# Recordant L'Àngels

## *Candidas* en UCI: 35 años de estudio

## "Del estudio EPCAN a nuestros días"

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SOCMIC sesión
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# Guión

1.- Trayectoria profesional /proyectos de investigación
2.- Estudios clínicos realizados
3.- Estudios clínicos derivados
    - CS. Utilidad clínica
    - Biomarcadores (BG, CAGTA)
    - Biomarcadores (BG, CAGTA, Mananos, *Candida* PCR)
4.- Consecuencias clínicas prácticas
5.- Futuro

# Questions to ask before starting any study / project

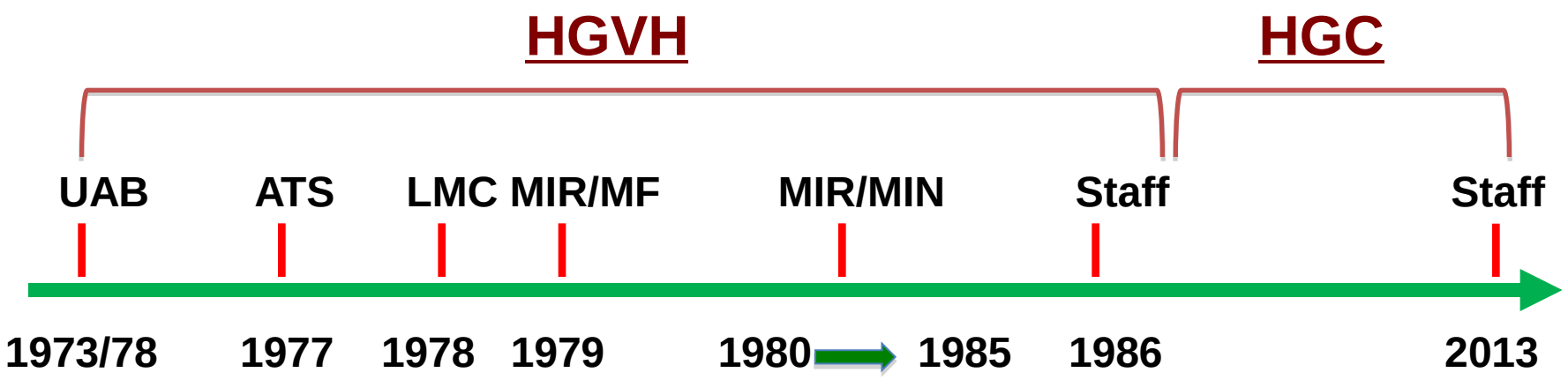
1. What is already known on this topic ?
2. What question this study/project addressed ?
3. What this study/project adds to our knowledge ?
4. How this is relevant to clinical practice ?

# 1. What is already known on this topic ?

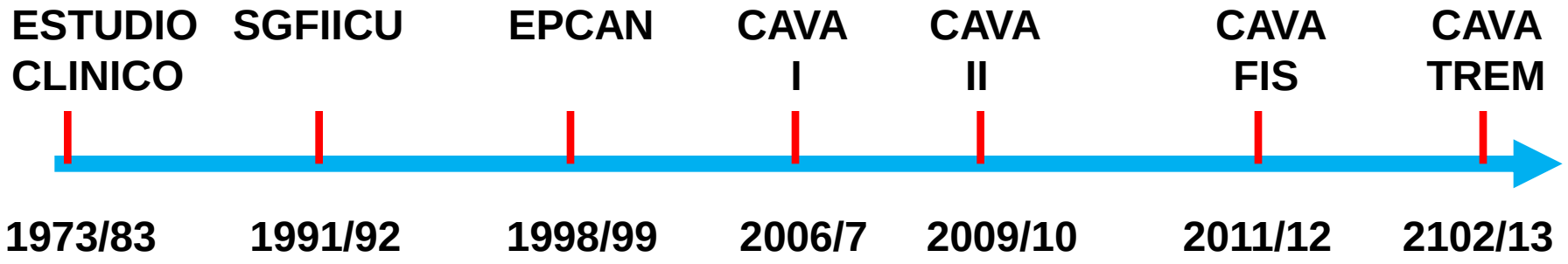
1. Introducción: aumento frecuencia, pacientes graves, mort. 60-80%.
2. El germen.
3. Factores predisponentes.
   - Enfermedad basal importante
   - Antibióticos
   - Esteroides
   - Alt. metabólicas y hormonales: DM, hipocalcemia.
4. Puertas entrada.
5. Responsabilidad patógena candidiasis y candidemia.

Etiopatogenia de las sepsis por *Candida*.
J. Figueras, C. Leon, A. Tomasa, R. Peracaula, M. Soler, FJ de Latorre, J. Padró.
Med Clin (Barc) 1974; 62;425-32

# Angels: trayectoria profesional/proyectos tema




## PROYECTOS



# Funguemia 1973-83. Análisis de 67 pacientes

Sanchez Rodriguez C, **León Regidor MA,** Capell Font S, Pérez Campos A, Planes Reig A, León Gil C.

**Med Clin (Barc) 1985;84:549-53**

- Estudio observacional, unicéntrico, retrospectivo
- 67 pacientes/68 episodios
- EB: **Patología GI** 62.6 % (42/67)
- FR: CVC, antibioterapia, NPT, cirugía abdominal (68%)
- Clínica: **indistinguible de una bacteriemia** (9 casos SS).
- Infecciones bacterianas asociadas 49/67
- Estratificación: **Funguemia Transitoria/Diseminada** (**45**/22)
- TAF: **28 pacientes tratados**, (9 con AFBD)
- Mortalidad global 58.5% (39/67), Relacionada 32.8% (22/67)

1. **Alta proporción de CRC**
2. **Concepto: Candidemia RC es autolimitada y no requiere trato**
3. **Retraso de inicio de tratamiento antifúngico**

# Funguemia 1973-83. Estudio epidemiológico

Capell Font S, Pérez Campos A, Sanchez Rodriguez C, **León Regidor MA**, Planes Reig A, León Gil C.

**Med Clin (Barc) 1985;84:600-5**

- Estudio unicéntrico retrospectivo
- 67 pacientes/68 episodios
- Funguemia nosocomial /1.000 ingresos:
  - **UCI: 17.5**
  - Resto Servicios: 0.3
- UCI: media 8 casos x año
- Aparición entre **la 2 y 3º semana**

| Semanas | Pacientes ingresados (n.º de casos) | Pacientes con funguemia (n.º de casos) (%) |
|---|---|---|
| 1 | 7.163 | 5 (0,06) |
| 2 | 1.406 | 13 (0,92) |
| 3 | 522 | 13 (2,49) |
| 4 | 301 | 8 (2,65) |
| 5 | 141 | 5 (3,54) |
| 6 | 90 | 3 (3,33) |
| 7 | 63 | 5 (7,93) |
| 8 | 34 | 7 (20,58) |
| 9 | 30 | 0 — |
| 10 | 14 | 2 (14,28) |
| 11 | 20 | 2 (10) |
| 12 | 16 | 1 (6,25) |

| Servicio | Total |
|---|---|
| UCI - Hospital General | 147/78 |
| Hematología | 18/11 |
| Servicios Médicos | 51/31 |
| Servicios Quirúrgicos | 26/17 |
| UCI - Traumatología | 13/7 |
| UCI - Hospital Infantil | 36/20 |
| Resto de Servicios Hospital Infantil* | 38/21 |
| Total | 329/185 |

# Candidiasis y candidemia. Reexamen de una problemática actual

Sánchez Rodríguez C, León Gil C, **León Regidor MA**, Capell Font S, Pérez Campos A.

**Med Clin (Barc) 1985;85:464-71**

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- Revisión 121 referencias
- Epidemiologia
- Definición de términos
- Población susceptible. Etiología
- Recursos clínicos (I): EF, lesiones cutáneas, miositis, catéteres y TF supurada, endoftalmitis
- Recursos clínicos (II). Valoración focos metastásicos, miocarditis/pericarditis, artritis y osteomielitis, encefalitis/meningitis, afección pulmonar
- Recursos analíticos y microbiológicos
- Diagnostico serológico
- A quien tratar ?

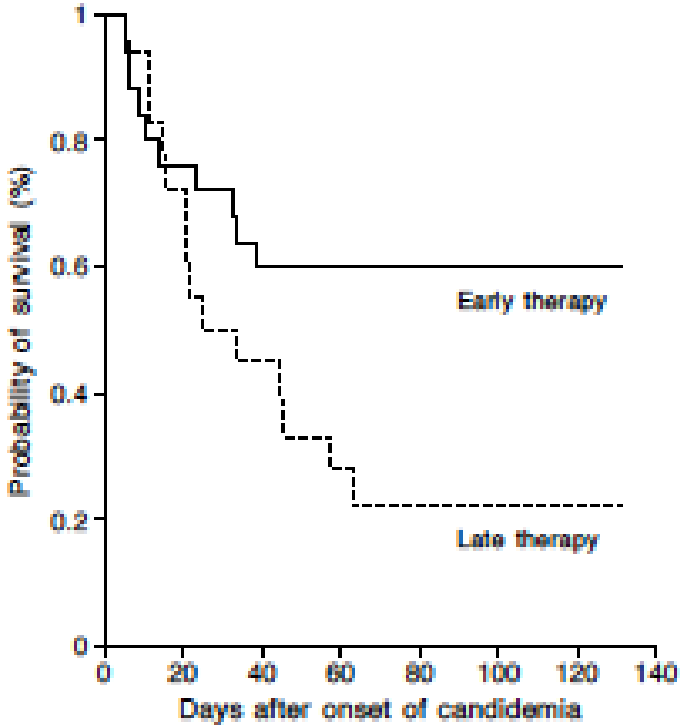
1. Candidemia: Aumento número de casos/número de pacientes con candidemia.
2. Difícil establecer diferencias entre la **CT y CD.**
3. Durante los episodios de CT “pudiera” haber un cierto grado de diseminación.
4. Apuesta: desarrollo de mejores métodos diagnósticos/diagnostico temprano/TAF adecuado.

