FUNGAL INFECTIONS IN THE ICU PATIENTS
– State of the Art –

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FUNGAL INFECTIONS IN THE ICU PATIENTS

Why is this topic important ?

Increasing problem

Mortality higher than in bacterial infections

Early diagnosis is a challenging problem

New strategies for recognition and treatment

Good example of a multidisciplinary approach

FUNGAL INFECTIONS IN THE ICU PATIENTS

Topics to be addressed

Epidemiology

Physiopathology

Risk factors

Clinical diagnosis

Laboratory diagnosis

Therapeutic approaches

FUNGAL INFECTIONS IN THE ICU PATIENTS

Organisms addressed

Candida

Aspergillus

Mucorales

Organisms not addressed

Cryptococcus

other yeasts

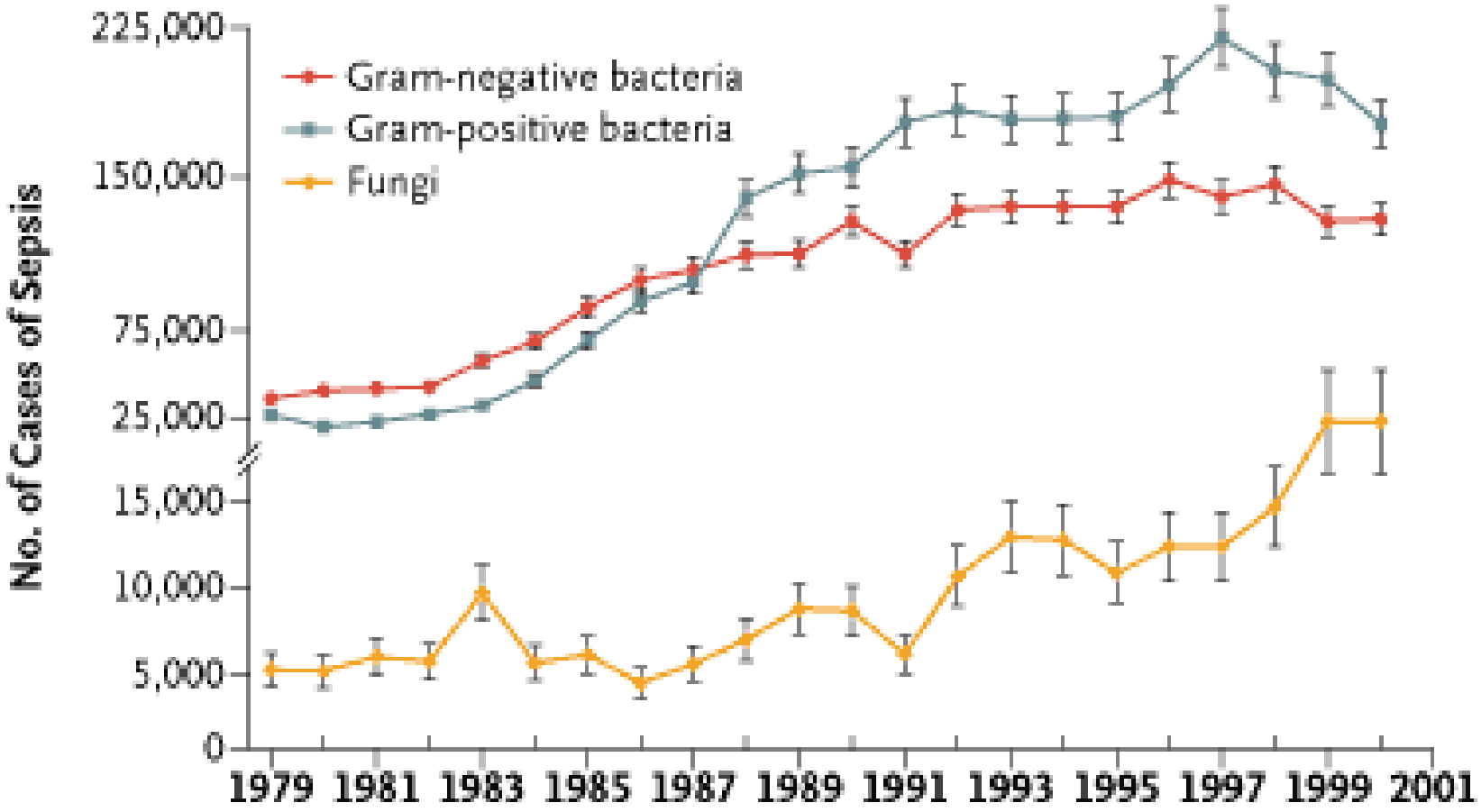
other mould

dimorphic fungi

FUNGAL INFECTIONS IN THE ICU PATIENTS

Epidemiology

General trends



Martin C.S. et al., *N Engl J Med* 2003; 348: 1546.

FUNGAL INFECTIONS IN THE ICU PATIENTS

Epidemiology

Invasive candidiasis – Candidemia

0.2 - 3 / 1000 hospital admissions
2 - 12 / 1000 ICU patients

DK 2003-4	**0.49 / 1000**	**discharges**	**(Arendrup 2005)**
SE 1998-9	**0.32 / 1000**	**admissions**	**(Klingspor 2004)**
NO 1993-6	**0.29 / 10'000**	**pt days**	**(Sandven 1998)**
CH 1991-2000	**0.49 / 10'000**	**pt days**	**(Marchetti 2004)**
EU 1997-9	**0.2-0.38 / 1000**	**admissions**	**(Tortorano 2004)**

