Risk Factors for Candidemia in ICU

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IFI in ICU - Challenges

Magnitude of Problem

- Crude mortality ≈ 50-70% and attributable mortality ~ 40%
- IFI - 85% Candida, 15% other fungi

**Delay in antifungal therapy leads to increased mortality**

- Every hour of delay - 7.5% increase
- 12-24 hour delay – Two fold increase

Early diagnosis is often elusive

- Non-specific manifestations
- Culture based microbial diagnosis is poorly sensitive and slow
- Non-culture based techniques are not yet standardised for ICU patients

ICU Blood Isolates :
Jan 2008 - Dec, 2010 (n = 2299)
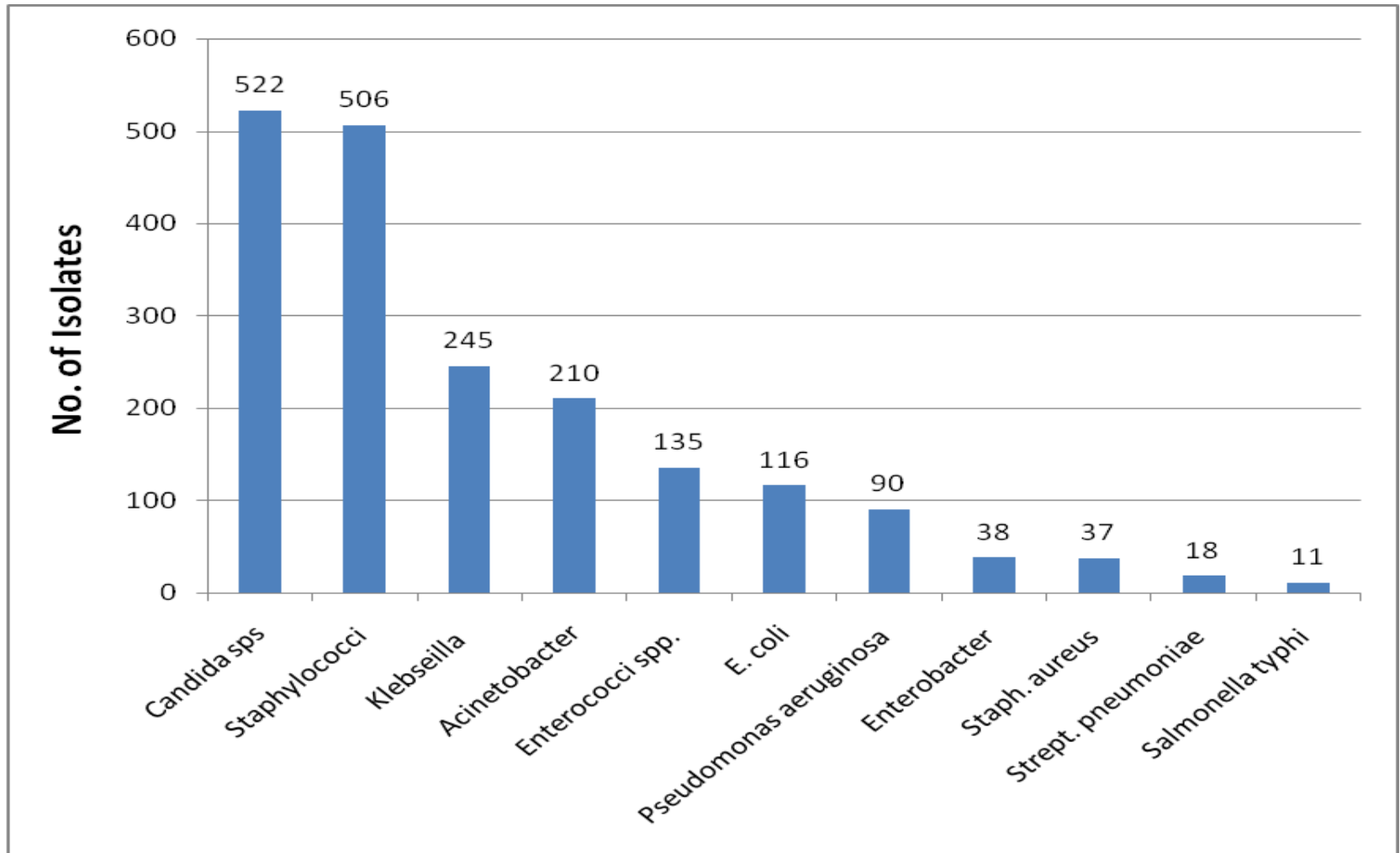
Candidemia is the 4th most common cause of nosocomial blood stream infections accounting for a high mortality