# Candidemia in non-neutropenic critically ill patients: analysis of prognostic factors and assessment of systemic antifungal therapy.

Nolla-Salas J, Sitges-Serra A, León-Gil C, Martínez-González J, **León-Regidor MA**, Ibañez-Lucía P, Torres-Rodríguez, PM and Study Group of Fungal Infection in the ICU.

**Intensive Care Med 1997; 23:23-30**

- Multicenter, prospective, observacional
- 28 ICUs, 15 months (Oct 1991-Dcber 1992)
- 418 bed, 22937 admissions
- **Candidemia 46, mean age 59 y**.
- 1 episodio/500 ICU admissions
- Surgical/medical: **30**/16
- *Candida* specie: *C. albicans* (60%), *parapsilosis* (17%)
- **TAF 43**: FCNZ: 27, AFBD 10, sequential therapy 6.
- Overal mortality 56%, attributable 21,7%.
- **Apache II (time of diagnosis) and survival: 20**
- **Time of diagnosis /start of AFT: "early", late"**

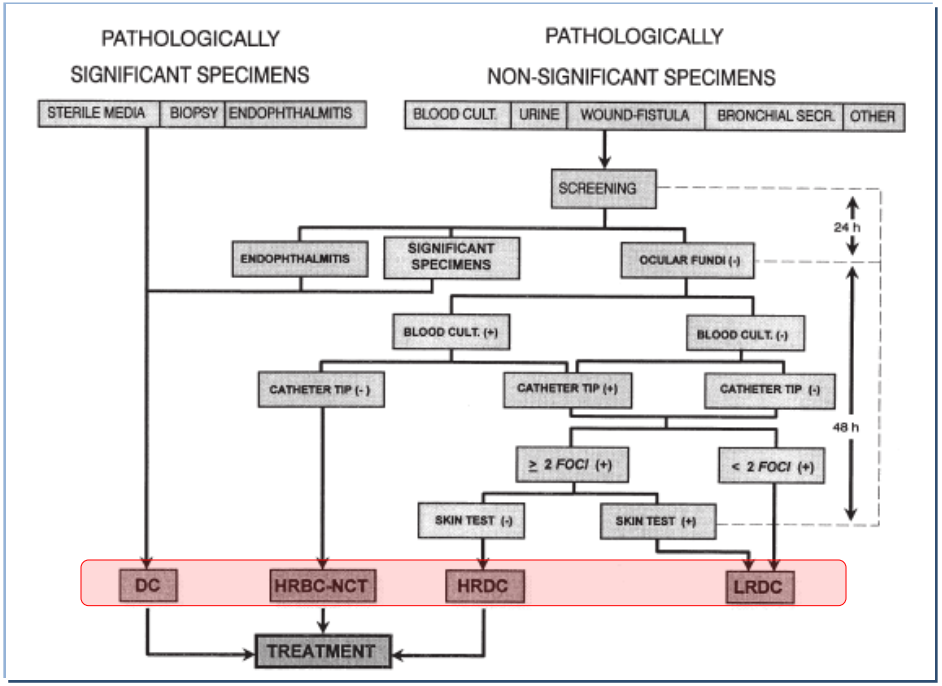


# The utility of serology in diagnosing candidosis in non-neutropenic critically ill patients (1).

Ibañez-Nolla J, Torres-Rodríguez JM, Nolla M, **León MA,** Méndez R, Soria G, Díaz RM, Marrugat J.

**Mycoses 2001;44:47-53**

- Prospective, cohort, one UCI (HGC)
- Sept 1988-Oct 1995 **(8 y).**
- Inclusion: all patients with at least one sample + *Candida*
- Screening and optional samples
- Cutaneous test/ophthalmologic evaluation/post morten study
- Serology: Antibodies (IHA, IFA), antigens (Cand-Tec/Pastorex)



# The utility of serology in diagnosing candidosis in non-neutropenic critically ill patients (2).

Ibañez-Nolla J, Torres-Rodríguez JM, Nolla M, **León MA,** Méndez R, Soria G, Díaz RM, Marrugat J.

**Mycoses 2001;44:47-53**

- 3389 pts, ICU LOS 6 days (1-112), **mortality 10%**
- **145 cases included** (overall mortality 46%)
- 120 cases with multifocal colonization, **Candidemia 24 (18 pts), Endopht 2 cases**
- **ATF Therapy 109 (75%)**

**Table 3.** Characteristics of all positive antibodies by multifocality and mortality

| Antibodies | Multifocality | | *P* |
|---|---|---|---|
| | Monofocal (14) | Multifocal (79) | |
| Negative (%) | 6 (43) | 35 (44) | NSS |
| Positive (%) | 8 (57) | 44 (56) | |
| **Antibodies** | **Mortality** | | ***P*** |
| | Survivors (50) | Deaths (43) | |
| Negative (%) | 17 (34) | 24 (56) | 0.034 |
| Positive (%) | 33 (66) | 19 (44) | |

| Test | Sensitiv. | Specif. |
|---|---|---|
| Antibodies | 37% | 78% |
| Antigens | 0 % | 90 % |

**Significant relation between mortality and low levels of antibodies**

# Fungal colonization and/or infection in non-neutropenic critically ill patients: results of the EPCAN observational study.

León C, Álvarez-Lerma F, Ruiz-Santana S, **León MA**, Nolla J, Jordá R, Saavedra P, Palomar M, and EPCAN Study Group.

**Eur J Clin Microbiol Infect Dis 2009;28:233-42**

- Prospective, cohort, observational, multicenter study
- Adult non-neutropenic pts, **73 ICUs M/S** (70 hospitals)
- **9 months** (May 1998-January 1999)
- Underlying diseases, comorbidities, reasons for ICU admission, RF (presence and duration)
- 7 days of ICU admission: Once a week: APACHE II, Clinical situation, microbiological *screening (*TA, pharyngeal exudates, gastric aspirates, and urine)
- Antifungal treatment and outcome
- **1765 patients,** age 57.9 y, APACHE II ICU admission: 18. 5,
- Overall mortality 43.5%, Intra ICU: 33.8%
- No C/I (785), Colonized (883), **infected (97).**
- **18,385 samples**: 13,849 (surveillance) and 4,536 (optional)
- ***C. albicans* 72.1%** (screening), and 69,7 % (optional).

# Economic Impact of *Candida* Colonization and *Candida* Infection in the Critically Ill Patient.

Olaechea PM, Palomar M, León-Gil C, Álvarez-Lerma F, Jordá R, Nolla-Salas J, **León-Regidor MA**, and **EPCAN Study Group**.

**Eur J Clin Microbiol Infect Dis 2004;23:323-30**

- Prospective, cohort, observational, multicenter study
- 1765 adult non-neutropenic pts, 73 ICUs mixed (70 hospitals)
- 9 months (May 1998-January 1999)
- 7 days of ICU admission: Once a week: APACHE II, SOFA, Clinical situation, and microbiological *screening*
- **No C/I, Colonized, Infected**. Comorbidities and RF. ATF therapy. Outcome

Cost (2000)
ICU: 1,153 E
Hospit: 406 E

| Patient group | Length of ICU stay in days (no. of patients) | | |
|---|---|---|---|
| | No antifungal therapy ($n$=1300) | Antifungal therapy ($n$=405) | $P$ value |
| Non-colonized, non-infected | 14 (675) | 18 (45) | 0.6 |
| *Candida* colonization | 18 (610) | 28 (270) | <0.001 |
| *Candida* infection | 17 (15) | 30 (90) | 0.003 |

**Direct Cost (1 day)**
- *Candida* colonization: 8,000
- *Candida* infection: 16,000

# A bedside scoring system *("Candida score")* for early antifungal treatment in nonneutropenic critically ill patients with *Candida* Colonization.

Cristóbal León, Sergio Ruiz-Santana, Pedro Saavedra, Benito Almirante, Juan Nolla-Salas, Francisco Álvarez-Lerma, José Garnacho-Montero, **María Ángeles León,** and EPCAN Study Group.

**Courtesy by J. Mensa**

| Variable | Proven Candidal Infection % | | *p* Value | Crude Odds Ratio (95% Confidence Interval) | Adjusted Odds Ratio (95% Confidence Interval) |
|---|---|---|---|---|---|
| Surgery on ICU admission | | | | | |
| No | | 1 | | | |
| Yes | | | <.001 | 2.69 (1.76–4.10) | 2.71 (1.45–5.06) |
| Total parenteral nutrition | | | | | |
| No | | 1 | | | |
| Yes | | | | | (1.16–5.31) |
| Severe sepsis | | | | | |
| No | | 2 | | | |
| Yes | | | | | (4.14–14.22) |
| *Candida* species colonization | | | | | |
| No | | | | | |
| Yes | | 1 | <.001 | 3.20 (1.85–5.53) | 3.04 (1.45–6.39) |

**Score ≥ 2.5** — **Sensitivity 81%** **Specificity 74%**

**Crit Care Med 2006; 34:730-37**

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Courtesy byJ. Mensa

| Variable | Proven Candidal Infection % | *p* Value | Crude Odds Ratio (95% Confidence Interval) | Adjusted Odds Ratio (95% Confidence Interval) | |
|---|---|---|---|---|---|
| Surgery on ICU admission | | | | | 1 |
| No | 6.9 | | | | |
| Yes | 6.5 | <.001 | 2.69 (1.76–4.10) | 2.71 (1.45–5.06) | |
| Total parenteral nutrition | | | | | 1 |
| No | | | | | |
| Yes | | | | 2.48 (1.16–5.31) | |
| Severe sepsis | | | | | 2 |
| No | | | | | |
| Yes | 8.8 | <.001 | 8.63 (5.49–13.56) | 7.68 (4.14–14.22) | |
| *Candida* species colonization | | | | | 1 |
| No | 4.2 | | | | |
| Yes | 2.3 | <.001 | 3.20 (1.85–5.53) | 3.04 (1.45–6.39) | |

**Score ≥ 2.5** { **probability of *Candida* infection x 7.75**

**Crit Care Med 2006; 34:730-37**

# Usefulness of the *"Candida score"* for discriminating beween *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients. A prospective multicenter study.

