



## Грибковые инфекции при трансплантации паренхиматозных органов

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### Fungal infections in solid organ transplantation

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В последние годы количество эпизодов развития кандидоза значительно увеличилось.

Клиническими факторами, способствующими высокому риску развития грибковой инфекции после трансплантации печени, являются:

- ретрансплантация печени,
- релапаротомия в ближайшие несколько суток после трансплантации печени,
- формирование холедохоеюностомы как варианта желчеотводящего анастомоза,
- большой объем компонентов крови, использованных в интраоперационном периоде,
- дисфункция почек,
- фульминантное течение печеночной недостаточности,
- сопутствующая цитомегаловирусная инфекция.

Кроме того, факторами риска развития кандидоза могут быть:

- нейтропения,
- использование центрального венозного катетера,
- колонизация *Candida*,
- использование антибиотиков широкого спектра действия,
- продолжительное время нахождения в палате интенсивной терапии,
- продолжительная искусственная вентиляция легких,
- гемодиализ,

- сахарный диабет,
- использование кортикостероидов,
- иммуносупрессивная терапия,
- мочевого катетер.

Анидулафунгин – это новый эхинокандин, который не взаимодействует с цитохромом р450, и не требует снижения дозы в зависимости от функции почек, печени, веса пациента.

Приведу результаты собственного исследования микробиологической и клинической эффективности анидулафунгина при лечении кандидоза у пациентов после трансплантации печени.

Проведено проспективное, открытое, одноцентровое исследование у пациентов после трансплантации печени с подозрением или диагнозом кандидоза. Анидулафунгин назначали как эмпирическую терапию, как предупреждающую терапию и для лечения подтвержденной кандидемии. Пациентам назначали анидулафунгин внутривенно.

Первичной конечной точкой исследования являлся общий ответ на терапию анидулафунгином, вторичными конечными точками служили эффективность интравенозной терапии, 90-суточная выживаемость пациентов, взаимодействие с иммуносупрессантами.

В исследование были включены 42 пациента.

Виды *Candida* распределились в следующем порядке: *C. albicans* (50 %), *C. glabrata* (12,5 %), *C.*

*parapsilosis* (12,5 %), *C. crusei* (12,5 %), *C. lusitaniae* (6,2 %), *C. tropicalis* (6,2 %), др. (25 %).

Грибы высеивались из желчи, крови, центрального венозного катетера, бронхоальвеолярного смыва, из брюшной полости.

Два пациента (15,4 %) умерли вследствие тяжелого сепсиса и полиорганной недостаточности.

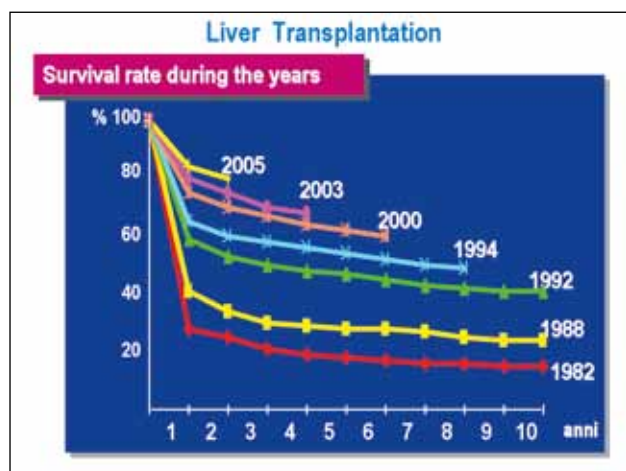
Исследование показало, что анидулафунгин является эффективным, безопасным и хорошо переносимым препаратом.

