



**Agorà penitenziaria 2016**  
Roma, 16 Settembre, 2016



# **Le micosi invasive**

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**Università "La Sapienza"**

**Roma**

# Mario Venditti

## disclosures

### ■ Research grants

- Pfizer, Novartis, MSD,

### ■ Advisor/consultant

- Pfizer, MSD, Angelini, Gilead, Sanofi

### ■ Speaker/chairman

- Astra Zeneca, Astellas, Pfizer, MSD, Gilead, Zambon, Novartis

# Evoluzione della patologia fungina nel tempo

## prima del 1960:

- micosi endemiche: criptococcosi, istoplasmosi, coccidiomicosi, blastomicosi.

## 1960- 1980;

- micosi invasive in oncoematologia:  
11

candidosi invasiva, epatite focale da candida, aspergillosi, zigomicosi, fusariosi, tricosporonosi etc

## 1980- 2000:

- micosi su dispositivi impiantati:  
candidemie, candidosi invasiva, aspergillosi

1960-80

2000-

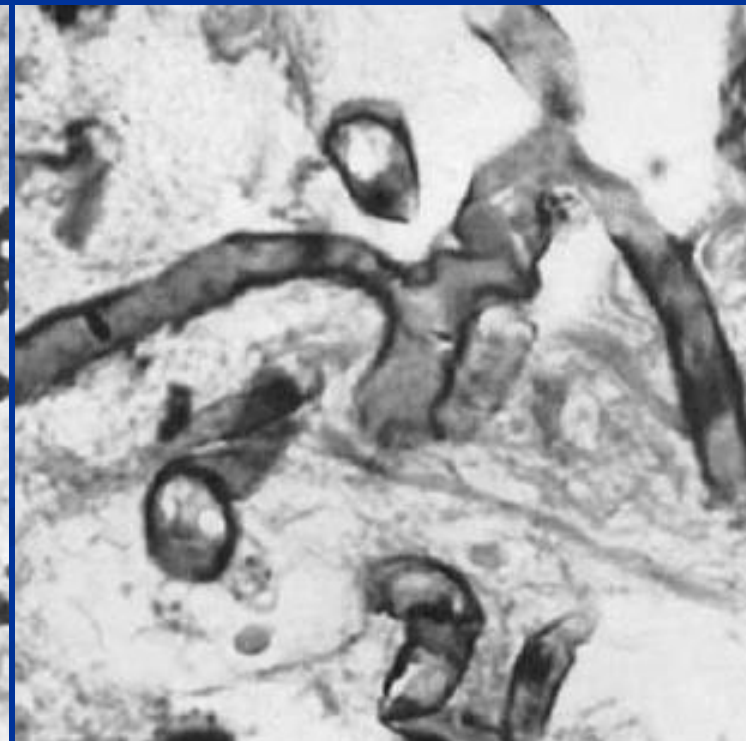
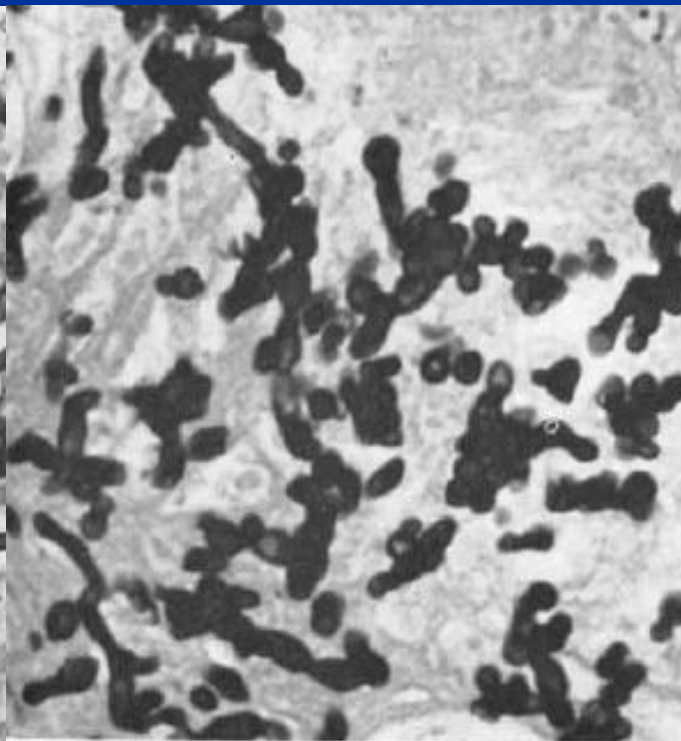
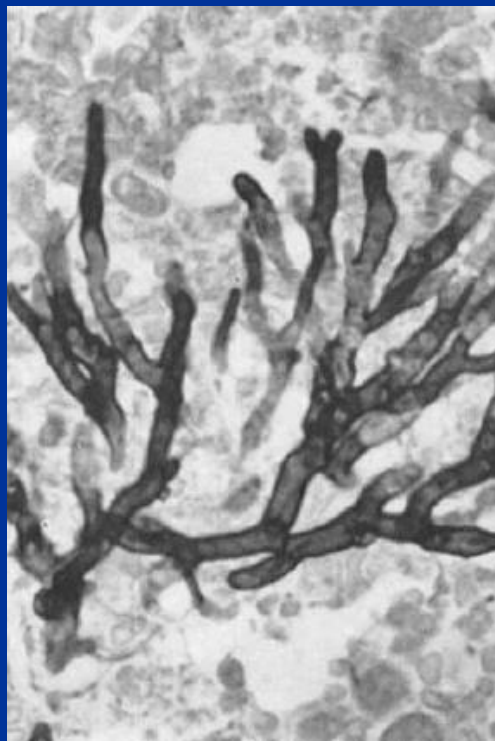
# PULMONARY COMPLICATIONS OF ACUTE LEUKEMIA

GERALD P. BODEY, MD, RALPH D. POWELL, JR., MD, EVAN M. HERSH, MD,  
ARLENE YETERIAN, BS, AND EMIL J FREIREICH, MD

CANCER *June* 1966

The lungs of 50 consecutive autopsied cases of acute leukemia were studied and cultures were obtained from 36. Thirty-one patients had major pulmonary lesions. Most of these were not recognized antemortem. Infection was the most common pulmonary complication. Pulmonary disease was present in 95% of

rhage was higher in patients with severe thrombocytopenia. Thirty-one major and 29 minor pulmonary infections were found in 40 of the patients. Many of these were unrecognized clinically and the offending organism was seldom isolated antemortem. The most frequently identified pathogens were *Pseudomonas* sp., *Candida* sp., and *Aspergillus* sp.





# Funghi filamentosi non *Aspergillus* causa di infezione

Douglas AP et al *Clin Microbiol Infect* 2016

## Famiglia

## specie emergenti

### - Mucormycetes

*Mucor, Rhizopus*  
& *Lichtheimia*

*Apophysomyces*

*Saksenaea, Syncephalastrum*

### - Hyalohyphomycetes

*Fusarium, Schedosporium*

Simil IPA in leucemia & BMT

Simil ABPA

Simil IPA in MGC & fibrosi cistica

Infezioni su corpi estranei

### - “Funghi neri”

*Alternaria, Bipolaris*  
*Cladophialophora*  
*Exophiala*

Simil IPA nell'immunodepresso e nel  
TOS

# *Candida* colonization and systemic infection in neutropenic patients. A retrospective study.

Martino P, Girmenia C, Venditti M, Micozzi A, Santilli S, Burgio V, Mandelli F  
*Cancer*64(10):2030-4;1989

## Colonizzazione da *Candida*

- Siti multipli non contigui
- Sito unico
- Non documentata

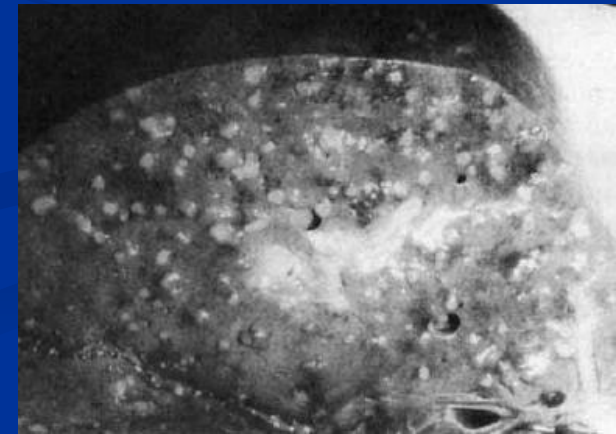
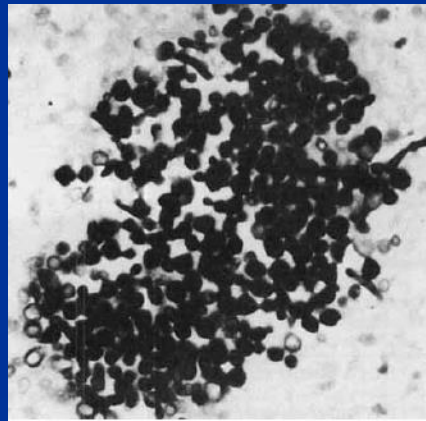
## Candidiasi sistemica\*

18/56(32%) \* §

2/170(1.2%)\*

1/198(0.5%) §

\* § :  $P < 0.00001$



# Fluconazole treatment of catheter-related right-sided endocarditis caused by *Candida albicans* and associated with endophthalmitis and folliculitis

Venditti M, Micozzi A, Cassone A, & Martino P *Clin Infect Dis.* 1992 Feb;14(2):422-6.

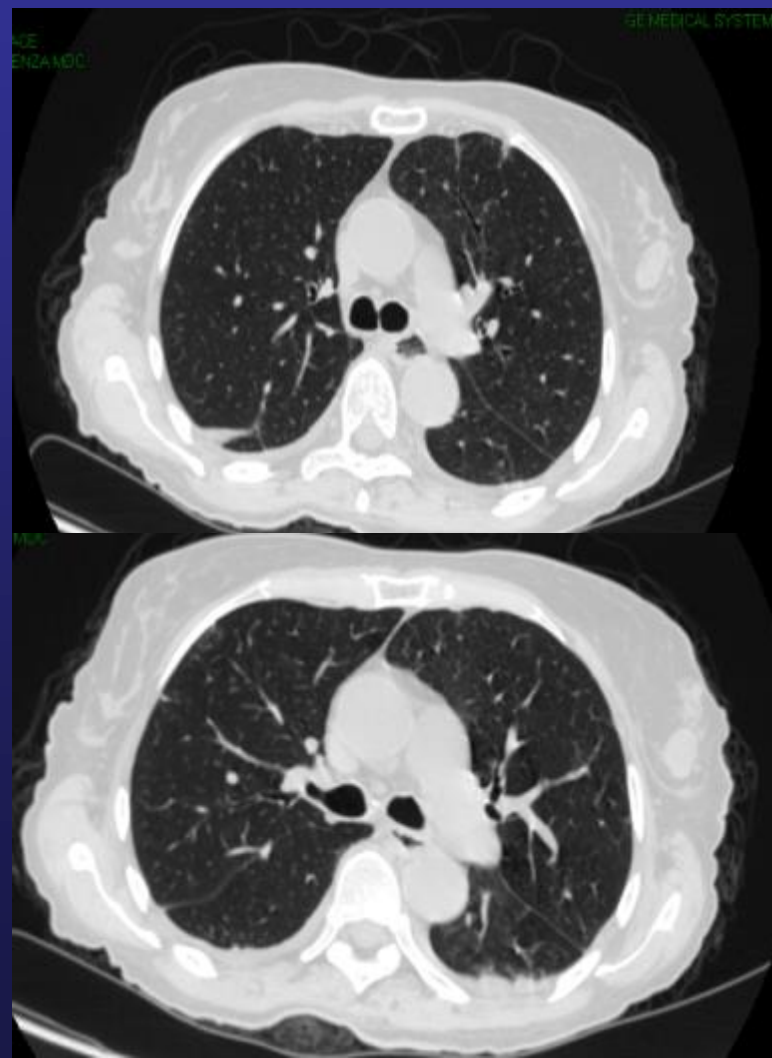
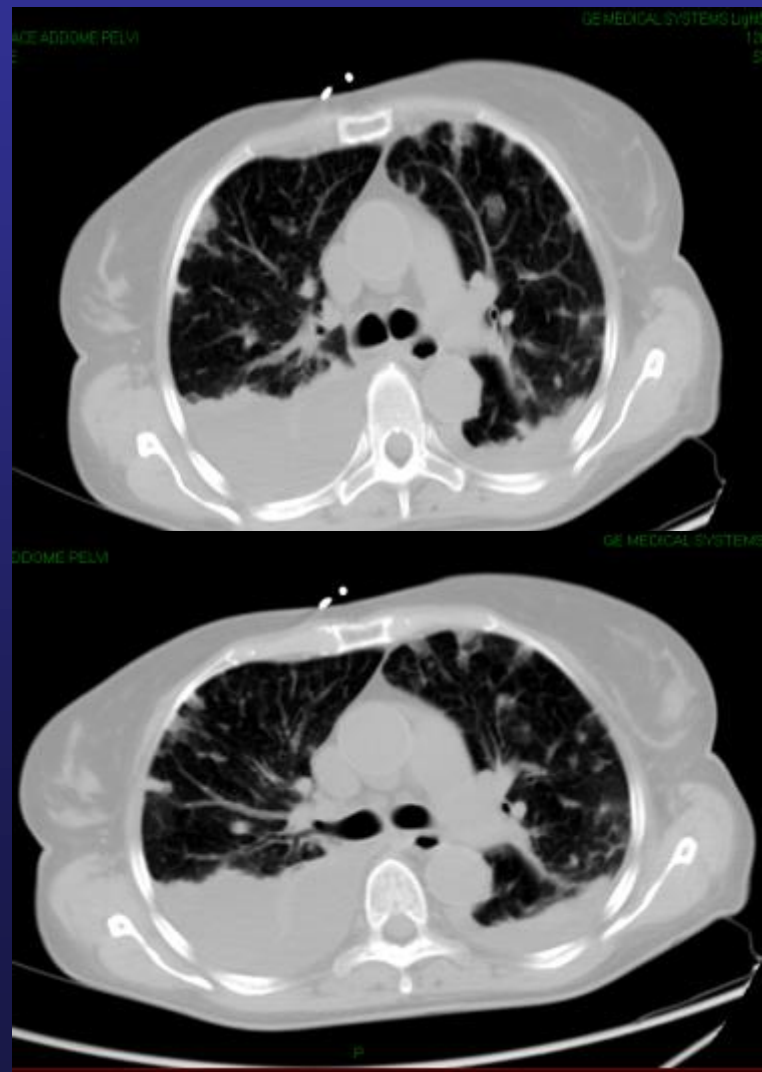
An unusual case of catheter-related right-sided endocarditis, endophthalmitis, and extensive folliculitis, apparently caused by a single DNA biotype of *Candida albicans*, was successfully treated with a 6-month course of fluconazole .....The patient was a 21-year-old man who underwent colectomy for diffuse polyposis and developed the clinical syndrome just described following total parenteral nutrition for the treatment of purulent anal fistulas.....