C. León, S. Ruiz-Santana, P. Saavedra, B. Galván, A. Blanco, C. Balasini, A. Utande, FJ. González, MA. Blasco, MJ. López, PE. Charles, A. Hernández, and **Cava I Study Group**.

- Prospective, cohort, observational, multicenter study
- Adult non-neutropenic pts, **36 ICUs M/S** (32 hospitals)
- **14 months** (April 2006-June 2007)
- Underlying diseases, comorbidities, reasons for ICU admission, RF (presence and duration)
- Antifungal treatment and outcome
- **7 days of ICU admission: Once a week**: APACHE II, SOFA, Clinical situation, and microbiological *screening* **(5)** TA, pharyngeal exudates/gastric aspirates, urine, perirectal swab, skin and optional samples
- **1107 patients**, age 60 y., *ICU admission: APACHE II: 18.4, SOFA: 7 (median)*
- No C/I (215), Colonized (834), **infected (58)**
- Overall mortality 30.5%, Intra ICU: 21.7%
- **ATFT 49 (84.4%) patients**. Time between ICU admission and administration of ATFT **17.3 days**
- 240 patients with *Candida* species colonization or IC (18): **(1–3)-beta-D-glucan serum levels**

**Crit Care Med 2009; 37:1624 –33**

**Usefulness of the *"Candida score"* for discriminating beween *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients. A prospective multicenter study.**

C. León, S. Ruiz-Santana, P. Saavedra, B. Galván, A. Blanco, C. Balasini, A. Utande, FJ. González, MA. Blasco, MJ. López, PE. Charles, A. Hernández, and Cava I Study Group.

## Abdominal Surgery

| **Candida Score** | < 3 | = 3 | > 3 |
|---|---|---|---|
| IC rate medical / surgical patients (n = 1,107) | 2.3 % | 5.9 % | 11.5 % (5.1 - 17.8) |
| IC rate Abdominal Surgery (n = 182) | 2.3 % | 12.5 % | **30.3 % (19.2 - 41.4)** |

**Crit Care Med 2009; 37:1624 –33**

**Usefulness of the *"Candida score"* for discriminating beween *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients. A prospective multicenter study.**

C. León, S. Ruiz-Santana, P. Saavedra, B. Galván, A. Blanco, C. Balasini, A. Utande, FJ. González, MA. Blasco, MJ. López, PE. Charles, A. Hernández, and Cava I Study Group.

Table 4. Rates of invasive candidiasis according to the *Candida* score

| Cutoff Value | Incidence Rate (%) (95% CI) | Relative Risk (95% CI) |
|---|---|---|
| <3 | 2.3 (1.1–3.5) | 1 |
| 3 | 8.5 (4.2–12.7) | 3.7 (1.8–7.7) |
| 4 | 16.8 (9.7–23.9) | 7.3 (3.7–14.5) |
| 5 | 23.6 (12.4–34.9) | 10.3 (5.0–21.0) |

CI, confidence interval.

Crit Care Med 2009; 37:1624 –33

## Candiduria in critically ill patients admitted to intensive care medical units.

Francisco Álvarez-Lerma, Juan Nolla-Salas, Cristobal Leon, Mercedes Palomar, Ricard Jorda, Nieves Carrasco, Felipe Bobillo (**EPCAN Study Group**).

**Intensive Care Med 2003;29:1069–76**

- 1765 adult non-neutropenic pts, (< 7 days): **Candiduria 389 patients (22%)**
- Age 61 y, Apache II 19.
- Incidence density : 9.5 episodes/1.000 days
- Length of ICU stay since presence of candiduria: 16 days
- Risk factor associated: age over 65 y, female gender, LOS in hospital before ICU admission, diabetes, TPN, MV, previous use of antibiotics (C. no *albicans*).
- ***C. albicans* 266 (68.4%),** *C. glabrata* 32 (8.2%), *C. tropicalis* 14 (36%).
- **Candiduria is a risk factor for ICU/hospital mortality (OR 1.58).**

## Risk factors for candidaemia in critically ill patients: a prospective surveillance study.

Jordá Marcos R, Alvarez-Lerma F, Jurado M, Palomar M, Nolla-Salas J, **León MA**, León C. and **EPCAN** Study Group.

**Mycoses 2007;50:302-10**

- 1765 adult non-neutropenic pts, (< 7 days): **Candidemia: 63 pts,**
- Age 63 y, Apache II 18, ICU/hospital stay: 28/48, **Surgical 29 (46%), Medical 26 (41.3 %)**
- **ATF treatment 48/63 (76%):**
  - FCNZ 32 (66.7%), AFBD 8 (16%), LAFB 5 (10.4), AFBLC 3 (6.3%).
- ICU/hospital: Mortality 34 (54%)-39 (73%)

**Table 3** Risk factors for candidaemia. Results of multivariate analysis

| Variable | Odds ratio | 95% Confidence interval | *P*-value |
|---|---|---|---|
| Haemofiltration procedures | 1.96 | 1.06–3.62 | 0.032 |
| Elective surgery | 2.75 | 1.17–6.45 | 0.020 |
| Total parenteral nutrition | 3.89 | 1.73–8.78 | 0.001 |
| *Candida* spp. colonisation | 4.12 | 1.82–9.33 | 0.001 |

**Assessment of candidemia-attributable mortality in critically ill patients using propensity score matching analysis.**

Francisco J González de Molina, Cristóbal León, Sergio Ruiz-Santana and Pedro Saavedra, for the **CAVA I Study Group**.

**Crit Care 2012,16: R105**

- 1,107 pts, **38 (3.4%) candidemias** **Propensity score matching analysis (Candidemia: 70 no, 35 yes).**

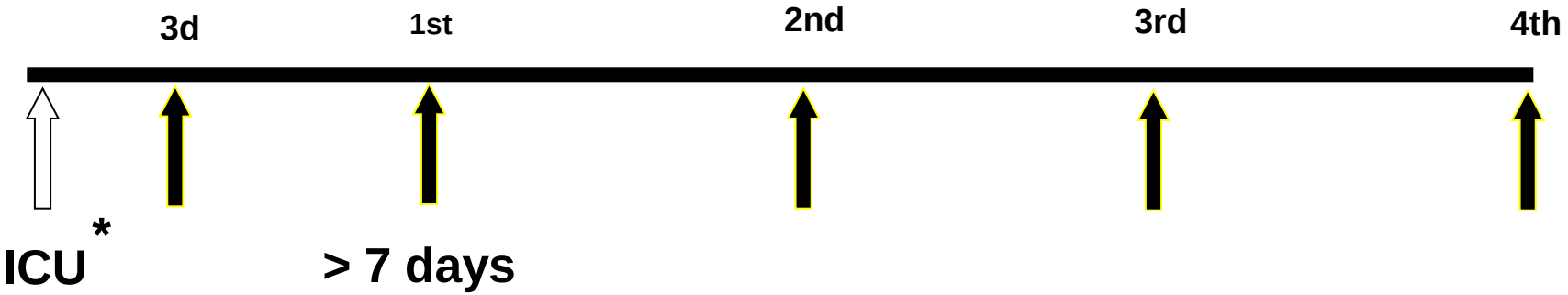
- The use of propensity score matching analysis to control for all potential confounding variables allowed the **assessment of candidemia-attributable mortality** in critically ill patients.
- Candidemia **was not associated with an increase in either ICU or hospital mortality**.
- Earlier treatment of bloodstream infection and better monitoring (surveillance sampling weekly), resulting in appropriate antifungal agent may contribute to increased survival.
- **APACHE II** at the time of diagnosis of candidemia was the **only predictor of death** in patients with candidemia.

Critical Care 2012, 16:R105

**Value of B-D-glucan and *Candida albicans* germ tube antibody for discriminating between *Candida* colonization and invasive candidiasis in patients with severe abdominal conditions.**

León C, Ruiz-Santana, Saavedra P, Castro C, Úbeda A, Loza A, Martin E, Blanco A, Jerez V, Ballús J, Álvarez L, Utande A, Fariñas O, and the **Study Group Cava II**

Multicenter, observational, prospective:
C. Score; biomarkers & IC
18 ICUs; n = **176 (S.A.C.)**; 4 wks. Study; 2009-10




C Score, BG, CAGTA, others → Weekly (x 2) screening
Optional Samples related clinical situation / follow up

Variables: demographics; APACHE II, SOFA (admission; weekly x 2, starting antifungals); comorbid diseases; risk factors; antifungal therapy and outcome.

*Adult patients, admitted ICU ≥ 7 days
S.A.C. = Severe Abdominal Conditions
CAGTA = *Candida albicans* germ-tube antibody

**Intensive Care Med 2012; 38:1315-25**

# Value of B-D-glucan and *Candida albicans* germ tube antibody for discriminating between *Candida* colonization and invasive candidiasis in patients with severe abdominal conditions.

León C, Ruiz-Santana, Saavedra P, Castro C, Úbeda A, Loza A, Martin E, Blanco A, Jerez V, Ballús J, Álvarez L, Utande A, Fariñas O, and the **Study Group Cava II**.

## CART prediction rule model

- Patients with *Candida* colonization → A **model for IC prediction** was obtained
  **C**lassification **A**nd **R**egression **T**rees (**CART**).

- Variables used → maximum values biomarkers before / during development IC, or highest value when IC did not developed (Apache-II, BG, CAGTA).

- CART through a process of binary recursive spliting of the datasets based on rules of the form *if-then-else*, identifies a set of predictors of IC estimating the probabilities of IC according to the values of predictors.

- The discriminate value of the probabilities of IC obtained by the CART was evaluated by the receiver characteristic operating (ROC) curve .