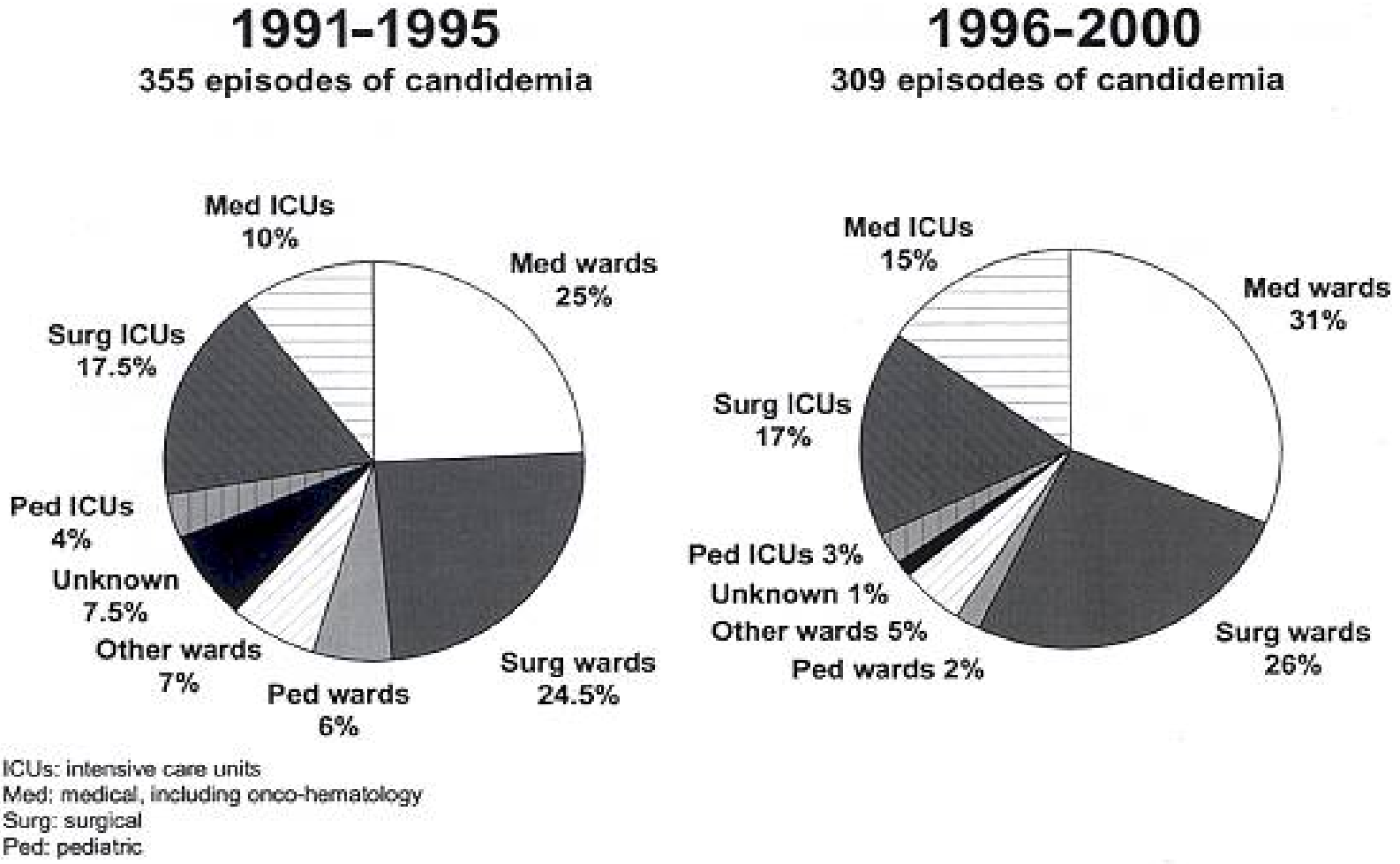
Epidemiology

1'417 ICUs in 17 European countries
(EPIC Study 1992)

	Total (%)	BSI	wound	UTI
S. aureus	**30.0**	**21.9**	**26.5**	**6.0**
P. aeruginosa	**28.7**	**9.7**	**21.2**	**18.7**
CN Staph.	**19.1**	**44.9**	**0**	**0**
Yeasts	**17.1**	**9.3**	**8.3**	**21.2**
Enterococci	**11.7**	**10.9**	**18.2**	**14.8**

Vincent J.L. et al. (EPIC), *JAMA* 1995; 274: 639-44.
Spencer et al., *ESCMID* 1996; 15: 281.

Epidemiology – Contribution of ICUs



Marchetti O., Bille J. et al., *Clinical Infectious Diseases* 2004; 38: 311.

