

Intraabdominal candidosis – Myth or Fact?

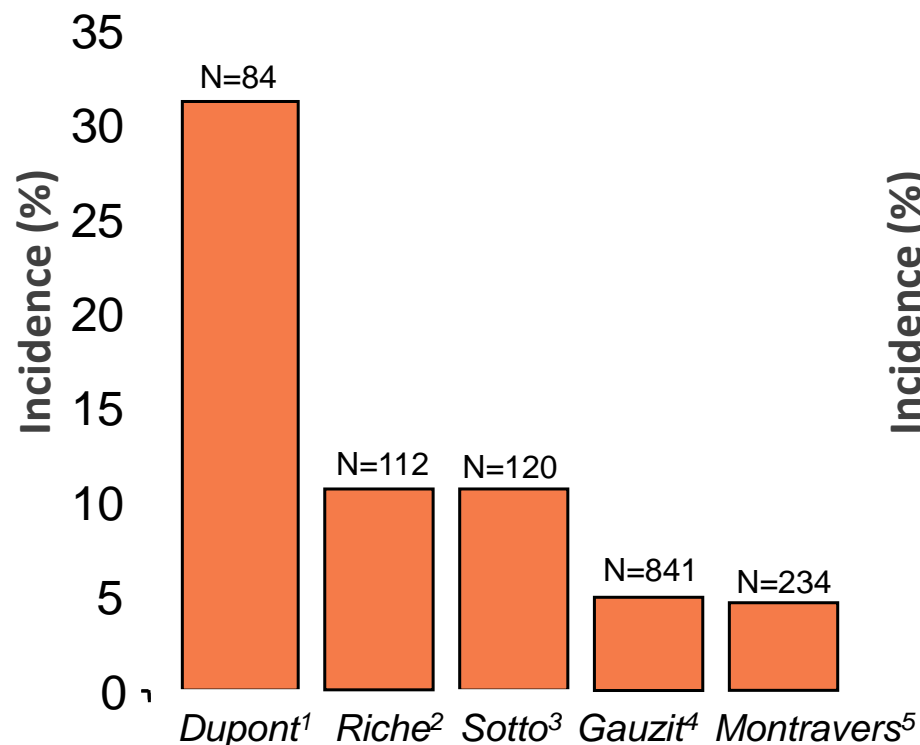
V. Adamková – Clinical Microbiology and ATB center; General University Hospital,
Prague, Charles University