### FACTORS RELATED WITH THE INCREASE OF NOSOCOMIAL CANDIDA INFECTIONS IN ICU

- Patients with more severe underlying diseases
- More elderly patients
- Immunosuppression
  - Antineoplastic chemo-radio-therapy
  - Transplant surgery
- Increase in survival rate in critical illness  
... .. and prolonged ICU stay

### Frequency of major fungal infections in organ transplant recipients

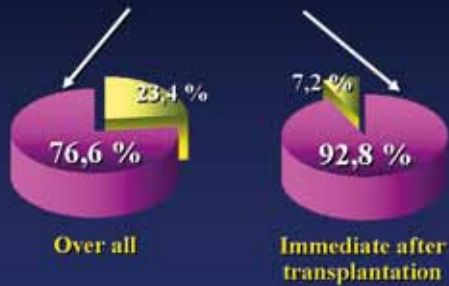
	Incidence of invasive fungal infections*	Infections due to Aspergillus	Infections due to Candida
Renal	1.4 - 14%	0 - 10%	2.0 - 100%
Heart	5 - 21%	77 - 91%	8 - 23%
Liver	7 - 42%	9 - 34%	35 - 91%
Lung and heart-lung	15 - 35%	25 - 50%	43 - 72%
Small-bowel	40 - 59%	0 - 3.6%	80 - 100%
Pancreas	18 - 38%	0 - 3%	97 - 100%



- ### Liver Transplantation
- #### CAUSES of FAILURE
- inadequate surgical technique
  - peri-operative management
  - surgical post-operative complications
  - rejection
  - severe infections
  - organ toxicity
  - organ dysfunction/failure

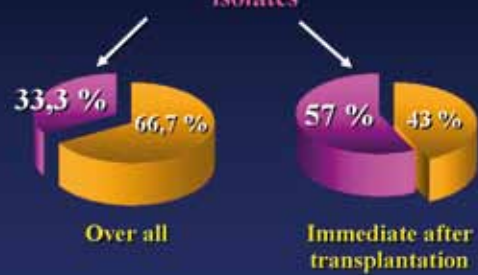
**Bacterial Infections in Liver Transplantation**  
45 consecutive patients

Percentage of bacterial isolates

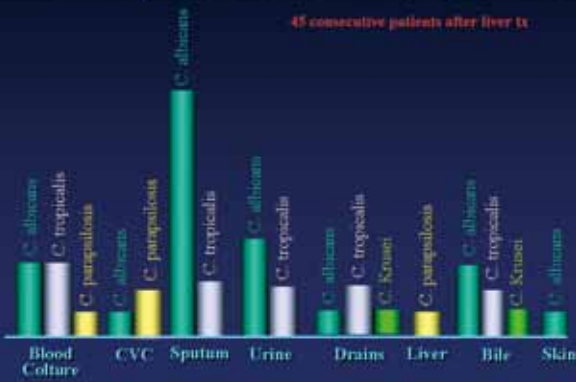


**Fungal Infections in Liver Transplantation**  
45 consecutive patients

Percentage of fungal species isolates

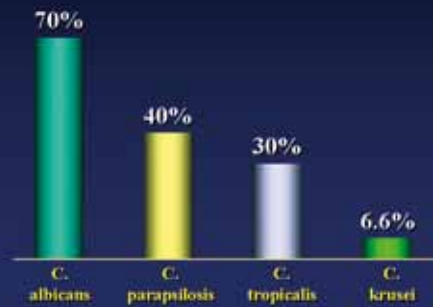


**Proportion of Candida species most commonly recovered from clinical specimens**  
45 consecutive patients after liver tx



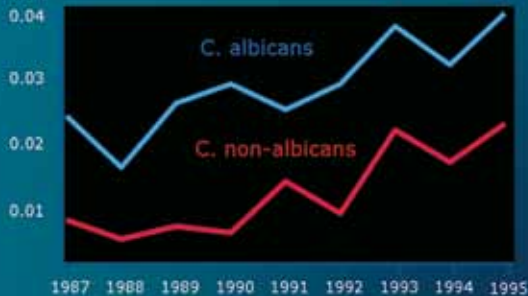
**Fungal Infections in Liver Transplantation**  
45 consecutive patients