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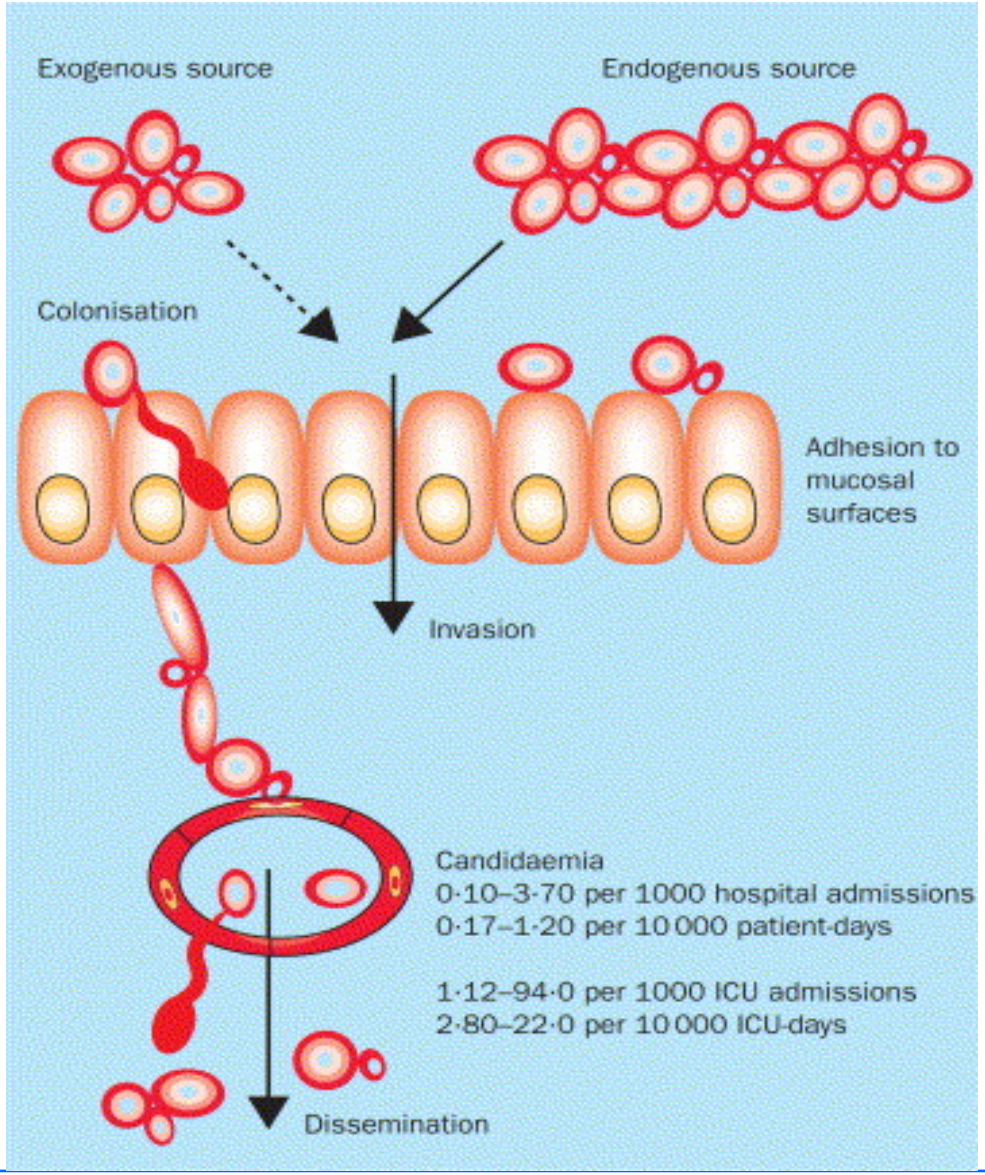
Physiopathology



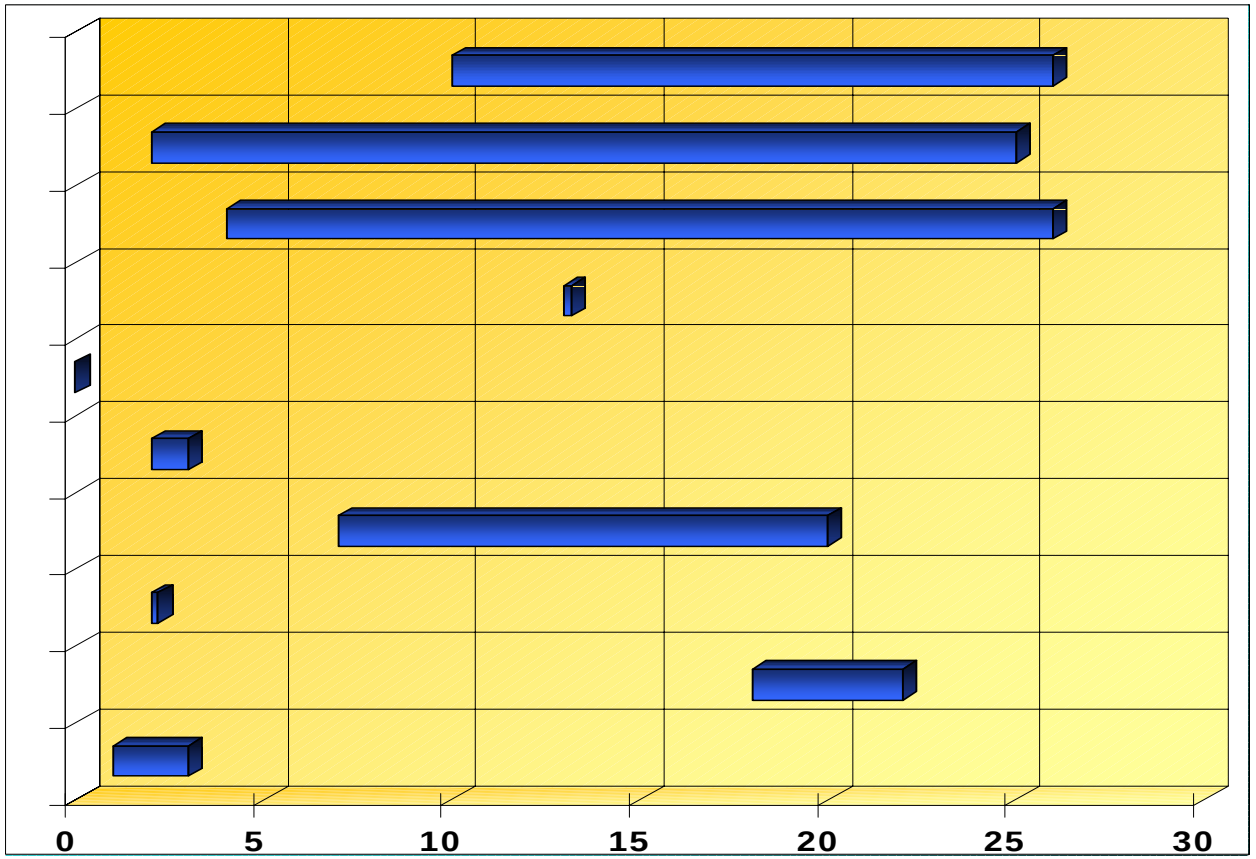
Eggimann P. et al., *Lancet Infectious Diseases* 2003; 3: 690.