# Septic bilateral pulmonary candidiasis successfully treated with anidulafungin therapy in two patients with peritoneal carcinomatosis

Falcone M Accarbio V, Venditti M *J Antimicrob Chemother* 65:2266,2010

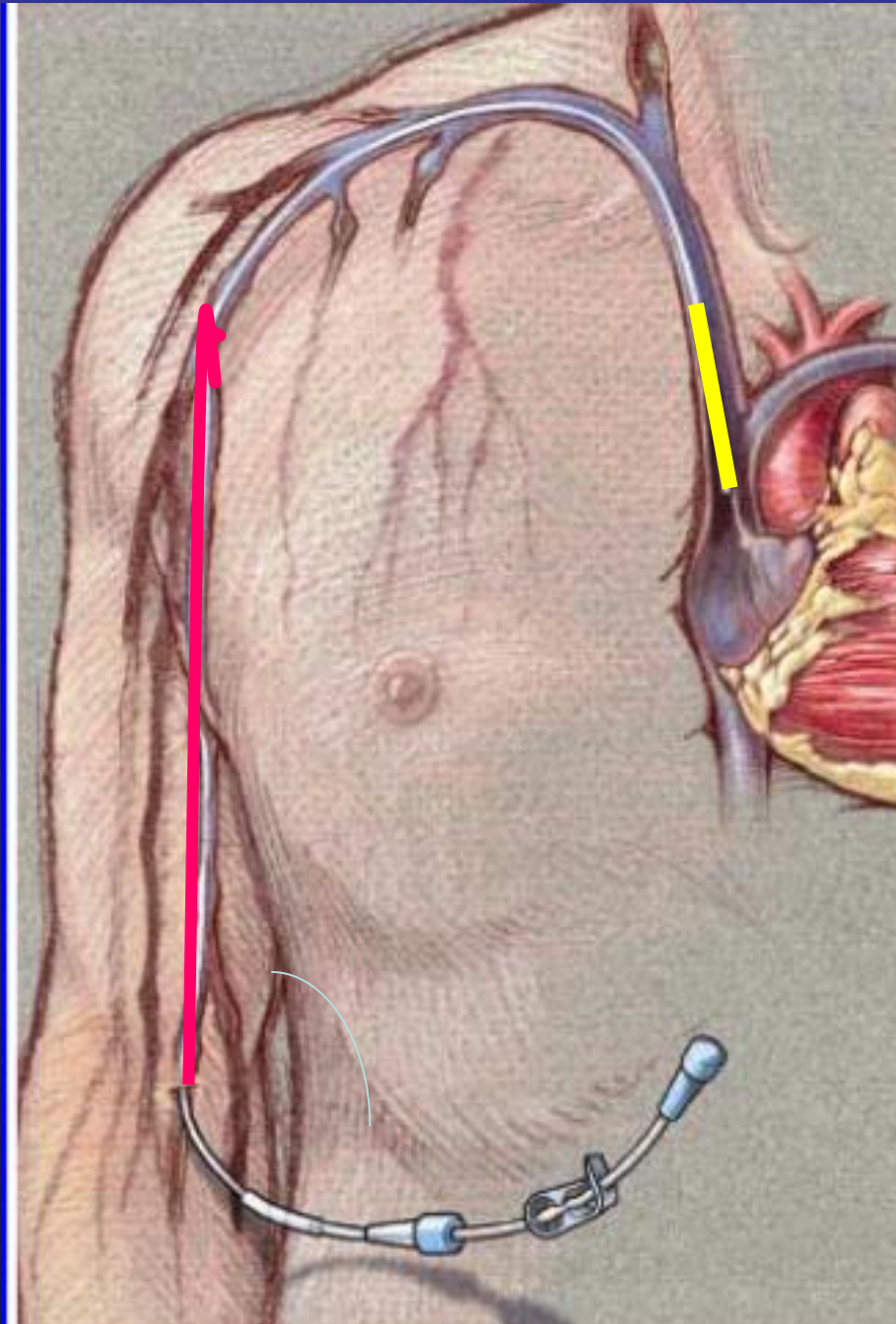
Giorno 5

Giorno 20





# ER PIIC!



# Peripherally inserted central catheter as a predominant risk factor for candidemia in critically ill pts in IMW in Italy

Tascini C et al *Intensive Care Medicine* 2015

Clinical characteristics and outcomes of patients	Patients in General Internal Medicine wards (n = 50)	p value	Patients in Intensive Care Units (n = 22)
Clinical characteristics			
Age (years)	78 ± 13	<0.05	66 ± 12
Charison score	6.69 ± 2.52	ns	7.16 ± 3.14
Admission from home	34/50 (68 %)	≤0.001	2/22 (9 %)
Transfer from surgical ward	1/50 (2 %)	≤0.001	13/22 (59 %)
Hospital stay (days)	11 [6–20]	≤0.001	40 [30–72]
Time to onset of candidemia (days)	4 [1–11]	<0.001	21 [9–36]
Very early onset candidemia (<48 h from admission)	23/50 (46 %)	≤0.001	1/22 (5 %)
Early onset candidemia (2–10 days from admission)	13/50 (26 %)	ns	6/22 (27 %)
Late onset candidemia (>10 days from admission)	14/50 (28 %)	<0.05	15/22 (68 %)
Patient therapy and outcomes			
Therapy with azole	33/50 (66 %)	<0.05	6/22 (27 %)
Therapy with echinocandins	2/50 (4 %)	≤0.001	14/22 (64 %)
No treatment	15/50 (30 %)	ns	2/22 (9 %)
Continuous infusions	29/50 (58 %)	<0.05	19/22 (86 %)
Nasogastric tube	16/50 (32 %)	≤0.001	17/22 (77 %)
Central venous catheter	9/50 (18 %)	≤0.001	17/22 (77 %)
Peripherally inserted central catheter	36/50 (72 %)	≤0.001	1/22 (5 %)
Overall mortality	17/50 (34 %)	≤0.001	14/22 (64 %)



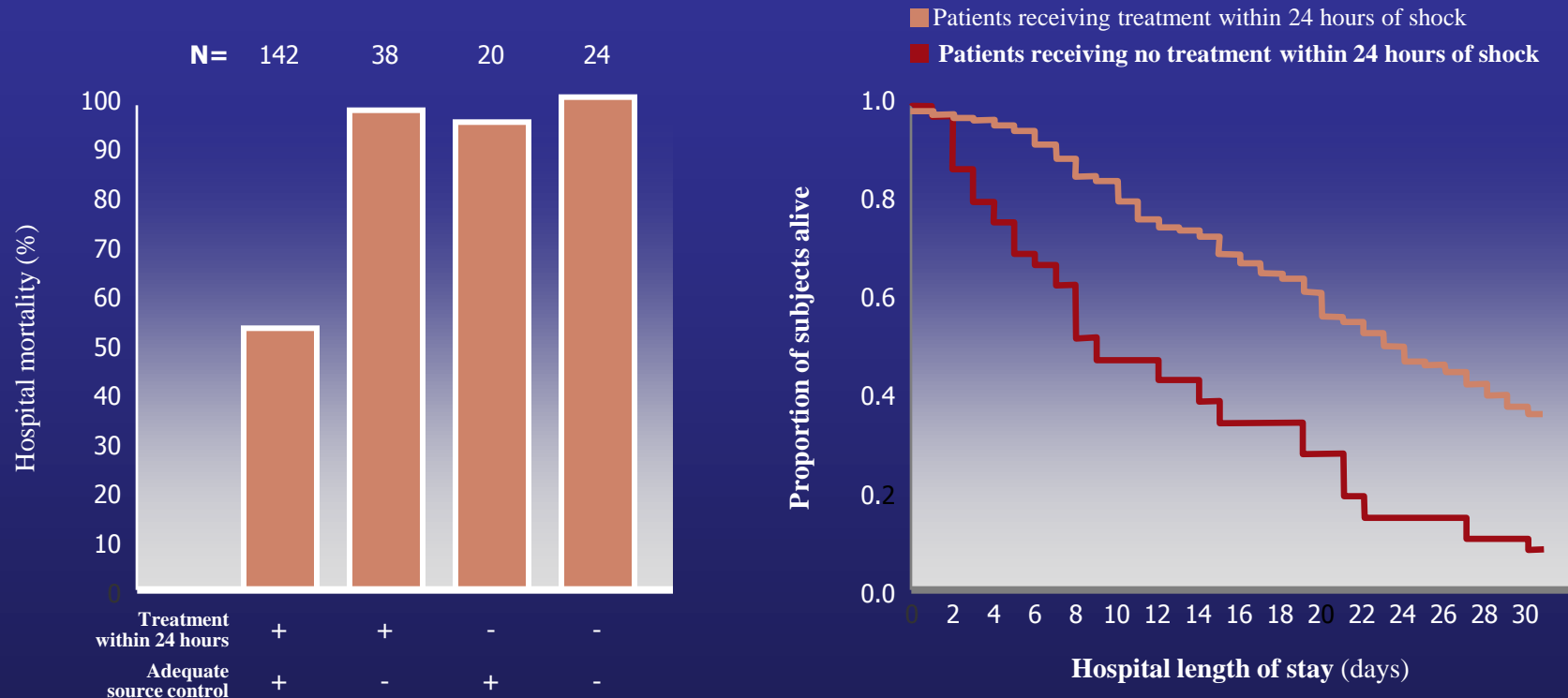
# Rate of candidemia per 10 000 days of admission per year observed at three large Italian tertiary-care university hospitals, 2012–2013

Tascini C et al *Clin Microbiol Infect* 2015

Ward	Pisa	Udine	Florence
All	3.45	1.65	2.46
MWs (general+ specialized MWs)	4.51	1.29	3.33
General MWs	10.2	1.3	4.85
Specialized MWs	1.94	1.27	1.27
ICU	9.35	2.06	12.45
Surgical wards	2.59	3.9	1.05

