

Catheter-related Candidemia

Preceptorship Program Sesion 3

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Case 1

**Liver Transplant patient
with fever 6 weeks after
transplantation**

Presentation

62 year old lady with Liver Tx 6 weeks ago.

Intestinal leak. Reinterventions on days + 10 and + 20.

Receiving Meropenem

Total Parenteral Nutrition and a Hickman catheter since 3 weeks ago

Presentation

Shaking chills and fever (39°C)

Hemodynamically stable

No particular physical findings

Chest examination: normal

Chest X-Ray: normal

Wounds in good healing

Abdominal echography: No new findings



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Topics selected for initial discussion

Incidence and dimension of the problem

The empirical use of antifungals

The assessment of the catheter involvement

The biofilm penetration by antifungals

Candida species and the relative risk

Topics selected for initial discussion

To keep or to retrieve the line

Guidewire for the replacement?

Is lock-therapy an alternative?

What is the antifungal treatment of choice.

How long to treat?

In your opinion what sentence defines best
the incidence of Catheter-Related
Candidemia?

Catheter related candidemia causes:

- 1.- 20 to 30% of all episodes of CRI.
- 2.- 10-19% of all episodes of CRI
- 3.- 5-10% of all episodes of CRI
- 4.- < 5% of all episodes of CRI
- 5.- I don't know a figure

Catheter related candidemia causes:

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5.- I don't know a figure

Candidemia species in the whole institution

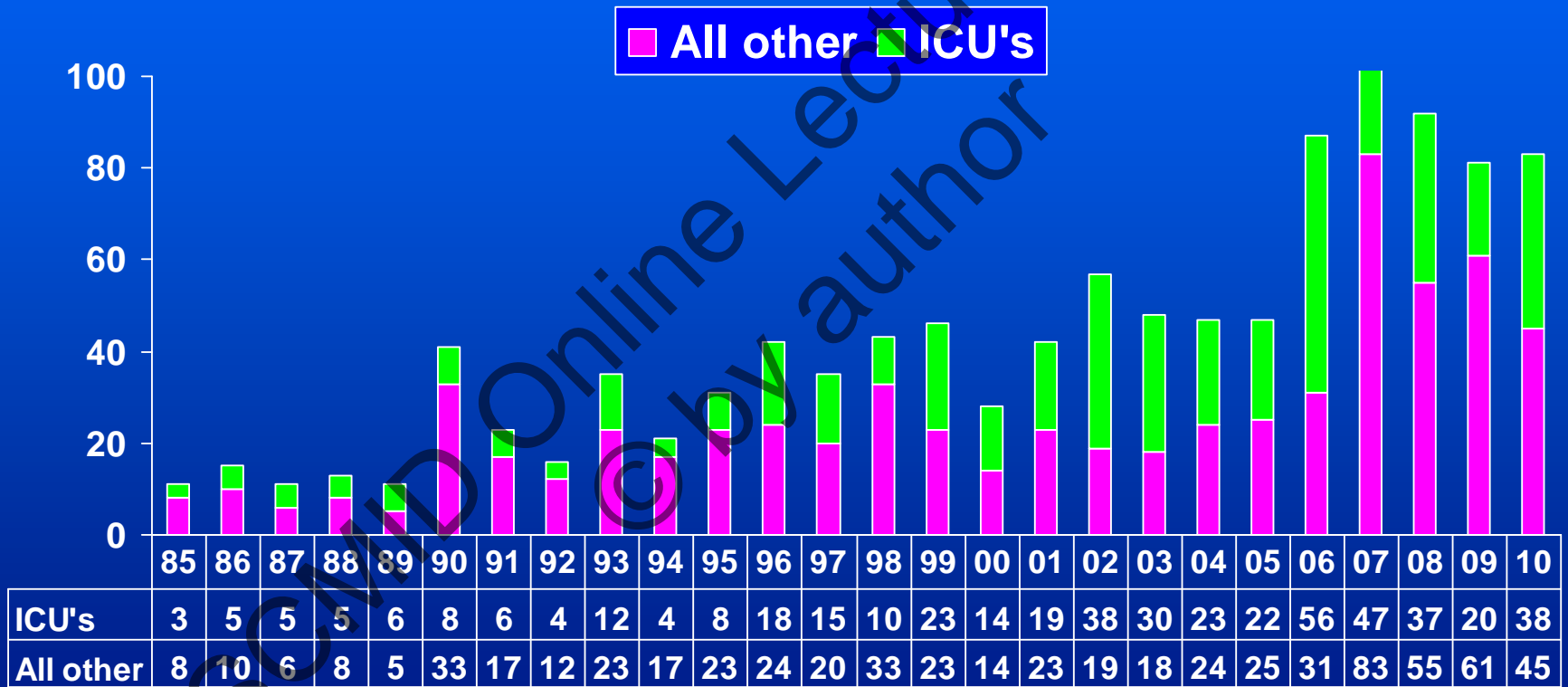
1985-2010

■ C. albicans ■ Candida no alb.