Table 1. Rank order of nosocomial bloodstream pathogens and the associated crude mortality among 49 hospitals throughout the United States.

Rank	Pathogen	No. of isolates	%	Crude mortality (%)
1	Coagulase-negative staphylococci	3,908	31.9	21
2	*Staphylococcus aureus*	1,928	15.7	25
3	Enterococci	1,354	11.1	32
4	*Candida* species	934	7.6	40
5	*Escherichia coli*	700	5.7	24
6	*Klebsiella* species	662	5.4	27
7	*Enterobacter* species	557	4.5	28
8	*Pseudomonas* species	542	4.4	33
9	*Serratia* species	177	1.4	26
10	Viridans streptococci	173	1.4	23

Mortality due to infections in febrile neutropenia

55.276 episodes
Mean costs per episode: US$19,110

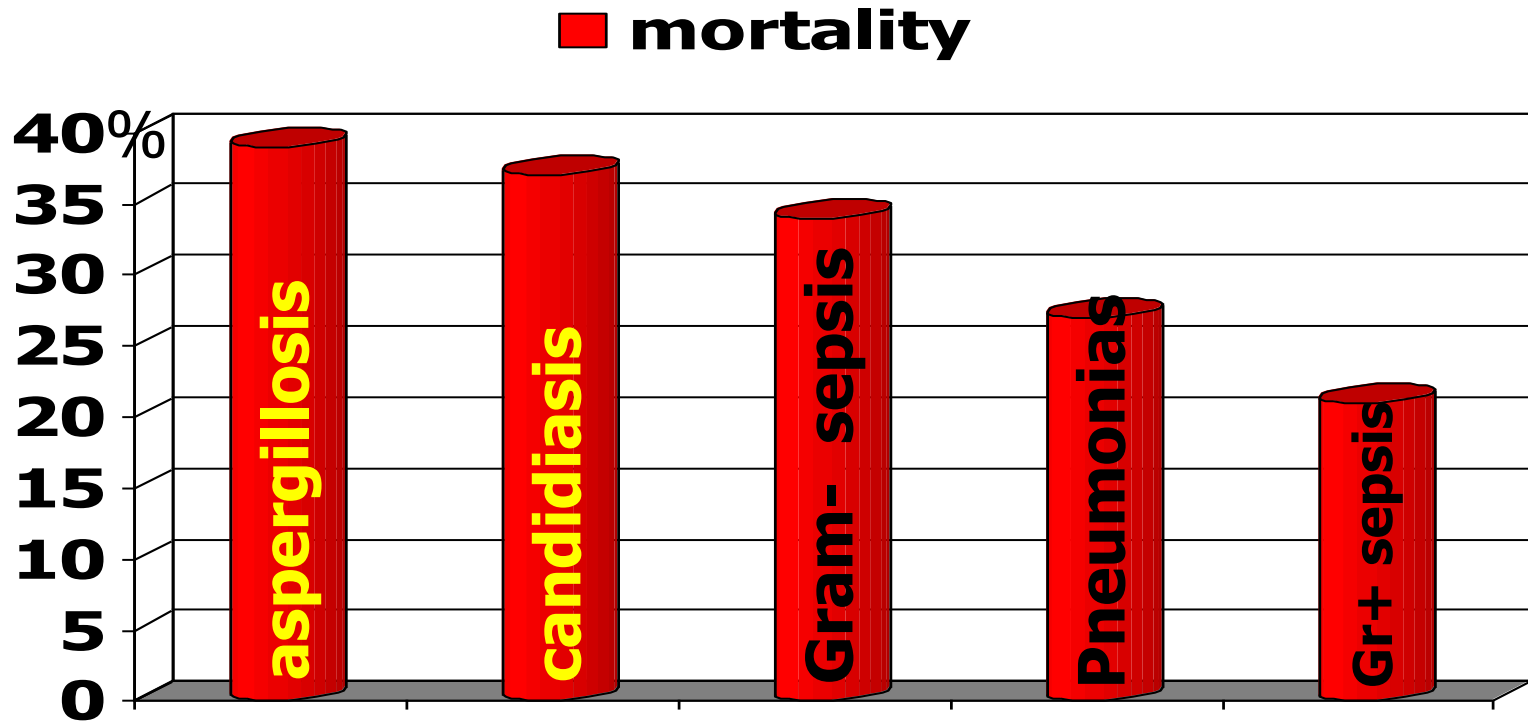*Kuderer et al. Cancer 2006; 106:2258-2266*