FUNGAL INFECTIONS IN THE ICU PATIENTS

Risk factors for invasive candidiasis

OR (multivariable analyses)

- **Colonisation**
- **Antibiotics**
- **Vascular access**
- **Bladder catheter**
- **Neutropenia**
- **TPN**
- **Surgery**
- **AF prophylaxis**
- **Renal failure**
- **Disease severity**



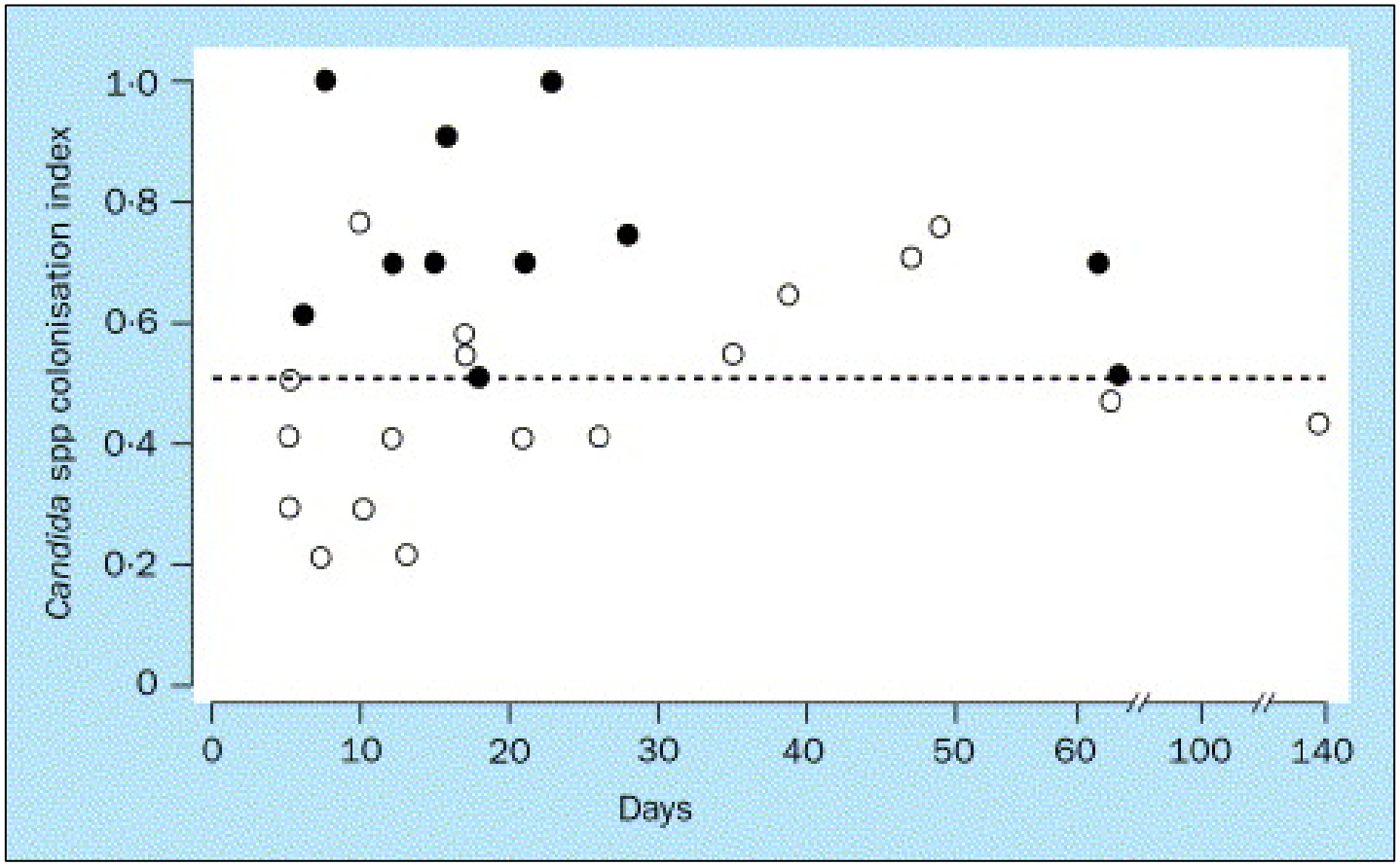
Adapted from Eggimann P. et al., *Lancet Infectious Diseases* 2003; 3: 685.

Risk factors Colonisation

Spread from abdominal cavity to other body sites
Heavy or increased growth from peritoneal cavity
High amounts in stool
Multiple site colonization
Patient specific strain carriage
Colonisation rate at entry 5-15%
during prolonged ICU stay 50-85%

Risk factors

Candida colonisation



Colonisation index: ratio of the nb of body sites colonised to the total nb of body sites cultured

Eggimann P. et al., *Lancet Infectious Diseases* 2003; 3: 685.

Clinical Diagnosis

Problematic

Clinical presentation variable and non specific

fever	**80%**
leukocytosis	**50%**
chorioretinitis	**25%**
endophtalmitis	**10-20%**