# Septic shock attributed to Candida infection: importance of empiric therapy and source control

Kollef M, et al. *Clin Infect Dis* 2012;54(12):1739–46



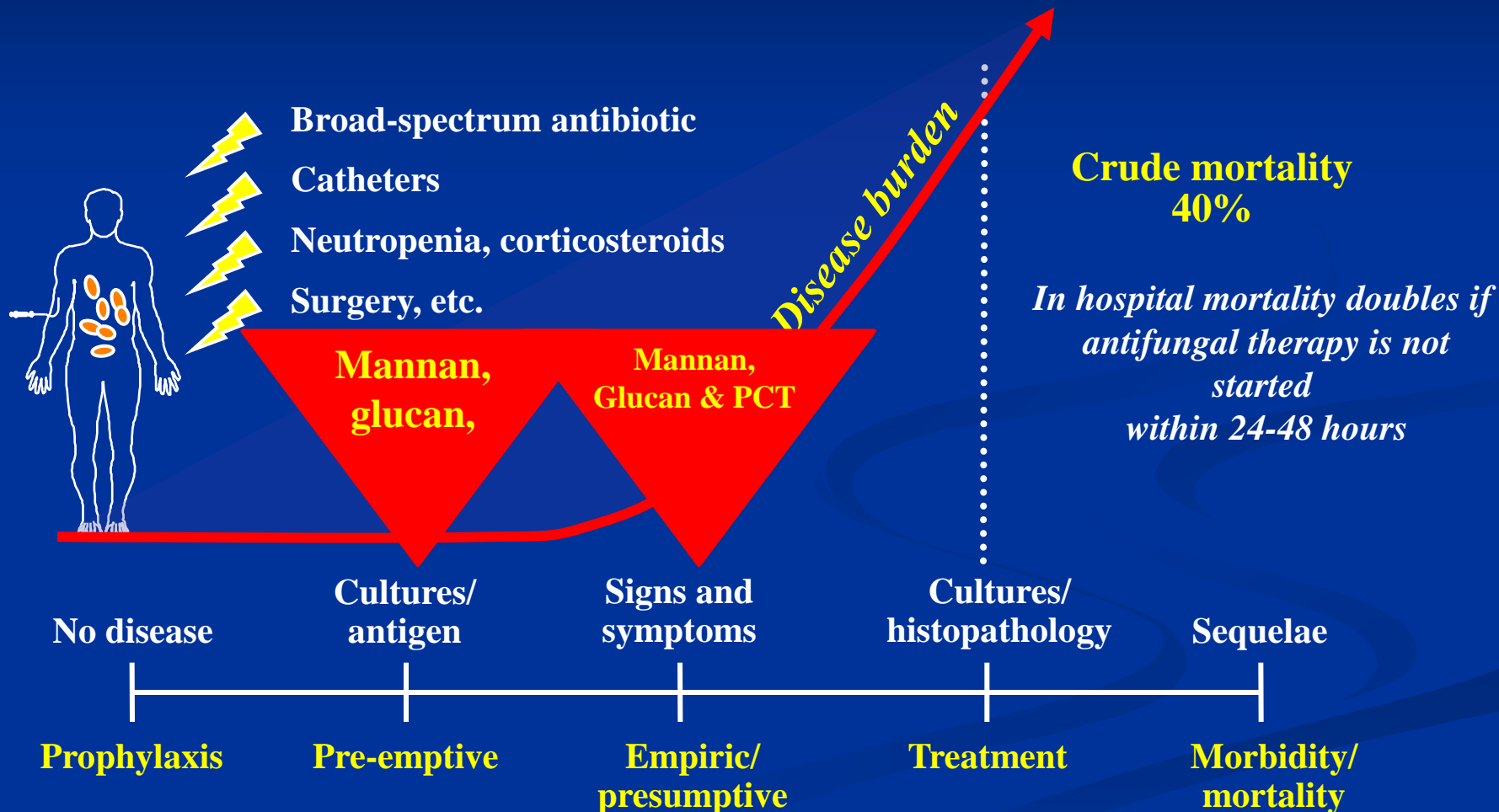
- Hospital mortality according to whether or not patients received antifungal therapy and adequate source control within 24 hours of the onset of septic shock ( $P < 0.001$  for the comparison of patients receiving both antifungal therapy and adequate source control within 24 hours of the onset of shock to the other 3 groups)

# ITALIC definitions of treatment strategies of invasive candidiasis

Scudeller L, Viscoli C, Menichetti F, Del Bono V, Cristini F, Tascini C, Bassetti M, Viale P *Infection* 42: 263, 2014

<u>Treatment strategy</u>	<u>Certainty of diagnosis</u>	<u>Risk factors</u>	<u>Clinical signs</u>	<u>Biomarkers (BDG)</u>	<u>Microbiological diagnosis</u>
Prophylaxis	.....	+	-	.....	.....
Pre-emptive	probable	+	-	+(?)	-
Empirical	possible	+	+	-	-
Presumptive	probable	+/-	+	+	-
Targeted	proven	+/-	+/-	+/-	+

# Difficulties in the diagnosis of invasive candidiasis



# **criteri per la profilassi antifungina nel paziente critico post-chirurgia**

## **Criteri maggiori**

- **Almeno 24 ore di terapia antibiotica sistemica**
- **CVC**

**(almeno un criterio)**

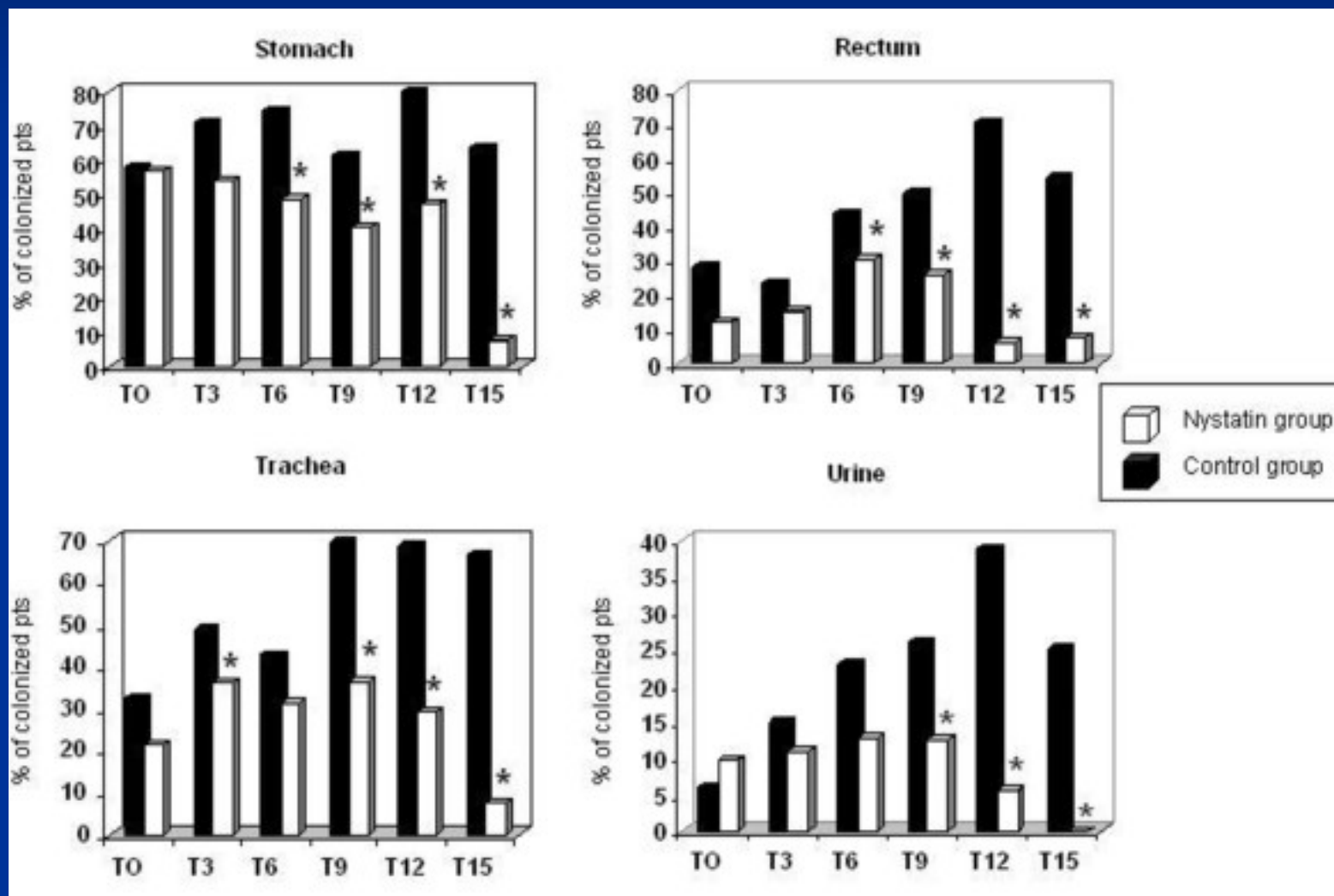
## **Criteri minori**

- **NPT**
- **Dialisi**
- **Chirurgia maggiore**
- **Pancreatite acuta**
- **Terapia steroidea**
- **Terapia immunosoppressiva**

**(almeno due criteri)**

# Oral nystatin prophylaxis in surgical/trauma ICU patients

Giglio et al. *Critical Care* 2012 16:R57

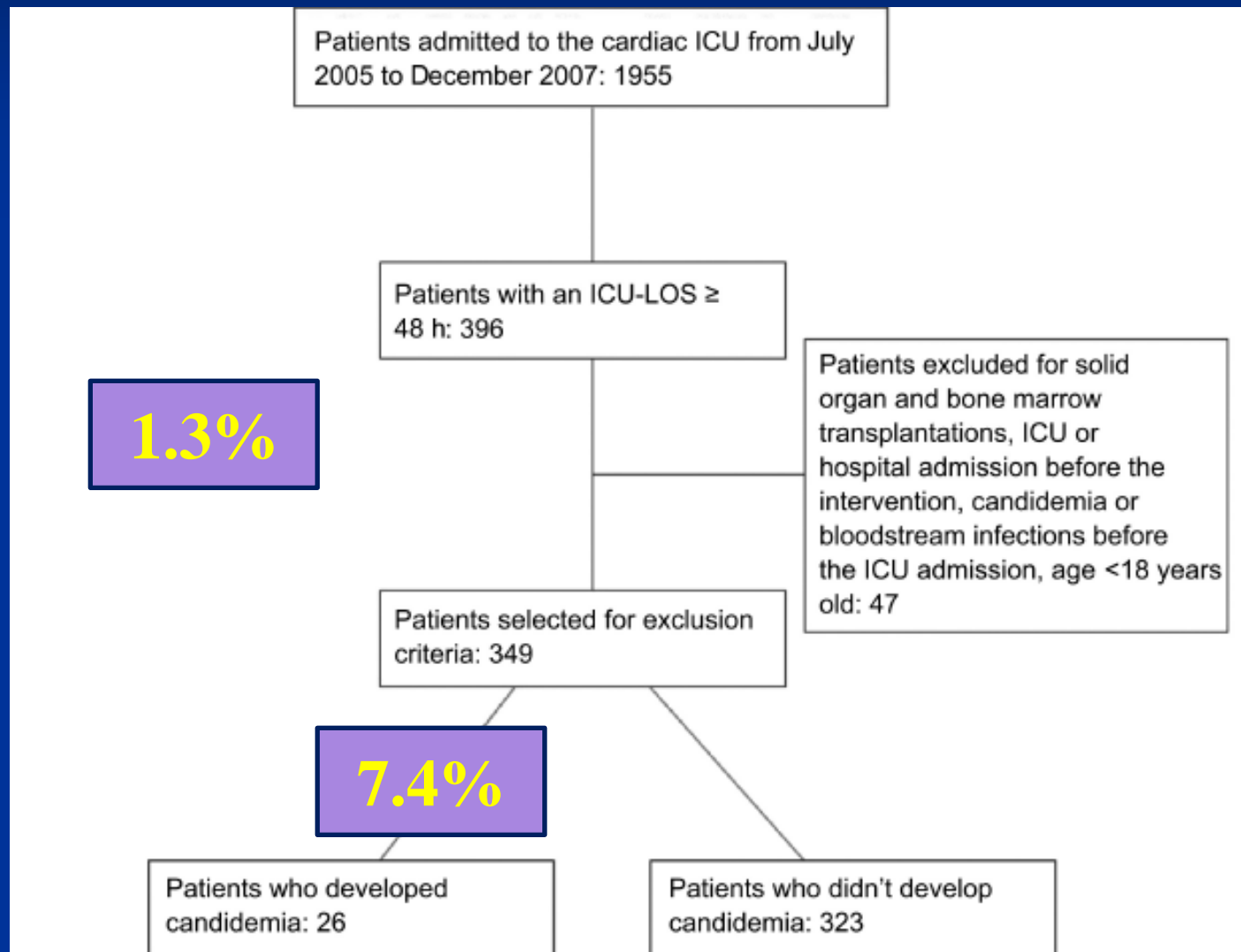




# Candidemia after cardiac surgery in the intensive care unit: an observational study

Pasero D, De Rosa FG, ... & Di Perri G *Interact CardioVasc Thorac Surg* 2011;12:374-378

The flow diagram showed patients admitted to the cardiac ICU and selected for ICU-LOS  $\geq 48$  hours and exclusions criteria. ICU-LOS, intensive care unit length of stay.