- Predictive rule → identify patients have an IC risk, when probability to develop IC is ≥ 30%.(cut-off chosen by CART algorithm to minimize error measurement = deviance)

- Obtained rule: estimated →Sensitivity, Specificity, PPV, NPV.

- Data analysis → carried out using R-package.

**Intensive Care Med 2012; 38:1315-25**

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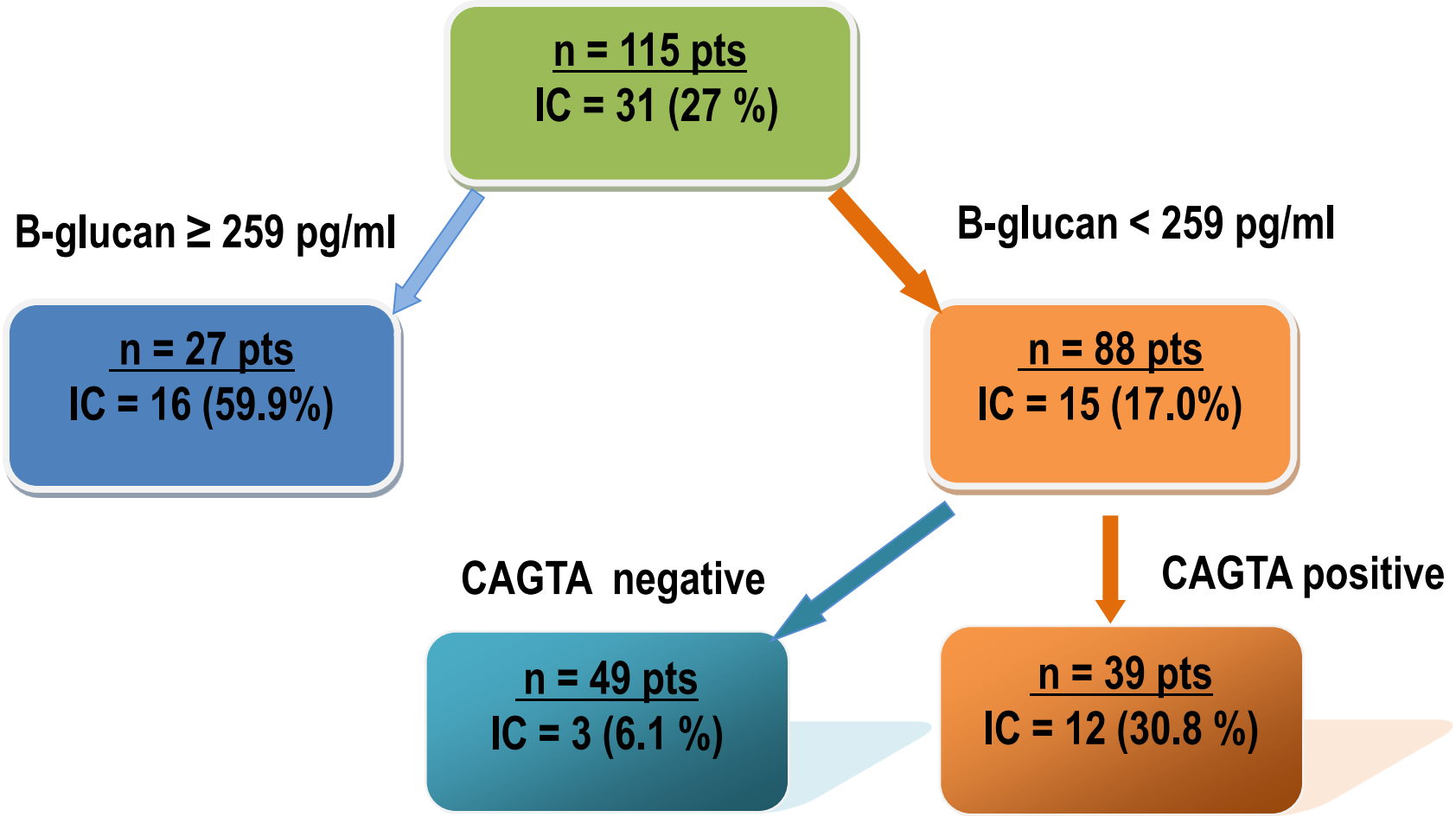
León C, Ruiz-Santana, Saavedra P, Castro C, Úbeda A, Loza A, Martin E, Blanco A, Jerez V, Ballús J, Álvarez L, Utande A, Fariñas O, and the **Study Group Cava II**




Intensive Care Med 2012; 38:1315-25

# Diagnostic accuracy of *CART-derived prediction rule*, BG (cut-off: > 259 pg/mL), CAGTA (cutt-off: positive) and CS for IC diagnosis

| | Area under ROC curve (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) | Predictive value | |
|---|---|---|---|---|---|
| | | | | Positive % (95% CI) | Negative % (95% CI) |
| **CART analysis** | **0.78 (0.76-0.81)** | **90.3 (75.1-96.6)** | **54.7 (44.1-65.0)** | **42.4 (31.2-54.4)** | **93.9 (83.5-97.9)** |
| **BG** | 0.67 (0.59-0.74) | 51.6 (34.8-68.0) | 86.9 (78.0-92.5) | 59.3 (40.7-75.5) | 83.0 (73.8-89.4) |
| **CAGTA** | 0.67 (0.63-0.70) | 71.0 (53.4-83.9) | 57.3 (46.5-67.5) | 38.6 (27.1-51.6) | 83.9 (72.2-91.3) |
| **CS** | 0.62 (0.58-0.66) | 93.5 (79.2-98.2) | 18.1 (11.3-27.7) | 29.9 (21.7-39.6) | 88.2 (65-7-96.7) |

**CART** classification and regression tree analysis; **BG**: beta-D-glucan; **CAGTA:** *Candida albicans* germ tube antibody. Total number of patients with Candida spp. colonization = 115.

# Usefulness of the (1→3)-β-D-Glucan and *Candida albicans* germ tube antibody in the Diagnosis of Invasive Candidiasis in Non-neutropenic Critically Ill Patients (non selected).

***CAVA FIS PROJECT***

2011/12. One ICU (HUV). 105 **NNCIP non selected**. > 7 days
Twice a week: Clinical status, APACHE II, SOFA, and *Candida score, candida* colonization cultures (rectal swabs, tracheal, pharyngeal or gastric aspirates, and urine), and serum BG and CAGTA. **Were collected factors can interfere with the levels of BG (RRT, AC / PT, use of blood transfusions, surgery…)**

| | NCNI (n = 42) | Colonized (n = 52) | Candidemia (n = 6) | Peritonitis (n =5) | *P* value |
|---|---|---|---|---|---|
| Age, years, mean (range) | 66 (50-73) | 63 (54-76) | 68 (62-78) | 67 (62-70) | 0.820 |
| Male/female patients | 32/10 | 25/27 | 4/2 | 5/0 | 0.007 |
| BG, pg/mL | | | | | |
| Median (IQR) | 44 (31-102) | 40 (31-140) | 72 ( 31-300) | 31 (31-31) | 0.527 |
| Maximum (IQR) | 77 (31-140) | **150 (47-500)*** | **194 (120-300)*** | **50 (31-80)** | **0.037** |
| CAGTA positives, n (%) | 13 (31.0) | 26 (50.0) | 3 (50.0) | 1 (20.0) | 0.203 |

NCNI: neither colonized nor infected, BG: B-D- glucan, IQR: interquartile range (25th-75th percentile), CAGTA: Candida albicans germ tube antibodies. *Significant differences as compared with the NCNI group.

## Conclusions

Patients with candidemia and *Candida* spp. colonization showed significantly higher values of serum BG than neither colonized or infected patients.

**Instituto Salud Carlos III. Madrid. Spain (FIS PI 10/02110)**

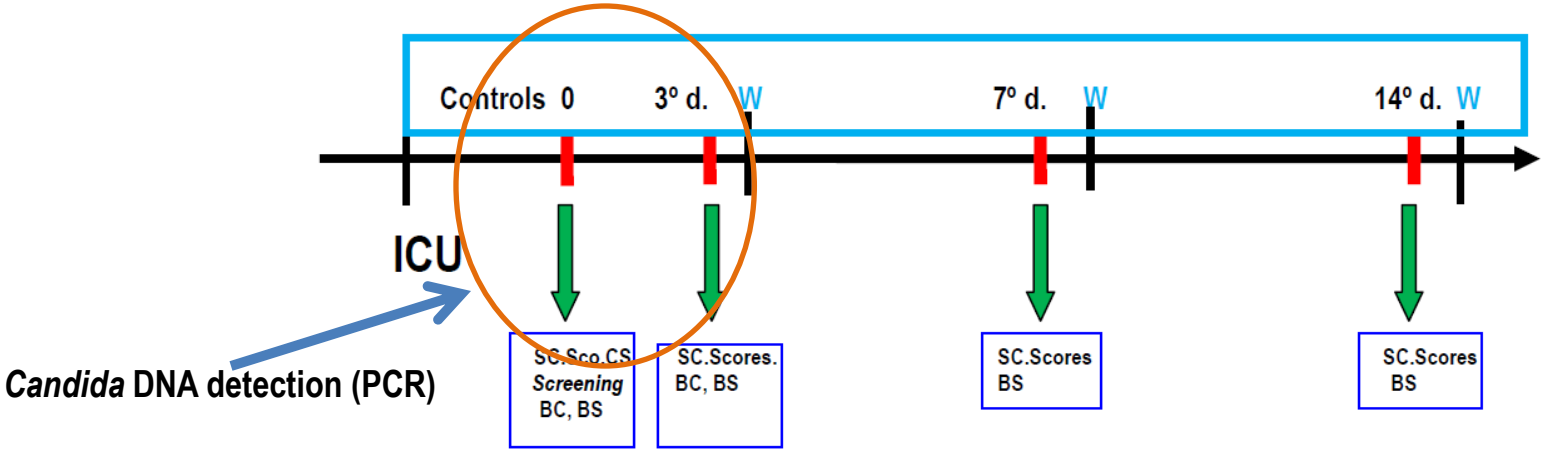
**ICAAC 2013 (M-1380)**

**Invasive Candidiasis in the critically ill patients. Diagnostic utility of 1-3-Beta-D-Glucan(BDG), anti-mycelium antibodies (CAGTA), mannan/antimannan antibodies (MAA), and detection of *Candida DNA (PCR)*" *CAVA TREM PROJECT***

Prospective, cohort, observational, multicenter study
**2012/14.** 12 ICUs **NNCIP selected (SAC)**. > 7 days
Twice a week: Clinical status, APACHE II, SOFA, and *Candida score, candida* colonization cultures (rectal swabs, tracheal /pharyngeal, urine), and serum (BG and CAGTA)
***Preliminary data (October 2013): 215 pts included, 117 CC, 26 IC, AFT 94% (44.6%)***

**Phase II: antifungal therapy**

Clinical and microbiological controls



# Evaluation of "Candida score" in critically ill patients: a prospective, multicenter, observational, cohort study.

Leroy G, Lamblotte F, Thevenin D, Lemaire C, Parmentier E, Devos P, Leroy O.