skin lesions

muscle abscesses

septic arthritis

high grade candiduria in non catheterized patients

signs of multi-organ failure

Skin – **Candidemia**

Candida – **Retinitis**

Laboratory diagnosis

Candida – Conventional methods

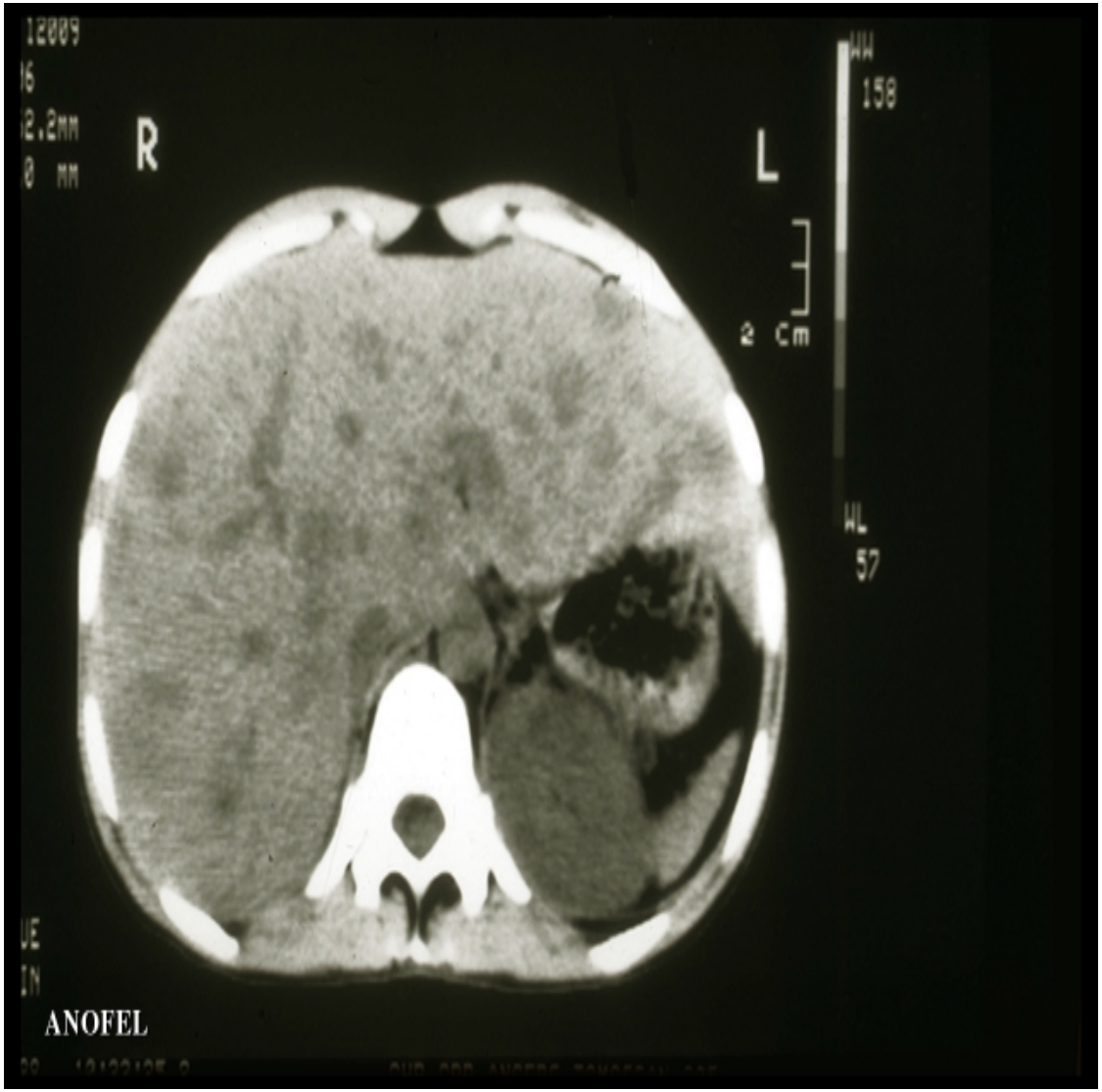
- **Culture** **blood**
  other sterile body sites
  urines
  other sites (dd colonisation-infection)