Roma, 20.-22.10.2016

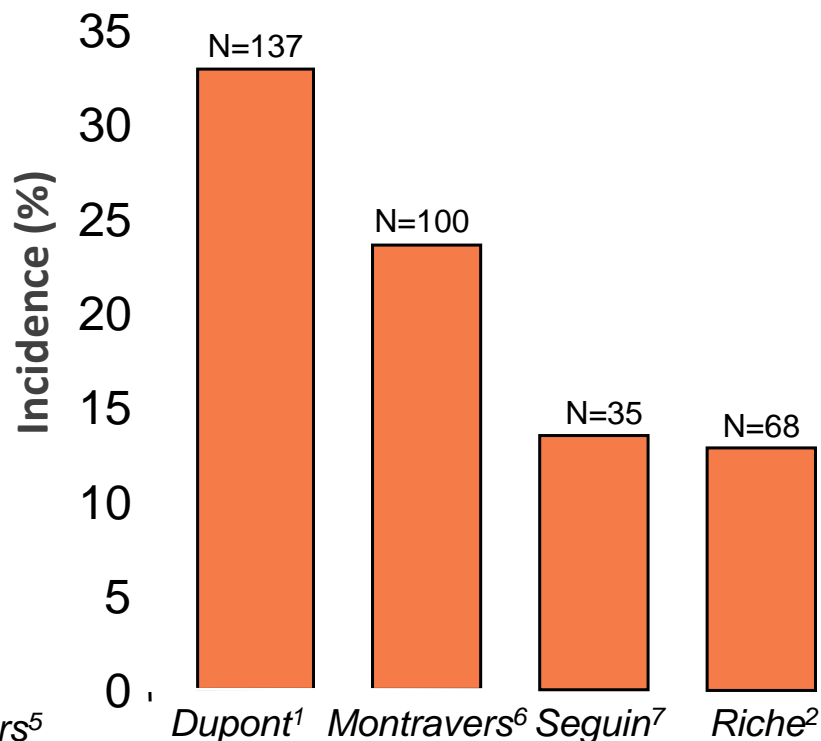


Incidence of *Candida* peritonitis

Community-acquired peritonitis



Postoperative peritonitis



1. Dupont H. Crit Care Med 2003;31:752-7;

2. Riche F. Crit Care 2009;13:R99;

3. Sotto A. J Antimicrob Chemother 2002;50:569-76;

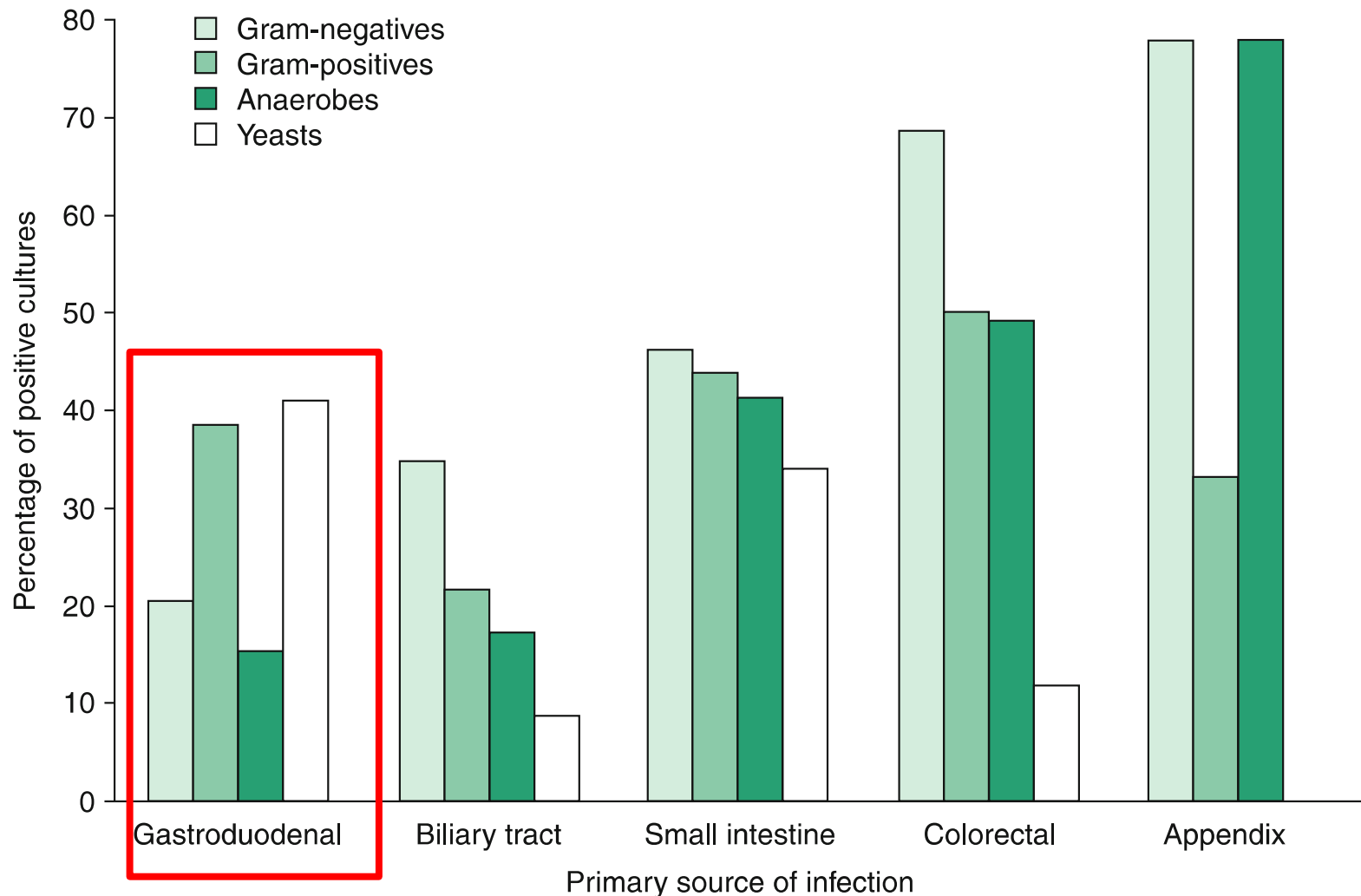
4. Gauzit R, et al. Surg Infect 2009;10:119-27;

5. Montravers P, et al. J Antimicrob Chemother 2009;63:785-94;

6. Montravers P. Clin Infect Dis 1996;23:486-94;

7. Seguin P. Clin Microbiol Infect 2006;12:980-5

Culture results in SP and TP: % positive findings with relation to primary source of infection



Man 1942

- 8/2015 – GIT bleeding for gastric ca
- 4.11. gastrectomy; anastomotic leak
- 12.11. oesophageal stent
- 19.11. worsening again
- 20.11. stent dislocation, revision
- 22.11. lungs auscultation, susp.
mediastinitis?????? – therapy MER, VAN -> shock
- 23.11. transfer to ICU; CRRT
- 24.11. exitus lethalis



PIP/TAZ



Autopsy findings:

- **Thrombosis of vena cava sup., thrombosis of v. femoralis dx, persistent foramen ovale, st. p. gastrectomy, left liver lobe necrosis, spleen infarctions, septic spleen activation, pleural exudate, peritoneal exudate, heart ventricles hypertrophy and dilation, lung oedema, oesophageal stent**



Microbiological findings:

- Thrombus – *C.albicans* +++
- Spleen tissue - *C.albicans*

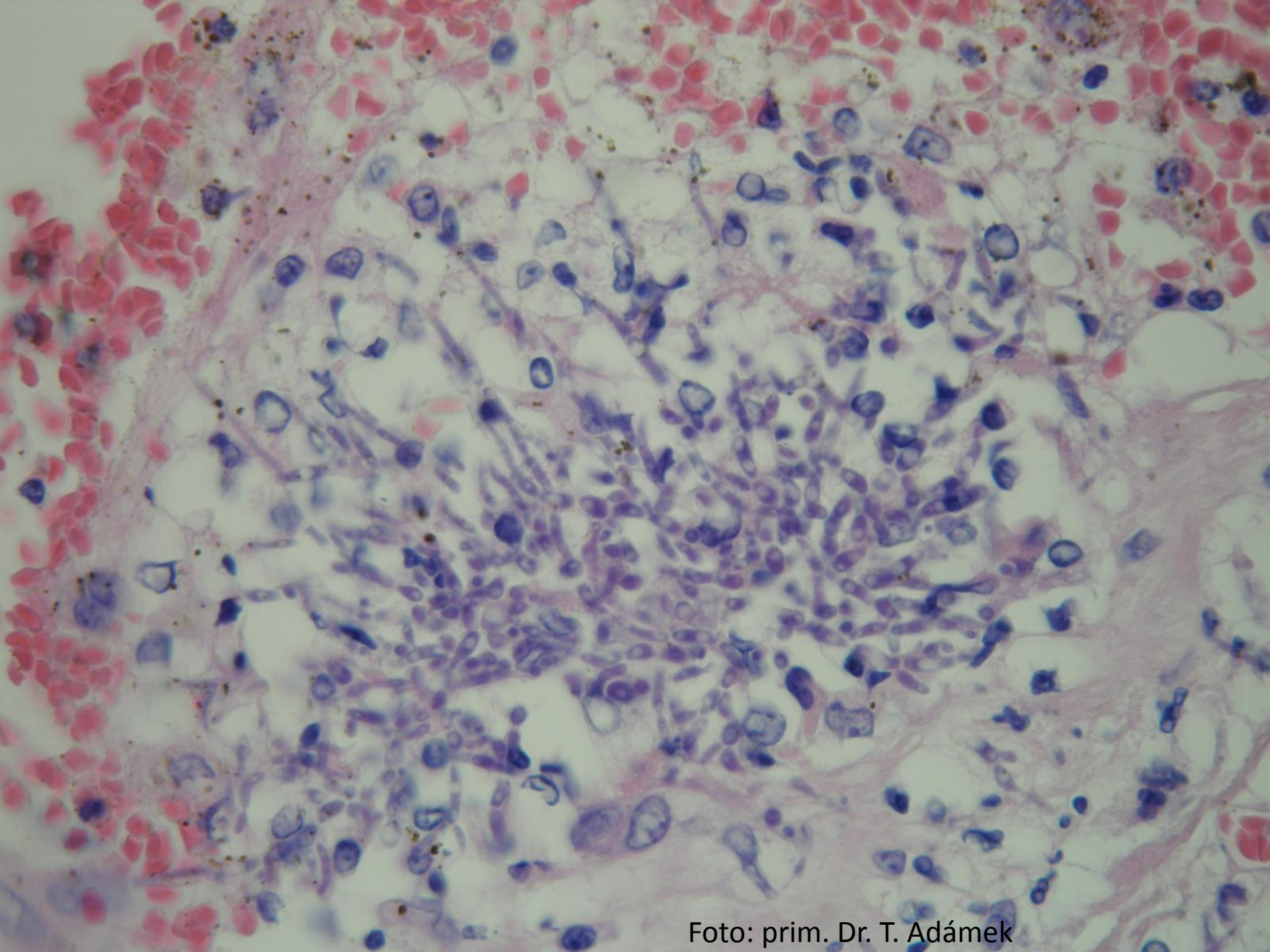