Over all proportion of candidal species isolates



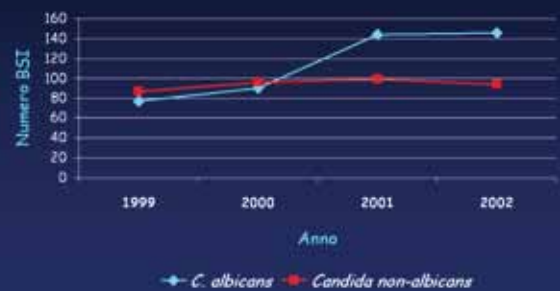
**Candidemia in 5 dutch University Hospitals**

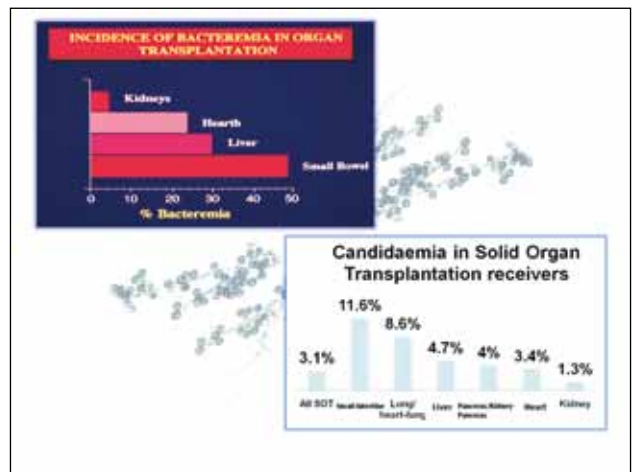
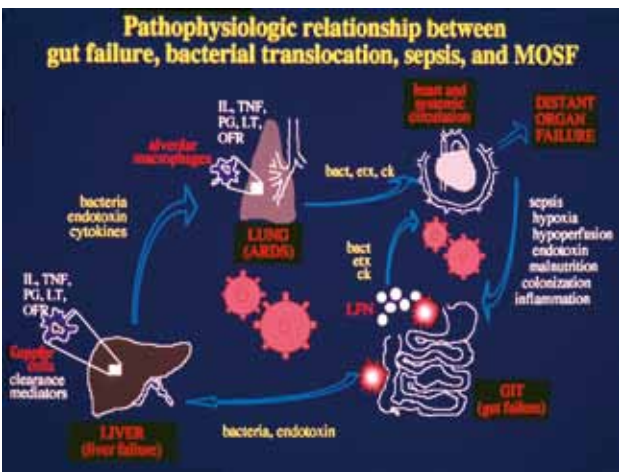
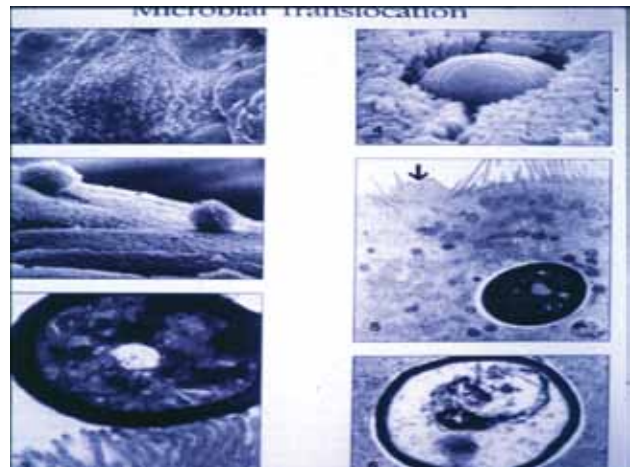
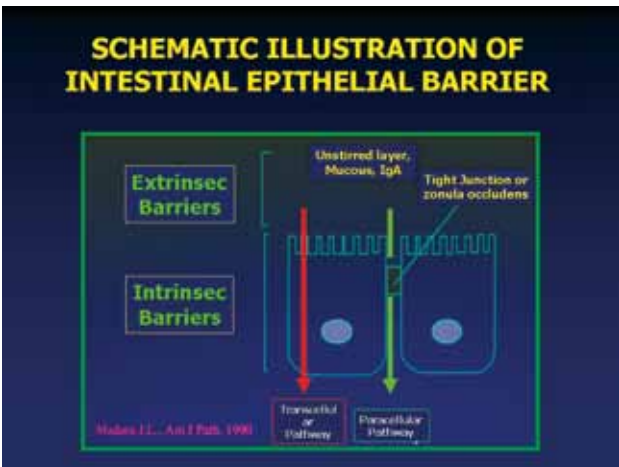
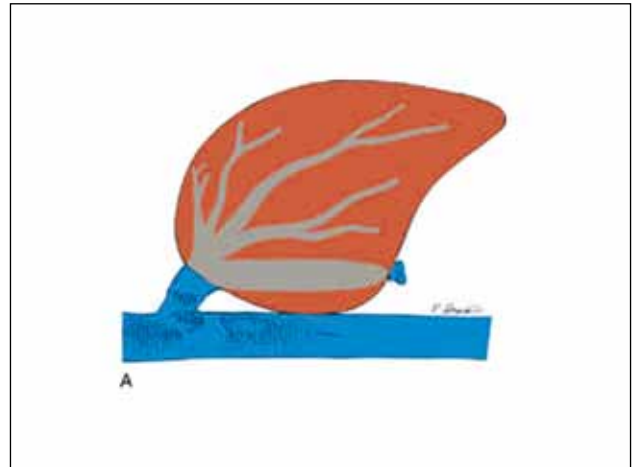
Episodes/1000 patient-days