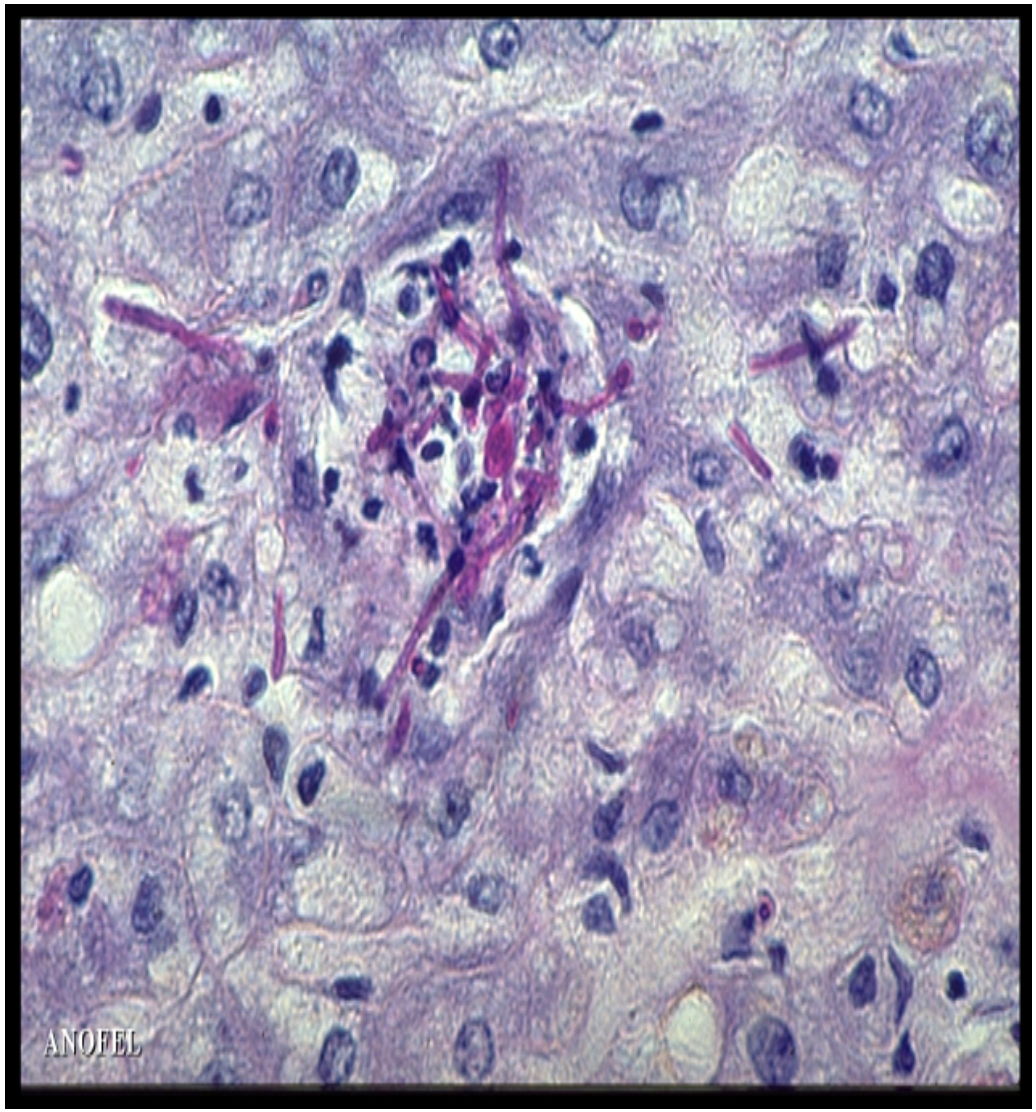
⊖ **insensitive**
slow

⊕ **identification to species level**
antifungal susceptibility testing

- **Histology** **biopsies (liver, skin)**

FUNGAL INFECTIONS IN THE ICU PATIENTS





Laboratory diagnosis

***Candida* – indirect tests**

- **antigen-antibodies**
- **fungal DNA detection**

Mostly evaluated in onco-hematology patients

Very few studies in ICU patients

Very few commercially available tests

FUNGAL INFECTIONS IN THE ICU PATIENTS

Diagnosis of invasive *Candida* infections

Antigen based tests

	detection limit	
Mannan	**0.1 μg/mL**	**specific to *Candida* spp**
β-1-3 D glucan	**0.1 pg/mL**	**non specific to *Candida* spp**

Diagnosis of invasive *Candida* infections
Mannan (+ antimannan)

Frequency of testing
2-3 times/week
ag peak very short

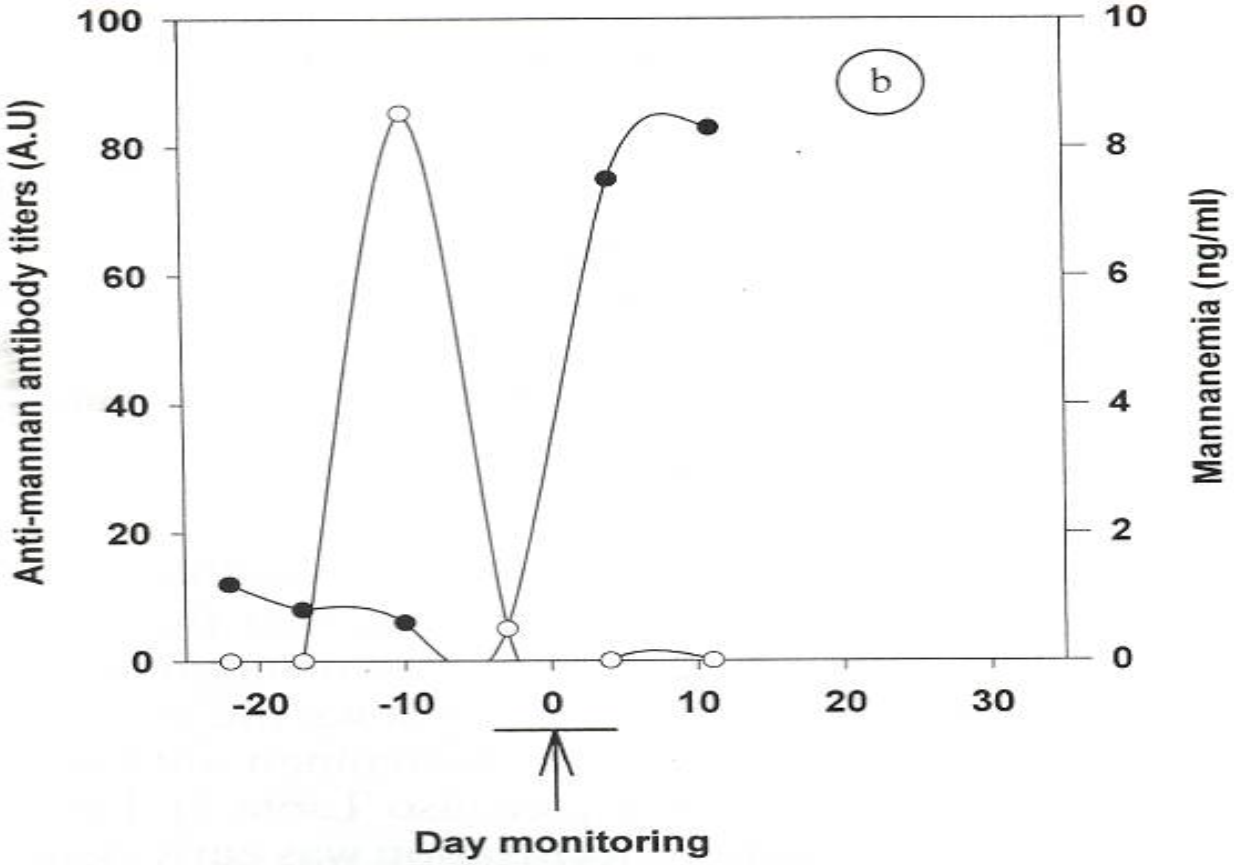


FIG. 4. Examples of kinetic evolution of antigenemia (○) and antimannan antibody response (●) detected by EIA. Patients 39 (a) and 43 (b) had systemic candidiasis. The arrow marks the date of mycological isolation of *C. albicans* from blood and a drain. The curves are drawn by using the interpolate regression.

Sendid, *JCM* 1999; 37: 1514.