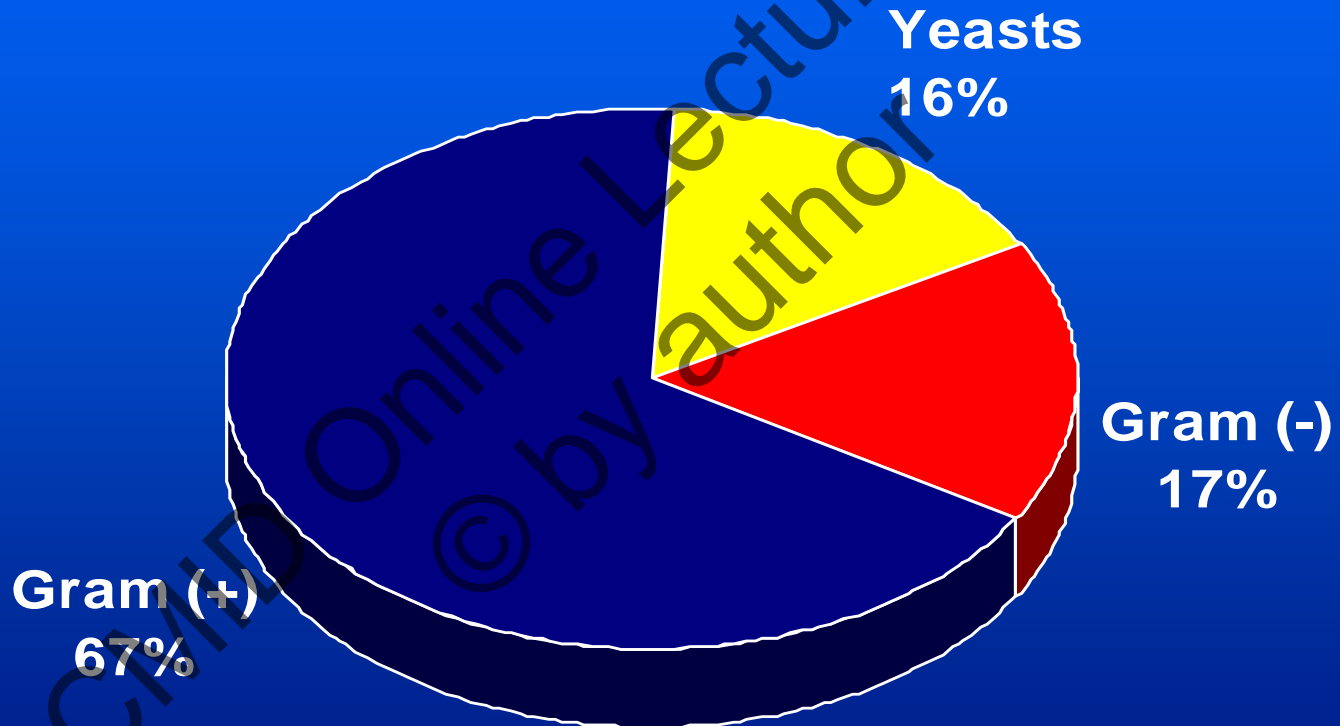
Candidemia in ICU's

1985-2010



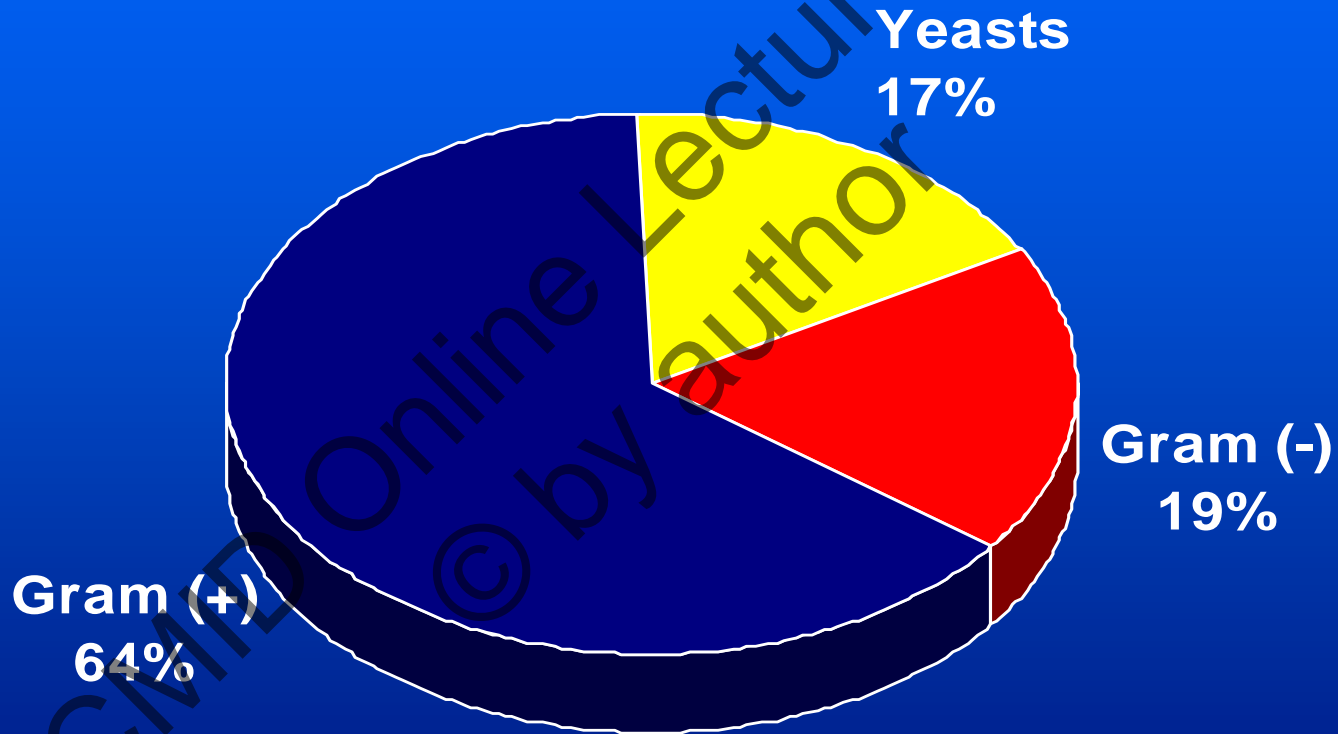
All Catheter related BSI (2003-2010). HGUGM

1234 episodes microbiologically proven



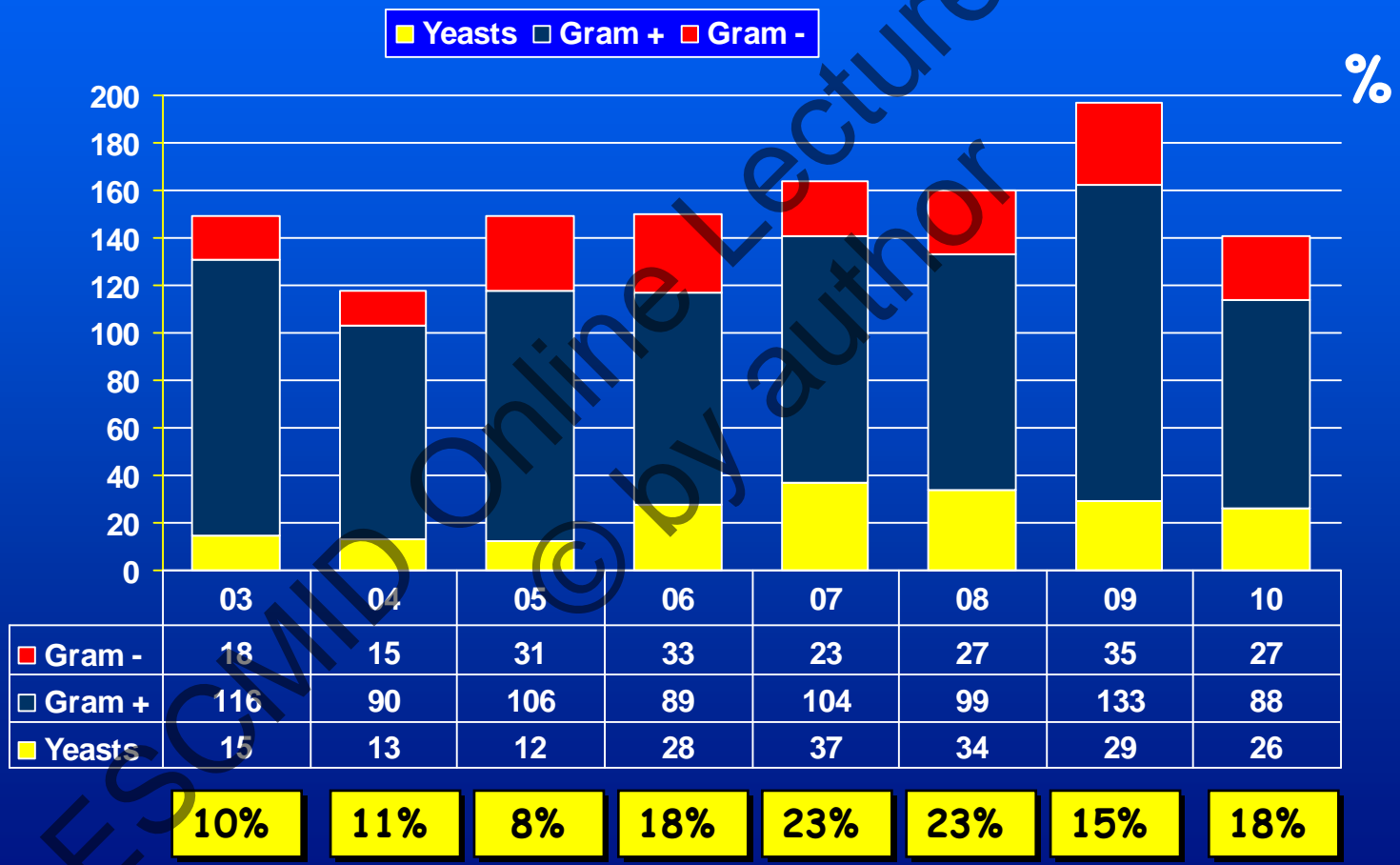
Catheter related BSI in ICUs (2003-2010). HGUGM

429 episodes microbiologically proven



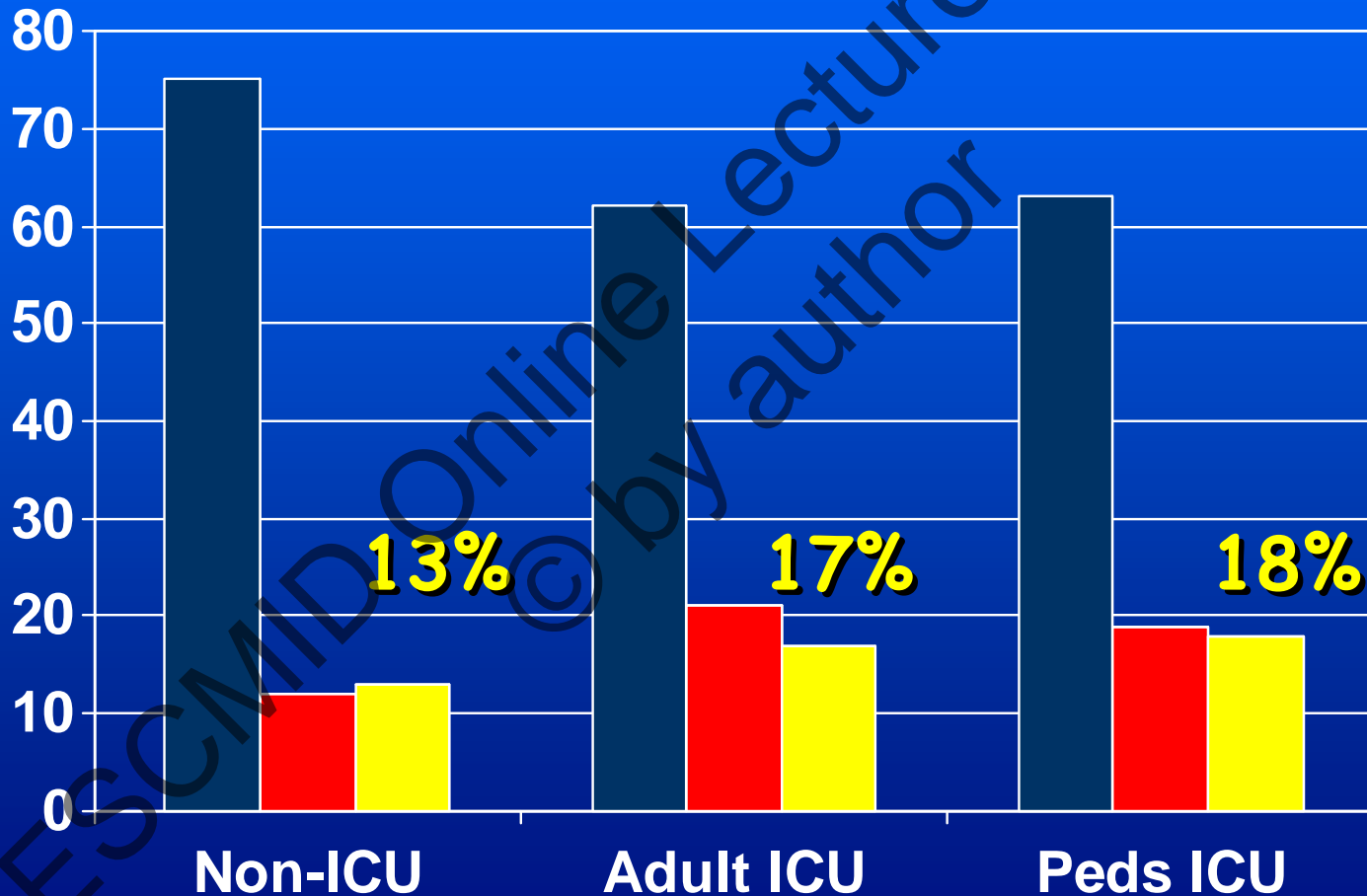
Catheter related BSI (2003-2010). HGUGM

1234 episodes. Evolution of Candida proportion



Catheter related BSI in HGUGM (2003-2010)

1234 episodes microbiologically proven



Incidence of Candidemia:

4th Leading BSI microorganism (USA)

Causing 5-10% of all BSI in ICU's

6th-10th BSI microorganism (E.U.)