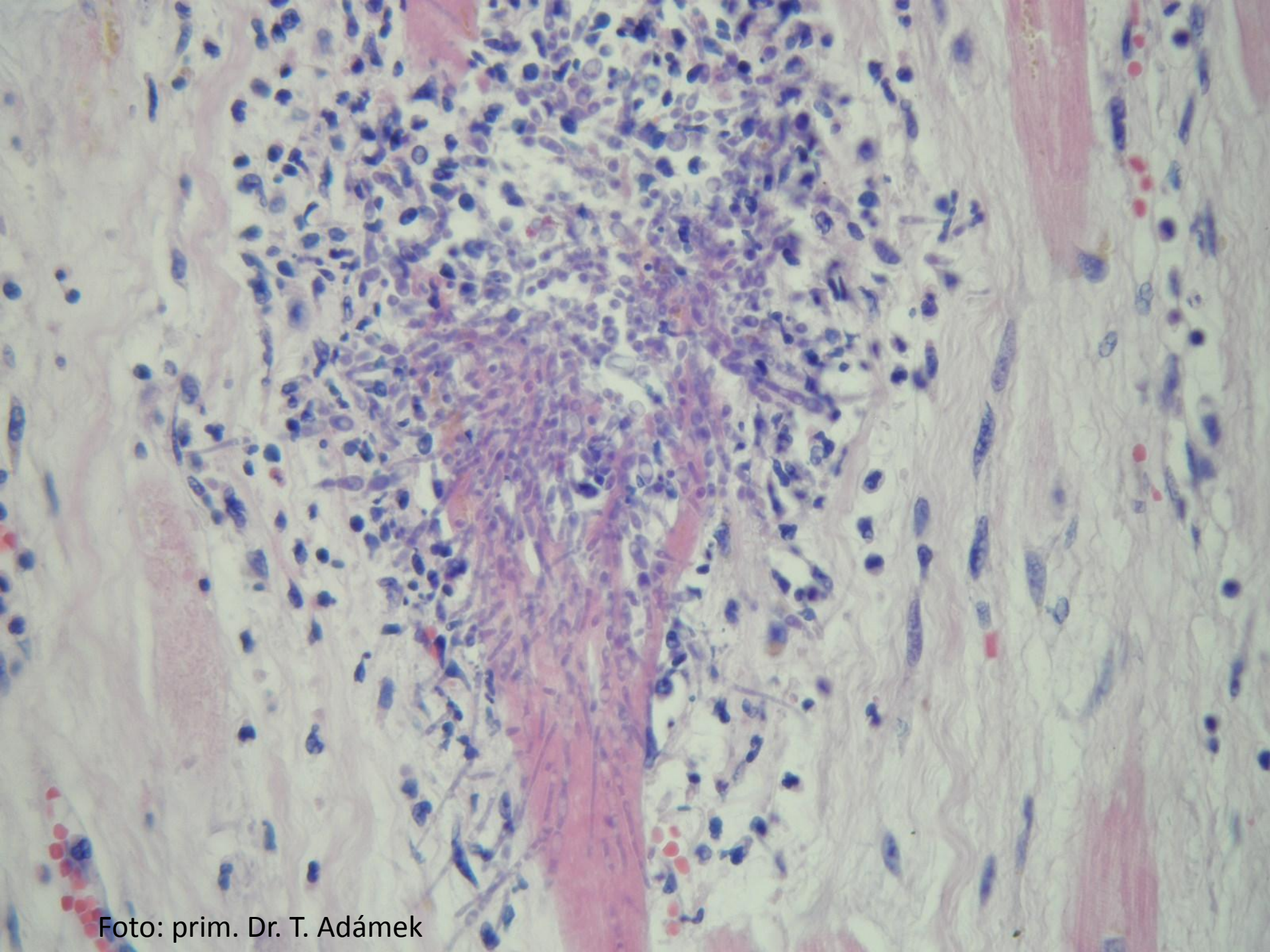
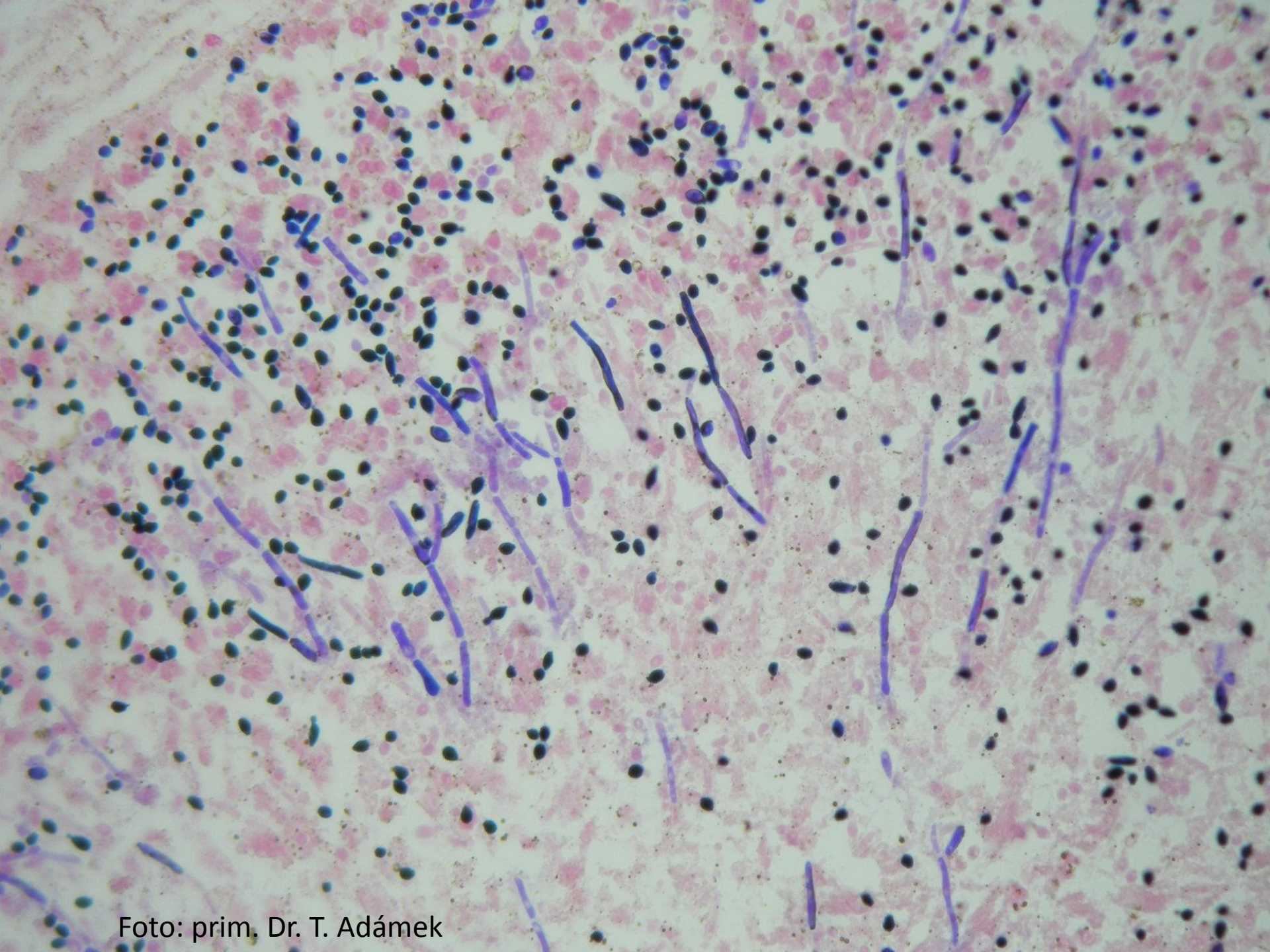