# Fattori predittivi indipendenti di candidemia e di morte secondaria a candidemia dopo chirurgia cardiotoracica

<u>Variabile</u>	<u>OR</u>	<u>P</u>	<u>sens</u>	<u>spec</u>	<u>PPV</u>	<u>NPV</u>	<u>accuratezza</u>
<b>- Candidemia</b>							
VM>10 gg	28.2	<.001	97%	99%	97%	99%	99%
Inf. Batterica	9.4	<.001	100%	92%	76%	100%	94%
<b>CPBP&gt;120 min</b>	<b>8.1</b>	<b>&lt;.01</b>	<b>70%</b>	<b>85%</b>	<b>54%</b>	<b>92%</b>	<b>82%</b>
Diabete mellito	2.4	<.01	60%	70%	33%	87%	68%
Modello globale			53%	100%	100%	90%	90%
<b>- Morte per candidemia</b>							
APACHE II	21.7	<.001	80%	80%	67%	89%	80%

**Michalopoulos AS et al CHEST 124: 2244, 2003**

Nella Terapia Intensiva di un Ospedale di II livello,  
4 pazienti nel giro di due mesi sviluppano febbre con  
emoculture positive per *Saccharomyces spp.*

Caratteristiche comuni dei 4 pazienti

- **Trasmissione:**

- aereosol al momento della apertura  
delle bustine**

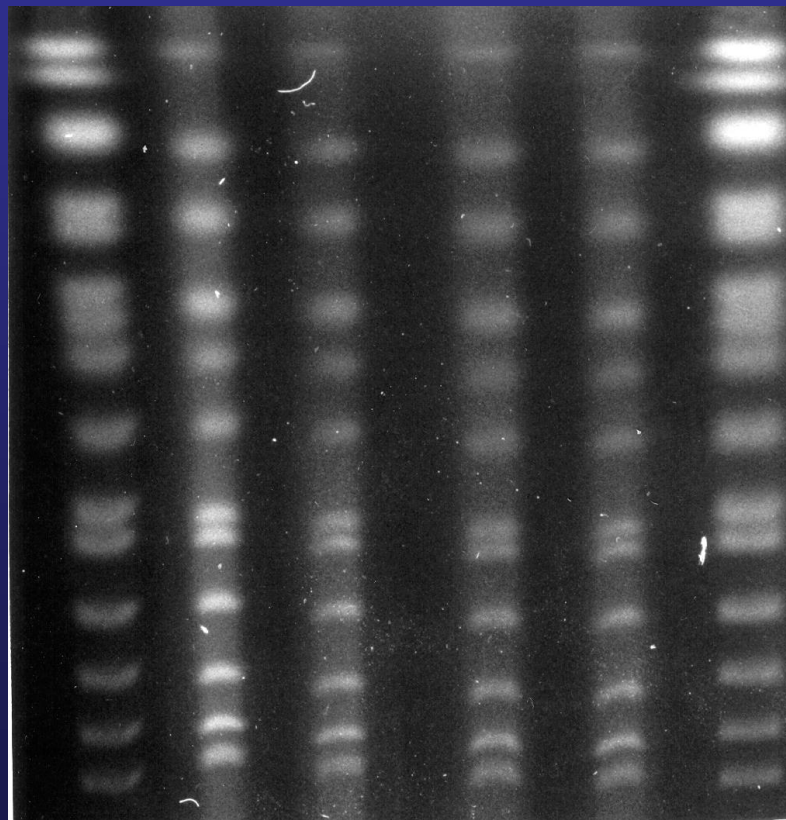
- +/- mani del personale**

- In

- somministrazione **NO**

# Pulsed Field Gel Electrophoresis (PFGE) di *S.boulardii* isolato da emocolture e da preparato commerciale (Codex)

Line 1   Line 2-3   Line 4-5   Line 6  
marker   CODEX   *S. boulardii*   marker



# Fungemia da *S. cerevisiae* subspp *boulardii* in una UTI post CCH e assunzione di probiotico

<u>probiotico</u>	<u>fungemia</u>	<u>no fungemia</u>
si	3	2
no	0	38
<b>totale</b>	<b>3</b>	<b>40</b>

Analisi della letteratura. 57 casi : 45% dopo assunzione del probiotico, 9% in pazienti prossimi a chi assumeva il probiotico, mortalità associata 28%.

**Munoz & Bouza CID July 2005**

# Fattori predisponenti la candidemia nei pazienti cardiocirurgici

- Pressione antibiotica

**Selezione a favore di *Candida***



**Aumentata traslocazione di  
*Candida***

che

- Altri fattori di rischio concomitanti

- cvc, NPT, insufficienza renale acuta +/- CAVH, chirurgia recente, diabete mellito .....



# OPEN HEART SURGERY

RISK FACTORS FOR CANDIDEMIA  
(NPT, SEVERE SEPSIS, ANTIBIOTICS, ACUTE  
RENAL FAILURE, *CANDIDA* COLONIZATION,  
STEROIDS ETC)

POST-OPERATIVE CANDIDEMIA\*  
FROM DAMAGED INTESTINAL MUCOSA  
OR CVC

direct intraoperative  
contamination  
or  
unsuccessful antifungal  
therapy & surgical  
debridement of previous  
*Candida* ie

adherence of *Candida* on  
prosthetic valve

biofilm formation

resistance to antifungals, no evidence of IE  
at echocardiography !

Late appearance of vegetations at echocardiography  
and/or clinical symptoms of IE

DIAGNOSIS OF  
*CANDIDA* PVE

**At least 25%  
of post-  
operative  
candidemias  
develop  
endocarditis!**

# Agents of BSI after 393 episodes of CDAD

Falcone M, Russo A, Carfagna P, Goldoni P, Vullo V & Venditti M

*Antimicrob Agents Chemother* early on line 2015

**19% out of 393 CDAD were complicated by BSI**

**12% candidemia +/-  
enterobacteriaceae &  
*Enterococcus***

# Proposed management of patients with CDI at risk for candidemia

Falcone M, Venditti M, Sanguinetti M & Posteraro B. *Exp Rev Antiinfect Ther*, in press 2016

Advanced age, Severe CDI, relapse or  
relapse>1, Rybotipe 027

**Avoid high dose oral vancomycin**

Reduce microbiota  
alteration in favor of  
*Candida*

Reduce *C. difficile*  
toxins synthesis  
Reduce toxin effects

Clinical worsening despite  
CDI therapy  
(i.e. severe sepsis)

Oral nystatin prophylaxis  
&  
Fidaxomicin therapy

Fidaxomicin therapy  
&  
bile salt or MABs

Risk of gram negative BSI  
(KPC rectal colonization?)  
Treat accordingly!!

**Plan early frozen-and-thawed or fresh FMT**

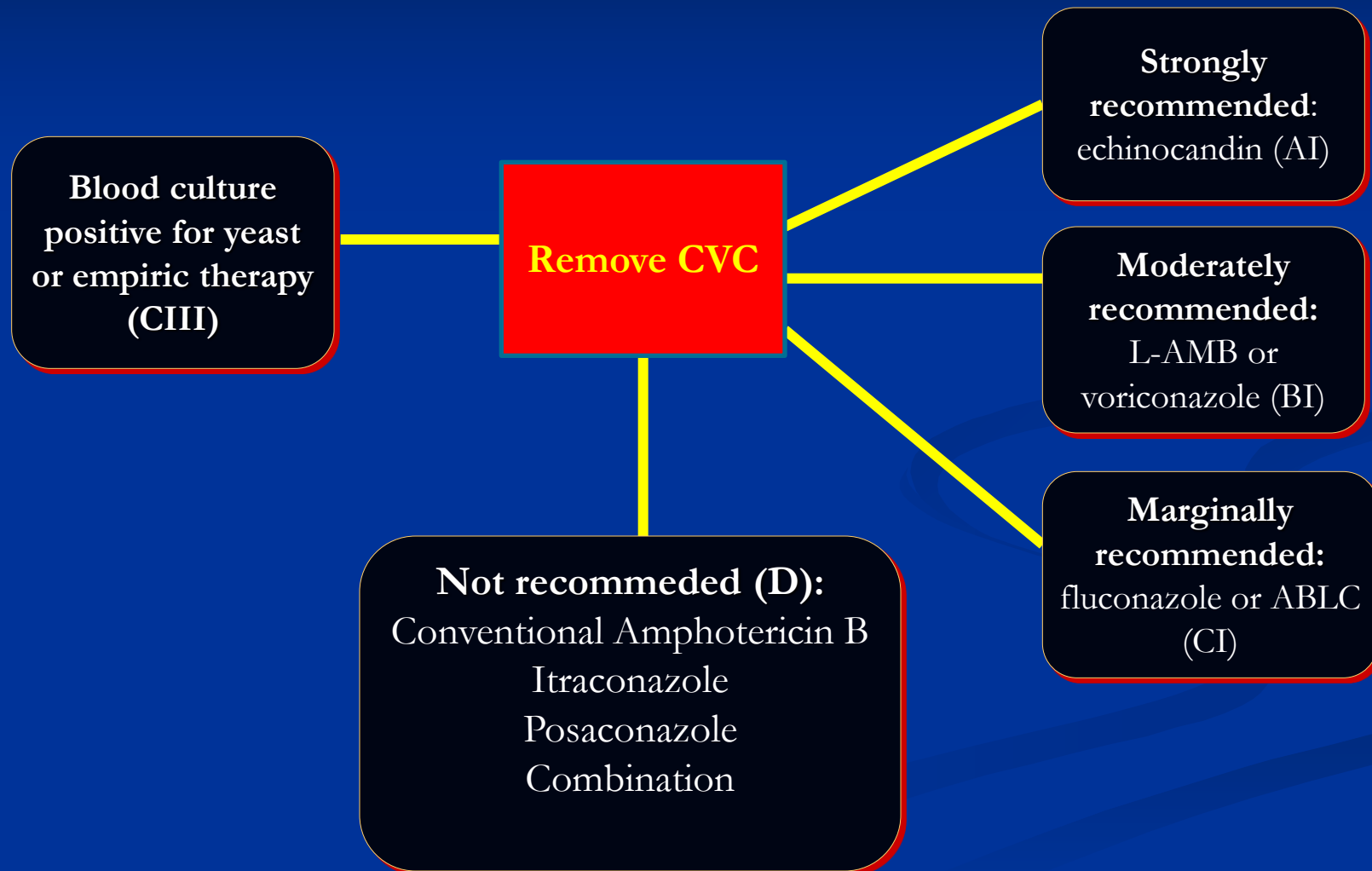
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Prophylaxis	.....	+	-	.....	.....
Pre-emptive	probable	+	-	+(?)	-
<b>Empirical</b>	<b>possible</b>	+	+	-	-
<b>Presumptive</b>	<b>probable</b>	+/-	+	+	-
<b>Targeted</b>	<b>proven</b>	+/-	+/-	+/-	+

# Treatment of candida in non-neutropenic patients (ESCMID guidelines 2012)

Cornely OA et al. *Clin Microbiol Infection*, 2012



# Candidosi invasive....

## +/- candidemia nel paziente chirurgico

### CVC relate

1. Endocardite
2. tromboflebite,
3. Endoftalmite
4. Nefrite
5. Etc
6. Etc, etc,

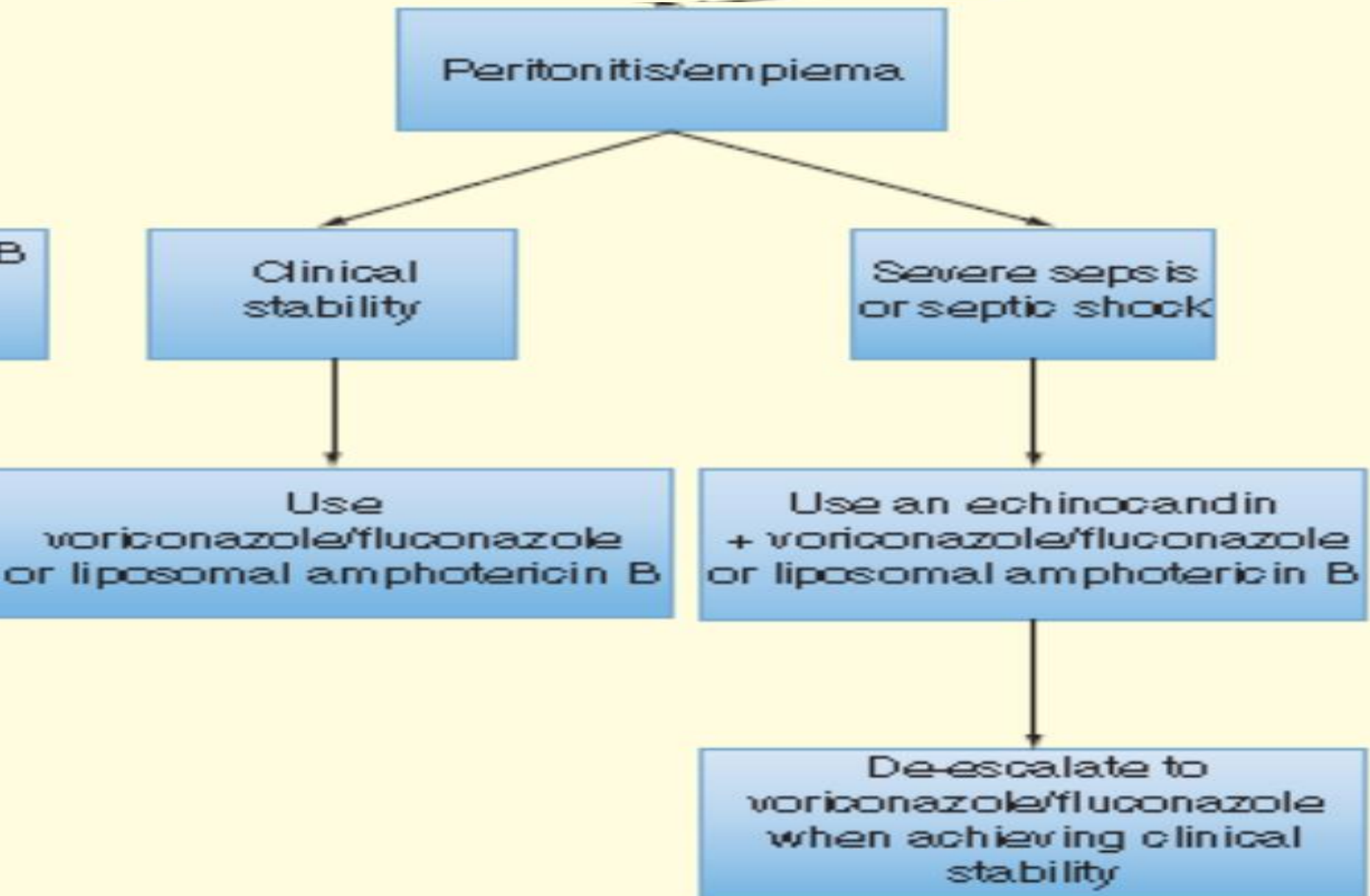
### non CVC relate

1. Peritoniti  
secondarie/terziarie  
nosocomiali
2. Cistopielite CATUR  
relata
3. Infezioni di ferita con  
corpo estraneo (protesi  
ortopediche, ventricoliti  
su shunt...)
4. Tromboflebite pelvica
5. .... E di nuovo  
l'endocardite.....