FUNGAL INFECTIONS IN THE ICU PATIENTS

Diagnosis of invasive *Candida* infections

Mannan (+ antimannan)

Sensitivity factors

main variables:

- **type of disease** **candidemia in:**
  - **oncohematology**
  - **ICU patients**

  hepatosplenic candidiasis
- **species of *Candida***
- **stage of the disease (antibodies)**
- **frequency of testing (per test or per episode evaluation)**

Mannan – antimannan
Kinetics according to the type of patients

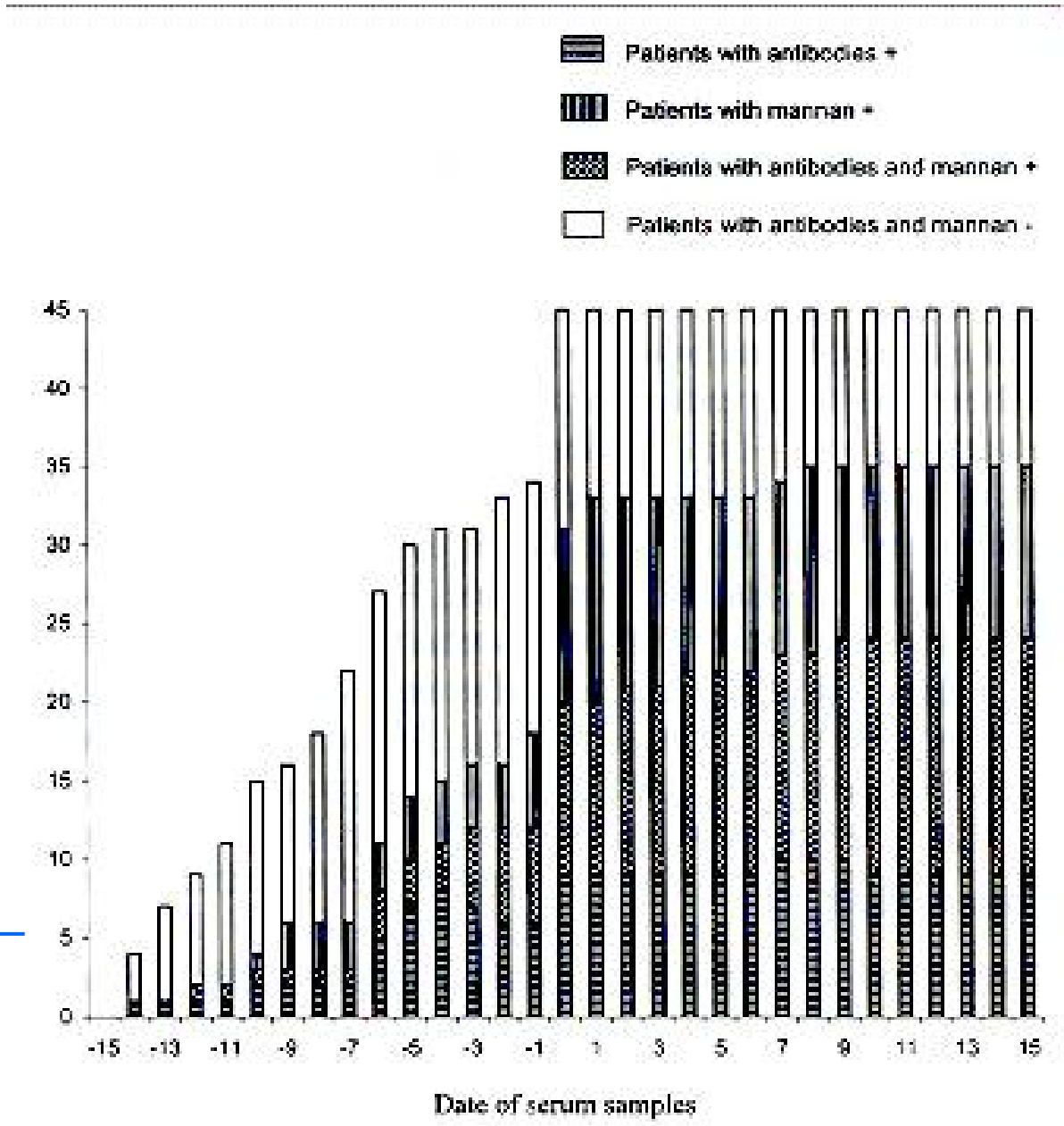
	n=	+ test before BC	ag +	ab +
Hemato-oncol.	11	100%	82%	36%
ICU pts	15		40%	33%
Surgical pts	17		47%	65%
Total		73%		

Yera H. et al., *Eur J Clin Microbiol Infect Dis* 2001; 20: 864.

FUNGAL INFECTIONS IN THE ICU PATIENTS

Mannan – antimannan Kinetics

45 patients with positive blood culture



Yera H. et al., *Eur J Clin Microbiol Infect Dis* 2001; 20: 864.

Mannan – antimannan
Sensitivity according to species

	n=	+ test before +BC	%
C.albicans	**23**	**74%**	**17/23**
C.tropicalis	**9**	**100%**	**9/9**
C.parapsilosis	**5**	**60%**	**3/5**
C.glabrata	**4**	**50%**	**2/4**
C.krusei	**4**	**50%**	**2/4**

Yera H. et al., *Eur J Clin Microbiol Infect Dis* 2001; 20: 864.

FUNGAL INFECTIONS IN THE ICU PATIENTS

Mannan screening in ICU patients

Prospective study of 105 ICU patients (>7 days in ICU)
Screening 1x/week

IC n=10 (2 proven, 3 probable)