Richards MJ. I.Cont.Hosp.Epi. 2000

Rangel-Frausto MS. C.I.D. 1999

Wisplinghoff H. C.I.D. 2003.

Nolla-Salas J. Int.Care.Med. 1997

Bouza E. Clin.Microb.Infect. 1999

Incidence of Candida-CR-BSI

Prowle et al. *Critical Care* 2011, **15**:R100
<http://ccforum.com/content/15/2/R100>



CRITICAL CARE

RESEARCH

Open Access

Acquired bloodstream infection in the intensive care unit: incidence and attributable mortality

Candida, Staphylococcus and Gram negatives associated with increase in death

Prowle JR. Crit.Care. 2011

Incidence of Candida-CR-BSI

6339 ICU admissions

330-BSI (5.2%)

34-Proven CR-BSI (10%)

Candida: 15.5% of all ICU acquired BSI

Population-based study in Barcelona

345 episodes of Candidemia

4.3 cases/100,000 inhabitants

0.5 cases/1,000 hospital discharges

0.7 cases/10,000 patient-days

57.4% likely related to the catheter

When confronted with a septic patient with suspicion of catheter origin. When do you include antifungal empiric treatment?

Empirical treatment

- 1.- All patients on broad spectrum antibiotics
- 2.- All patients already colonized by Candida
- 3.- Patients with a femoral line
- 4.- All solid and Bone Marrow transplants
- 5.- All of the above

Empirical treatment

- 1.- All patients on broad spectrum antibiotics
- 2.- All patients already colonized by Candida
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- 5.- All of the above

Empirical treatment of Candida if:

Total parenteral nutrition
Broad-spectrum abx.
Hematologic malignancy
Bone marrow transplantation
Solid-organ transplant
Femoral catheterization,
Colonization due to Candida species at
multiple sites



B-II

Empirical treatment of Candida:

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Empirical antifungal therapy should be considered for critically ill patients with risk factors for invasive candidiasis and no other known cause of fever, and it should be based on clinical assessment of risk factors, serologic markers for invasive candidiasis, and/or culture data from nonsterile sites (B-III).

Empirical treatment of Candida if:

27. In addition to coverage for gram-positive pathogens, empirical therapy for suspected CRBSI involving femoral catheters in critically ill patients should include coverage for gram-negative bacilli and *Candida* species (A-II).

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Empirical treatment of Candida:

Zilberberg et al. *BMC Infectious Diseases* 2010, **10**:150
<http://www.biomedcentral.com/1471-2334/10/150>



RESEARCH ARTICLE

Open Access

Inappropriate empiric antifungal therapy for candidemia in the ICU and hospital resource utilization: a retrospective cohort study

90% inadequate treatment in first 24 h
Delays 95%, Inadequate dosage 26%

Zilberberg MD. *BMC Infect.* 2010

What approach do you trust more to assess
if the catheter is the origin?

The assessment of catheter causality

- 1.- Differential quantitative blood cultures
- 2.- Differential time to positivity
- 3.- Superficial cultures permit to rule out the catheter origin if negative
- 4.- None of the above
- 5.- All of the above

The assessment of catheter causality

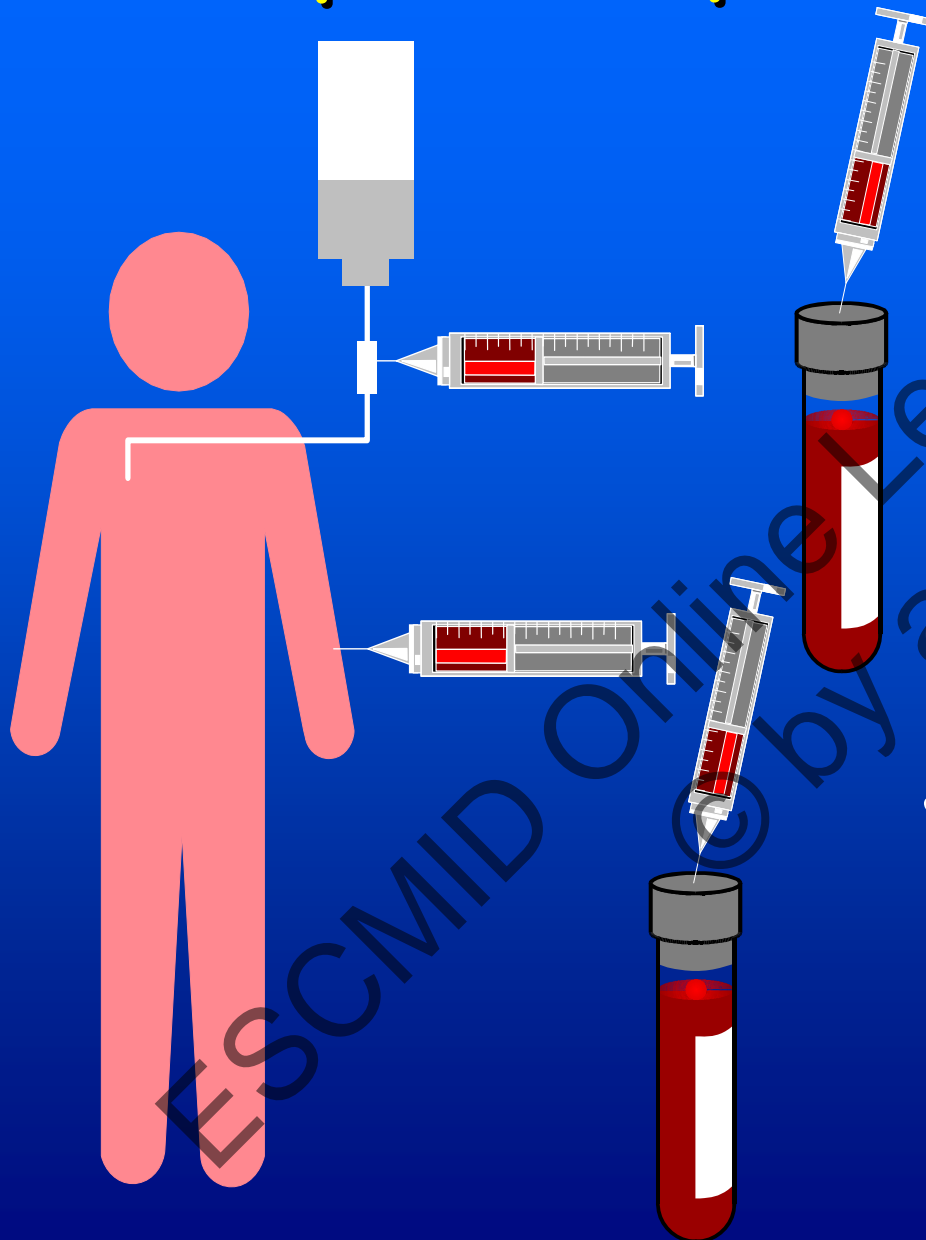
- 1.- Differential quantitative blood cultures
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- 3.- Superficial cultures permit to rule out the catheter origin if negative
- 4.- None of the above
- 5.- All of the above

DX: Differential time to positivity

Blot. J.Clin.Microbiol. 1998



DX: Comparative quantitative bacteremia



> 5 times

Specificity 100%

Sensitivity >80%

Mosca . Surgery 1987

Differential Time to Positivity: A Useful Method for Diagnosing Catheter-Related Bloodstream Infections

Issam Raad, MD; Hend A. Hanna, MD, MPH; Badie Alakech, MD; Ioannis Chatzinikolaou, MD; Marcella M. Johnson, MS; and Jeffrey Tarrand, MD

Background: Catheter-related bloodstream infections are associated with recognized morbidity and mortality, especially in critically ill patients. Accurate diagnosis of such infections results in proper management of patients and in reducing unnecessary removal of catheters.

Objective: To evaluate differential time to positivity as a method for diagnosing catheter-related bacteremias caused by both short-term and long-term use of central venous catheters.

Design: Prospective study design.

Setting: M.D. Anderson Cancer Center, Houston, Texas, a tertiary care cancer center.

Patients: All patients, between September 1999 and November 2000, who had the same organism isolated from blood cultures drawn simultaneously through the central venous catheter and the peripheral vein.

Measurements: Time necessary for the blood cultures from the central venous catheter and the peripheral vein to become positive, as well as other relevant patient information.

Results: 191 bloodstream infections with positive simultaneous central venous catheter and peripheral vein blood cultures were included. One hundred eight patients had catheter-related bacteremias, and 83 had non-catheter-related bacteremias. Catheter-related bacteremias were more frequently caused by staphylococci and less likely to be associated with underlying hematologic malignant conditions, neutropenia, and longer duration of hospitalization. As a diagnostic tool for catheter-related bacteremia (using a composite definition reference standard according to the Infectious Diseases Society of America guidelines), differential time to positivity of 120 minutes or more was associated with 81% sensitivity and 92% specificity for short-term catheters and 93% sensitivity and 75% specificity for long-term catheters.

Conclusion: Differential time to positivity of 120 minutes or more is highly sensitive and specific for catheter-related bacteremia in patients who have short- and long-term catheters.

Ann Intern Med. 2004;140:18-25.