# Current pharmacological concepts for wise use of echinocandins in the treatment of *Candida* infections in septic critically ill patients

Pea F. *Expert Rev. Anti Infect. Ther.* 11(10), 989–997 (2013)

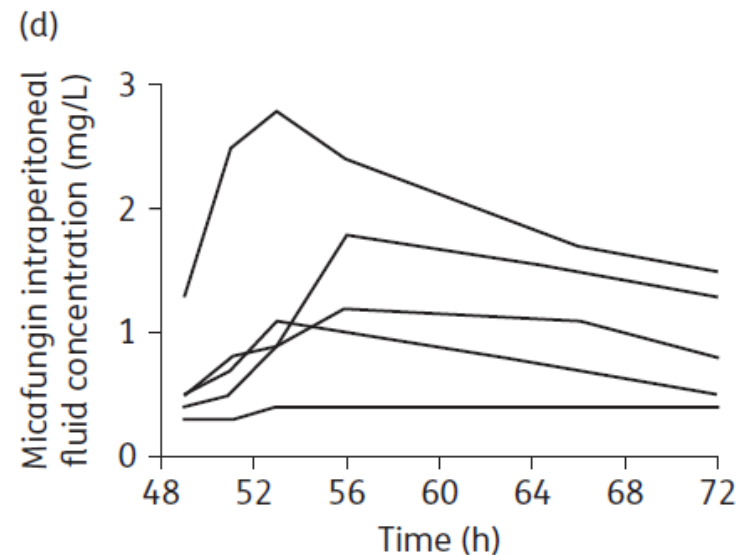
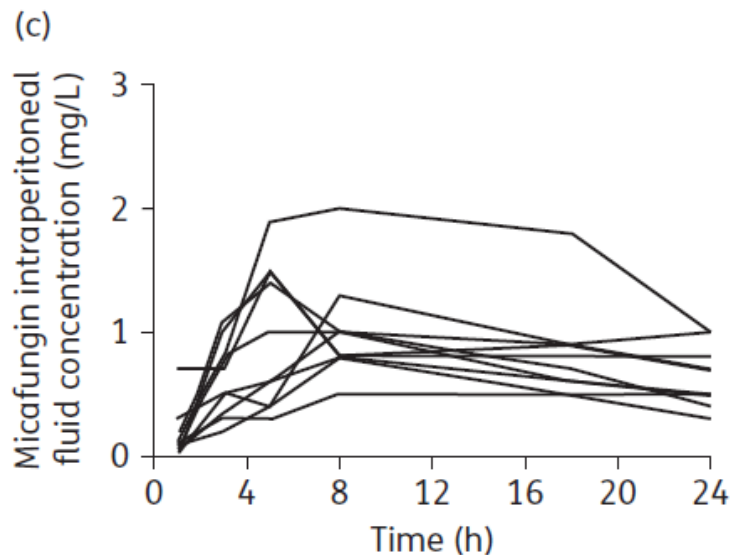
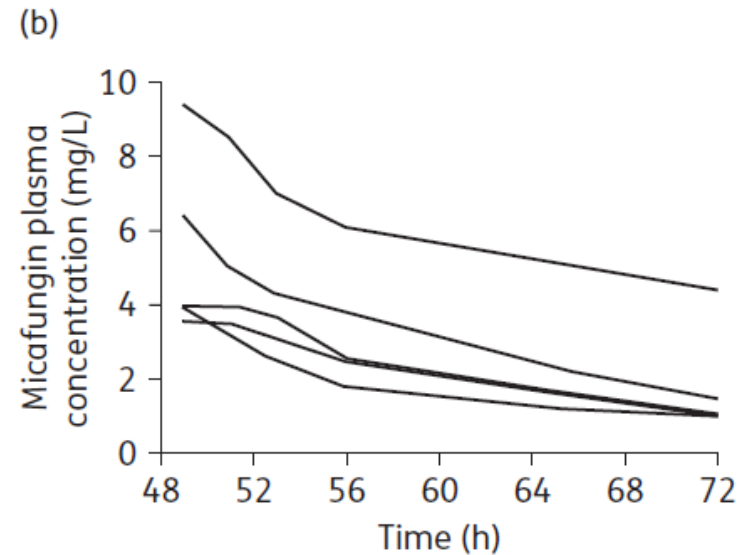
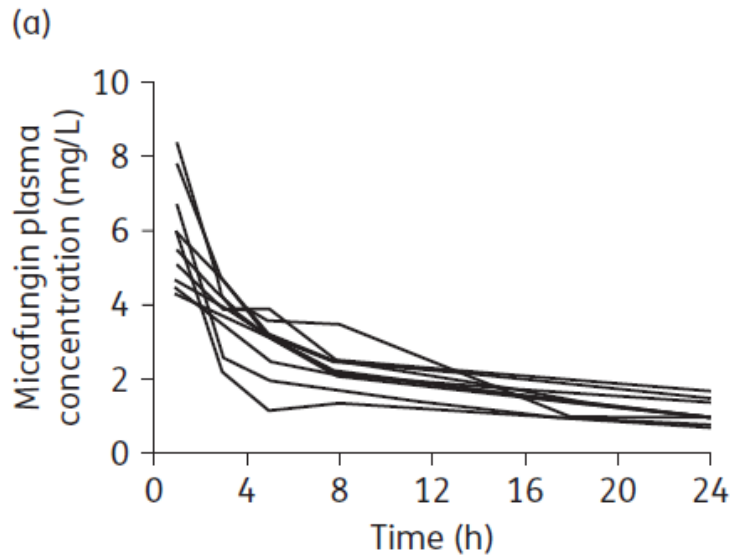


# Caso clinico

**Sfebbra definitivamente con  
fluconazolo in monoterapia...**

# Plasma and peritoneal fluid population pharmacokinetics of micafungin in post-surgical patients with severe peritonitis.

Grau S et al *J Antimicrob Chemother.* 2015 Oct;70(10):2854-61



# Candidosi invasive....

## +/- candidemia nel paziente chirurgico

### CVC relate

1. Endocardite
2. tromboflebite,
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5. Etc
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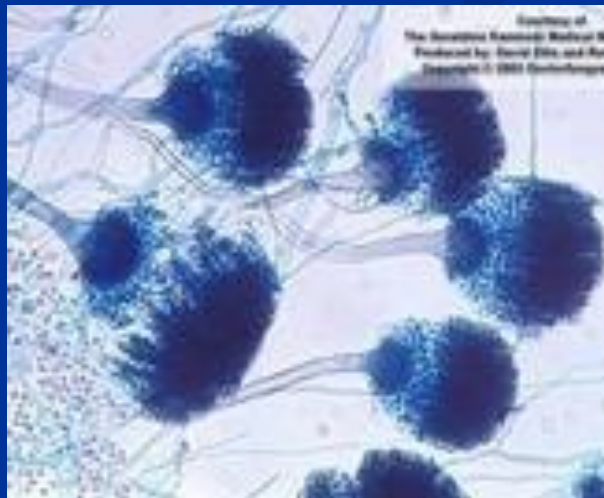
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3. Infezioni di ferita con  
corpo estraneo (protesi  
ortopediche, ventricoliti  
su shunt...)
4. Tromboflebite pelvica
5. .... E di nuovo  
l'endocardite.....

# *Aspergillus*

Catalogato nel **1729** dal sacerdote e biologo italiano  
**Pier Antonio Micheli**

La vista dei funghi al microscopio  
gli fece venire in mente la  
forma di un ASPERSORIO  
(latino *aspergillum*)



# Epidemiology of *Aspergillus* spp. infections

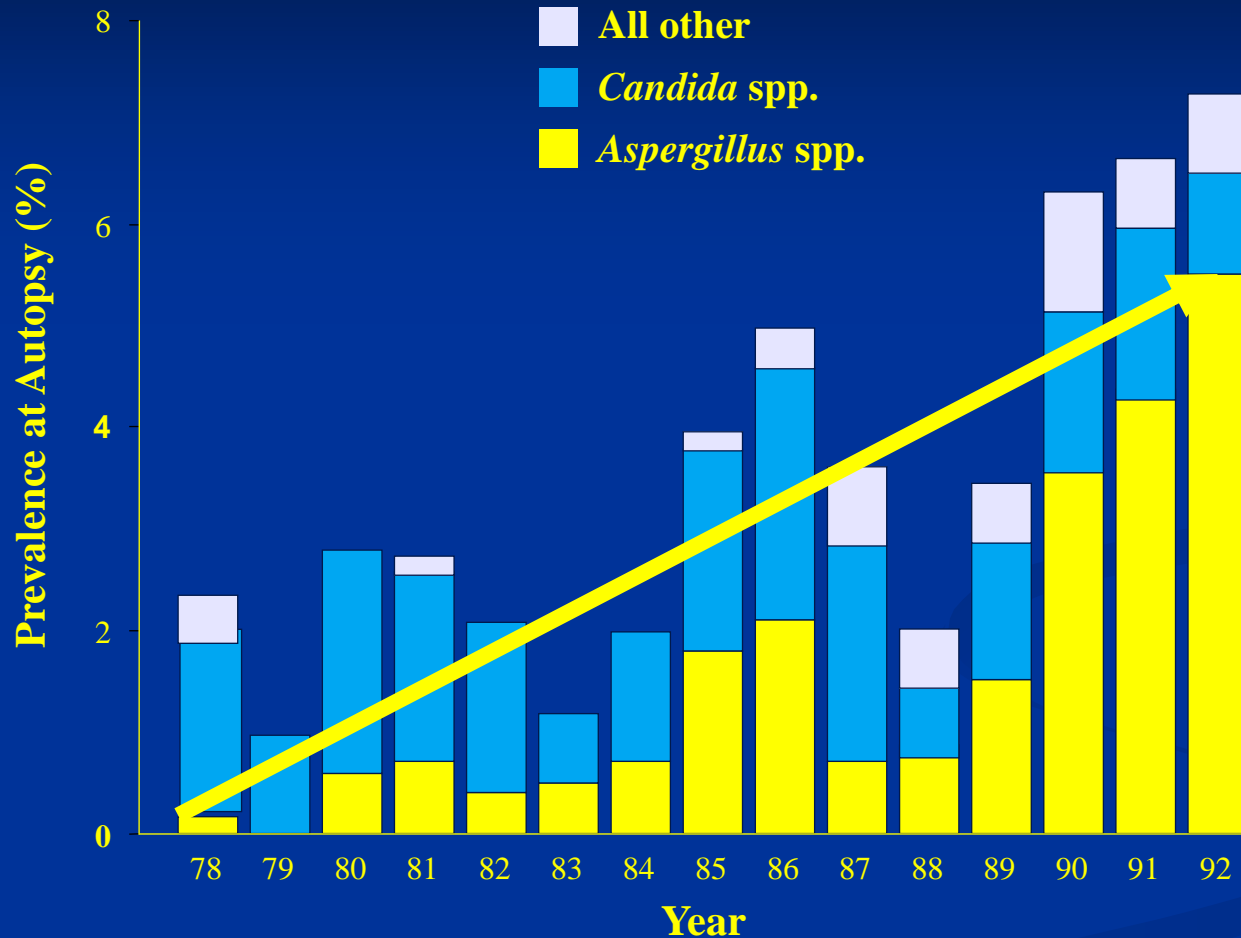
<sup>1</sup>Warnock DW. Jpn J Med Mycol 2007; 48:1-12 <sup>2</sup>Perkhofer S, et al. Int J antimicrob Agents 2010;36(6):531-536 <sup>3</sup>Lortholary O, et al. Clin Microbiol Infect 2011;17(12):1882-1889  
<sup>4</sup>Tong KB, et al. Int J Infect Dis 2009;13(1):24-36

- Invasive aspergillosis (IA), including invasive pulmonary aspergillosis (IPA), is the most clinically important form of *Aspergillus* infection
- IA is considered a rare disease
  - Occurs predominantly in immunocompromised patients
- Epidemiological data on the incidence of IA are limited, but indicate significant increases over time<sup>1</sup>
  - Estimated 10,190 aspergillosis hospitalisations in 1996 annually in the US, resulting in 1,970 deaths and \$633 million in cost<sup>1</sup>
  - Current EU and US reports indicate an incidence of 2 - 4 cases per 100,000 population<sup>2-4</sup>
- *Aspergillus fumigatus* is the most common species<sup>2</sup>
  - *A. terreus* and *A. flavus* are becoming more frequent<sup>2</sup>



# Prevalence of IA at autopsy

Groll A, et al. *J Infect* 1996;33:23-32



In 1992,  
60% of the IA  
patients were  
diagnosed at  
autopsy and had no  
treatment

# Aspergillosis in ICU patients: epidemiology and economic outcomes

Baddley et al. *BMC Infectious Diseases* 2013, 13:29

- **412 (6.4%) ICU patients with IA were identified.**
- Mean age was 63.9 years
- Co-morbidities included acute respiratory failure (76%), acute renal failure (41%) and diseases requiring steroid use (77%).
- **In-hospital mortality was 46%.**
- The most frequently used AF was voriconazole (71%).
- **Mean LOS was 26.9 days and mean total hospital cost was \$76,235.**
- Each 1 day lag before initiating AF therapy was associated with 1.28 days longer hospital stay and 3.5% increase in costs ( $p < 0.0001$  for both).

