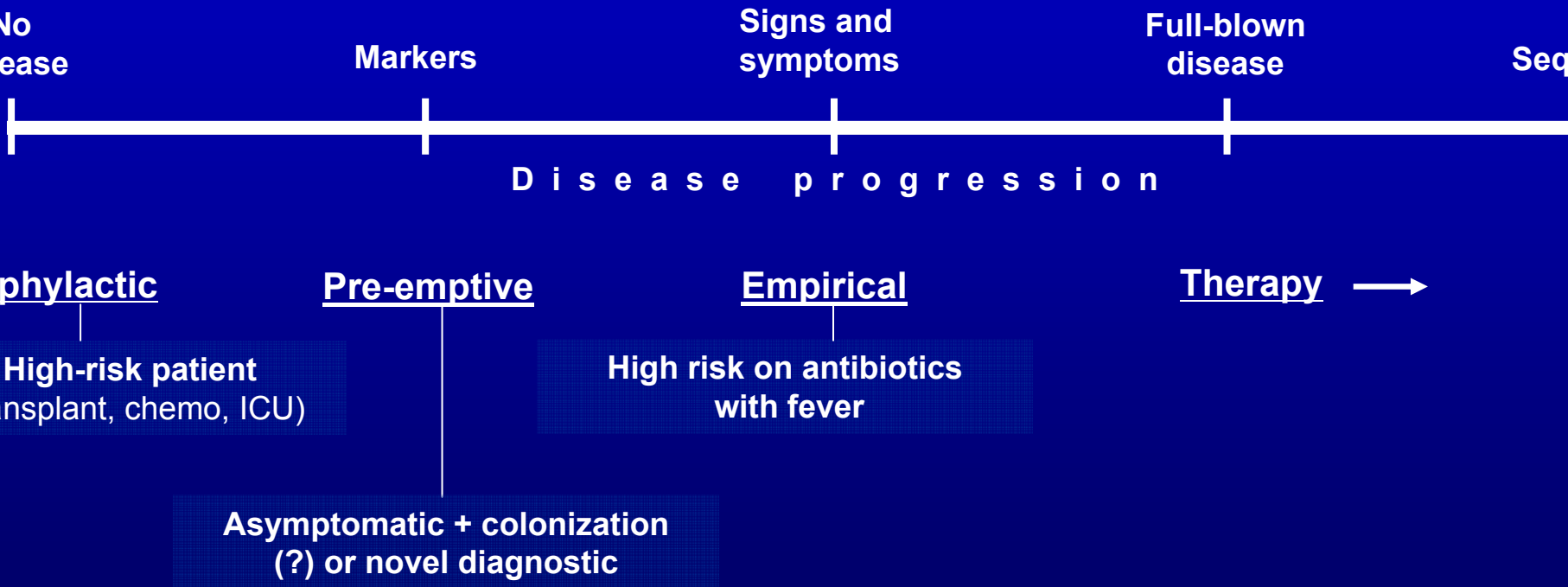


Antifungal Prophylaxis in the Surgical Patient

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Prophylactic, Empirical, or Pre-emptive Therapy



Selective Antifungal Prophylaxis

Not all patients (surgical or SICU) are at the same risk

Not all patients are at **High** risk

Definition of high risk?

- Overall risk of candidiasis ICU ~2%
- High risk ~ $\geq 10\%$

Justification of antifungal prophylaxis benefits > risks and costs

Goals and Objectives of Antifungal Prophylaxis

- ↓ candidemia
- ↓ invasive candidiasis
- ↓ empirical use of antifungals
- ↓ hospital/crude mortality
- ↓ attributable mortality

Goals of Antifungal Prophylaxis

↓ *Candida* colonization
↓ Candiduria

> No

Indications for Antifungal Prophylaxis

Dr Smith (1)	Elective gastrectomy	No
Dr Smith (2)	Acute perforated gastric ulcer	Yes/No
Dr Smith (3)	Missed or delayed diagnosis of perforated GU	Yes/No
Dr Smith (2)	Intraoperative swab, culture positive. Prophylactic? Pre-emptive? Early treatment?	Yes/No
Dr Smith	Post-gastrectomy anastomotic leak – indicated?	Yes/No

Indications for Antifungal Prophylaxis/Therapy

Based upon:

- **Clinical status**
- **Likelihood of invasive candidiasis**
- **Risks of treating**
- **Risks of non-treating**

Indications for Antifungal Prophylaxis/Therapy

- **Past:** Amphotericin B.
Threshold for use: High
- **Present:** Azoles/Echinocandins.
Threshold dropped: Toxicity ↓