For author affiliations, see end of text.

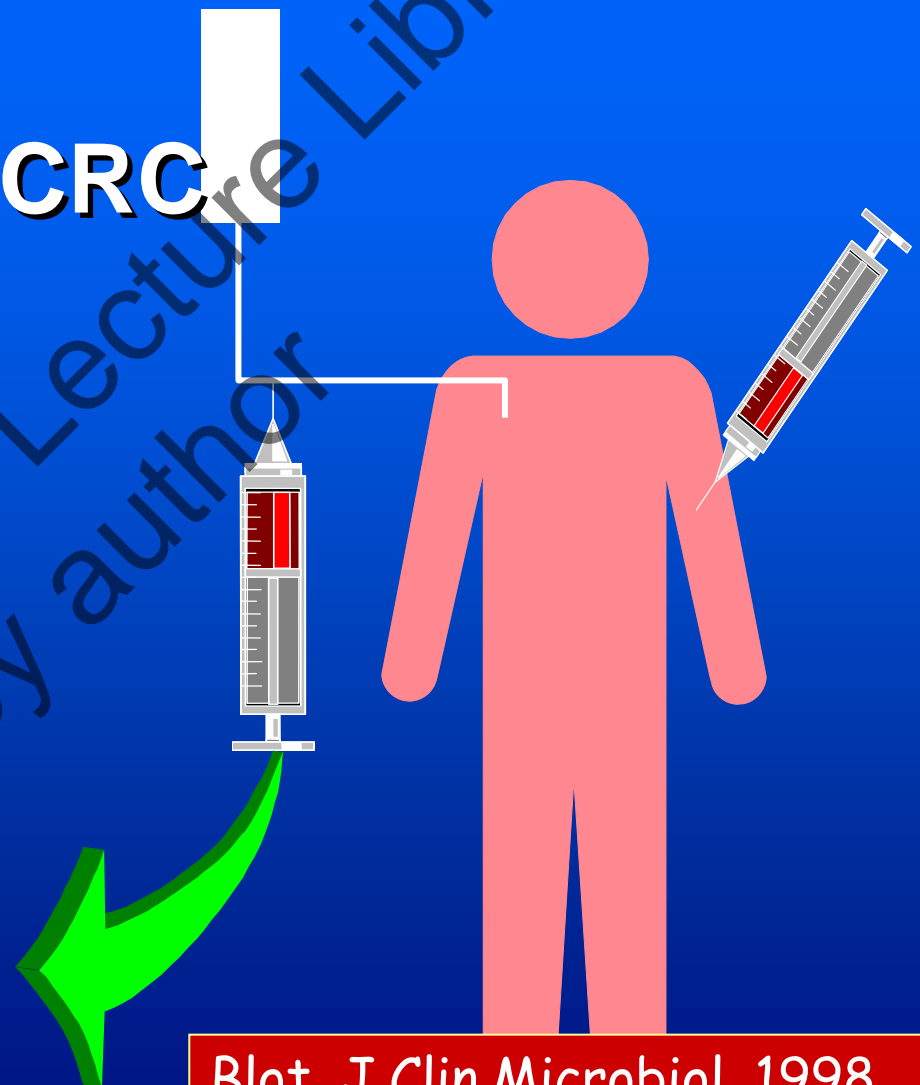
See editorial comment on pp 62-64.

www.annals.org

Raad I. Ann.Intern.Med. 2004

DX: Differential time to positivity

> 2 h suggestive of CRC



Blot. J.Clin.Microbiol. 1998

Raad I. Ann.Intern.Med. 2004

Differential time to positivity



- 204 ICU patients included
 - 26 CRB
 - 29 BSI from other origins
 - 36 Cath colonization

6 candidemias

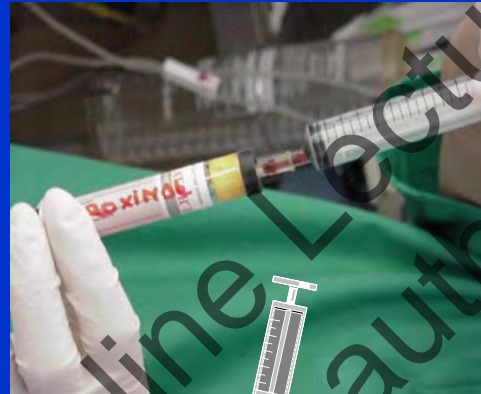
	Superficial	DQC	DTTP
Sensitivity	78.6	71.4	96.4
Specificity	92.0	97.7	90.3
PPV	61.1	83.3	61.4
NPV	96.4	95.6	99.4
Accuracy	90.2	94.1	91.2

DTP: In Intensive Care Units

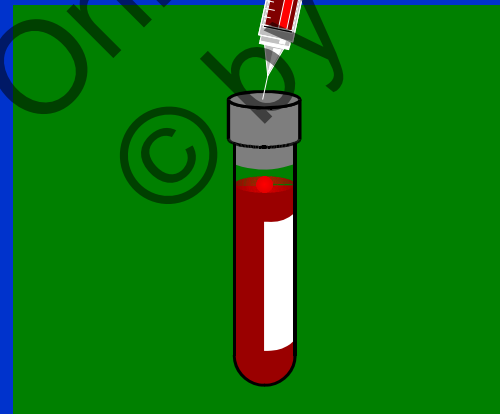
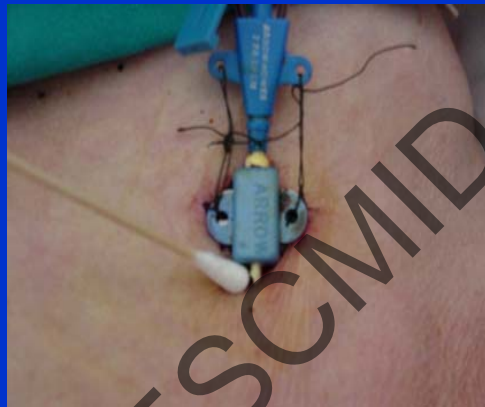
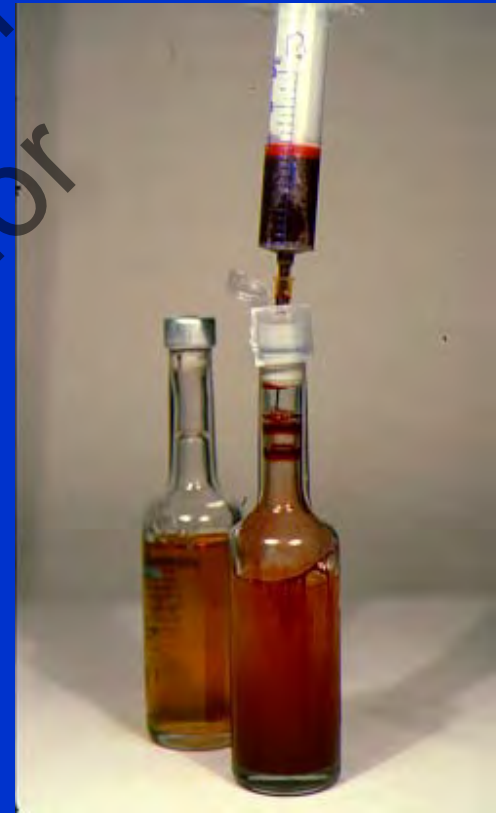
Superficial



DQC:Lysis



DTP



DTP: In Intensive Care Units





	Superficial	DQC	DTTP
Sensitivity	78.6	71.4	96.4
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The challenge of anticipating catheter tip colonization in major heart surgery patients in the intensive care unit: Are surface cultures useful?

Emilio Bouza, MD, PhD; Patricia Muñoz, MD, PhD; Almudena Burillo, MD, PhD;
Javier López-Rodríguez, MD; Cristina Fernández-Pérez, MD, PhD; María Jesús Pérez, RN;
Cristina Rincón, RN; and the Cardiovascular Infection Study Group



Preliminary results in candidemia: PPV 100%, NPV 75%

 Sensitivity	83.5%	(73.6-90.4)
 Specificity	67.1%	(60.6-72.9)
 PPV	47.6%	(39.5-55.9)
 NPV	91.9%	(86.5-95.3)

Time to positivity and candidemia

JOURNAL OF CLINICAL MICROBIOLOGY, July 2008, p. 2222–2226

0095-1137/08/\$08.00+0 doi:10.1128/JCM.00214-08

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Time to Blood Culture Positivity as a Marker for Catheter-Related Candidemia[▽]

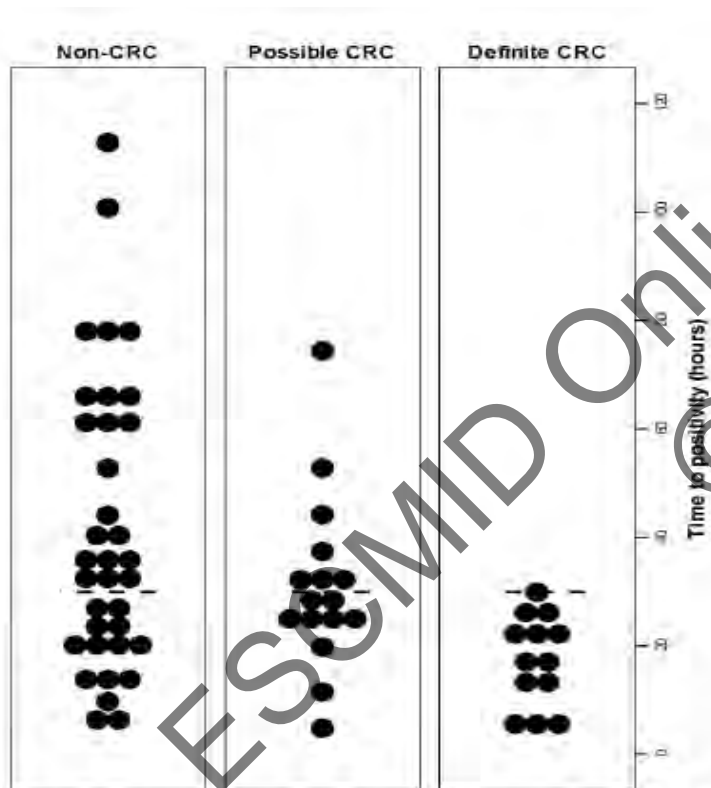


FIG. 1. Time to positivity among patient populations with different likelihoods of catheter-related candidemia. The short horizontal dashed lines mark the 30-h cutoff.