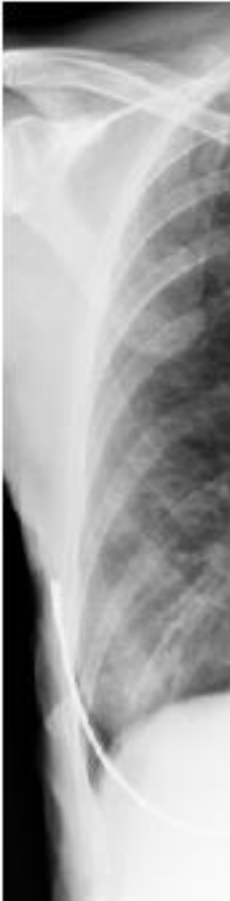
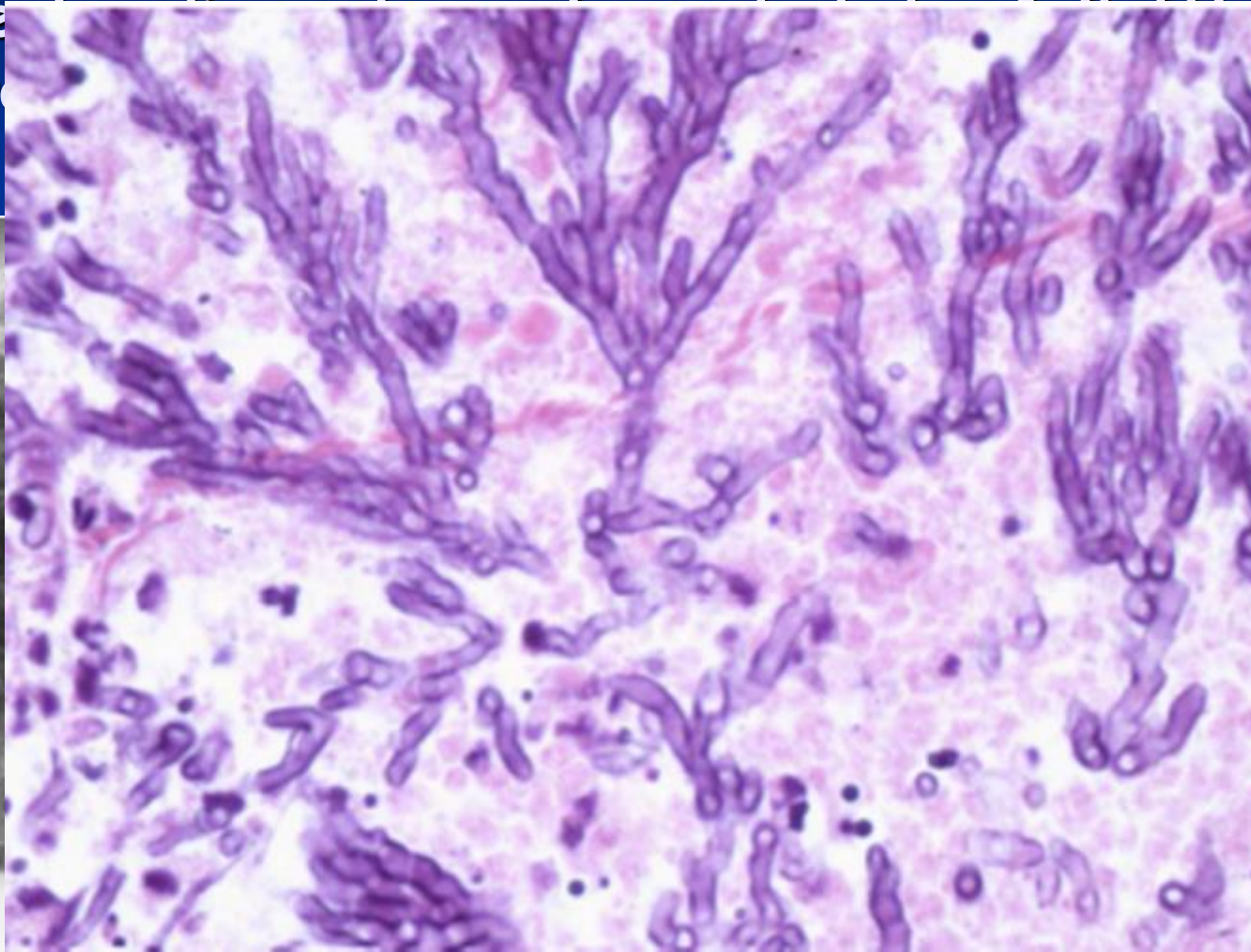
# Malattia da *Aspergillus*

- Sudbdoia e indolente → capace di accelerare in una progressione fatale
- Necessità e possibilità di diagnosi precoce con surrogati marker?
- Nuove categorie a rischio
- Prospettive terapeutiche....

# Fatal Invasive Pulmonary Aspergillosis Complicating Influenza A (H1N1)v Infection

Carfagna P, Brandimarte P, Caccese R, Campagna D, Brandimarte C, Venditti M.  
*Mycoses on line early, 2011*

Chest CT scan showing bilateral consolidation (left) and showing bilateral consolidation (right) S.



## **Risk of IPA: from IMW to ICU**

- Prolonged treatment with steroids before admission (> 3 weeks).
  - Chronic obstructive pulmonary disease.
    - Liver cirrhosis
    - HIV infection.
- Systemic diseases requiring immunosuppressive therapy.
  - SOT.
  - Diabetes mellitus.
  - Renal failure with RRT.
  - Influenza A (H1N1) infection.
- Post extracorporeal membrane oxygenation (ECMO).

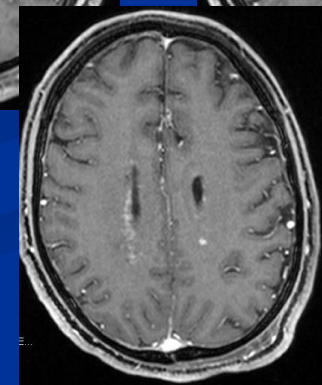
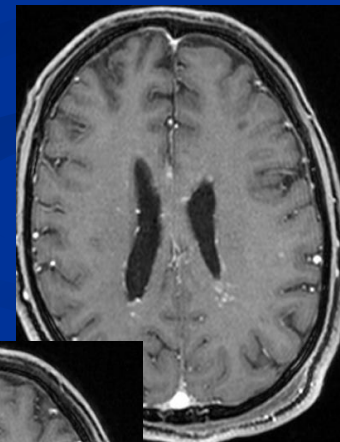
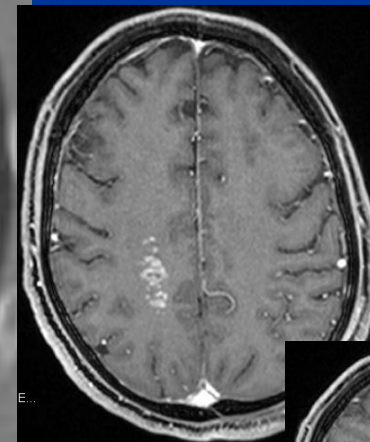
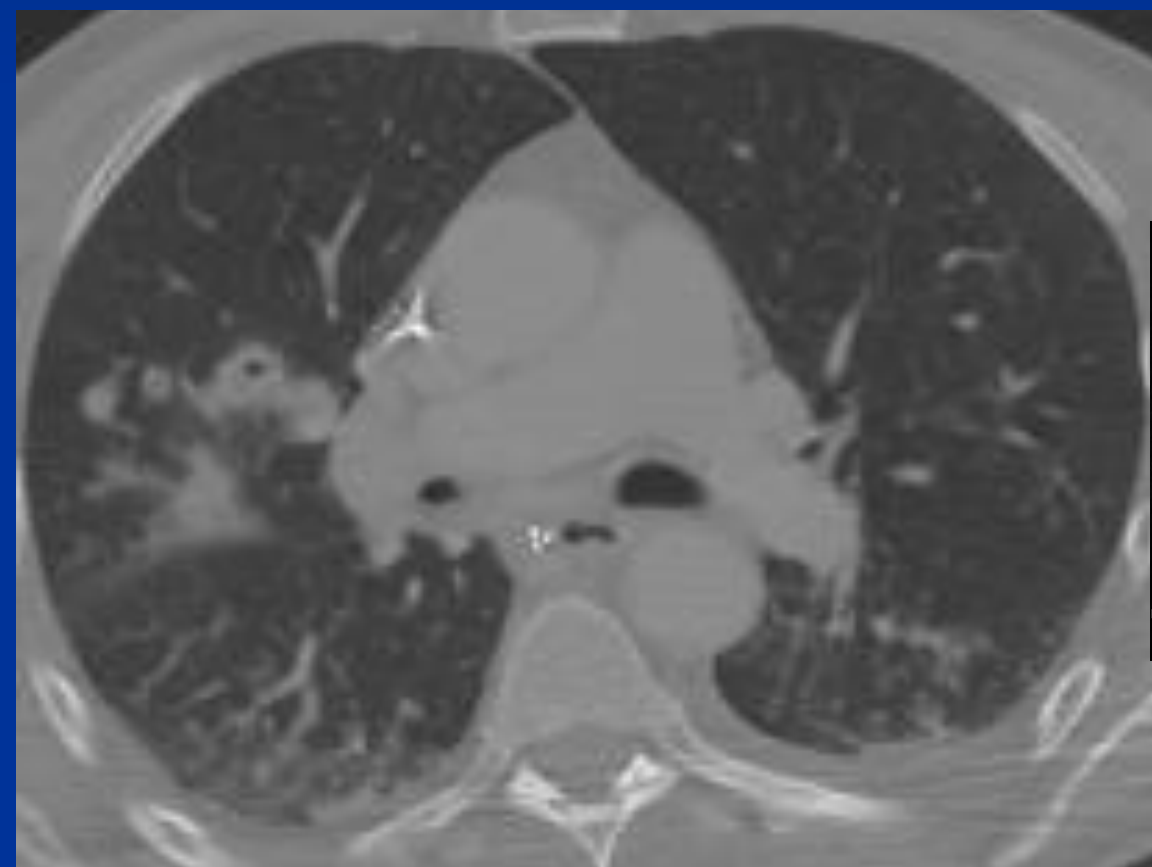


- Uomo, 58 anni, non comorbidità si ricovera per febbre , coma e insufficienza respiratoria.
- negativi tutti gli accertamenti per virus, batteri, micobatteri nel sangue, BAL e liquor ....
- linfociti NKCD3-, CD16/56+: 19 uL (range 90-550)