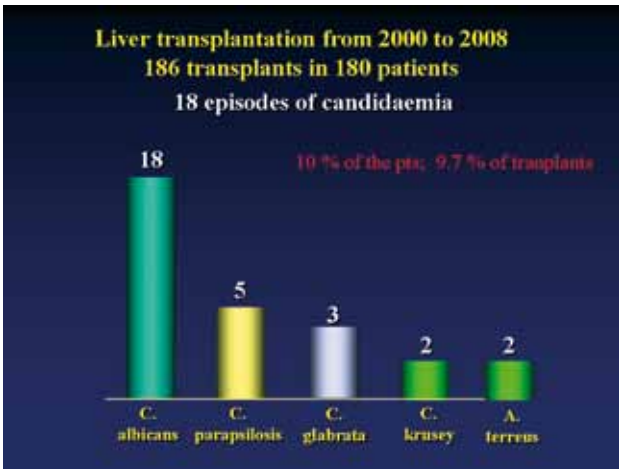


Voss Europ J Clin Microbiol Infect Dis 1996

**Incidence of BSI due to *C. albicans* and *Candida non-albicans* at the Policlinico "A. Gemelli" Hospital - Rome (1999-2002)**





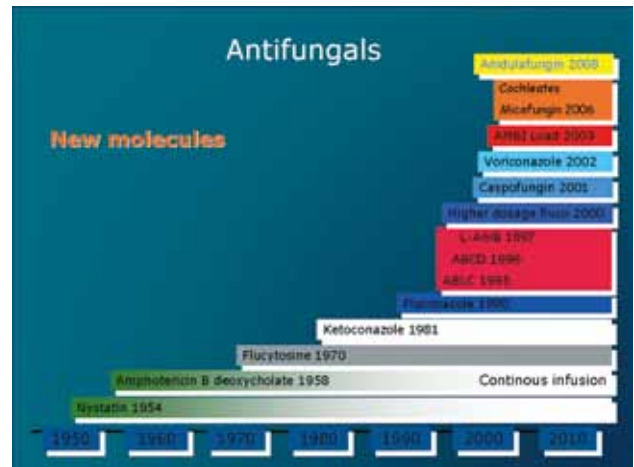


Invasive fungal infection  
 Parenchymal infection  
 Fungal  
 Septic high risk pts  
 Persistent fever despite ant. ther.  
 Septic Shock