Table 1. Risk factors for invasive candidiasis in the intensive care setting

Adult Intensive Care Patients	Neonatal and Pediatric Intensive Care Patients
Prolonged length of stay	In addition to the adult risk factors
High acuity	Prematurity
Diabetes	Low APGAR score
Renal failure	Congenital malformations
Hemodialysis	
Broad-spectrum antibiotics	
Central venous catheter	
Parenteral nutrition	
Immunosuppressive drugs	
Cancer and chemotherapy	
Severe acute pancreatitis	
Candida colonization at multiple sites	
Surgery	
Transplantation	

APGAR, American Pediatric Gross Assessment Record.

Risk Factors

Two main factors predispose to infections with *Candida spp.*:

colonization of skin and mucous membranes with *Candida*

alteration of natural host barriers (wounds, surgery, and insertion of indwelling intravascular and urinary catheters)

Other Risk Factors

Colonization with *Candida also* *induced by profound alteration of the endogenous* **flora resulting from prolonged broad-spectrum antibiotic therapy**

loss of integrity of skin and mucosal barriers - **surgery (especially of the abdominal compartment)**

Total parenteral nutrition, acute renal failure, haemodialysis and treatment with immunosuppressive agents

Dimopoulos G, Karabinis A, Samonis G, Falagas ME: Candidemia in immunocompromised and immunocompetent critically ill patients: a prospective comparative study. *Eur J Clin Microbiol Infect Dis 2007, 26:377-384.*

Candida Score

A prospective, cohort, observational, multicentre study that included
73 medical-surgical ICUs in Spain
'Candida score' was developed

Aim to initiate antifungal therapy early.

An adjusted logit model indicated a *Candida score* of 2.5 or more were 7.5 times more likely to have *Candida infections than patients with a score of less* than 2.5

Leon C et al.: A bedside scoring system ('*Candida score*') *for early antifungal treatment* in nonneutropenic critically ill patients with *Candida colonization. Crit Care Med 2006, 34:730-737.*

Candida Score

Variable
Surgery on ICU admission No   Yes
Total parenteral nutrition No   Yes
Severe sepsis No   Yes
Candida species colonization No   Yes

Score >2.5

will help intensivists select patients who will benefit from early anti-fungal administration.

Ostrosky's Score

Most recently, an analysis of risk factors in 2,890 patients who stayed in the ICU for more than 4 days led to the development and validation of a clinical prediction rule for the early diagnosis of invasive candidiasis in the ICU

a combination of the following factors:
any systemic antibiotic
presence of central venous catheter
and at least two other risk factors, including total parenteral nutrition, major surgery, pancreatitis, any use of steroids and use of immunosuppressive agents.
This prediction rule exhibited a sensitivity of 34%, a specificity of 90%, a positive predictive value of 10% and a negative predictive
value of 97%.