Foto: prim. Dr. T. Adámek

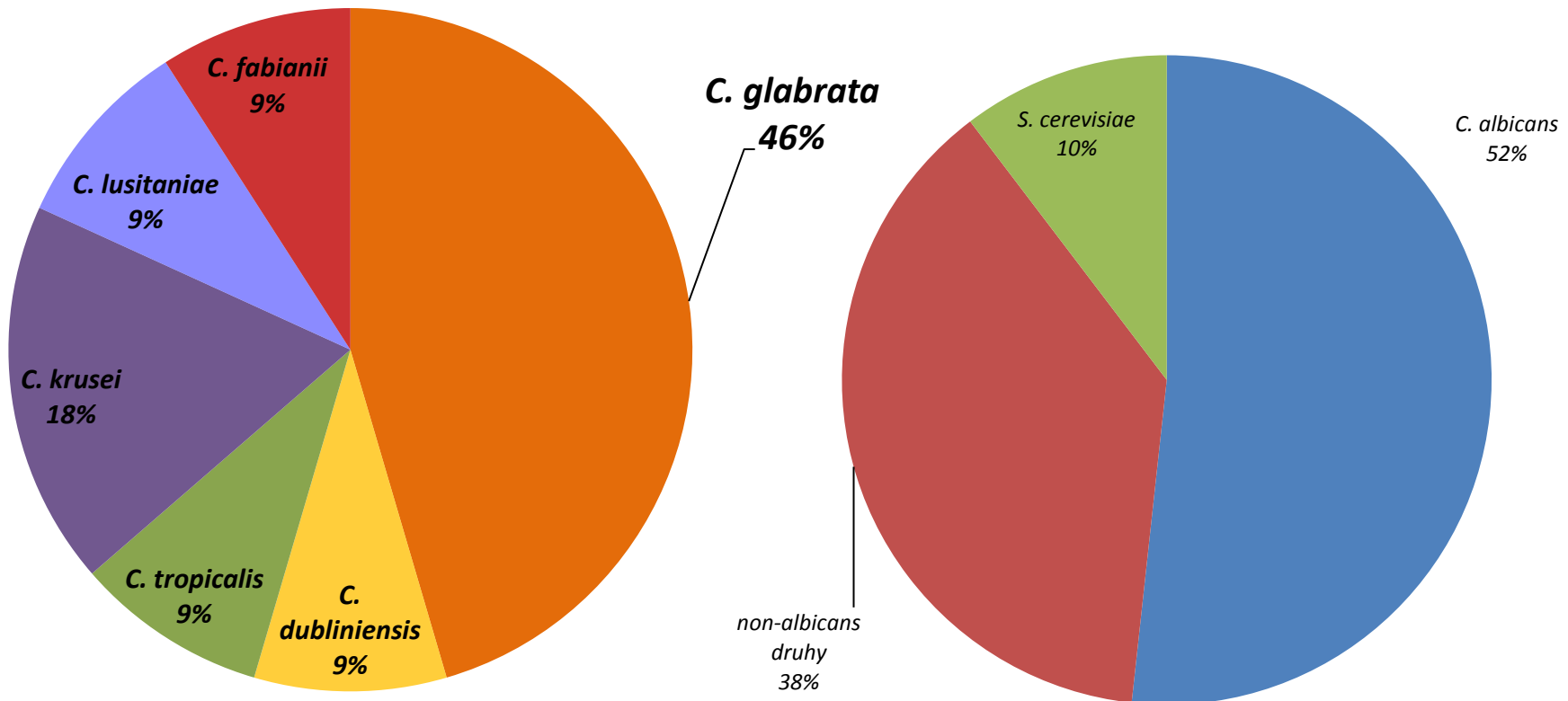


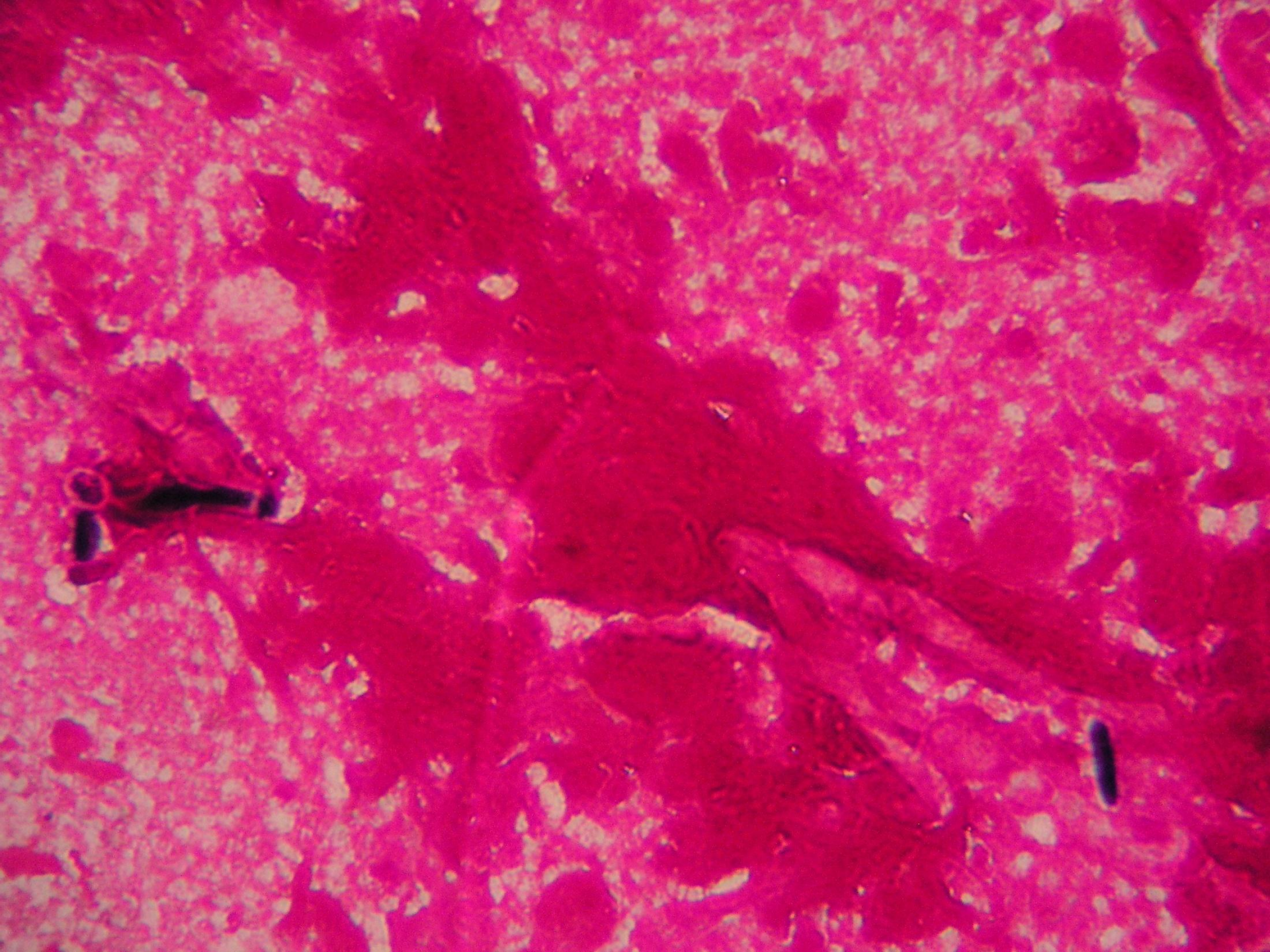


SMARTSurgical department – 6 m, 123 patients

Rapid detection of Sepsis

- Yeasts in 28 patients (9 % of all findings). 13 patients with rupture of upper GIT. The most frequent isolates: *Candida albicans*, *C. glabrata* a *S. cerevisiae*.