-*Aspergillus* cresce dal BAL

- Indice di galattomannano nel BAL:  
4.90

- PCR positiva nel liquor per  
*Aspergillus*







# Infezione fungina invasiva "probabile"

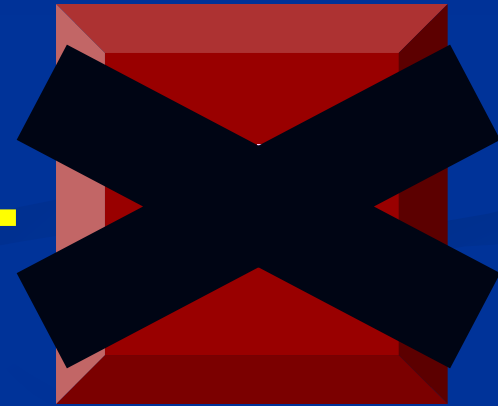
Fattori  
dell'ospite

+

Micologia

+

Caratteristiche  
cliniche e  
radiologiche



# Infezione fungina invasiva "provata" o "probabile"

Fattori  
dell'ospite

+

Micologia

+

Istologia

Caratteristiche  
cliniche e  
radiologiche

Conferma  
diagnosi

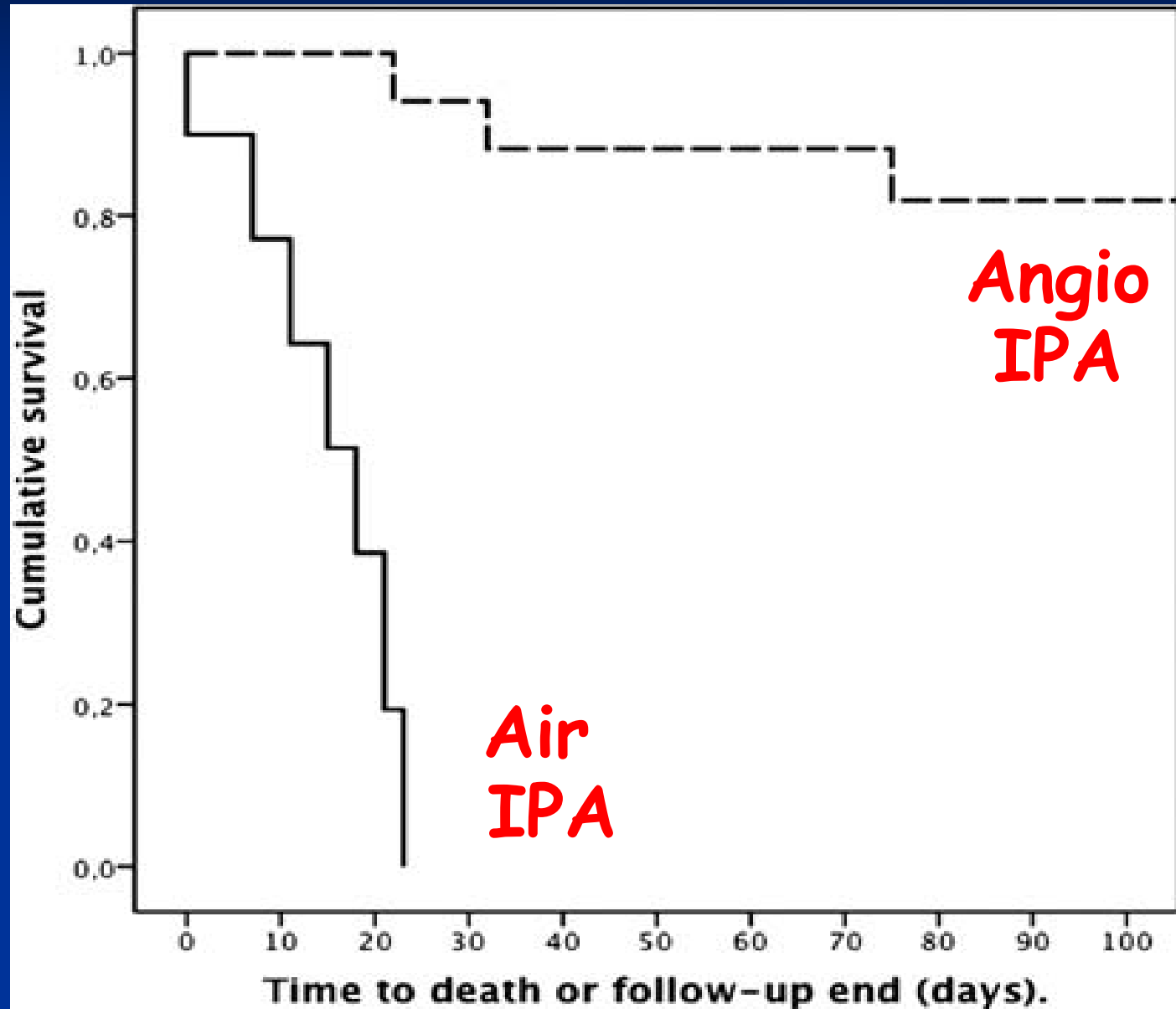
# Standard Glossary of CT Imaging Definitions to Categorize Pulmonary Lesions

(Park et al. Journal of Infection 2011 63, 447-456)

lesioni	Definizioni
Noduli	Opacità ovoidale di tessuto molle < 3cm che nasconde completamente la vascolarizzazione bronchiale sottostante. Sottocategorie di noduli includono: <ul style="list-style-type: none"><li>•Macronoduli (noduli grandi con diametro <math>\geq</math> 1cm)</li><li>•Raggruppamenti di piccoli noduli (diametro &lt; 1cm)</li></ul>
Lesioni delle vie respiratorie periferiche	Presenza di attenuazione a mosaico, air trapping, a tree-in-bud sign, o opacità peribronchiale.
Opacità a vetro smerigliato /GGO: Ground-glass opacity	Attenuazione offuscata del polmone con una consistenza intermedia tra aria e liquido che non nasconde la vascolarizzazione bronchiale sottostante.
Halo sign (Segno dell'alone)	Macronodulo circondato da una zona a vetro smerigliato.
Air-crescent sign (Segno della mezza luna)	Tasca gassosa a forma di mezza luna che occupa l'interfaccia di separazione tra un sequestro polmonare attribuibile a necrosi e un perimetro di polmone ancora funzionante.
Consolidamento <sup>a</sup>	Aumento omogeneo dell'attenuazione del parenchima polmonare che nasconde i margini dei vasi e le pareti delle vie respiratorie (può essere presente un broncogramma aereo)
CT Massa <sup>a</sup>	Qualsiasi lesione polmonare osservata in una radiografia del torace con un'opacità di diametro > 3cm.

# IPA in heart transplant recipients: two radiologic patterns with different prognosis

Munoz P et al J Heart Lung Transpl 2013



# PREDICTORS OF MORTALITY IN NONNEUTROPENIC PATIENTS WITH INVASIVE PULMONARY ASPERGILLOSIS (IPA): DOES GALACTOMANNAN HAVE A ROLE?

Russo A, Giuliano S, Vena A, Falcone M, Lucidi C, Merli M & Venditti M *Diagn Microbiol Infect Dis* 2014

Univariate analysis of factors associated with death among patients with IPA.

Variable	<u>Number (%) of patients</u>		P	RR (95% CI)
	Survivors (n=17)	Nonsurvivors (n=7)		
Cirrhosis	1 (5.9)	6 (85.7)	>.01	1.45 (2.12-100)
Voriconazole	15 (88.2)	2 (28.6)	>.01	.17 (.04-.66)
GM index (mean $\pm$ SD)	1.9 $\pm$ .6	3.6 $\pm$ 2.8	.02	...

## Not significant variables:

age, sex, steroid & immunosuppressive therapy, other comorbidities (hematologic malignancies, solid tumor, BPCO, HIV infection...), presence of fever or leukocytosis, concomitant antibiotic therapy...

# Terapia

## Prima scelta

Voriconazolo

6 mg/kg ev ogni 12 ore 1° giorno  
poi 4 mg/kg ev ogni 12 ore

Oppure

orale 200 mg ogni 12 ore  
(assorbimento intestinale intatto)

## Alternative

Ruolo della echinocandina nel  
trattamento iniziale

*Walsh et al (IDSA guidelines) Clin Infect Dis 46: 327, 2008*  
*Trof RJ et al Intensive Care Med 33: 1694, 2007*

# Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes

CID 2008; 46:201-11

Andres Pascual,<sup>1</sup> Thierry Calandra,<sup>1</sup> Saskia Bolay,<sup>1</sup> Thierry Buclin,<sup>2</sup> Jacques Bille,<sup>3</sup> and Oscar Marchetti<sup>1</sup>

<sup>1</sup>Infectious Diseases Service, <sup>2</sup>Division of Clinical Pharmacology, and <sup>3</sup>Institute of Microbiology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

Variable	Voriconazole trough blood level		P
	≤1 mg/L (n = 13)	>1 mg/L (n = 39)	
Route of voriconazole administration			.05
Intravenous	4 (31)	24 (61)	
Oral	9 (69)	15 (39)	
Voriconazole dosage, median mg/kg/day (range)			
Overall	7 (2.5–9)	8 (2–11)	NS
Intravenous	7.5 (7–8)	8 (6–11)	NS
Oral	6 (2.5–9)	7 (2–11)	NS
Response to anti-fungal therapy			
Interval between first and second trough blood level (range)	21 (10–120)	17.5 (10–180)	NS
Treatment success			.02
Overall	7 (54) <sup>a</sup>	34 (88)	
Complete response	5	27	
Partial response	2	7	
Lack of response	6 (46)	5 (12)	
Persistence	3 (23)	0 (0)	
Progression	3 (23)	4 (10)	
Breakthrough IFI	0 (0)	1 (2)	

All 6 patients responded after increase of voriconazole doses

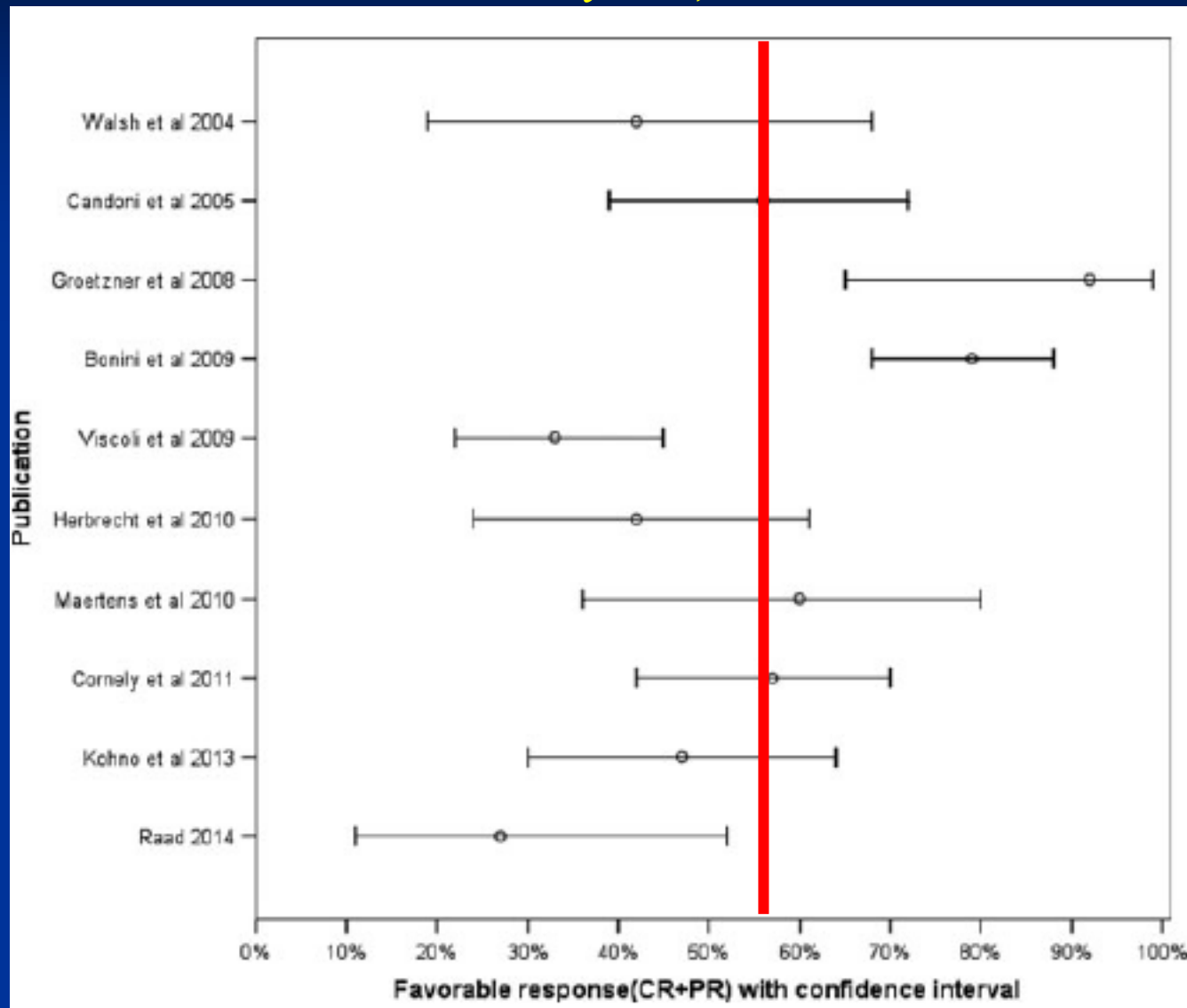


# Voriconazole through levels a safety of antifungal therapy

Variable	Vor trough blood level		P
	≤5.5 mg/L (n = 36)	>5.5 mg/L (n = 16)	
Vor route			.07
Intravenous	15 (42)	13 (81)	
Oral	21 (58)	3 (19)	
Vor dosage, median mg/kg/day (range)			
Overall	7 (2–11)	8 (6–11)	.13
Intravenous	7.5 (6–10)	8 (6–11)	NS
Oral	6 (2–11)	7 (6–8)	NS
Serious adverse event			
Encephalopathy			
Incidence	0	5 (31)	.002
Interval after start of Vor, days (range)	NA	9 (5–30)	
Cholestatic hepatopathy			
Incidence	3 (8)	3 (19)	NS
Interval after start of Vor, days (range)	50 (5–150)	13 (6–20)	NS
Concomitant therapy			
Omeprazole	6 (17)	7 (44)	.04
Tacrolimus	0	1 (6)	NS

# Clinical evidence for caspofungin monotherapy in the first-line and salvage therapy of invasive *Aspergillus* infections