- To evaluate **CS performance** ICU patients developing hospital-acquired **severe sepsis or septic shock**.
- Prospective, multicenter (5 ICUs France), cohort study
- n = 94 recruited (IC = 5 → 5.3 %)
- IC rates: CS = 2 or 3 → 0%; CS = 4 → 17.6%; CS = 5 → 50% ($p < 0.0001$).
- **CS > 3 → Benefit early S.A.T.**

**Table 2 Risk factors for invasive candidiasis, according to the value of "*Candida* score"**

| Risk factors | *Candida* score = 2 (n = 44) | *Candida* score = 3 (n = 29) | *Candida* score = 4 (n = 17) | *Candida* score = 5 (n = 4) |
|---|---|---|---|---|
| Severe sepsis or septic shock | 44 | 29 | 17 | 4 |
| Total parenteral nutrition | 0 | 8 | 15 | 4 |
| Surgery | 0 | 10 | 17 | 4 |
| Multifocal *Candida* colonization | 0 | 11 | 2 | 4 |
| Invasive mechanical ventilation | 30 | 23 | 11 | 2 |
| Central venous catheter | 39 | 27 | 15 | 4 |
| Urinary catheter | 42 | 27 | 17 | 4 |
| Antibiotherapy > 5 days within the past 2 weeks | 39 | 25 | 14 | 4 |
| Renal replacement therapy | 8 | 10 | 4 | 1 |
| Insulin-dependent diabetes mellitus | 7 | 4 | 0 | 0 |
| Immunosuppression | 4 | 3 | 2 | 0 |

**Ann Intens Care 2011;1:50**

## Systemic antifungal therapy in critically ill patients without invasive fungal Infections.

Azoulay E, Dupont H, Tabak A, Lortholary O, Stahl JP, Francais A, Martin C, et al.

- To determine → nº patients, w /o documented IC, received S.A.T.
- 1-day cross-sectional cohort study; 169 ICUs France / Belgium
- n = 2,047 recruited
- n = 154 (7.5%) with SAT (only 54 with IC)
- Independent predictors SAT:
  - Center-related factors: Hospital < 800 beds (OR: 2.9); organ transplant activity (OR:2.6); use fluoroquinolones (OR:2.3); use SAT unresolved sepsis (OR:1.9 / 2.2/ 2.0)
  - Patient related factors: Candida colonization (OR: 12.4); severe sepsis and septic shock (OR:4.7); emergency surgery (OR: 2.4); hematologic malignancies (OR:7.1)
- **Trend greater impact SAT on survival when CS = 4 or 5**

**Crit Care Med 2012;40:813-22**

S.A.T Systemic Antifungal Treatment

**Systemic antifungal therapy in critically ill patients without invasive fungal Infections.** Azoulay E, Dupont H, Tabak A, Lortholary O, Stahl JP, Francais A, Martin C, et al.

## Impact SAT on 28-d mortality according CS

A

| Candida score class | Alive with SAT | Dead with SAT | Crude HR [95%CI], P value | Adjusted HR ‡ [95%CI], P value |
|---|---|---|---|---|
| Candida score 0 or 1 (n=1019) | 7 (100%) | 0 (0%) | 0 [0 – Inf] ; p=0.97 | 0 [0 – Inf] ; p=.99 |
| Candida score 2 or 3 (n=664) | 34 (75.6%) | 11 (24.4%) | 0.99 [0.54 – 1.83] ; p=0.97 | 0.76 [0.26 – 2.18] ; 0.61 |
| Candida score 4 or 5 (n=310) | 39 (81.3%) | 9 (18.8%) | 0.78 [0.39 – 1.57] ; p=0.49 | 0.09 [0.01 – 1.49] ; 0.09 |

B

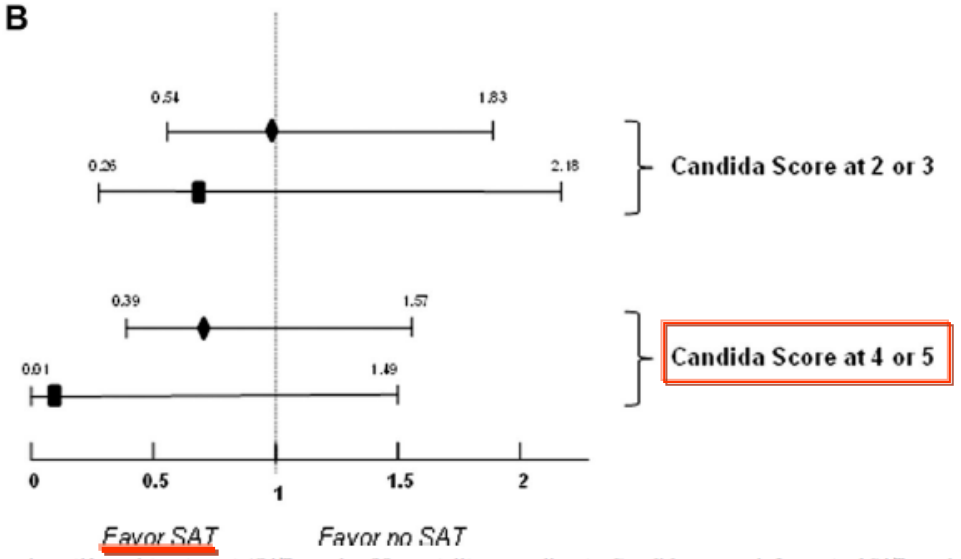



Figure 4. Impact of systemic antifungal treatment (*SAT*) on day 28 mortality according to *Candida* score. *A*, Impact of SAT on day 28 survival according to three classes of *Candida* score. ‡Adjusted hazard ratios were obtained by adjustment on propensity score for day 28 mortality and with stratification on the center. *B*, Unadjusted (lozenges) and adjusted (*squares*) hazard ratio (*HR*) and 95% confidence intervals depicting the impact of SAT on day 28 mortality in patients with *Candida* score at 2 or 3 or with *Candida* score at 4 or 5.

**Crit Care Med 2012;40:813-22**

# Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1- 3)-B-D-glucan assay, *Candida score*, and colonization index.

Posteraro B, De Pascale G, Tumbarello M, Torelli R, Pennisi MA, Bello G, Maviglia R, Fadda G, Sanguinetti M, Antonelli M.

- Prospective, single center, observational study
- To compare diagnostic value BG, **CS**, CI ICU patients risk IC
- n = 95 (LOS > 5 days): clinical sepsis onset → BG; blood cultures,
- Clinical data / surveillance cultures
- **Of 14 IC patients:13 candidemias**.
- **Combination positive BG and CS ≥ 3** improved IC diagnosis:

  **Sensitivity** [100% (95% CI, 76.8% to 100%)]

  **NPV** [100% (95% CI, 94.6% to 100%)] *vs.* 92.9% and 98.7% for BG test alone.

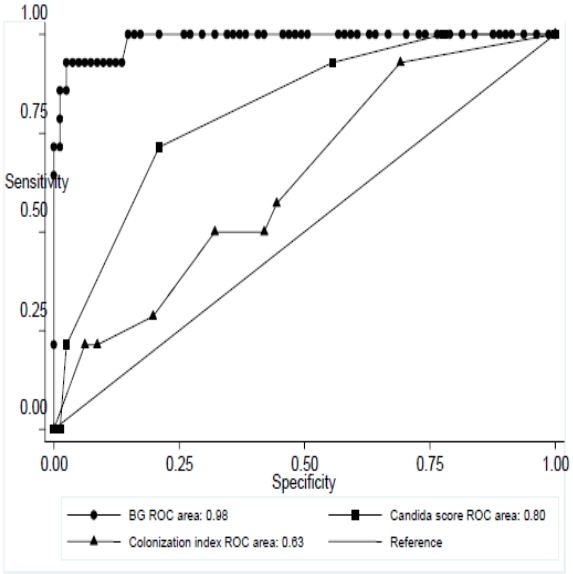



**Table 3 Performances of (1→3)-β-D-glucan assay (BG), *Candida* score (CS), and colonization index for detection of invasive candidiasis in 95 patients**

| | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | PPV (%) (95% CI) | NPV (%) (95% CI) | PLR (%) (95% CI) | NLR (%) (95% CI) |
|---|---|---|---|---|---|---|
| BG cut-off value, 80 pg/mL | 92.9 (66.1 to 99.8) | 93.7 (85.8 to 97.9) | 72.2 (46.5 to 90.3) | 98.7 (92.8 to 99.9) | 14.74 (4.65 to 47.52) | 0.07 (0.02 to 0.39) |
| CS ≥3 | 85.7 (57.2 to 98.2) | 88.6 (79.5 to 94.7) | 57.1 (34.0 to 78.2) | 97.2 (90.3 to 99.7) | 7.51 (2.79 to 18.29) | 0.16 (0.02 to 0.54) |
| Colonization index ≥0.5 | 64.3 (35.1 to 87.2) | 69.6 (58.2 to 79.5) | 27.3 (13.3 to 45.5) | 91.7 (81.6 to 97.2) | 2.12 (0.84 to 4.25) | 0.51 (0.16 to 1.11) |

# Beta-Glucan Antigenemia Anticipates Diagnosis of Blood Culture-Negative Intra-Abdominal Candidiasis

Tissot F, Lamoth F, Hauser PM, et al.