Colonization rate : 70%

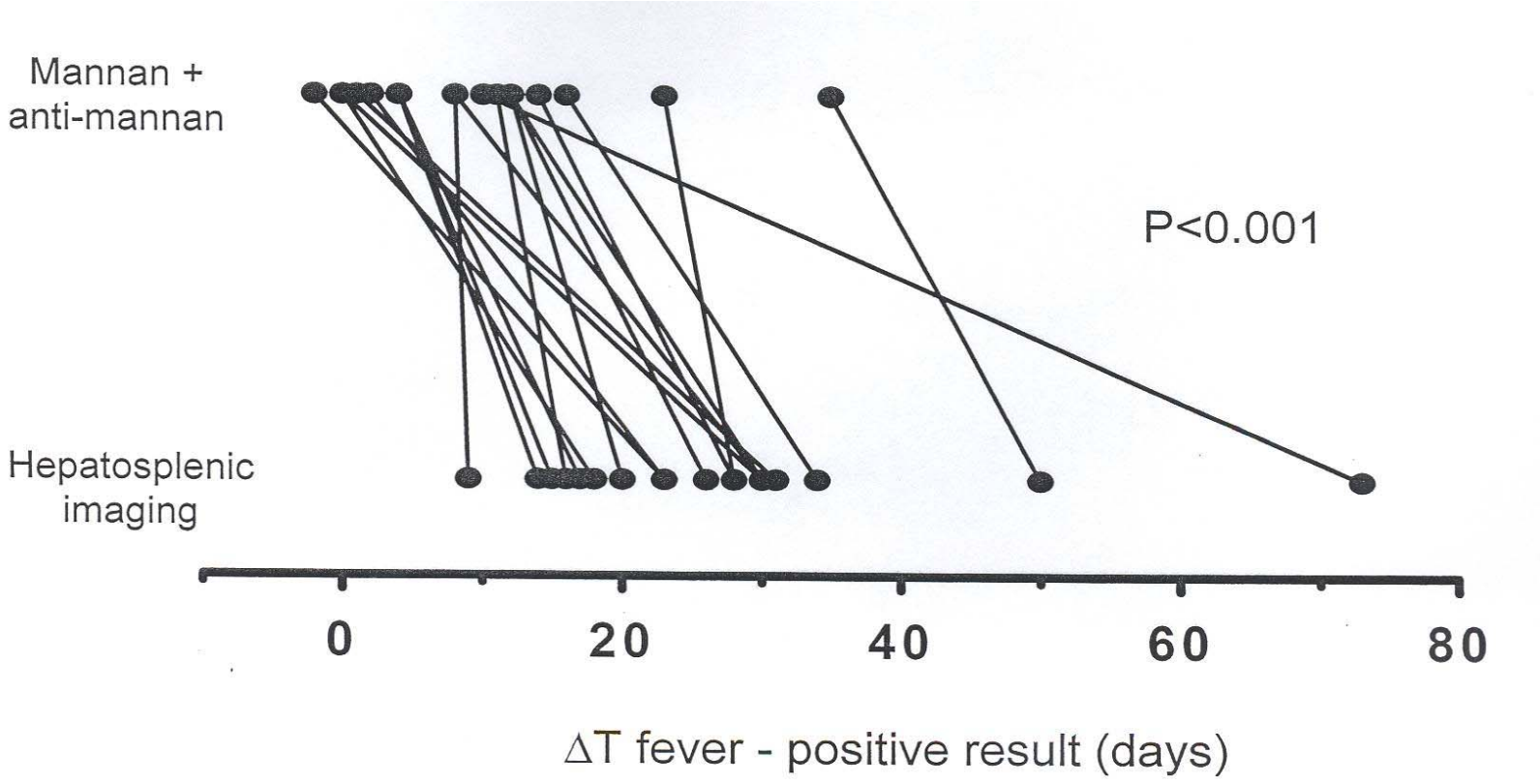
Mannan positive in 60% pt with IC
43% pt colonized
25% pt without colonization

20% of false positive results !

Ibara A.S. et al., *J Mycol Med* 2004; 14: 34-42.

Laboratory diagnosis – *Candida*

Detection of mannan and antimannan in hepatosplenic candidiasis



Prella M., Bille J., et al. *Diagnostic Microbiology and Infectious Disease* 2005; 51: 95.

Multicenter Clinical Evaluation of β-D-glucan Assay

163 patients with IFI, 170 without - **1 sample taken within 72 hours after diagnosis**

107 patients with proven candidiasis

sensitivity	**81.3%**	

All patients	**sensitivity**	**70%**
	specificity	**87%**
	PPV	**83.8%**
	NPV	**75.1%**

Ostrosky-Zeichner et al., *Clinical Infectious Diseases* 2005; 41: 654.

β-D-glucan for diagnosis of IFI in patients with acute infections

	BG assay positive	
	(Digby 2003)	***(Pickering 2005)***
IFI confirmed	**96% (25/26)**	**87% (13/15)**
Bacteremia	**73% (8/11)**	**56% (14/25)**
No infection	**22% (2/9)**	

Low positive predictive value

High negative predictive value (≥ 95%)

Pickering JW et al., *J. Clin Microbiol* 2005; 43: 5957.
Digby J et al., *Clin Diag Lab Immunol* 2003; 10: 882.

Molecular based tests

DNA detection (PCR)

Single species/genus versus panfungal

High sensitivity (1-10 fg of DNA)

Applied to various body fluids : blood, serum, CSF, BAL

Quantification possible (response to antifungal therapy, differentiation colonization-infection)

No standardized (commercial) assay

→ no prospective multicenter large studies

UPDATE ON DIAGNOSIS OF INVASIVE CANDIDA INFECTIONS

Nucleic acid detection in patients with *Candida* fungemia and/or invasive candidiasis (IC)

Patients (%) with positive NA test		Controls (%) with positve NA test		Sample	Reference	
11/14	(79%)	0/29	(0%)	serum	Kan	JID 168: 779, 1993
15/16	(93%)	0/34	(0%)	blood	Jordan	JCM 32: 2962, 1994
16/18	(89%)	0/6	(0%)	serum	Chryssanthou	Scand JID 26: 479, 1994
28/28	(100%)	3/31	(10%)	serum	Burnie	EJCMID 16: 346, 1997
8/8	(100%)	3/100	(3%)	blood	Einsele	JCM 35: 1353, 1997
13/14	(93%)	18/58	(31%)	blood	Morace	JCM 37: 1871, 1999
28/30	(95%)		(3%)	blood	White	JCM 43: 2181, 2005

Adapted from Yeo and Wong, *Clin. Microbiol. Rev.* 15, 465, 2002.