Preventing invasive candida infections. Where could

Pathophysiological characteristics of invasive candidiasis according to immune status

Pathophysiological characteristics	Immunocompromised patients	Critically ill patients
Immunity		
Neutrophils	Decreased	Increased
Macrophages	Decreased	Increased
T-cells	Decreased	Normal
Ulcerations of mucosal surfaces		
Oropharyngeal	++ to +++	0 to +
Upper digestive tract	++ to +++	0 to +
Lower digestive tract	++ to +++	0 to +
Typhlitis	++ to +++	0
Digestive surgery	0	++ to +++
Antibiotic exposure	++ to +++	+ to ++
Organ failure	+ to ++	++ to +++
Candida colonization	++ to +++	++ to +++
Invasive candidiasis		
Candidaemia	++ to +++	0 to +
Non-candidaemic systemic candidiasis	0 to +	++ to +++

Intensive Care Med (2013) 39:2226–2230
DOI 10.1007/s00134-013-3134-2

EDITORIAL

Philippe Montravers
Herve Dupont
Philippe Eggimann

Intra-abdominal candidiasis: the guidelines— forgotten non-candidemic invasive candidiasis

Table 1 Limitations of current clinical/biological tools in the diagnosis and treatment of intra-abdominal candidiasis

Current clinical/biological tools	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Usefulness to guide empirical antifungal treatment
Clinical risk factors					
Colonization index	Medium high	Medium	++	+++	++ if dynamics is followed
<i>Candida</i> scores	Medium	Medium high	++	+++	++
Predictive rules (+colonization)	Medium	Medium (high)	++	++ (+)	++ (+ if ongoing studies positives)
Biomarkers					
C-reactive protein	Low	Low	+	++	Not useful
Procalcitonin	Low	Medium	+	+++	++ if added to <i>Candida</i> score
Mannan/anti-mannan antibodies	Very high	High	++	+++	+++ if dynamics is followed
Beta-D-glucans	Very high	Very high	+++	+++	+++ in high risk patients
Secondary peritonitis					
+ <i>Candida</i> and nosocomial infection	High	Very high	++	++	++ (but overtreatment)
+ <i>Candida</i> + upper digestive tract perforation	High	Very high	++	++	++ (but overtreatment)
+Septic shock	High	Very high	++	++	++ (but overtreatment)
Tertiary peritonitis					
Anastomotic leakage	Very high	Very high	+++	+	+++ (>35 % risk of candidiasis)
Repetitive surgery	Very high	Very high	+++	+	+++ (>50 % risk of candidiasis)

?????

Pathophysiological role of *Candida* spp isolated from the peritoneum

Distinction between colonization and infection

Prophylaxis and preemptive antifungal treatment

Therapeutic challenges

- Synergisms and antagonisms with bacteria (*Pseudomonas* spp, *Enterococci*, *Staphylococci*...)
- Mechanisms of adhesion/invasion of the epithelial intestinal cell
- Role of biofilms
- Role of host defense mechanisms (innate immunity)
- Enhanced predictivity of described tools in high risk groups:
 - Exclusion of low risk patients by negative predictive value of colonization index, of clinical scores and of predictive rules
 - Positive predictive value of biomarkers in these patients
- Role of fungi isolated from mixed cultures
- Time course of colonization and infection
- When, how, to whom, what drug
- What dose, for how long time
- Comparison of antifungal agents (fungicidal versus fungistatic)
- Effects of combinations of antifungals
- In different but homogenous clinical settings:
 - Severe or mild to moderate fungal infection
 - Community-acquired versus nosocomial/health-care associated infections
 - Prolonged or persistent fungal peritonitis
 - Clinical and biological makers of clinical and microbiological response
 - Optimal duration of treatment
 - Feasibility and advantages of de-escalation

Philippe Montravers
Herve Dupont
Philippe Eggimann

Intra-abdominal candidiasis: the guidelines— forgotten non-candidemic invasive candidiasis