**Please, treat!**

Candida in BAL  
 Candiduria  
 Candida in sputum drains  
 Candida in wound  
 Candida in cvc  
 Suppurative phlebitis

**PPP**



**General patterns of susceptibility of *Candida* species.**

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosine	Amphotericin B	Candins
<i>Candida albicans</i>	S	S	S	S	S	S	S
<i>Candida tropicalis</i>	S	S	S	S	S	S	S
<i>Candida parapsilosis</i>	S	S	S	S	S	S	S to R*
<i>Candida glabrata</i>	S-OD to R	S-OD to R	S-OD to R	S-OD to R	S	S to I	S
<i>Candida krusei</i>	R	S-OD to R	S	S	I to R	S to I	S
<i>Candida lusitanae</i>	S	S	S	S	S	S to R	S

**NOTE:** I, intermediately susceptible; R, resistant; S, susceptible; S-OD, susceptible dose-dependent.  
 \* Echinocandin resistance among *C. parapsilosis* isolates is uncommon.

**IDSA GUIDELINES**  
 Clinical Infectious Diseases 2009; 48:503-25

## Echinocandins

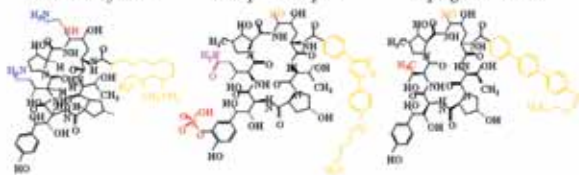
- Only intravenously
- Fungicidal
- 3 molecules
  - Caspofungin
  - Anidulafungin
  - Micafungin
- Different metabolisms

## Echinocandins

**Caspofungin**  
*Glarea flocyrenis*

**Micafungin**  
*Coleophoma cesperti*

**Anidulafungin**  
*Aspergillus nidulans*



- Side chains are key determinants of lipophilicity, solubility, antifungal activity, and toxicity

Adapted from Micafungin US Prescribing Information, Anidulafungin US Prescribing Information, Caspofungin US Prescribing Information, Collins M, Isonoe KJ, Arora R, et al. Antimicrob Agents Chemother 2004;48:471-487, DeBorja W et al. J Med Chem 2002;45:2271-2280

## Pharmacology: Metabolism, Elimination, Bioavailability, and Protein Binding

	Caspofungin	Micafungin	Anidulafungin
<b>Metabolism</b>	Hepatic metabolism by hydrolysis and N-acetylation Spontaneous nonhepatic chemical degradation	Hepatic metabolism by acyltransferase and catechol-O-methyltransferase	Nonhepatic chemical degradation
<b>Elimination/excretion</b>	Urine 41% Feces 34%	Urine + Feces 82.5% Feces 71%	Urine <3% Feces <10%
<b>Protein Binding</b>	97%	>99%	>99%
<b>Oral Bioavailability</b>	<5%	<5%	<5%
<b>Dialyzable</b>	No	No	No

Adapted from Micafungin US Prescribing Information, Anidulafungin US Prescribing Information, Caspofungin US Prescribing Information, Collins M, Isonoe KJ, Arora R, et al. Clin Infect Dis 2004;41:226-230

## In Vitro Susceptibility of Invasive Isolates of *Candida* spp. to Anidulafungin, Caspofungin, and Micafungin: Six Years of Global Surveillance<sup>7</sup>

TABLE 2. In vitro susceptibility of 3,241 clinical isolates of *Candida* spp. to anidulafungin, caspofungin, and micafungin