Focus on Invasive Candidiasis in Surgical ICU

- Major problem – attributable mortality 40-50%
- ICU's have 10-fold higher incidence than wards
- ↑ incidence
 - Why?
 - Expansion of pool of high risk patients
 - Advanced technologies e.g. vascular catheters
 - i.e. ↑ risk factors

Risk Factors for Invasive Candidiasis in Surgical ICU Patients

- **Prolonged length of stay**
- **High acuity**
- **Diabetes**
- **Renal failure**
- **Hemodialysis**
- **Broad spectrum antibiotics**
- **Central venous catheters**
- **TPN**
- **Immunosuppressive drugs**
- **Severe acute pancreatitis**
- **Recent surgery (transplantation)**
- ***Candida* colonization at multiple sites**

Invasive Candidiasis in Surgical ICU Patients

- Incidence peaks ~day 10 in ICU
- Uncommon before day 8
- *Candida* colonization ↑ after day 8

Invasive Candidiasis in Surgical ICU Patients

Risk factors for death/bad prognosis:

- **Age**
- **APACHE score**
- **Failure to remove central lines**
- **Malnutrition**
- **Candidemia**
- ***Non-albicans Candida* fungemia**
- **Delay in antifungal therapy**

Invasive Candidiasis in the ICU

Autopsy studies suggest **mortality** actually higher because of **undiagnosed** and therefore **untreated** infection

Why **undiagnosed**?

- i. Nonspecific risk factors
- ii. Nonspecific clinical manifestations
- iii. Low sensitivity of microbiological culture
- iv. Unavailability of deep tissue culture because of risks

Invasive Candidiasis in the ICU

Also:

Culture diagnosis **delays** treatment by 2-3 days which contributes to mortality.

Invasive Candidiasis in the ICU

**Groundwork established for anti-*Candida*
prophylactic or pre-emptive or
empirical therapy.**

Invasive Candidiasis in the ICU – Prophylactic Therapy

Role remains controversial

Practiced in some ICU's only – Why?

Several trials but data contradictory – Why?

- Low statistical power**
- Choice of outcomes**

Invasive Candidiasis in the ICU – Prophylaxis Studies

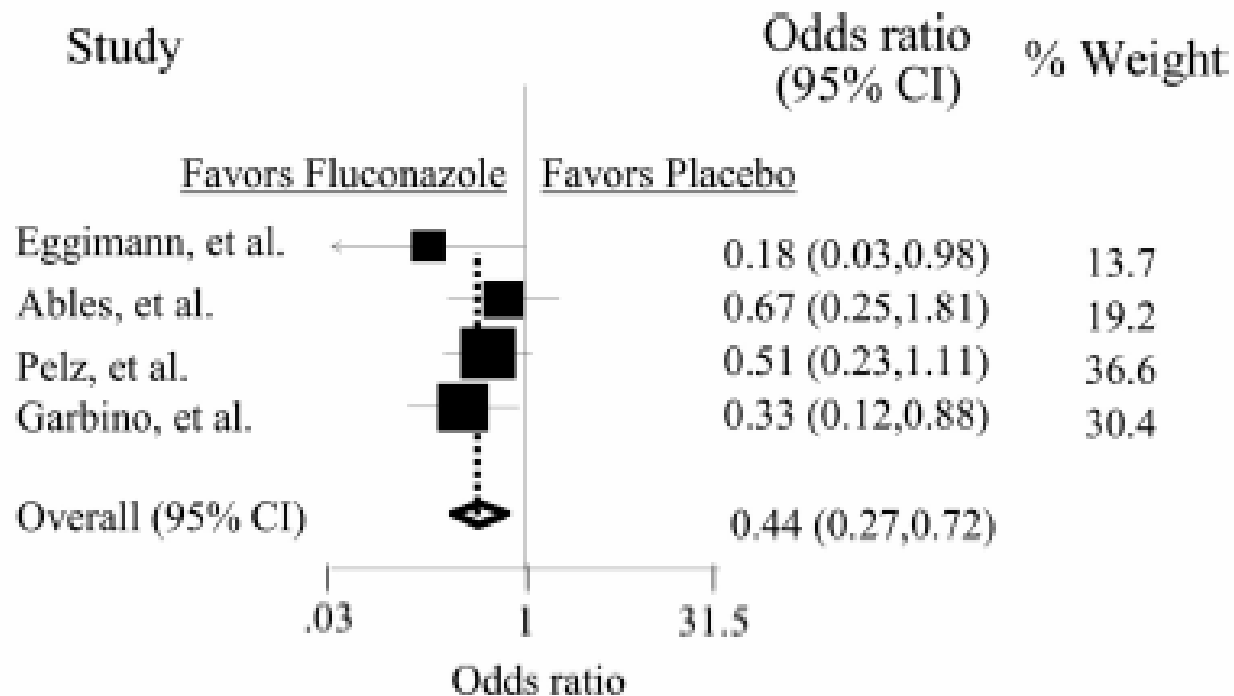


Figure 1. Impact of fluconazole prophylaxis on candidal infections. *CI*, confidence interval.