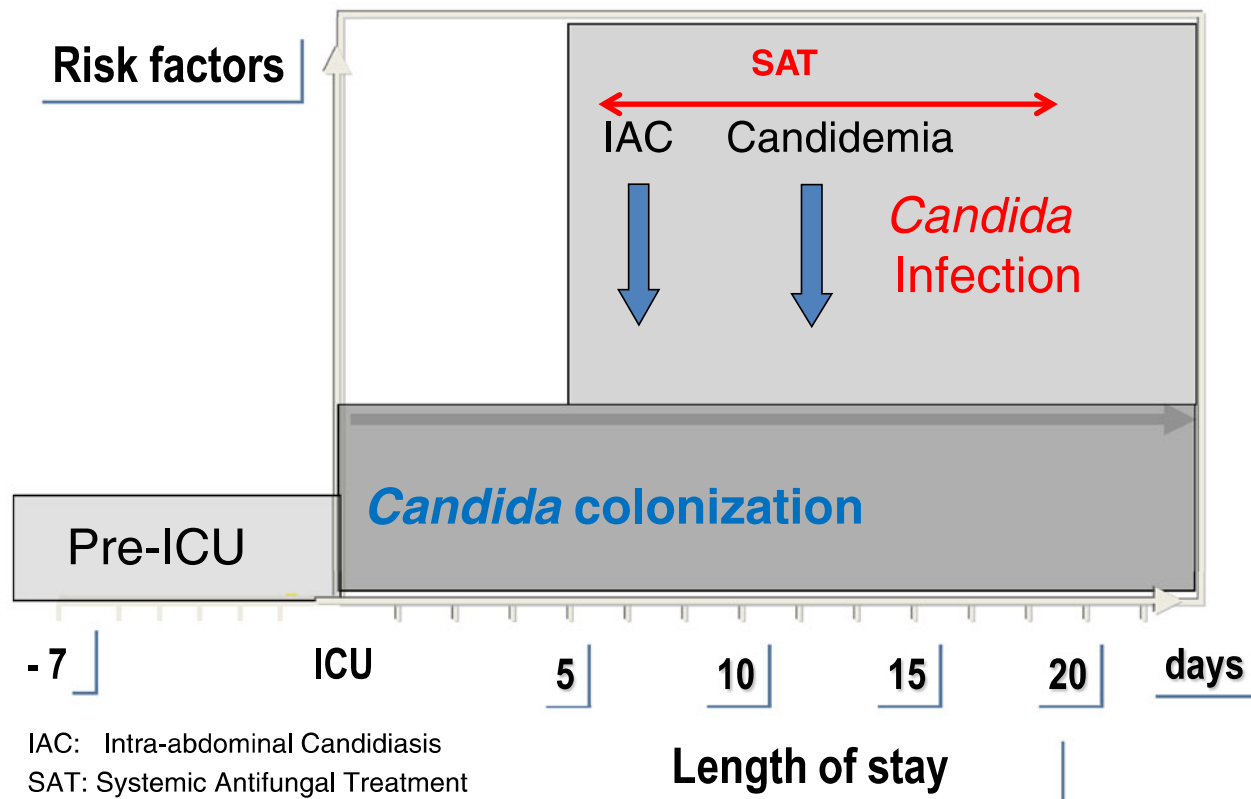


Fig. 1 Invasive candidiasis in ICU. Natural history

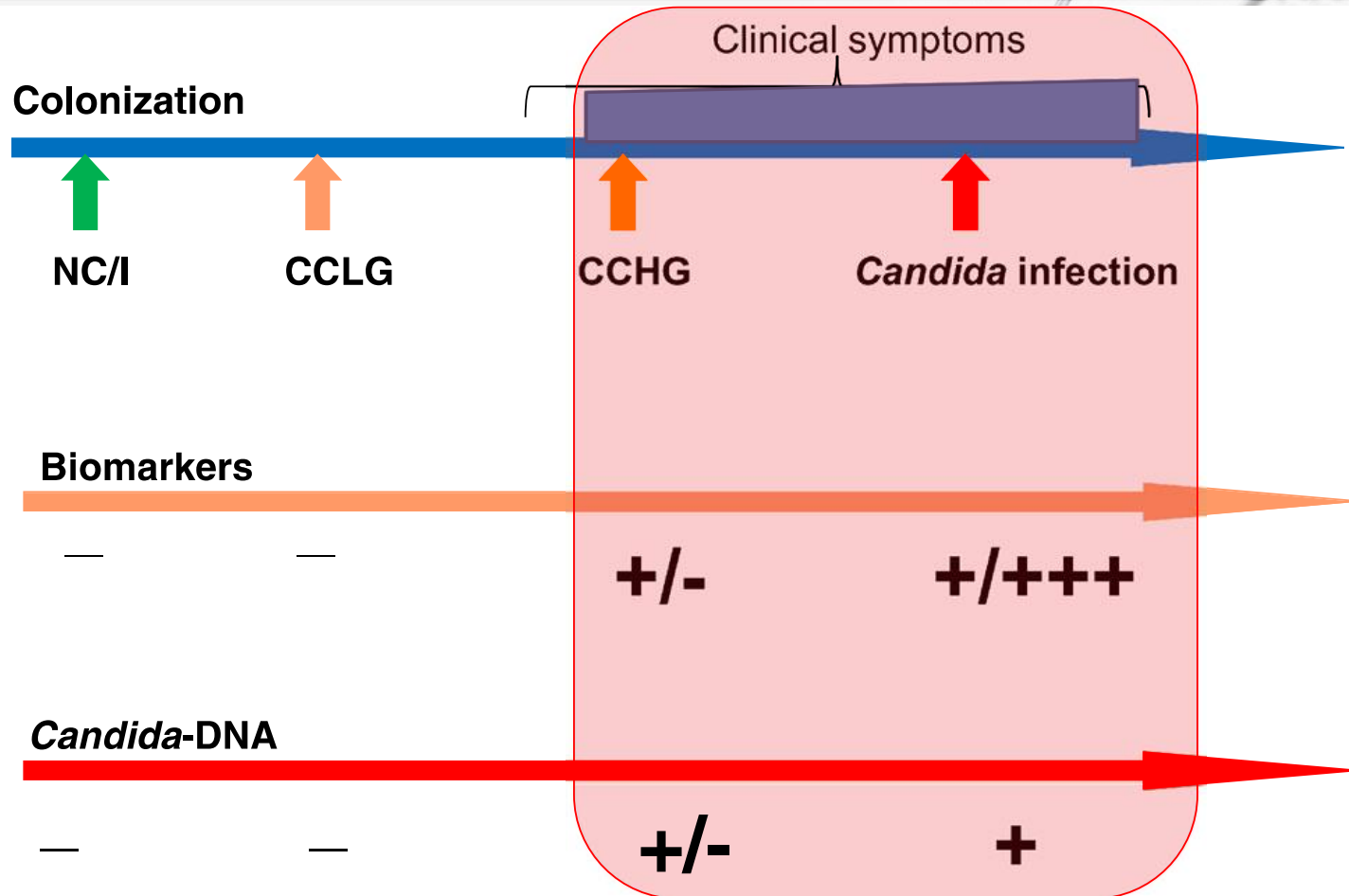
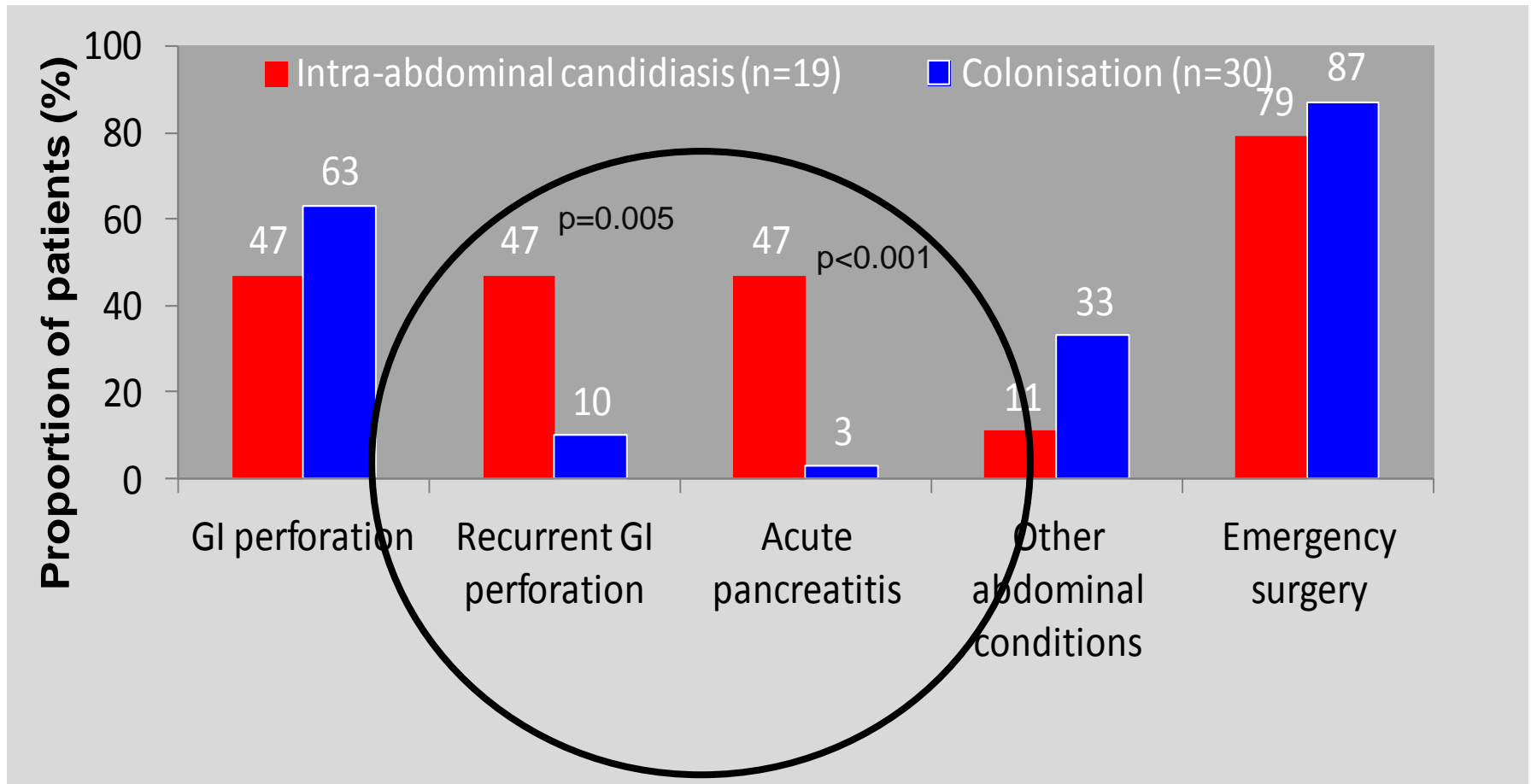