Ostrosky-Zeichner L, Sable C, Sobel J, Alexander BD, Donowitz G, Kan V, Kauffman CA, Kett D, Larsen RA, Morrison V, *et al.:* Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. *Eur J Clin Microbiol Infect Dis 2007,* 26:271-276.

colonization index (CI)

In the past, researchers have tried to predict infection by measuring the Candida colonization of distinct body sites (upper respiratory or stomach samples, urine and wound swabs) divided by the number of sites tested, which became known as the colonization index (CI)
Although the negative predictive value was 100%, the positive predictive value for candidaemia was relatively low (66%) and could only be improved if the CI was corrected by quantitative culture

Pittet D, Monod M, Suter PM et al. Candida colonization and subsequent infections in critically ill surgical patients. Ann Surg 1994; 220: 751–8.
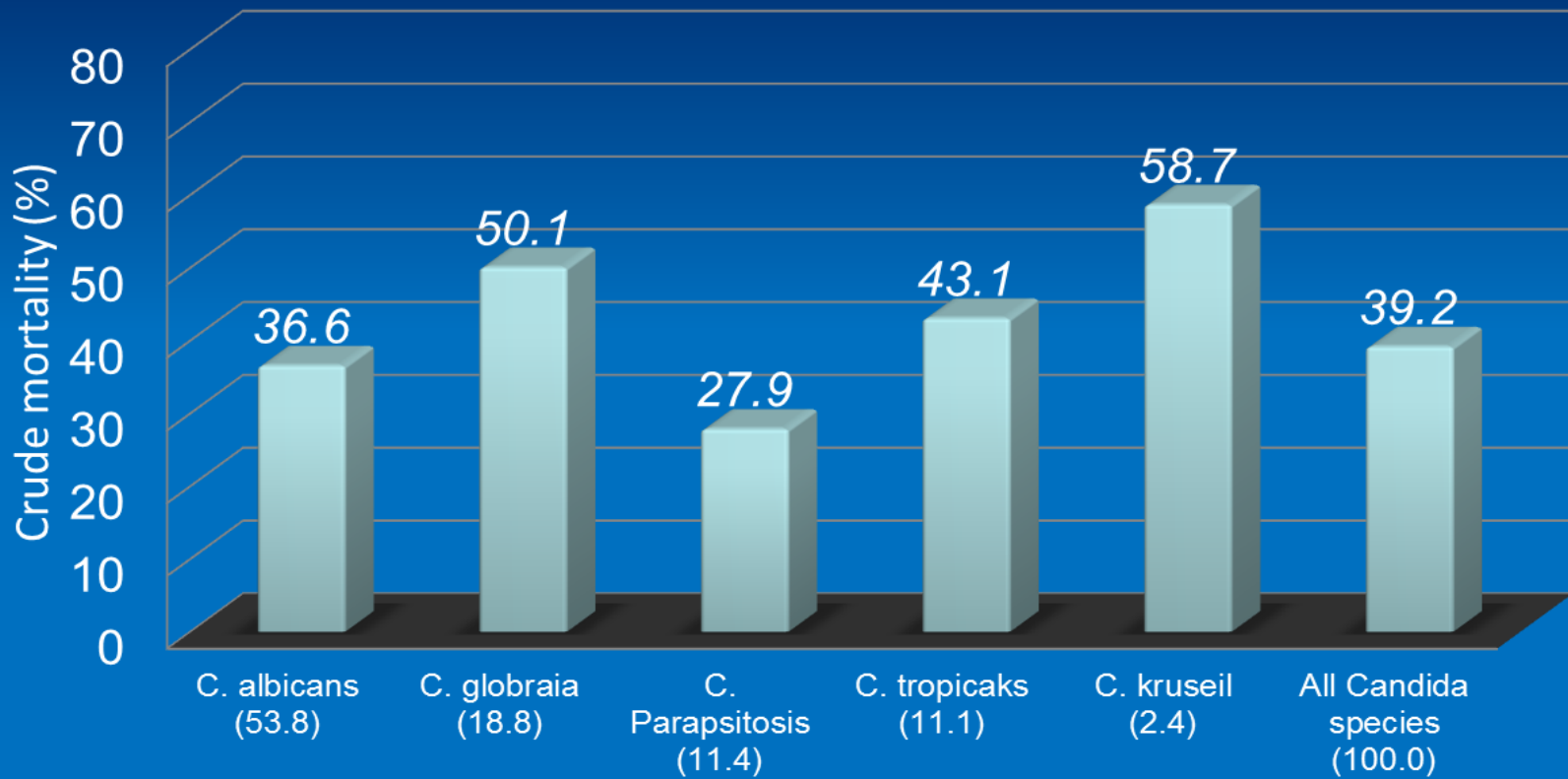
Candidemia