- Prospective, cohort study **(FUNGINOS)**
- 89 (20.5%) / 434 patients high-risk IAC studied (ICU stay ≥72h):→ **29 IAC + negative blood culture (27/29).**
- BG **preceded** microbiological documentation IAC and start SAT by five / six days (median), respectively.
- **Conclusion: BG is superior to cultures, CS, CI, CCI for anticipating diagnosis of blood-culture-negative post-surgical IAC.**

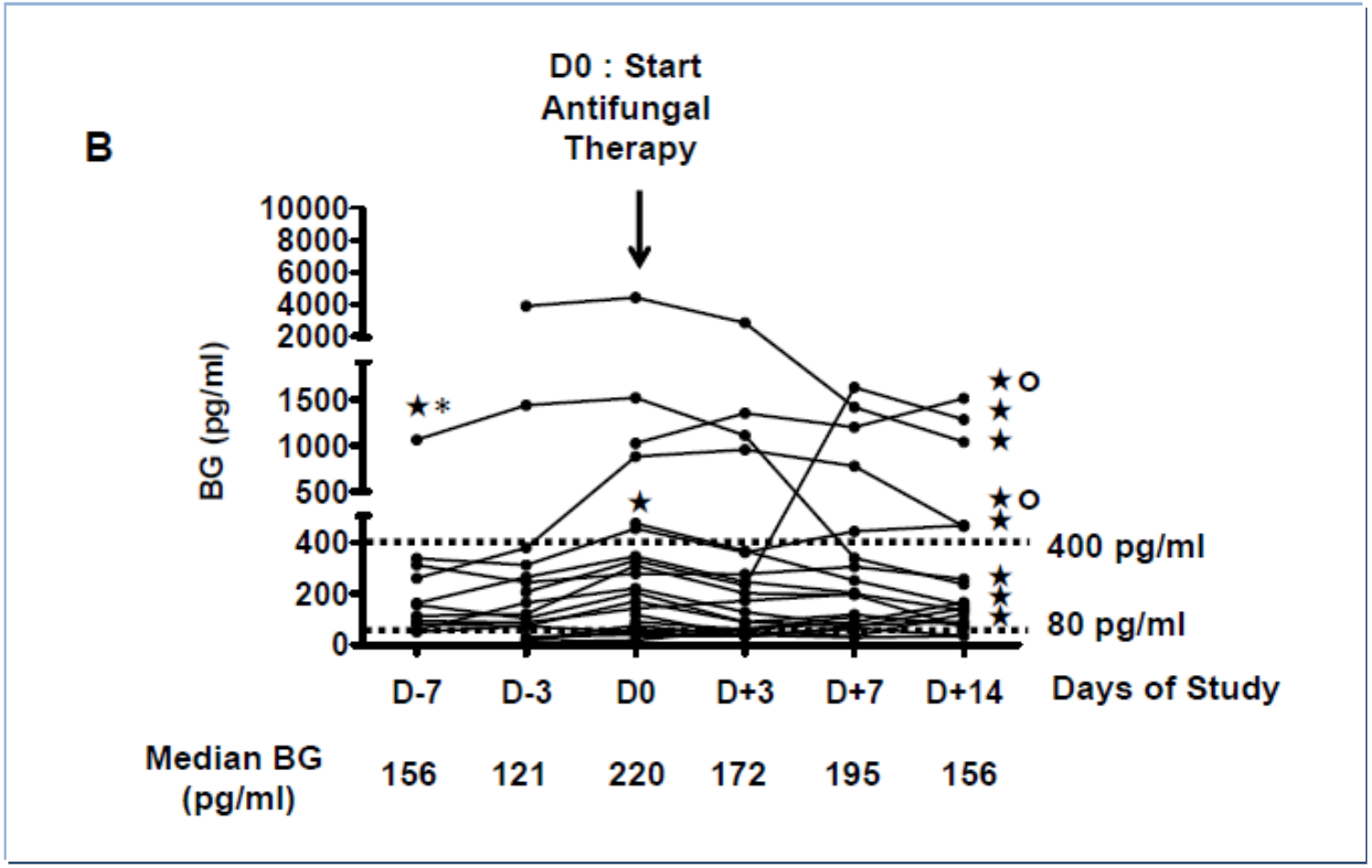
| | Sensit. (95%CI) | Specif. (95%CI) | PPV (95%CI) | NPV (95%CI) |
|---|---|---|---|---|
| **BG ≥ 80 pg/ml 1 x** | 0.83 (0.64 -0.94) | 0.40 (0.26-0.57) | 0.49 (0.34-0.64) | 0.77 (0.55-0.92) |
| **BG ≥ 80 pg/ml 2 x** | **0.65 (0.46-0.62)** | **0.78 (0.63-0.90)** | **0.68 (0.48-0.84)** | **0.77 (0.61-0.68)** |
| **CS ≥ 3** | 0.86 (0.68-0.96) | 0.38 (0.23-0.54) | 0.49 (0.35-0.63) | 0.80 (0.56-0.94) |

Am J Respir Crit Care Med 2013 Jun 19. [Epub ahead of print )

# Beta-Glucan Antigenemia Anticipates Diagnosis of Blood Culture-Negative Intra-Abdominal Candidiasis

Tissot F, Lamoth F, Hauser PM, et al.

**Individual BG kinetics in IAC patients receiving antifungal therapy (n=26)**




Am J Respir Crit Care Med 2013 Jun 19. [Epub ahead of print )

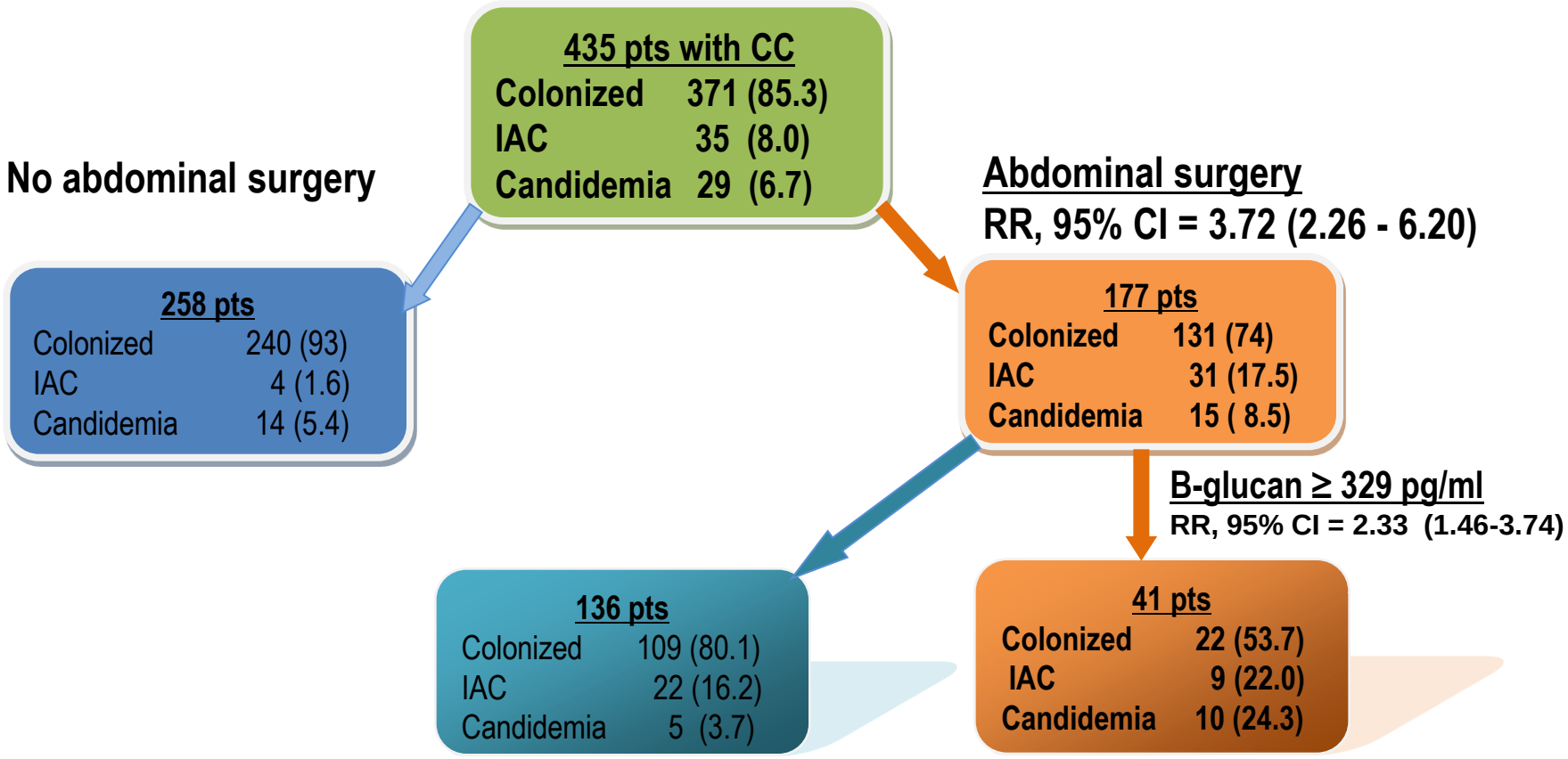
# Comparison of BDG test findings in non-neutropenic critically ill adult patients

| Author, year | Patient´s type | Number Pts./samples (mean) | IC Type | Cut-off | Sensit.(%) (95% CI) | Spec.(%) (95% CI) | PPV (%) (95% CI) | NPV (%) (95% CI) | Proven IC BG ** (median) |
|---|---|---|---|---|---|---|---|---|---|
| Tissot, 2013 | Surgical Pancreatitis | 89/921 (9) | IAC | ≥ 80 | 65 * (46-82) | 78 * (63-93) | 68 * (52-88) | 77 * 63-89) | **253** |
| León, 2012 | SAC | 176/766 (4.3) | C, IAC | ≥ 80 | 51.6 (34-69) | 86.9 (78-92) | 59.3 (40-75) | 83.0 (73-89) | **259** |
| Del Bono, 2011 | Surgical | 152/152 (1) | C | ≥ 80 | 62 | 98 | 98.4 | 57.3 | **324** |
| Posteraro, 2011 | Medical | 95/130 (1.3) | C | ≥ 80 | 92.9 (66-99) | 93.7 (85-90) | 72.2 (46-90) | 98.7 (92-99) | **500** |
| Mohr, 2011 | Med/Surg | 57/239 (4.1) | C | ≥ 80 | 100 * | 59 * | NDA | NDA | **171** |
| Presterl, 2009 | Med/Surg | 197/ NDA | C, IAC, HC | ≥ 40 | 52.2 (31-76) | 75.9 (62-85) | 46.2 27-66) | 80 (66-89) | **44** |