Time to positivity
< 30 h
Sensitive but non-specific
> 30 h Rule out
Catheter origin

Ben-Ami R. J.Clin.Microb. 2008

Withdrawing the catheter

Management of Central Venous Catheters in Patients with Cancer and Candidemia

Early catheter removal (< 72 h) improves response to antifungal agents in cases with a catheter-related fungemia

Factors of secondary origin: Neutropenia, disseminated disease, poor response to antifungal treatment, prior chemotherapy, corticosteroid treatment

Raad I. C.I.D. 2004

Could you assess the catheter as a potential origin without initial catheter withdrawal?

- ☞ Clinical diagnosis inaccurate (<25%)
- ☞ Help from the lab
 - **Is the catheter colonized?**
 - ◆ Superficial cultures
 - **Has the patient CRBSI?**
 - ◆ Differential time to positivity > 2 hours
 - ◆ Time to positivity > 30 hours
 - ◆ >25 cfu/ml in peripheral blood (Telenti A)

Time to positivity in CR candidemia

- ➔ TTP in **peripheral** blood is a sensitive but nonspecific marker for catheter-related candidemia
- ➔ TTP of more than 30 h can help **exclude** an intravascular catheter as the possible source of candidemia

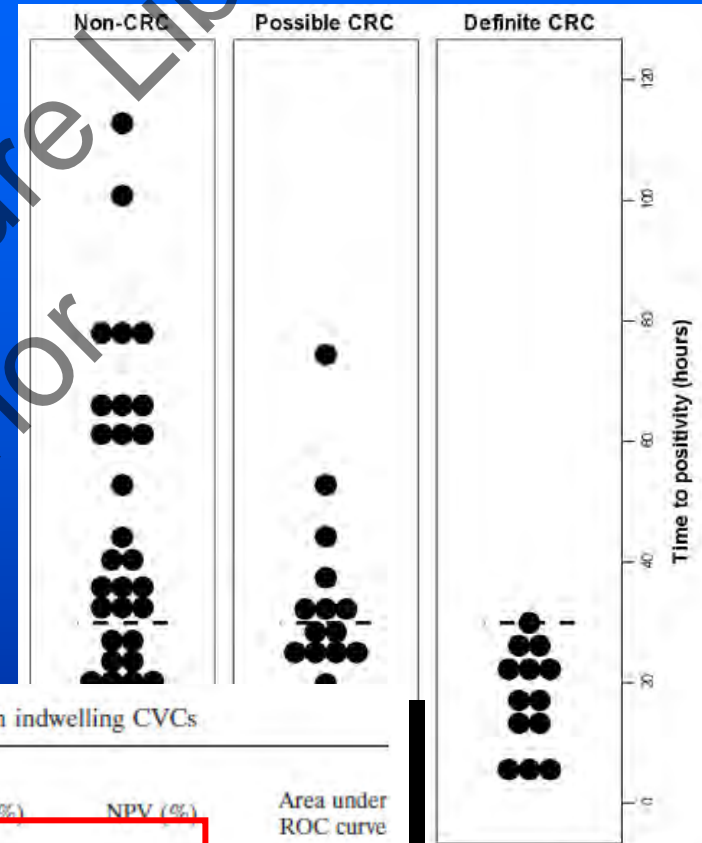
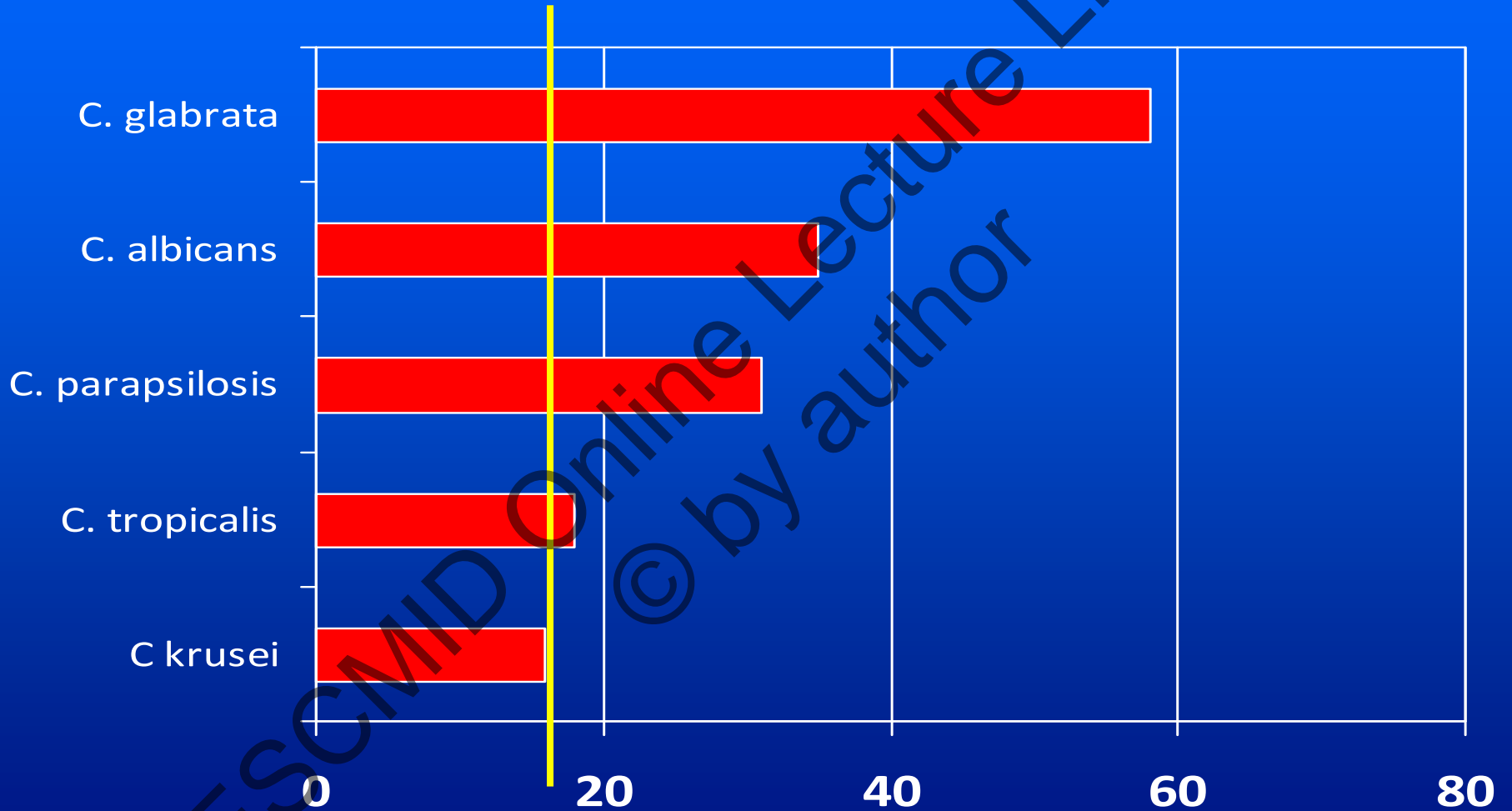


TABLE 3. Accuracy of a TTP cutoff of 30 h for the diagnosis of CRC in 50 patients with indwelling CVCs

Patient group	No. of patients with CRC diagnosis with the following TTP cutoff		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Area under ROC curve
	TTP ≤ 30 h	TTP > 30 h					
Definite CRC	13	0	100	51.4	41.9	100	0.76
Possible + non-CRC	18	19					
Definite + possible CRC	22	7	75.9	57.1	71.0	63.2	0.66
Non-CRC	9	12					

ent populations with different
mia. The short horizontal

Median time to positivity in Candidemia blood cultures (hours)



CRITICAL WINDOW: 12-24 H

How difficult to penetrate is Candida
biofilm?