Recent concern has centered around the increasing proportion of candidemia episodes caused by non-*albicans Candida* spp. given their association with fluconazole resistance

Ostrosky-Zeichner L, Pappas P: Invasive candidiasis in the intensive care unit. *Crit Care Med 2006; 34:857–863*
Pfaller MA, Diekema DJ: Epidemiology of invasive candidiasis: A persistent public health problem. *Clin Microbiol Rev 2007; 20:* 133–163

Increasing isolation of non albicans Candida

Candida species (% of isolates)

Crude mortality (%)

- C. albicans (53.8): 36.6
- C. globraia (18.8): 50.1
- C. Parapsitosis (11.4): 27.9
- C. tropicaks (11.1): 43.1
- C. kruseil (2.4): 58.7
- All Candida species (100.0): 39.2

Clin Infect Dis. 2004;39(3):309.

Candidemia in nonneutropenic critically ill patients: Risk factors for non-*albicans Candida* spp.

E. Geoffrey Playford, MBBS, MMed, FRACP, FRCPA; Deborah Marriott, MBBS, FRACP, FRCPA; Quoc Nguyen, BMedSci, MHA; Sharon Chen, PhD, FRACP, FRCPA; David Ellis, PhD; Monica Slavin, MD, FRACP; Tania C. Sorrell, MD, FRACP

Risk Factors for Non Albicans species

A prospective nationwide surveillance of all episodes of candidemia occurring within Australia (the Australian Candidemia Study) was undertaken over a 3-yr period (August 2001 to July 2004)

183 episodes of ICU-acquired candidemia in 183 patients were reported from 37 ICUs.

Candida albicans   111 (62%)
C. glabrata   *32 (17.9%)*
C. parapsilosis   *14 (7.8%)*
C. tropicalis   *10 (5.6%)*
C. krusei   *7 (3.9%)*
C. Dubliniensis   *02 (1.1%)*
unidentified *Candida* spp. 02 (1.1%)

C. curvata, C. famata, and C. lusitaniae one each (0.5%).

Independently significant variables associated with non-albicans candidemia included
prior exposure to systemic antifungal agents
prior gastrointestinal surgical procedures,
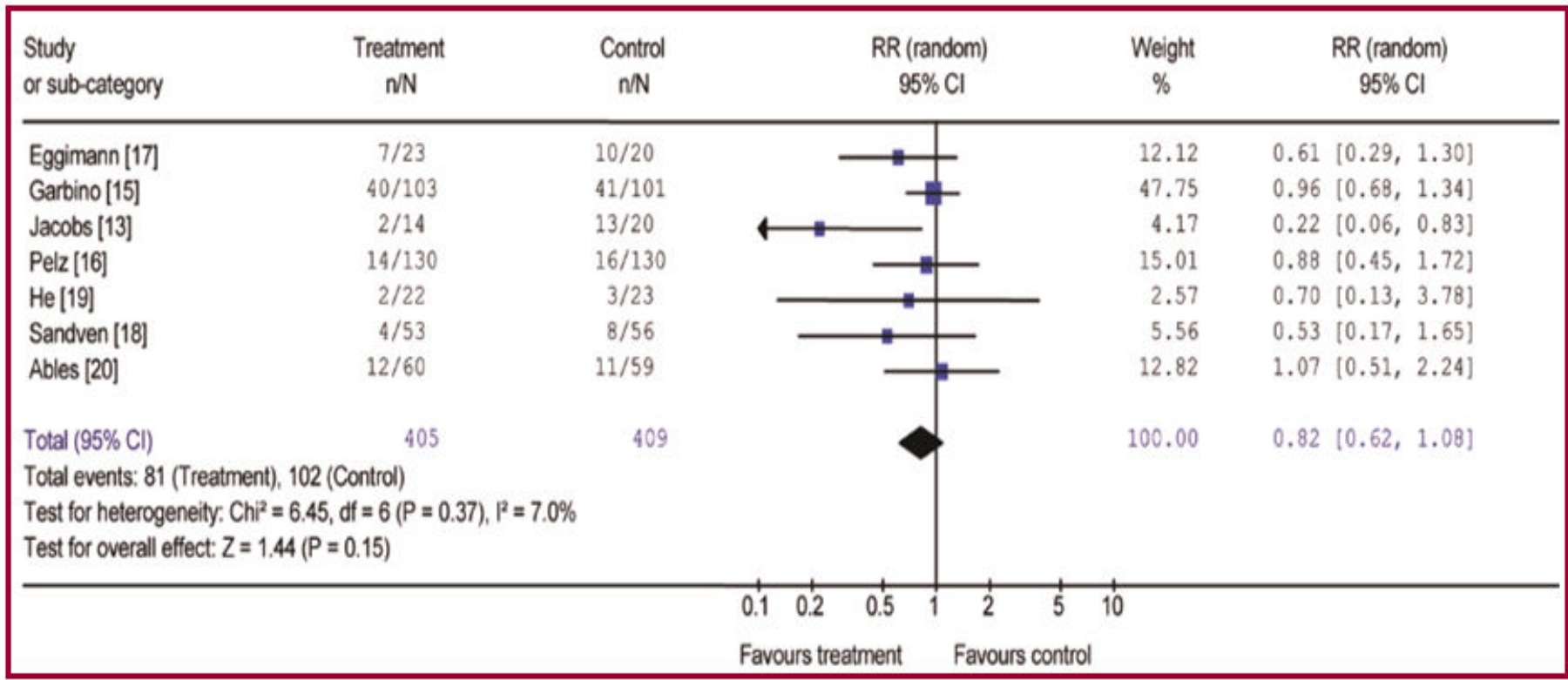**increasing age, and intravenous drug use.**