*Two consecutive BG determinations, ** pg/mL, CI: Confidence intervals
SAC: severe abdominal conditionsIC: Invasive Candidiasis, C: Candidemia, IAC: Intra-abdominal Candidiasis, HC: Hepatic Candidiasis, NDA: No data available

# Abdominal Surgery and BG in discriminating between C*andida* colonization and IC in non-neutropenic critically ill patients

- Prospective, multicenter, observational cohort studies (**Cava I, Cava II, Cava Fis**)
- 435 patients high-risk IC (ICU ≥ 7 days); medical / surgical **(177 with abdominal surgery)**
- 371 CC, **64 IC** (IAC 35, Candidemia 28, Chorioretinitis,1)
- Twice a week: surveillance cultures, Candida score and BG



# Diagnostic accuracy of CART-derived prediction rule for IC diagnosis in abdominal surgery patients

| Area Under ROC Curve | Sensitivity % (95% CI) | Specificity % (95% CI) | PPV % (95% CI) | NPV % (95% CI) |
|---|---|---|---|---|
| **0.713** | 71.8 (59.8 - 81.4) | 64.6 (59.7 - 69.3) | 25.9 (20.0 - 32.9) | 93.0 (89.2 - 95.5) |

## Risk of IC among patients with abdominal surgery (n=177)

| 1-3- β-D- glucan * | % IC | RR (95% CI) |
|---|---|---|
| ≤ 80 (n = 74) | 20.3 | 1 |
| > 80 (n = 103) | 30.1 | 1.48 (0.87;2.55) |
| < 329 (n = 136) | 19.9 | 1 |
| **≥ 329 (n = 41)** | **46.3** | **2.33 (1.46 ; 3.74)** |

* pg/ml

# Citaciones

| Num | Titulo/autores/revista | Citas |
|---|---|---|
| 1 | A bedside scoring system *("Candida score")* for early antifungal treatment in nonneutropenic critically ill patients with *Candida* Colonization. Cristóbal León, Sergio Ruiz-Santana, Pedro Saavedra, Benito Almirante, Juan Nolla-Salas, Francisco Álvarez-Lerma, José Garnacho-Montero, María Ángeles León, and EPCAN Study Group. Crit Care Med 2006; 34:730-37. | **307** |
| 2 | Candidemia in non-neutropenic critically ill patients: analysis of prognostic factors and assessment of systemic antifungal therapy. J. Nolla-Salas, A. Sitges-Serra, C. León-Gil, J. Martínez-González, M.A. León-Regidor, P. Ibañez-Lucía, J.M. Torres-Rodríguez, Study Group of Fungal Infection in the ICU. Intensive Care Med 1997; 23:23-30. | **227** |
| 3 | .Economic Impact of *Candida* Colonization and *Candida* Infection in the Critically Ill Patient. Olaechea PM, Palomar M, León-Gil C, Álvarez-Lerma F, Jordá R, Nolla-Salas J, León-Regidor MA, and EPCAN Study Group Eur J Clin Microbiol Infect Dis 2004;23:323-30. | **100** |
| 4 | Risk factors for candidaemia in critically ill patients: a prospective surveillance study. Jordá R, Alvarez F, Jurado M, Palomar M, Nolla-Salas J, León MA, León C, and EPCAN Study Group. Mycoses 2007;50:302-10. | **48** |
| 5 | Fungal colonization and/or infection in non-neutropenic critically ill patients: results of the EPCAN observational study León C, Álvarez-Lerma F, Ruiz-Santana S, León MA, Nolla J, Jordá R, Saavedra P, Palomar M, and EPCAN Study Group. Eur J Clin Microbiol Infect Dis 2009;28:233-42. | **33** |
| 6 | Ibañez-Nolla J, Torres-Rodriguez JM, Nolla M, León MA, Mendez R, Soria G, Diaz RM, Marrugat J. The utility of serology in diagnosing candidosis in non-neutropenic critically ill patients. Mycoses 2001;44:47-53. | **17** |

# The end of an era in defining the optimal treatment of invaslve candidiasis

Clancy CJ, Nguyen NH

**CID 2012;54:1123-5**

1.- Fraser VJ et al, CID **1992**
Barnes Hospital 1988-89 (20-fold increase in incidence)
Mortality : 63% (**in patients without AFT**).

2.- Rex JH et al. NEJM **1996**
**FCNZ** is as effective as AFBD.

3.- Mora-Duarte J et al. NEJM **2002**
**Caspofungin** and AFB.

4.- Andes DR et al. CID **2012**
Review 1915 patients (7 randomized clinical trials)
**Echinocandin** use is associated with improved survival and greater clinical success than azoles or AFB.

**Invasive candidiasis in critically ill patients: does progressing knowledge improve clinical management and outcome?**

Marchetti O, Eggimann P, Calandra T.

Current Opin Crit Care 2010,16:442–4

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"In summary, major advances in our understanding of the pathogenesis of *Candida* infections and recent improvements regarding diagnosis, clinical assessment and therapy of invasive candidiasis have opened new perspectives for better prevention and treatment of invasive candidiasis in critically ill patients".

# 3. What this study/project adds to our knowledge ?

1. Epidemiological aspects: *Candida* spp, rate of CC/IC, date of appearance time (CC/IC), etc.
2. Practical consequences: Mortality (attributable), ATFT (over)
3. Clinical scenario: surgical patients (abdominal)
4. IC prediction rules (better stratification):
   - Colonization index; Ostrosky rule; *Candida Score*
5. Candida Score & clinical use
6. Candida Score & biomarkers
7. *Candida* DNA detection (RT- in house PCR)

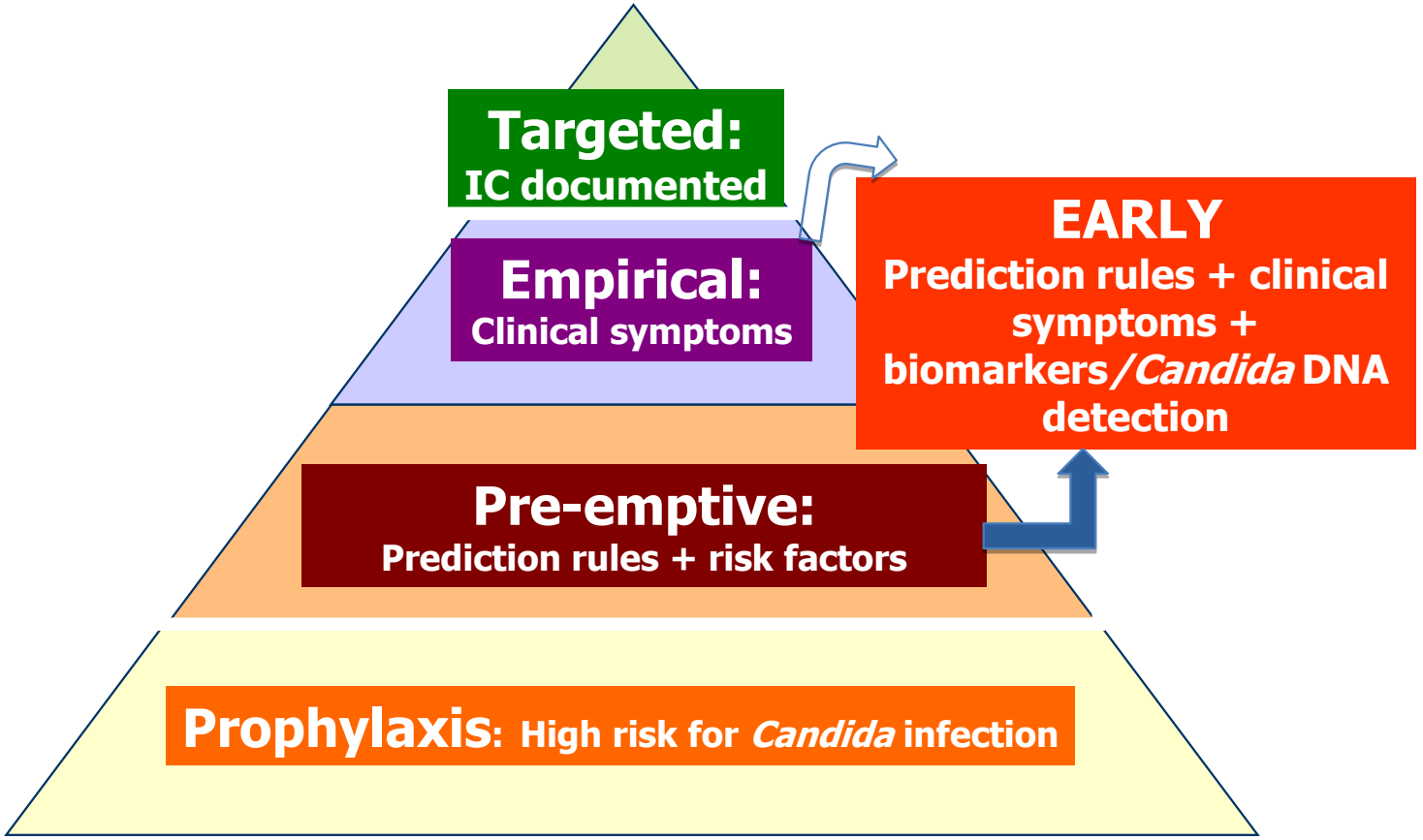
# Categorization of *Candida* colonization / infection in ICU