Species	No. of isolates tested	Antifungal used	Percentage of isolates susceptible to a 100 µg/ml agent (%)											
			0.001	0.002	0.004	0.008	0.012	0.016	0.024	0.032	0.048	0.064	0.096	
<i>C. albicans</i>	2,560	Anidulafungin	92.2	92.2	92.2	92.4	99.1	99.2	99.2	99.4	99.6	99.6	99.6	99.6
		Caspofungin	2.7	26.7	74.1	97.4	99.1	99.2	99.2	99.2	99.2	99.2	99.2	99.2
		Micafungin	10.4	69.6	76.2	92.1	99.1	99.2	99.2	99.2	99.2	99.2	99.2	99.2
<i>C. parapsilosis</i>	750	Anidulafungin	0.1	0.7	0.7	0.5	4.8	4.8	4.1	14.4	27.9	32.7	39.9	49.9
		Caspofungin	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
		Micafungin	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
<i>C. glabrata</i>	747	Anidulafungin	74.9	74.9	62.4	62.2	66.4	66.4	66.4	66.4	66.4	66.4	66.4	66.4
		Caspofungin	7.0	10.2	40.0	55.1	66.2	66.2	66.2	66.2	66.2	66.2	66.2	66.2
		Micafungin	12.7	10.4	40.0	55.1	66.2	66.2	66.2	66.2	66.2	66.2	66.2	66.2
<i>C. tropicalis</i>	407	Anidulafungin	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
		Caspofungin	0.3	10.8	76.7	95.8	99.0	99.7	99.7	99.8	99.8	99.8	99.8	99.8
		Micafungin	0.9	10.1	77.4	95.8	99.0	99.7	99.7	99.8	99.8	99.8	99.8	99.8
<i>C. krusei</i>	136	Anidulafungin	2.9	47.0	66.2	66.2	66.2	66.2	66.2	66.2	66.2	66.2	66.2	66.2
		Caspofungin	6.7	10.7	10.7	10.7	10.7	10.7	10.7	10.7	10.7	10.7	10.7	10.7
		Micafungin	2.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2	11.2
Total	5,240	Anidulafungin	1.7	21.1	48.9	72.8	92.0	92.0	92.0	92.0	92.0	92.0	92.0	92.0
		Caspofungin	2.2	19.7	74.4	79.6	94.9	94.9	94.9	94.9	94.9	94.9	94.9	94.9
		Micafungin	6.6	49.9	74.4	81.9	91.1	91.1	91.1	91.1	91.1	91.1	91.1	91.1

\*Values corresponding to MIC is in bold or blue 90% of isolates are classified as being in bold type

Pfaller et al. JCM 2008

### Summary of recommendations for the treatment of candidiasis.

#### ANTIFUNGAL PROPHYLAXIS FOR SOLID-ORGAN TRANSPLANT RECIPIENTS, ICU PATIENTS AT RISK OF CANDIDIASIS

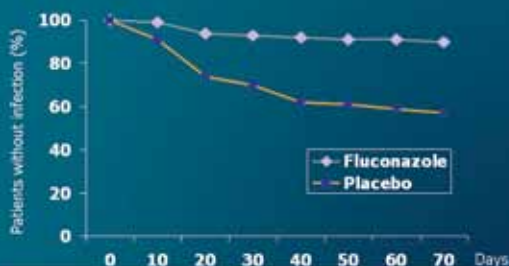
For solid-organ transplant recipients, fluconazole at a dosage of 200–400 mg (3–6 mg/kg) daily or LAmB at a dosage of 1–2 mg/kg daily, each for at least 7–14 days, is recommended as postoperative prophylaxis for high-risk liver (A-I), pancreas (B-II), and small bowel (B-III) transplant recipients.

For ICU patients, fluconazole at a dosage of 400 mg (6 mg/kg) daily is recommended for high-risk patients in adult units with a high incidence of invasive candidiasis (B-I).