Heinz et al *Mycoses*, 2016



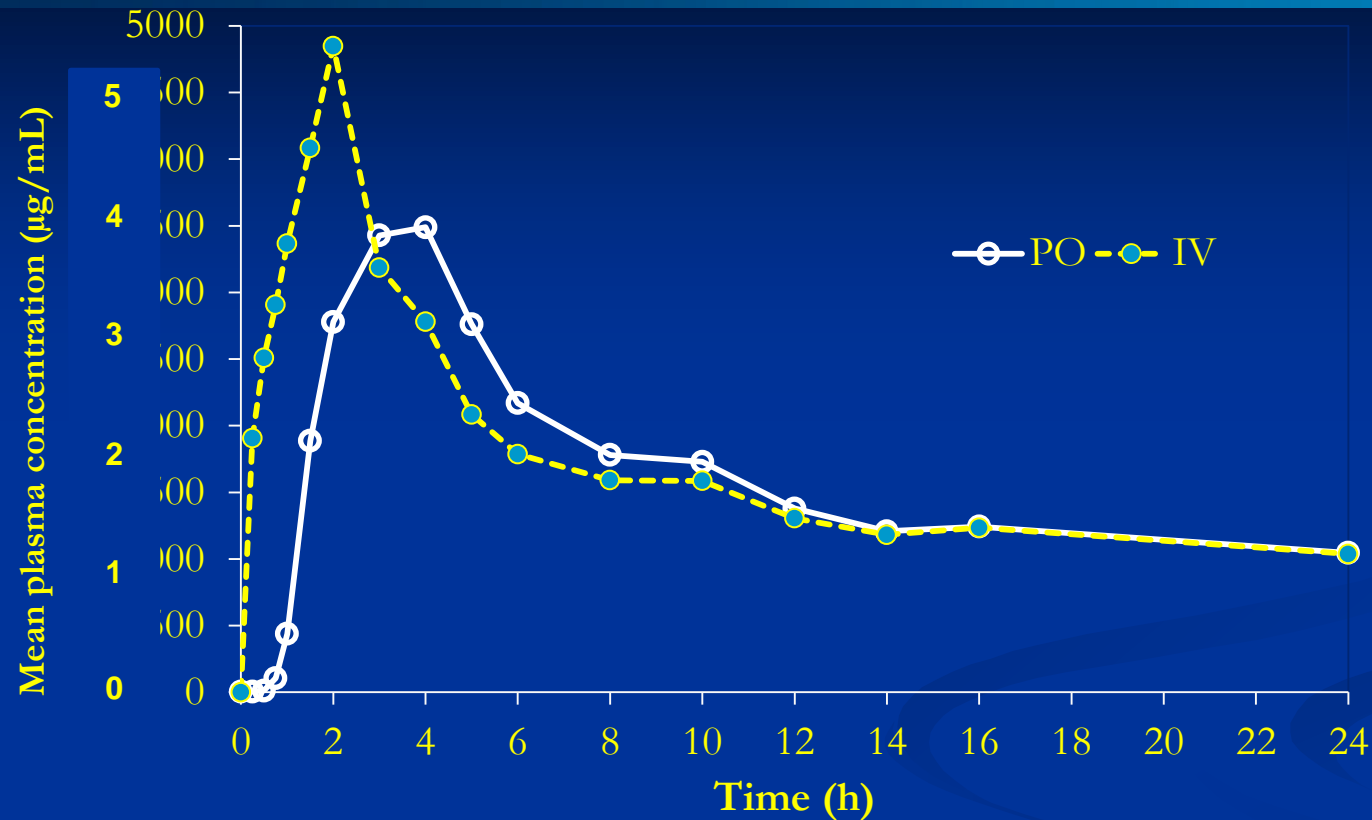
Circles indicate median favourable efficacy, and bars indicate confidence intervals.

# Isavuconazole: spectrum of activity

- Activity
- Variable activity
- Little or no activity

Organism	ISAV	POS	VRC	ITR	AmB	
<i>A. fumigatus</i>	Activity	Activity	Activity	Activity	Activity	Moulds
<i>A. flavus</i>	Activity	Activity	Activity	Activity	Activity	
<i>A. terreus</i>	Activity	Activity	Activity	Activity	Little or no activity	
<i>A. niger</i>	Activity	Activity	Activity	Activity	Activity	
<i>A. nidulans</i>	Activity	Activity	Activity	Activity	Activity	
<i>Fusarium spp.</i>	Variable activity	Variable activity	Variable activity	Little or no activity	Variable activity	
<i>Chromoblastomycosis</i>	Activity	Activity	Activity	Activity	Variable activity	
<i>Phaeohyphomycosis</i>	Activity	Activity	Activity	Activity	Little or no activity	
<i>Scedosporium apiospermum</i>	Variable activity	Variable activity	Variable activity	Variable activity	Variable activity	
<i>Scedosporium prolificans</i>	Little or no activity	Little or no activity	Little or no activity	Little or no activity	Little or no activity	Yeasts
Mucorales	Variable activity	Variable activity	Little or no activity	Little or no activity	Variable activity	
<i>Candida spp.</i>	Activity	Activity	Activity	Activity	Variable activity	
<i>Cryptococcus spp., Trichosporon spp.</i>	Activity	Activity	Activity	Activity	Variable activity	
<i>Histoplasma, Blastomyces, Coccidioides</i>	Activity	Activity	Activity	Activity	Activity	Dimorphic fungi

# Isavuconazole intravenous (IV) versus oral (PO) formulation



- IV (2-h infusion) and PO formulations are inter-changeable with PO bioavailability of 98%
- After PO administration  $C_{\max}$  is approx. 78% of that seen after IV dosing

# Primary end point (SECURE)

Maertens ECCMID 2014

## All-cause mortality (ACM) through Day 42 (ITT population)

	Isavuconazole N=258	Voriconazole N=258
All-cause mortality, n (%)	48 (18.6)	52 (20.2)
Adjusted treatment difference, % (95% CI) <sup>a</sup>	-1.0 (-7.8, 5.7)	
Deaths, n (%)	45 (17.4)	50 (19.4)
Unknown survival status, n (%) <sup>b</sup>	3 (1.2)	2 (0.8)

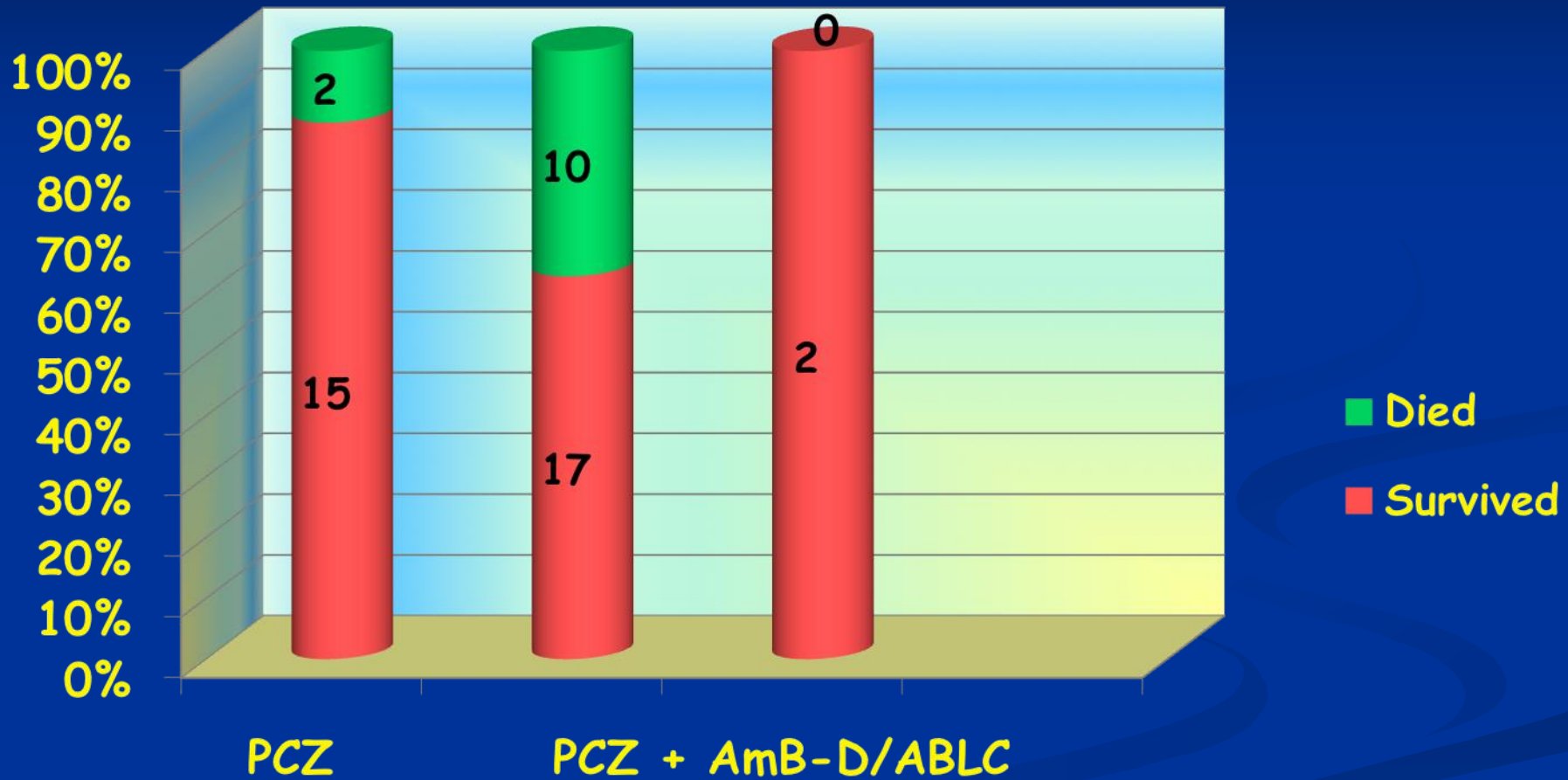
<sup>a</sup> Isavuconazole–voriconazole calculated by a stratified Cochran–Mantel–Haenszel method (strata: Geographic region, Allogeneic BMT/HSCT, and uncontrolled malignancy status)

<sup>b</sup> Patients with unknown survival status were counted as deaths

# Treatment-emergent adverse events (SECURE)

<b>Pts with Treatment-emergent Adverse Events (TEAEs)</b>	<b>Isavuco N=257 %</b>	<b>Vorico N=259 %</b>	<b>p-value</b>
Patients with any TEAE	96.1	98.5	NS
<b>Study drug-related TEAEs</b>	<b>42.4</b>	<b>59.8</b>	<b>&lt;0.05</b>
Serious TEAEs	52.1	57.5	NS
Study drug-related serious TEAEs	10.9	11.2	NS
<b>TEAEs leading to study drug discontinuation</b>	<b>14.4</b>	<b>22.8</b>	<b>&lt;0.05</b>
Study drug-related TEAEs leading to discontinuation	8.2	13.5	NS
Death	31.5	33.6	NS

# Pozaconazole in the treatment of zygomycosis: a review of the literature (1997-2012)





# **Mucormicosi: proposta di approccio terapeutico**

- 1. L-Ampho + Posaconazolo**
- 2. Livelli sierici di Posaconazolo  
adeguati**
- 3. Posaconazolo in monoterapia**
- 4. .. Rulo di isovuconazolo**

# Isavuconazole vs mucorales invasive infection: All-cause mortality (ACM) through Day 42

ACM (crude and weighted rates) was similar between isavuconazole (33.3%) and amphotericin B (crude 39.4%, weighted 41.3%) for the primary treatment of Mucormycosis.

	All-cause mortality n/N (%)	95% CI
Study 0103 <i>Mucorales</i> primary therapy cases	7/21 (33.3)	(14.588, 56.968) <sup>†</sup>
Amphotericin-treated matched-controls (crude mortality)	13/33 (39.4)	(22.907, 57.861) <sup>†</sup>
Amphotericin-treated matched-controls (weighted mortality)	(41.3)	(20.213, 62.326) <sup>‡</sup>

<sup>†</sup> Exact binomial CIs were calculated

<sup>‡</sup> 95% CI was calculated based on a normal approximation

Vehreschild ASH 2014

# Conclusioni

- La candidosi invasiva nella ultima decade si è dimostrata più frequentemente nei pazienti non critici degenti in Medicina Interna: può essere l'effetto di un aumento di nuovi immunodepressi, come complicanza della CDAD, oppure l'evoluzione indolente di una infezione contratta in UTI (es. EPV).
- La aspergillosi invasiva sta diventando un problema emergente nei pazienti non critici in virtù di nuove categorie di pazienti immunodepressi. I quadri clinici possono essere indolenti alla presentazione iniziale ed evolvere poi in virtù di nuovi "trigger" (es. H1N1) in maniera rapidamente progressiva . Voriconazolo, isovuconazolo & L ampho B i farmaci di scelta. Ruolo delle echinocandine?
- Per la mucormicosi, posaconazolo & isovuconazolo lasciano intravedere nuove prospettive di terapia medica. L-ampho ad alte dosi possibile alternativa, inizialmente in associazione con posaconazolo. Associazione ai fattori di crescita?.....ed alla ossigenoterapia iperbarica?

**Siate pronti, con la cintura ai fianchi e le  
lucerne accese (Lc, 12,35)**

**Grazie per la  
attenzione!**