Studies Demonstrating Clinical Utility of Prophylaxis

Eggiman et al (1999)

Non-neutropenic surgical patients with refractory GI leakage – fluconazole significantly ↓

Garbino et al (2002)

220 mechanically ventilated ICU (at least 3d) Fluconazole and selective gut decontamination → ↓ in superficial + 7% to 3%

Pelz et al (2001) n=260

Surgical ICU patients in single ICU, randomized to 400 fluconazole po - ↓ rate of IC by 55%

Swoboda et al in f/u of Pelz showed substantial benefit from fluconazole prophylaxis and no ↑ resistance

What We Learned From Prophylaxis Studies

Not **ALL** patients in ICU's are at significant **RISK** of invasive candidiasis (IC) and therefore not all ICU patients need prophylaxis.

Problem is identification of **HIGH RISK** patients likely to benefit from antifungal prophylaxis i.e. **SELECTIVE PROPHYLAXIS.**

Who is the High Risk Patient?

Some progress made in identifying patient **RISK** factors

- CVC
- Broad-spectrum antibiotics
- Surgery
- Diabetes
- TPN
- APACHE score
- Hemodialysis
- *Candida* colonization (?)

Needs early/rapid identification

Problem With Risk Factors

- Some still controversial e.g. *Candida* colonization
- **DO NOT CARRY EQUAL RISK**
- As single risk factors-problem of commonality

Fluconazole Prophylaxis for Severe Acute Pancreatitis

- n=46 critically ill (8 years)
- I.C. (intraabdominal) 17/46 (37%)
- *C. albicans* n=15
- Prophylactic fungal infections – 3/18 developed I.C. No impact on mortality.

Anti-*Candida* Prophylaxis in ICU – Identification of Prediction Rule

Recent Study By Ostrosky-Zeichner et al.

- Retrospective chart review and statistical modeling**
- 12 ICU's in US/Brazil**
- 2,890 patients**
- Training sample identified IC in at least 10%**

Anti-*Candida* Prophylaxis in ICU – Identification of Prediction Rule

ICU for > 4 days

+

**{ Any systemic antibiotic on days 1-3 in ICU
or
Presence of CVC on days 1-3 in ICU**

+

At least 2 of:

TPN on days 1-3 in ICU

Dialysis on days 1-3

Major surgery

Pancreatitis

Use of systemic steroids

Use of immunosuppression

} In 7 days prior to ICU

Invasive Candidiasis in ICU – Prediction Rule

- **Overall candidiasis RATE was 9.9% vs. 2.3%**
- **Rule captured 34.1% of cases R.R. 4.36**

Selecting High Risk Patients for Prophylaxis

Paphitou et al (2005)

Retrospective chart review of SICU patients who stayed ≥ 4 days

Any combination – Diabetes

New onset hemodialysis

TPN

Broad spectrum antibiotic

Rate of IC – **16%** versus **5%**

Applied to overwhelming **52%** of patients

Captured 78% of IC

Drawback – Definition of IC (problematic)

Fungal Surveillance Cultures

- Helpful in determining colonization
- IFI/IC > likely in heavily colonized patients
- Surveillance cultures **DO NOT** have a high positive predictive value in broad populations in ICU
- High negative predictive value

Where Are We Today With Regard Antifungal Prophylaxis in ICU??

- Still not the **standard of care**
- Only a (tiny) minority of patients are at high or sufficient risk of IC to benefit from prophylaxis
- We have made some progress in recognizing the higher risk patients viz
 - SICU i.e. surgical patients with **recent** but not all types of surgery
 - Patients likely to spend >3-4 days in ICU i.e. index of severity of illness
 - Constellation of risk factors taken together

Likely Candidiasis for Prophylaxis

- **Fluconazole (oral, parenteral)**
- **Voriconazole?**
- **Posaconazole?**
- **Caspofungin**
- **Micafungin**
- **Anidulafungin**

Next Step

Prospective SICU multicenter study enrolling **appropriate** patients – placebo versus antifungal to confirm efficacy

NOT YET GREEN LIGHT for widespread use.