The penetration of Candida biofilm

- 1.- Azoles penetrate very well
- 2.- Amphotericin B penetrates well
- 3.- Candins penetrate well in Candida biofilm
- 4.- Candins penetrate well but not equally
- 5.- I don't think penetration in biofilm matters for the treatment of CR-Fungemia

Candida biofilms



Revista Iberoamericana de Micología

www.elsevier.es/reviberoammicol



Actividad de la micafungina contra las biopelículas de *Candida*

Amphotericin B and azole drugs: poor penetration

Quindós G. Rev.IberoAm. Micol 2009

Candida biofilms



Revista Iberoamericana
de Micología

www.elsevier.es/reviberoammicol



Actividad de la micafungina contra las biopelículas de *Candida*

Candins

Good penetration in *Candida: albicans, dubliniensis, glabrata and krusei*

Variable in *Candida: parapsilosis and tropicalis*

Quindós G. Rev.IberoAm. Micol 2009

Candida biofilms: Activity of candins

Require 10-100 times concentrations than in planktonic cells

Inter-species variability

Depends on the substrate use in the study

Micafungin has a shorter period for action
Caspofungin and other candins are inactive in *Trichosporon ashaii* and *Cryptococcus neoformans* biofilms

Candida biofilms

International Journal of Antimicrobial Agents 37 (2011) 380–384

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

Journal homepage: <http://www.elsevier.com/locate/ijantimicag>



ELSEVIER



Short communication

Possible role of azole and echinocandin lock solutions in the control of *Candida* biofilms associated with silicone

8 *C. albicans* and 6 *C. glabrata*
Caspo, Mica and Posaconazole activity

Cateau E. Int.J.Antimicrob.Agents. 2011

Candida biofilms

Table 2
Reductions in the metabolic activity of young *Candida* biofilm yeasts induced by antifungal lock solutions.

<i>Candida</i> spp.	Post-lock interval (h)	Decrease in metabolic activity (%) ^a				
		Caspofungin		Miconazole		Posaconazole
		5 (mg/L)	25 (mg/L)	5 (mg/L)	15 (mg/L)	
<i>C. albicans</i>	24	81.3 ± 8.8	76.9 ± 12	75.1 ± 14.1	70.7 ± 11.3	54.2 ± 6
	48	76.8 ± 12.4	78.6 ± 11.1	77.7 ± 14.4	65.4 ± 18.3	49.7 ± 12
	72	78.6 ± 17.4	79.5 ± 8.3	81.2 ± 9.3	74.8 ± 13.3	41.3 ± 7.9
<i>C. glabrata</i>	24	76.7 ± 10.1	N/S	92.7 ± 0.4	N/S	None ^b
	48	55.8 ± 16.7	N/S	91.6 ± 20.7	N/S	None
	72	42.8 ± 19.1	N/S	92.4 ± 0.8	N/S	None

N/S, not studied.

^a Decreases are calculated as the mean reduction for each species (10 strains of *C. albicans* and 6 of *C. glabrata*; Table 1); mean reductions are presented for each antifungal concentration tested (5 mg/L and 25 mg/L caspofungin, 5 mg/L and 15 mg/L miconazole and 10 mg/L posaconazole) and for each post-lock interval studied (24, 48 or 72 h).

^b None indicates that no inhibition was measured.

Mica, Caspo and Posa reduce metabolic activity. No 100% inhibition
Miconazole has a more prolonged effect

Cateau E. Int.J.Antimicrob.Agents. 2011

Is the species of *Candida* present in blood of any help in assessing the catheter involvement?

Candida species and the catheter role

- 1.- All candida species can cause CR-BSI and the species does not help to assess the involvement
- 2.- *Candida parapsilosis* is particularly prone to CR-BSI
- 3.- *Candida krusei* is distinctly uncommon in patients with CR-BSI
- 4.- Candida with the crf gene are particularly prone to infect the catheter
- 5.- You don't have an opinion in this point

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Predictors of Adverse Outcome in Cancer Patients with Candidemia

Elias J. Anaissie, John H. Rex, Ömrün Uzun, Shahe Vartivarian

C. parapsilosis is more frequently associated to catheter infection and has a better prognosis

Risk of Candidemia

2,853 patients admitted into the ICU.

118 with candidemia

41.4 cases per 1,000 ICU admissions

2.09 per 1,000 hospital admissions

18.6% *C. albicans*

81.4% *C. non-albicans*

66% *C. parapsilosis*

12.7% *C. tropicalis*

2.5% *C. glabrata*

C. parapsilosis
strongly related
with catheters

If you are taking care of a patient with Candidemia presumptively related to the catheter, what is your attitude regarding retrieving the line?

Pulling or maintaining the line?

- 1.- I pull the line in all circumstances
- 2.- I keep the line if is badly needed, but treat with systemic antifungals
- 3.- I may keep the line for a few days but add lock therapy and systemic antifungals
- 4.- I keep the line, add lock and systemic antifungals and wait for the results of follow-up cultures
- 5.- I don't have an opinion on this point

Pulling or maintaining the line?

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Retrieving or Keeping the line

Remove the catheter

Candidemia + short term catheter
No obvious source of infection
Remove the catheter and the tip for culture
A-II

AI If positive tip with same Candida species:
Remove on guidewire and send tip for culture
B-II

Withdrawing the catheter

Year	Author	Journal	Catheter Removal
1995	Rex JH	Clin.Infect.Dis	Yes
1995	Nguyen MH	Arch.Int.Med	Yes
1996	Hung CC	J.Formos Med Ass	Yes
1998	Nucci M	I.C.H.E.	Yes
2000	Karkowicz MG	Pediatrics	Yes
2004	Raad I	Clin.Infect.Dis	Yes
2005	Almirante B	J.Clin.Microb	Yes
2009	Mermel L	C.I.D.	Yes
2009	Pappas P	C.I.D.	Yes

Withdrawing the catheter

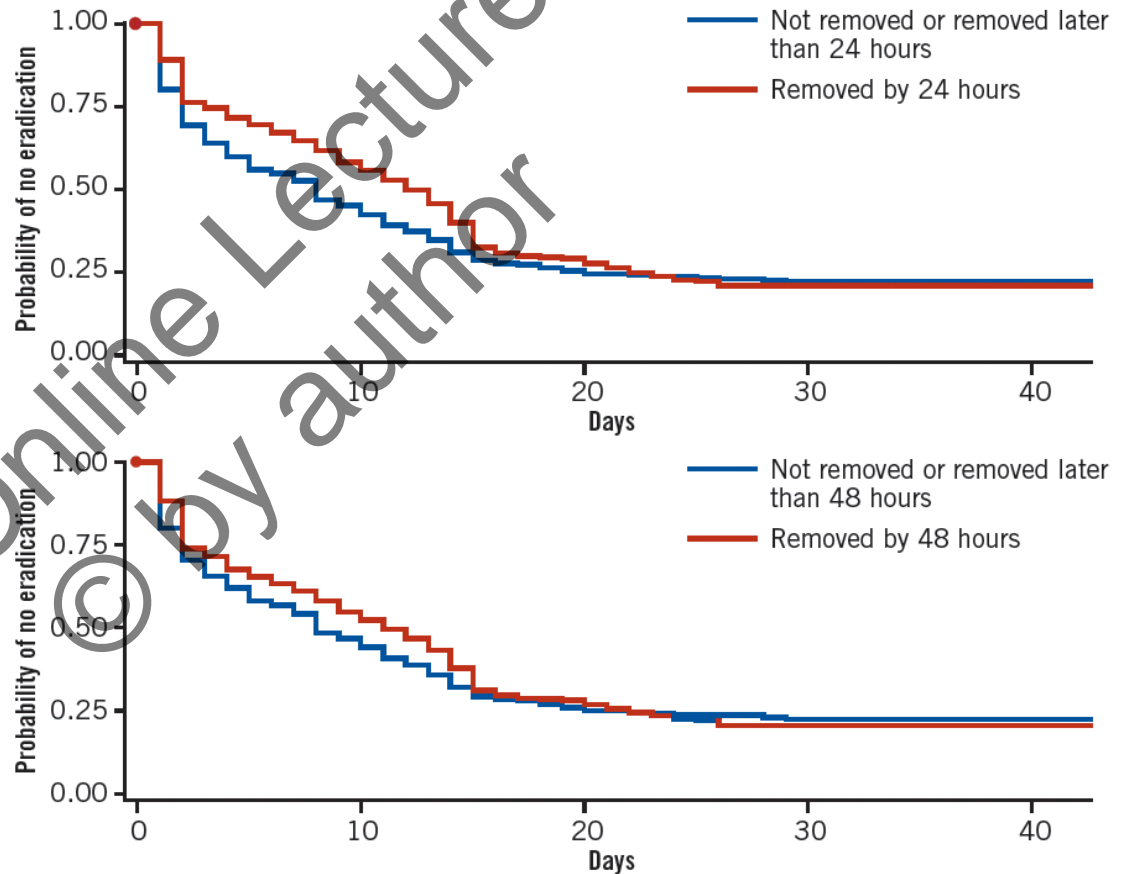
Early Removal of Central Venous Catheter in Patients with Candidemia Does Not Improve Outcome: Analysis of 842 Patients from 2 Randomized Clinical Trials

842 adults. Early removal of catheter (24-48h) was not associated with any clinical benefit.

Withdrawing the catheter

- Catheter removal by 24 or 48 hours after treatment initiation had no effect on:
 - Overall treatment success
 - Mortality
 - Mycological eradication
- Possible effect of removal after 48 hours was not assessed

Kaplan–Meier plots of time to mycological eradication by catheter removal status: CVC24 (top) and CVC48 (bottom).



In case you have to pull the line, what is your attitude regarding catheter replacement?