IOSA GUIDELINES

Clinical Infectious Diseases 2009;48:503–35

## Studies: Liver Transplantation Prophylactic Fluconazole vs. Placebo



	0	10	20	30	40	50	60	70
Fluconazole	108	107	102	100	99	98	98	97
Placebo	104	95	77	73	64	63	61	59

Winston Ann Intern Med 1999;131:729

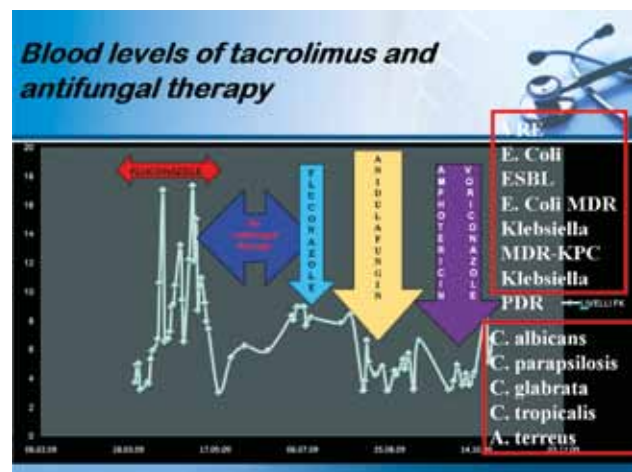
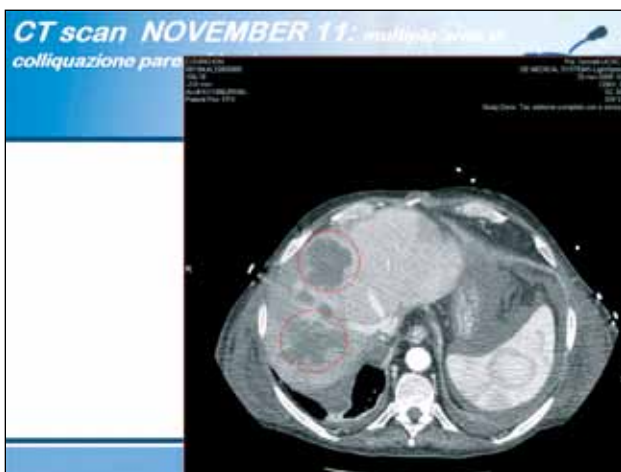
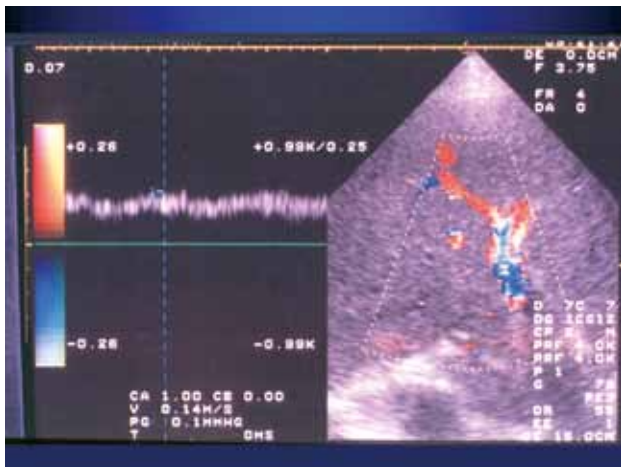


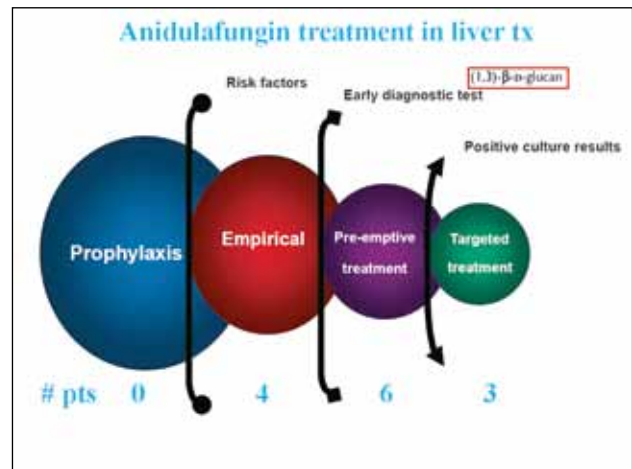
### IMPACT OF CANDIDA INFECTIONS ON MORBIDITY AND MORTALITY

	Mortality
Candida endophthalmitis	40-80% (Brooks '89, Menezes '94)
Candidemia	25-60% (Horn, 1985, Pittet 1993)
Directly attributable to Candidemia	38% (Wey 1988)

**EPIC study:**

6%	Candidemia alone
25%	fungi + Proteus
100%	fungi + Morganella or Providencia spp.