During such studies – identifying additional diagnostic aide e.g. colonization status, Fungitell[®], PCR to select patients for **prophylaxis** or **pre-emptive** antifungals

Invasive Candidiasis in the ICU

- **Recent introduction of β -glucan diagnostic test (Fungitell®) – not yet widely used**
 - **Sensitivity – 81%**
 - **Specificity – 84.1%**
 - **PPV – 83.8%**
 - **NPV – 75.1%**

Fluconazole Prophylaxis in Critically Surgical Patients

Reviewed 4 RCT comparing fluconazole with placebo
n=626 (2 multicenter)

Fluconazole PPX reduced incidence of fungal infections
p<0.001

However **NO SURVIVAL ADVANTAGE**

No ↓ in candidemia (2.2%)

Adding to **UNCERTAINTY**

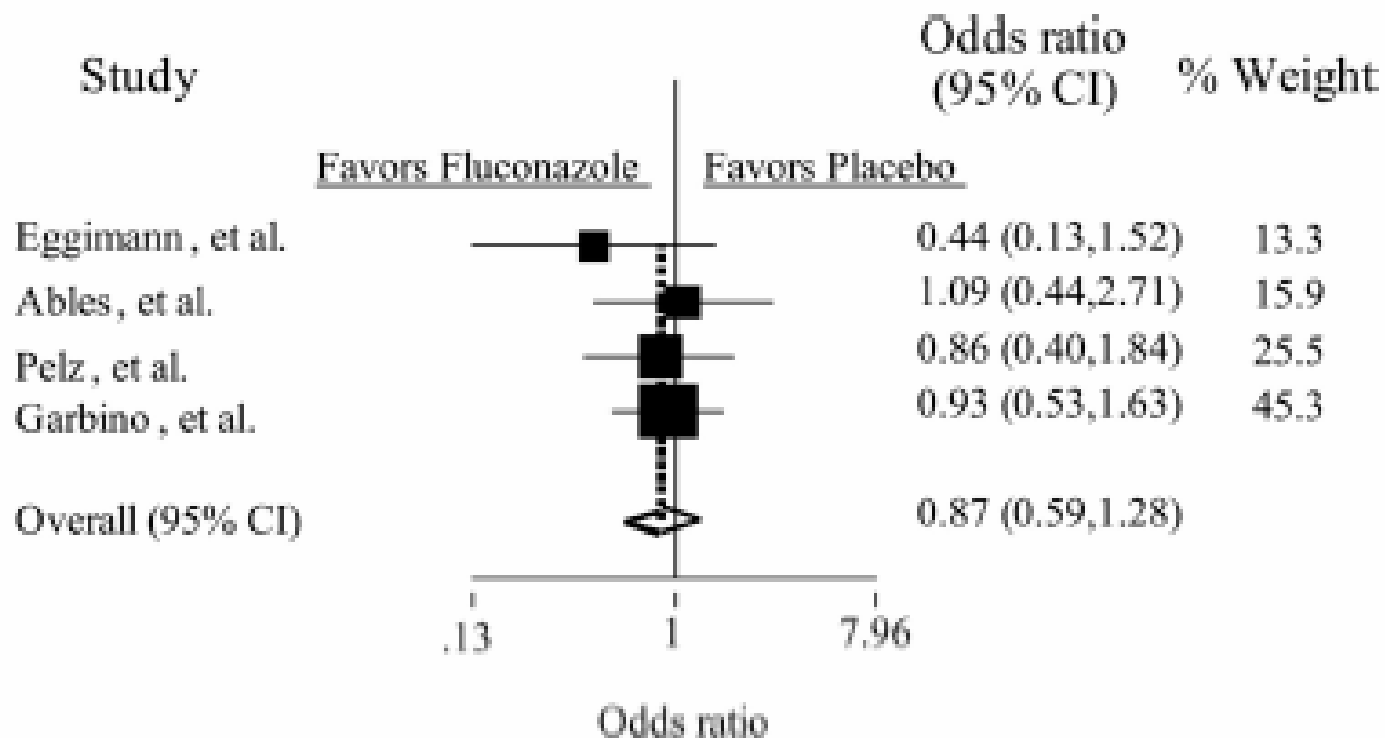


Figure 2. Effect of fluconazole prophylaxis on mortality. *CI*, confidence interval.

Conclusion

- 1. Antifungal prophylaxis has a role in selected high risk patients**
- 2. Although risk factors recognized, we still need next step in rapidly identifying and validating a prediction rule to select high risk patients**
- 3. Choice of antifungals at present – likely to be fluconazole**
- 4. Future? Glucan/or PCR testing?**

Outline of Antifungal Prophylaxis in Intensive Care Unit (ICU) Patients