Catheter replacement

- 1.- I replace by guidewire and wait for catheter tip results
- 2.- I replace by guidewire but use for replacement a catheter impregnated in antifungals
- 3.- I replace by guidewire and initiate antifungal lock for prevention
- 4.- I never replace by guidewire
- 5.- I don't have an opinion on this point

Catheter replacement

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Guidewire exchange

For patients with unexplained fever, if blood culture results are positive and the CVC or arterial catheter was exchanged over a guidewire, and the catheter has significant growth, then the catheter should be removed and a new catheter placed in a new site

B-II

Guidewire exchange

If other vascular sites are unavailable and/or the patient is at increased risk for bleeding diathesis in the setting of SI not complicated by an exit site infection, then exchange the infected catheter over a guidewire

B-II

ESCMID ©

Guidewire exchange for Candida

Alternatively, for patients with limited venous access, exchange the catheter over a guidewire and perform catheter tip cultures

B-II

If the catheter is colonized with the same species of Candida as found in a percutaneous blood culture, the catheter should be removed

A-II

Pulling the line

Novel Approach Using Antimicrobial Catheters to Improve the Management of Central Line-Associated Bloodstream Infections in Cancer Patients

Exchanging infected catheters on guidewires is safe if the new catheter is coated with Minocycline and Rifampin
No cases caused by Candida

What is your opinion regarding the present and future of lock therapy in patients with Candidemia related to the catheter?

Lock-therapy with antifungal agents

- 1.- I don't use Amphotericin B for locks
- 2.- I don't trust azoles for lock therapy
- 3.- I prefer candins for lock therapy
- 4.- Experimental models suggest that Micafungin is going to be the choice candin for lock therapy
- 5.- Lock therapy with anti-fungals is not established yet and should be considered in research phase

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Lock-therapy for Candida

Catheter removal is recommended for CRBSI due to *S. aureus* and *Candida* species, instead of treatment with antibiotic lock and catheter retention, unless there are unusual extenuating circumstances (e.g., no alternative catheter insertion site)

A-II

Lock-therapy for Candida

J Infect Chemother

DOI 10.1007/s10156-011-0224-3

ORIGINAL ARTICLE

In vitro effectiveness of antifungal lock solutions on catheters infected with *Candida* species

**In vitro antibiotic Lock-Model
Infected catheters *C. albicans* and *C. parapsilosis***

AmphoB, Caspo, Fluco, Itra, Vori.

300, 500, 1000 fold MIC

1,3,5,7 days

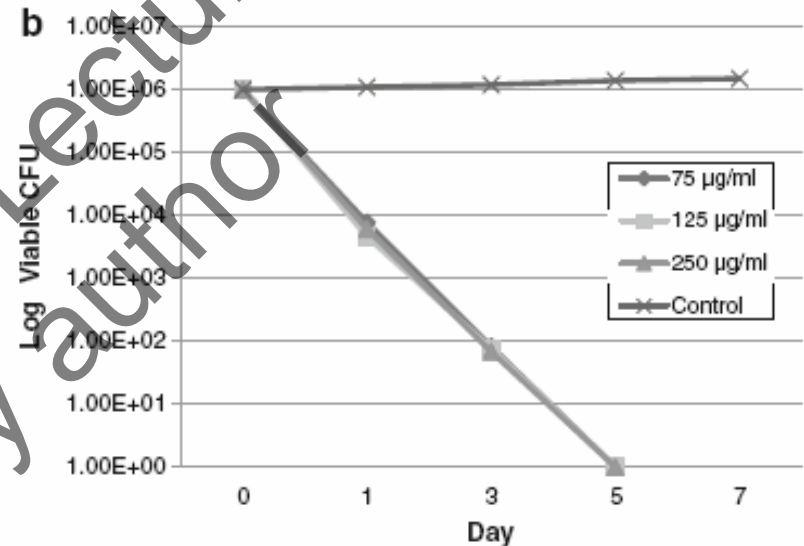
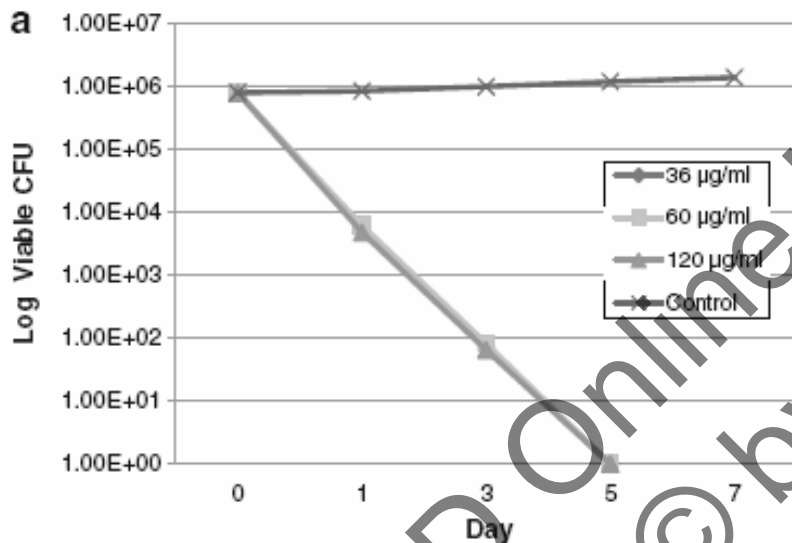
Oncu S. J.Infect.Chemother. 2011

Lock for Candida

Oncu S. J.Infect.Chemother. 2011

C. albicans

C. parapsilosis



Ampho B

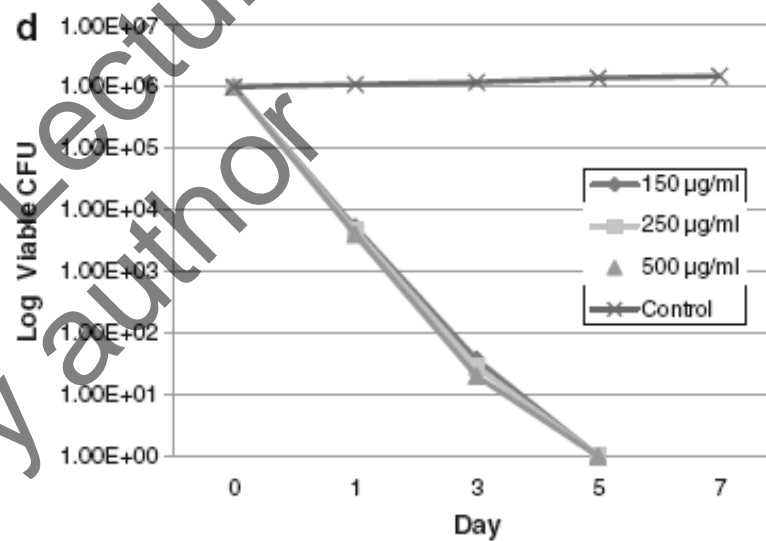
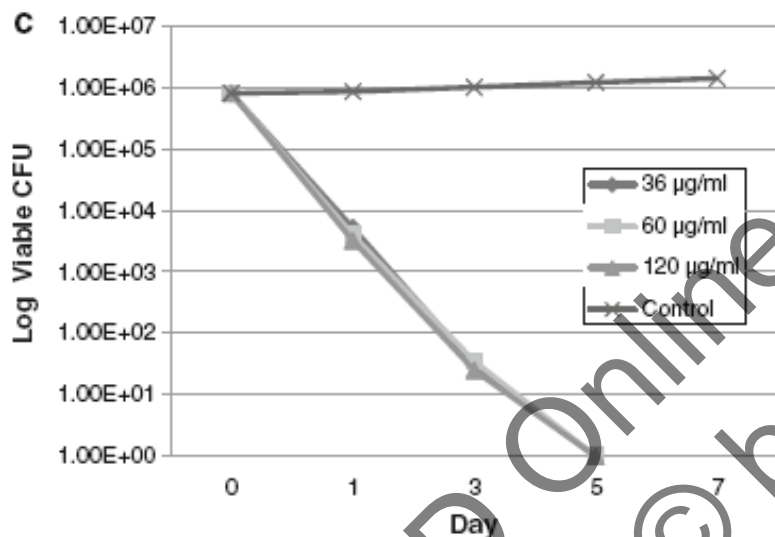
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Lock for Candida

Oncu S. J.Infect.Chemother. 2011

C. albicans

C. parapsilosis



Caspofungin

ESCMID

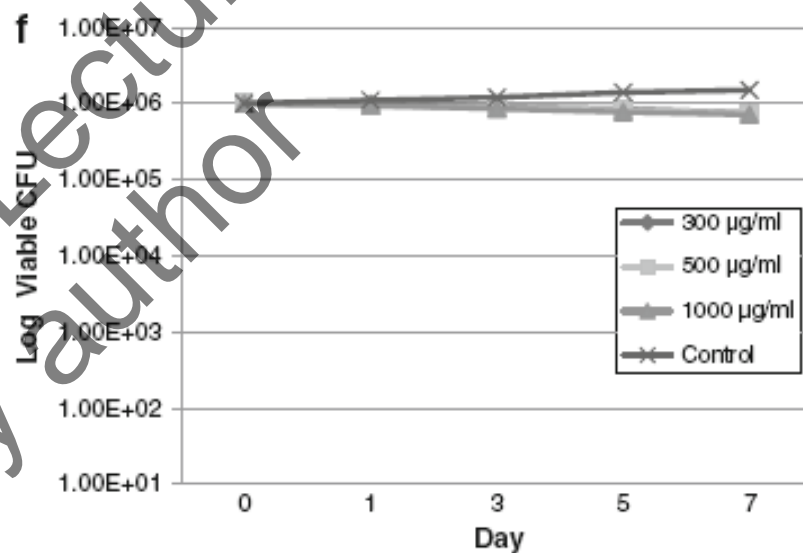
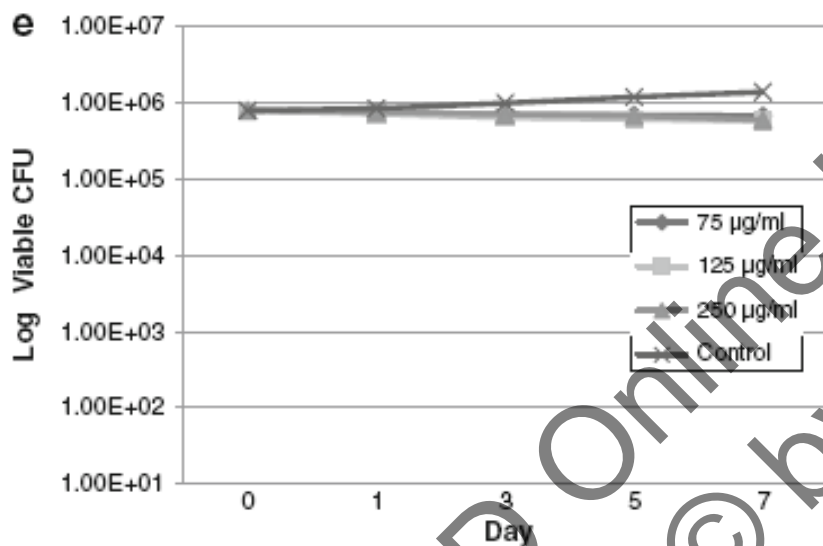
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Lock for Candida