Identify patients for Empirical Antifungal Therapy

Consider Empirical Antifungal

- **Persistent Fever without obvious source**

- **Fever not responding to antibiotics**

- **Positive serological marker (beta D Glucan)**

- **Candida colonisation of multiples sites in patient at risk of candidemia**

Azole Prophylaxis

No effect on mortality in medical / surgical ICU :

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Eggimann [17]	7/23	10/20		12.12	0.61 [0.29, 1.30]
Garbino [15]	40/103	41/101		47.75	0.96 [0.68, 1.34]
Jacobs [13]	2/14	13/20		4.17	0.22 [0.06, 0.83]
Pelz [16]	14/130	16/130		15.01	0.88 [0.45, 1.72]
He [19]	2/22	3/23		2.57	0.70 [0.13, 3.78]
Sandven [18]	4/53	8/56		5.56	0.53 [0.17, 1.65]
Ables [20]	12/60	11/59		12.82	1.07 [0.51, 2.24]
Total (95% CI)	405	409		100.00	0.82 [0.62, 1.08]

Total events: 81 (Treatment), 102 (Control)
Test for heterogeneity: $Chi^2 = 6.45$, df = 6 (P = 0.37), $I^2 = 7.0\%$
Test for overall effect: Z = 1.44 (P = 0.15)

0.1 0.2   0.5   1   2   5   10

Favours treatment   Favours control

Andrew F. Shorr et al. Fluconazole prophylaxis in critically ill surgical patients:
A meta analysis Crit Care Med 2005 Vol. 33, No. 9

Candidemia
in surgical ICU (SICU)

The burden of fungemia appears particularly high in surgical patients.

A recent prospective, observational study reported that the incidence of fungemia in surgical ICU (SICU) patients approached ten cases per 1,000 admissions
higher risk because of their underlying severity of illness, impaired gastrointestinal mucosal integrity, and frequency of treatment with both broad-spectrum antibiotics and parenteral nutrition

Blumberg HM, Jarvis WR, Soucie JM, et al: Risk factors for candidal bloodstream infections in surgical intensive care unit patients:
The NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. *Clin Infect Dis 2001; 33:177–186*

Indications for Candida Prophylaxis

- **High risk patient**
  - **Neutropenic**
  - **Solid organ transplant**
  - **BMT**
  - **Fluconazole : 400 mg (6 mg/kg) daily**
  - **Posaconazole : 200 mg three times /day**
  - **Echinocandin**