**Personal experience with Anidulafungin**  
 Baseline characteristics of the patients

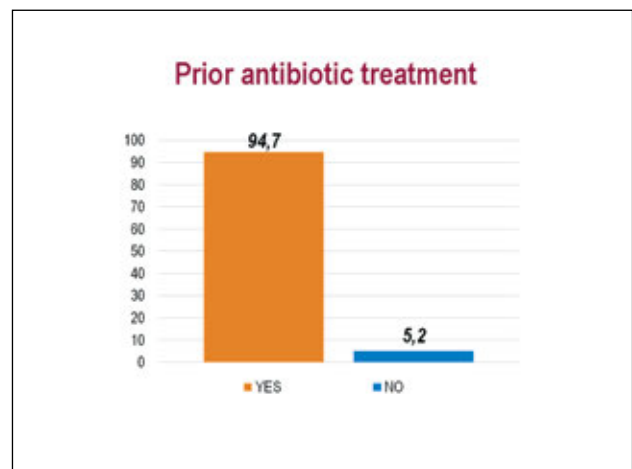
Anidulafungin (N=13)	
Male, n (%)	9 (69.2%)
Race, n (%)	
White	13(100%)
Age at enrollment (years) (mean ± SD)	48.7 ± 20.4
Range (years)	42-78
Patients aged ≥65 years, n (%)	5 (33.3%)
Pretreatment APACHE II score (mean ± SD)	15 ± 8.0
Percentages of patients with APACHE II score:	
<5	0
5-<10	32.9
10-<15	43.9
15-<20	9.9
>20	4.5

**Ophthalmoscopy**

- An OPHTHALMOSCOPY (*fundus oculi*) was taken to exclude intra-ocular Candida localization

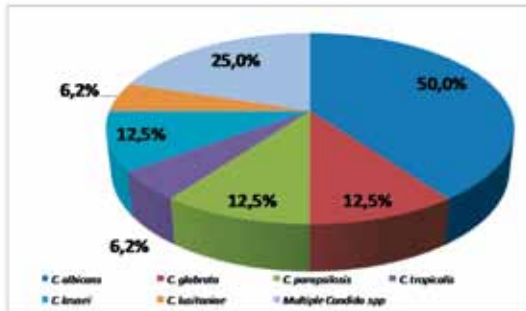
**Anatomical site of infection**

Site	Patients	%
Biliary tract	7	53.8
Colon	3	23.1
CVC	2	15.4
BAL	2	15.4
Pancreas	2	13.3
Peritoneum	1	7.7
Other	1	7.7





Distribution of Candida species (n=13 pts; 16 isolates)



### Adverse Events

ADVERSE EVENT	N° (%)
Nausea	2 (13.3%)
Vomiting	1 (6.7%)
Diarrhea	0
Thrombocytopenia	0
Phlebitis	0
Rash	0
Infection	0
↑ Bilirubinemia	1 (6.7%)
↑ ALT	1 (6.7%)
↑ AST	1 (6.7%)

### Tacrolimus plasma levels (Pt 5 N.G.)



### Conclusion

- Epidemiology and pathophysiology
  - Increased rate of non albicans
- Diagnosis
  - Remains difficult
- The molecules
  - Echinocandins have a prominent place
- Available guidelines
  - Association?





The E. Drouhet Lecture  
**Antifungal vaccines**

Prof. Antonio Cassone has proposed a revolutionary approach for protecting immunocompromised patients even against multiple mycoses with a single, well-defined  $\beta$ -glucan-protein conjugate vaccine.

The realization that fungicidal antibodies may be protective against most major fungal pathogens inspires the paradigm shift that, in analogy with bacteria and viruses, antifungal vaccine efficacy may not require cellular or other arms of the immune system.



Gabriele Spanga  
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