Oncu S. J.Infect.Chemother. 2011

C. albicans

C. parapsilosis



Fluconazole

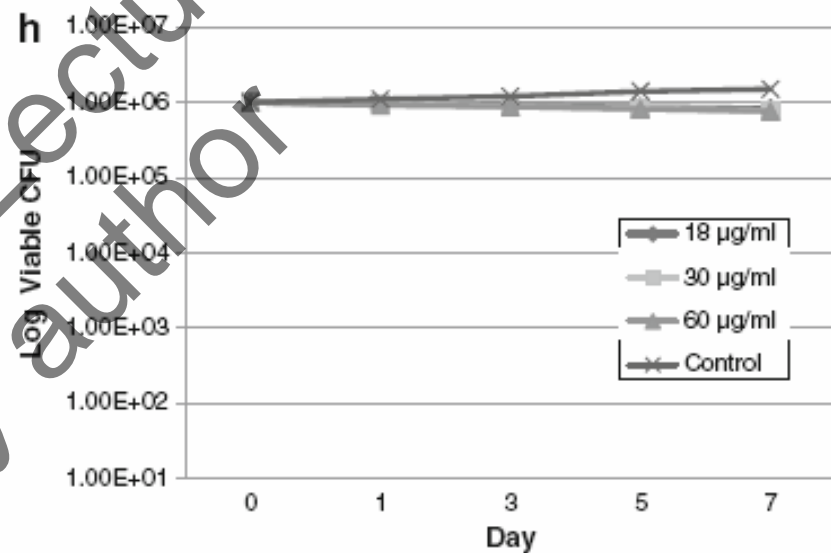
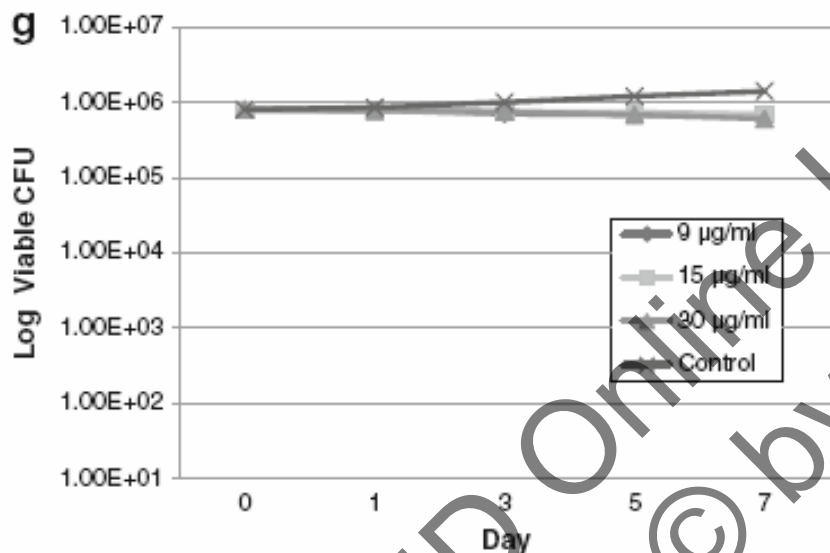
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Lock for Candida

Oncu S. J.Infect.Chemother. 2011

C. albicans

C. parapsilosis



Itraconazole

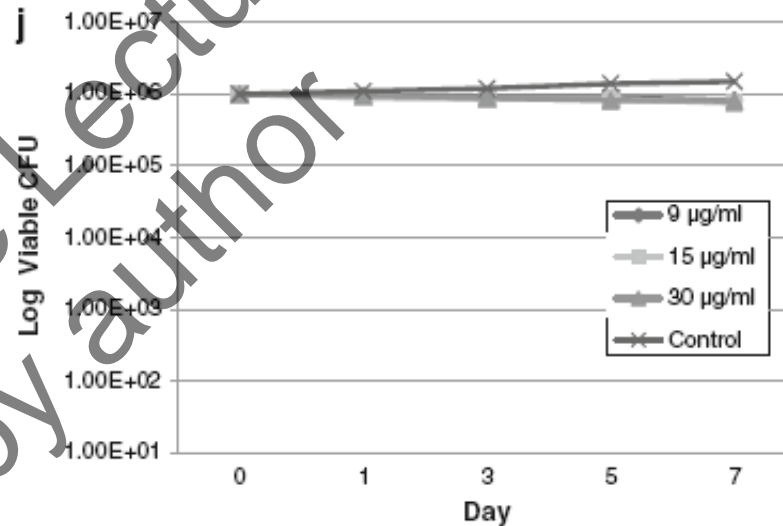
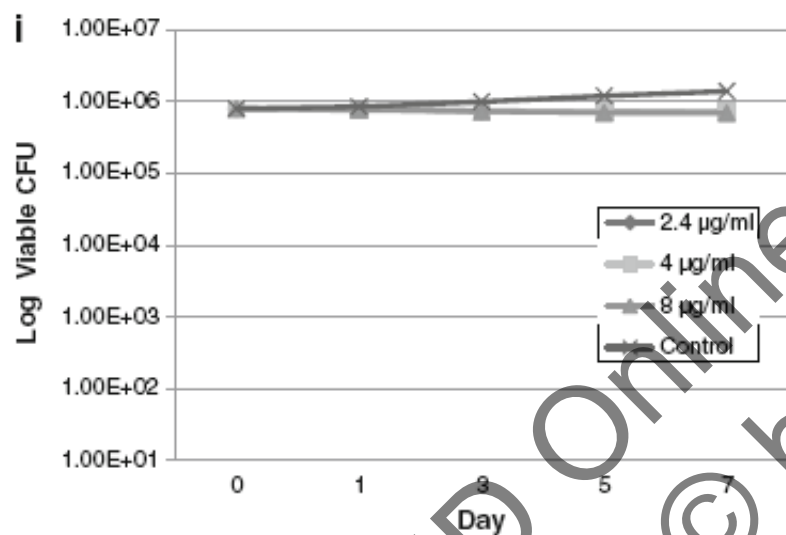
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Lock for Candida

Oncu S. J. Infect. Chemother. 2011

C. albicans

C. parapsilosis



Voriconazole

ESCMID

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How long would you treat patients with
Catheter-Related candidemia?

How long would you treat?

- 1.- For 2 weeks after first positive blood cultures
- 2.- For 2 weeks after the first negative follow up blood cultures
- 3.- For 2 weeks after negative BC's but with a long-term follow up
- 4.- For 4-6 weeks if TEE is not available or if retinal lesions were present and with a long term follow up
- 5.- I don't have an opinion on this point

How long would you treat?

- 1.- For 2 weeks after first positive blood cultures
- 2.- For 2 weeks after the first negative follow up blood cultures
- 3.- For 2 weeks after negative BC's but with a long-term follow up
- 4.- For 4-6 weeks if TEE is not available or if retinal lesions were present and with a long term follow up
- 5.- I don't have an opinion on this point

What is your attitude in patients with catheter tips colonized with *Candida*, without concomitant fungemia?

Candida Colonized Catheters (CCC)

- 1.- I do not prescribe antifungals on the basis of Candida colonization of the catheter tips and do not perform follow-up BC's
- 2.- I do not prescribe antifungals on the basis of Candida colonization of the catheter tips but carefully follow-up BC's.
- 3.- I treat the patient as if BC's were positive.
- 4.- I treat the patients with antifungals until follow-up cultures return negative.
- 5.- I never saw a patient in that situation

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Candida colonization without candidemia

Is *Candida* colonization of central vascular catheters in non-candidemic, non-neutropenic patients an indication for antifungals?

No differences in long term outcome between patients treated or not treated with antifungal therapy for *Candida* colonization of the catheter tips

Candida colonization of the CVC tip

Hospital	1.750 beds
Adult ICU's	60 beds
February 2003	February 2007

Patients with Candida in the CVC tip
Blood cultures without candidemia

Clinical improvement

Poor outcome

Bouza E. et al. Preliminary data. 2008

Candida colonization without candidemia

Is *Candida* colonization of central vascular catheters in non-candidemic, non-neutropenic patients an indication for antifungals?

We were unable to demonstrate that antifungal therapy was an independent variable influencing outcome (OR 0.82; 95% CI, 0.27–2.47; $P = 0.73$). *Conclusions:* Our data suggest that, in non-neutropenic critically ill patients with no concomitant candidemia and with CVC tips colonized by *Candida*, antifungal therapy does not seem to have a significant influence on clinical outcome.