1.- Neither *Candida* colonization/infection

*2.- Candida* colonization
- Low grade
- High grade (heavy)

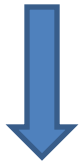
*3.- Candida* infection
- Candidemia
  - Candidemia primary
  - *Catheter-related* Candidemia
- Deep - seated infection
  - Intra-abdominal candidiasis
- *Others*
  - *Pleural candidiasis*
  - *Ocular candidiasis*
  - *Candida meningitis*
  - *Candida endocarditis*

# Systemic Antifungal Treatment. Modalities

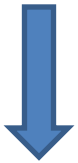


# 4. How this is relevant to clinical practice ?

High Risk of IC (Clinical Prediction Rules)

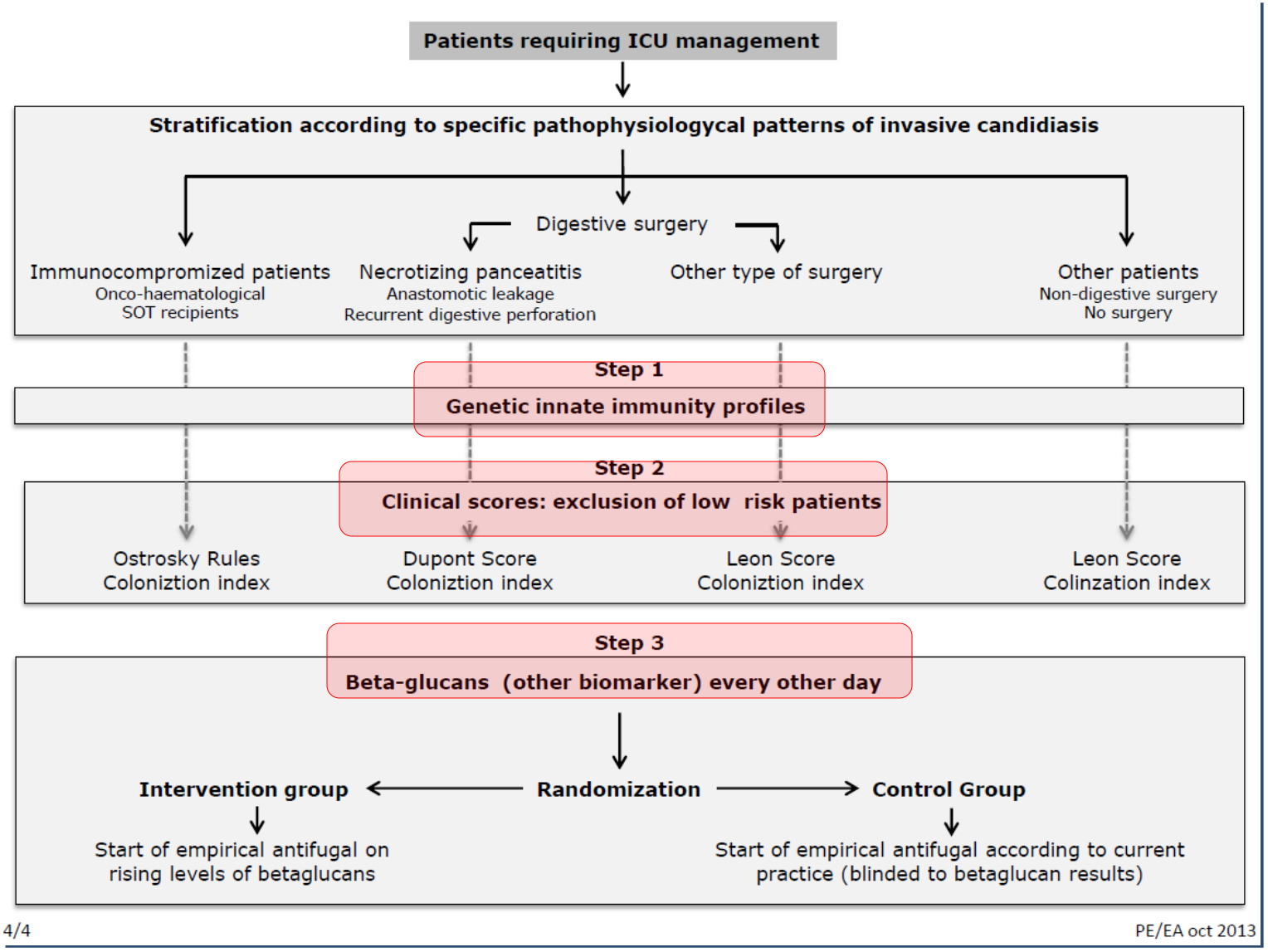


Biomarkers (combination*)/Candida* DNA detection



**ATF therapy**

# Future


Patients requiring ICU management
Stratification according to specific pathophysiologycal patterns of invasive candidiasis
Digestive surgery
Immunocompromized patients
Onco-haematological
SOT recipients
Necrotizing panceatitis
Anastomotic leakage
Recurrent digestive perforation
Other type of surgery
Other patients
Non-digestive surgery
No surgery
Step 1
Genetic innate immunity profiles
Step 2
Clinical scores: exclusion of low risk patients
Ostrosky Rules
Coloniztion index
Dupont Score
Coloniztion index
Leon Score
Coloniztion index
Leon Score
Colinzation index
Step 3
Beta-glucans (other biomarker) every other day
Intervention group
Randomization
Control Group
Start of empirical antifugal on
rising levels of betaglucans
Start of empirical antifugal according to current
practice (blinded to betaglucan results)

# T2 Magnetic Resonance Enables Nanoparticle-Mediated Rapid Detection of Candidemia in Whole Blood


This study shows that the nanoparticle- and T2MR- based detection method is rapid and **amenable to automation** and offers clinicians the opportunity to detect and identify multiple human pathogens **within hours(3)** of sample collection

Neely LA, et al. Science Translat Med 2013;5:182ra54

B. Galván, F. Mariscal, and J. García (Hospital Universitario La Paz, Madrid); A. Blanco and M.A. MA. Herranz and A. Gómez (Hospital Rio Hortega, Valladolid); F. Martín and L.M. Ruiz Velasco (Clínica Moncloa, Madrid); O. Rodríguez and C. Gimeno (Hospital Clínico Universitario, Valencia); R. Zaragoza and J.J. Camarena (Hospital Dr. Peset, Valencia); A. Martínez and A. Menasalva (Hospital Virgen de la Arrixaca, Murcia); L. de Janon and S. Arcieri (Hospital Universidad Abierta Interamericana-UAI, Buenos Aires, Argentina); M. Nieto and P. Merino (Hospital Clínico San Carlos, Madrid); J. Ballus and J. Ayats (Hospital de Bellvitge, Barcelona); J.R. Iruretagoyena and M. Alkorta (Hospital de Cruces, Bilbao); J. Luna and M. Pérez (Hospital Verga de la Cinta, Tortosa); J. Garnacho, JA. Márquez and M. Ruiz (Hospital Virgen del Rocío, Sevilla); R.M García and M.I. Blanco (Hospital de Cabueñes, Gijón); G. González and R. Blázquez (Hospital Morales Meseguer, Murcia); L. Vetere and M. R. Marcato (Hospital Vélez Sarsfield, Buenos Aires, Argentina); J.C. Pozo and M.C. Gamero (Hospital Reina Sofía, Córdoba); E. Maraví and X. Beristain (Hospital Virgen del Camino, Pamplona); J. Almirall and G. Sauca (Hospital de Mataró, Mataró, Barcelona), Spain; and P.E. Charles (Hôpital Le Bocage, Dijon), France.

B. Galván, F. Mariscal, and J. García (Hospital Universitario La Paz, Madrid); A. Blanco and M.A. MA. Herranz and A. Gómez (Hospital Rio Hortega, Valladolid); F. Martín and L.M. Ruiz Velasco (Clínica Moncloa, Madrid); O. Rodríguez and C. Gimeno (Hospital Clínico Universitario, Valencia); R. Zaragoza and J.J. Camarena (Hospital Dr. Peset, Valencia); A. Martínez and A. Menasalva (Hospital Virgen de la Arrixaca, Murcia); L. de Janon and S. Arcieri (Hospital Universidad Abierta Interamericana-UAI, Buenos Aires, Argentina); M. Nieto and P. Merino (Hospital Clínico San Carlos, Madrid); J. Ballus and J. Ayats (Hospital de Bellvitge, Barcelona); J.R. Iruretagoyena and M. Alkorta (Hospital de Cruces, Bilbao); J. Luna and M. Pérez (Hospital Verga de la Cinta, Tortosa); J. Garnacho, JA. Márquez and M. Ruiz (Hospital Virgen del Rocío, Sevilla); R.M García and M.I. Blanco (Hospital de Cabueñes, Gijón); G. González and R. Blázquez (Hospital Morales Meseguer, Murcia); L. Vetere and M. R. Marcato (Hospital Vélez Sarsfield, Buenos Aires, Argentina); J.C. Pozo and M.C. Gamero (Hospital Reina Sofía, Córdoba); E. Maraví and X. Beristain (Hospital Virgen del Camino, Pamplona); J. Almirall and G. Sauca (Hospital de Mataró, Mataró, Barcelona), Spain; and P.E. Charles (Hôpital Le Bocage, Dijon), France.

**Gracias por su atención !**