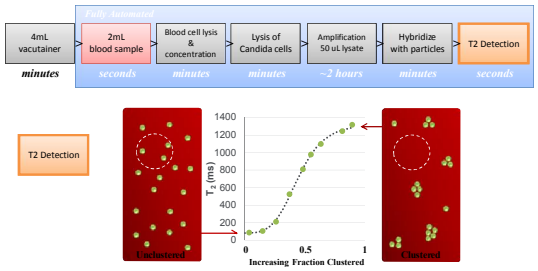
Figure 2. Sensitivity of serum polymerase chain reaction (PCR) and β-D-glucan (BDG) in diagnosing invasive candidiasis. PCR was superior to BDG, particularly among patients with deep-seated candidiasis. Overall, 55 patients with invasive candidiasis were enrolled. At the time of enrollment, 60% (33/55) of patients had deep-seated candidiasis in the absence of positive blood cultures (corresponding to group 3 in Figure 1). Thirty-one percent (17/55) had candidemia without evidence of deep-seated candidiasis (group 1), and 9% (5/55) had both candidemia and deep-seated candidiasis (group 2). Eighty-nine percent (34/38) of deep-seated candidiasis was intra-abdominal infections. Data shown for deep-seated and intra-abdominal candidiasis include patients with and without positive blood cultures. Results for deep-seated candidiasis without positive blood cultures did not differ from the data in the graph. (Adapted from [31].) Abbreviation: PCR, polymerase chain reaction.

Clancey NJ, Nguyen MH.Clin Infect Dis 2013; 56: 1284-92

Non-Culture Based Diagnosis of Invasive Candidiasis

Assay	Sens%	Spec%	NPV	Comments
β-D-Glucan	57-97	56-93	99	Best performance with 2 consecutive + results
Mannan	58	93	??	Best performance when used with antimannan EIA
Antimannan	59	83	??	Best performance when used with mannan EIA
PCR	95	92	??	Multiplex available in SEPTI-FAST® format

T2Dx Instrument Workflow



- Measuring the magnetic properties of the entire water population and not just the target provides breakthrough sensitivity in complex clinical samples

T2Candida vs BDG: Range of Predictive Values

T2 91.1% Sens. 99.4% Spec. from clinical trial
BDG 75% Sens. 85% Spec. from Meta Analysis (CID 2011;52:750-770)

Prevalence of disease	T2 91.1% Sens. 99.4% Spec.		BDG 75% Sens. 85% Spec.	
	PPV	NPV	PPV	NPV
2%	75.0%	99.8%	9.3%	99.4%
3%	81.8%	99.7%	13.7%	99.2%
5%	88.5%	99.6%	21.1%	98.5%
10%	94.8%	99.0%	35.7%	96.8%
30%	98.6%	96.3%	68.2%	88.8%

T2Candida and T2Dx are under review by the FDA and are not cleared for sale

Sepsis and IC

- Basic management principles.
  - timely (within 1h) appropriate antimicrobial therapy
  - hemodynamic resuscitation
  - adequate source control
- Initial empiric combination therapy targeting likely bacterial and/or fungal pathogens recommended to be administered within the first hour of recognition of severe sepsis/septic shock.
- Use of BDG, mannan/anti-mannan assays if available when IC is considered.

Dellinger et al, Crit Care Med 2013; 41:580-637

Surviving Sepsis Campaign

- Median time to initiation of effective antimicrobial therapy in septic shock
  - 5.5 h for bacteria
  - 31.5 h for *Candida* spp.
- Highlights the hesitancy of clinicians to initiate early antifungal therapy

Morrell et al AAC 2005;49:3640-5
Garey et al CID 2006;43:25-31

Candida: Emerging Resistance Issues

- *C. krusei*
  - Fluconazole resistant
- *C. glabrata*
  - Azoles (10-25% of all isolates)
  - Echinocandins (3-10% of all isolates)
  - Azole and echinocandin co-resistance (10-20% of azole-R isolates)
- *C. parapsilosis*
  - Echinocandins (elevated MICs, intrinsic)
  - Azoles (~4% acquired)
- Rare species
  - Intrinsic resistance to azoles and echinocandins
  - *C. guilliermondii*, *C. rugosa*

Pfaller et al. J Clin Microbiol 2007;45:1735-45

What is the Role of Empirical Treatment for Suspected IC in Non-Neutropenic Patients in the ICU?

Empirical antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis and/or culture data from non-sterile sites (Strong recommendation, moderate quality evidence).

Empirical antifungal therapy should be started as soon as possible in patients who have the above risk factors and who have clinical signs of septic shock (Strong recommendation, moderate quality evidence).

Pappas PG et al. IDSA 2016 management guidelines for candidiasis. Clin Infect Dis 2016

Preferred empirical therapy for suspected candidiasis in non-neutropenic patients in the intensive care unit is an echinocandin (caspofungin, loading dose of 70 mg, then 50 mg daily; micafungin, 100 mg daily; anidulafungin, loading dose of 200 mg, then 100 mg daily) (Strong recommendation, moderate quality evidence).

Fluconazole, 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily , is an acceptable alternative for patients who have had no recent azole exposure and are not colonized with azole resistant *Candida* species (Strong recommendation, moderate quality evidence).

Lipid formulation AmB, 3–5 mg/kg daily, is an alternative if there is intolerance to other antifungal agents (Strong recommendation, low quality evidence).

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Recommended duration of empirical therapy for suspected invasive candidiasis in those patients who improve is 2 weeks, the same as for treatment of documented candidemia (Weak recommendation, low quality evidence).

For patients who have no clinical response to empirical antifungal therapy at 4-5 days and who do not have subsequent evidence of invasive candidasis after the start of empirical therapy or have a negative non-culture based diagnostic assay with a high negative predictive value, consideration should be given to stopping antifungal therapy (Strong recommendation, low quality evidence).

Pappas PG et al. IDSA 2016 management guidelines for candidiasis. Clin Infect Dis 2016

Summary and Conclusions

- IC is an important and persistent public health problem.
- Despite AF agents with adequate spectrum and potency, morbidity and mortality remain unacceptably high.
- Current diagnostic tests are too slow and lack optimal sensitivity and specificity.
- The present strategies of empiric and/or preemptive therapy are not working.
  - timing, dose & duration
  - antifungal resistance (*C. glabrata*)
- We must develop rapid diagnostic methods to effectively guide early administration of antifungals