Risk factors for IC

Host factors

- Extremes of age
- Neutropenia and Immunosuppression
- Diabetes and Renal failure
- Higher APACHE II score $\geq$ 20
- Trauma ISS >20 and burn >50%
- Bowel perforation/Disruption of physiological barriers in the digestive tract
- Colonisation of several body sites and Candiduria >10^5 cfu/ml

Non-Specific to support start of prophylactic or pre-emptive treatment without knowing their true value

ICU related Recommendations

USA – IDSA 2009

- Empirical* antifungal therapy should be considered for critically ill patients with risk factors for IC
  - clinical risk factors
  - serologic markers
  - colonisation data - cultures from non-sterile sites

Europe – 2011 Congress of Clinical Microbiology and Infectious Diseases

- Risk factors are not specific
- Prediction rules can be helpful in "ruling out" IC
- Serial ß–glucan measurements may also help with early diagnosis

Pre-emptive antifungal therapy is justified in high risk sub-groups of ICU patients with severe sepsis

SSG Critical Care Medicine 32(11 Suppl):S495-512, 2004

Independent Risk factors for Candidiasis

Study	Design	Odds Ratio - Multivariate	Comments
Candida colonization			
Charles et al (2005)	Prosp Coh	*OR: 18.80;CI:5.21-67.79*	Colonization index
Pelz et al (2001)	Prosp Coh	*OR: 10.64; CI: 1.43-78.74*	CI> 0.50
Pittet et al. (1994)	Prosp Coh	*OR: 4.01; CI: 2.16 – 7.45*	
			Sites other than blood
Antibiotic use			
Wesse-Mayer et al. (1987)	Matc Case Cont	*OR : 1.74; CI: NS*	
Wey et al. (1989)	Matc Case Cont	*OR : 12.50; CI: 2.95 – 52.91*	3-5 agents
Central Venous catheters			
Wey et al. (1989)	Matc Case Cont	*OR : 7.23; CI: NS*	Hickman catheter
Blumberg et al. (2001)	Prosp Coh	*OR: 5.40; CI: 1.20-23.60*	Catheter and prior surgery
Parenteral nutrition			
Pelz et al. (2001)	Prosp Coh	*NS*	
Weese-Mayer et al. (1987)	Matc Case Cont	*NS*	Hyperalimentation with lipids
MacDonald et al. (1998)	Matc Case Cont	*NS*	Hyperalimentation

Study	Design	Odds Ratio - Multivariate	Comments
Surgery Blumberg et al. (2001) Petri etla. (1997)	Prosp Coh Prosp Coh	*OR: 7.30; Cl: 1.00 – 53.80* *NS*	Any type of surgery Abdominal drainage
Renal failure Blumberg et al. (2001) Wey et al. (1989)	Prosp Coh Matc Case Cont	*OR: 3.83; Cl: 2.10-8.30* *NS*	
Mechanical ventilation Wey et al. (1989) Weese-Mayer et al. (1987**)**	Matc Case Cont Matc Case Cont	*NS* *NS*	Duration 1-7 days Tracheal intubation
Length of Stay Wey et al. (1989)	Matc Case Cont	*NS*	
Severity of disease Pelz et al. (2001) Pittet et al. (1994)	Prosp Coh Prosp Coh	*OR : 1.02; Cl: 1.01-1.04* *OR: 1.03; Cl: 1.01-1.05*	APACHE III point APACHE II point

Conclusion

Invasive candidiasis is a serious condition in ICU patients that requires early and appropriate management in order to reduce morbidity and mortality.

The wide use of antifungal prophylaxis or screening is generally not recommended, although it may be of benefit for a highly selective small group of high-risk patients

Conclusion

Dilemma

- Culture based treatment may result in therapy started too late
- Over-interpretation of the clinical risk factors
  - problems and costs associated with needless treatments

Challenge

- To find out the right strategy which balances out the risks and benefits for prophylaxis and pre-emptive treatment based on clinical risk factors, surveillance data and serum/BAL markers

Thank you for your attention