Fig. 2 Interrelation between microbiology, clinical, biomarkers, and *Candida* DNA. *NC/I* no colonized/infected, *CCLG* *Candida* colonization low grade, *CCHG* *Candida* colonization high grade

Recurrent GI perforation is associated with IAC

49 sur.pts with positive culture of yeast in peritoneal fluid





Philippe Montravers
Olivier Leroy
Christian Eckmann

Intra-abdominal candidiasis: it's still a long way to get unquestionable data

- ❖ AmarCand 1 Study – IAC in 34 % ICU patients with proven IC
- ❖ IAC the second most frequent candidosis on ICU
- ❖ IAC - >10 % of all peritonitis
- ❖ Mortality 25 – 60 %

Matteo Bassetti
Monia Marchetti
Arunaloke Chakrabarti
Sergio Colizza
Jose Garnacho-Montero
Daniel H. Kett
Patricia Munoz
Francesco Cristini
Anastasia Andoniadou
Pierluigi Viale
Giorgio Della Rocca
Emmanuel Roilides
Gabriele Sganga
Thomas J. Walsh
Carlo Tascini
Mario Tumbarello
Francesco Menichetti
Elda Righi
Christian Eckmann
Claudio Viscoli
Andrew F. Shorr
Olivier Leroy
George Petrikos
Francesco Giuseppe De Rosa

A research agenda on the management of intra-abdominal candidiasis: results from a consensus of multinational experts

Table 2 Risk factors for intra-abdominal *Candida* infection

Risk factor	Notes	References
1. Specific		
Recurrent abdominal surgery	Laparoscopies included	[33]
GI tract perforations	Recurrent perforations and/or perforations untreated within 24 h ^a	[17]
Gastrointestinal anastomosis leakage	More severe if the leakage is in the upper GI tract ^b	[2, 3, 17, 31]
Multifocal colonization by <i>Candida</i> spp.		
2. Additional nonspecific		
Acute renal failure, central venous catheter placement, total parenteral nutrition, ICU stay, severity of sepsis, diabetes and immunosuppression, prolonged broad-spectrum antibacterial therapy		[20, 31]

^a Surgical control of upper gastrointestinal perforations is more problematic [65]

^b Gastroduodenal surgery, in particular that involving the esophagus

Principal recommendations on management of IAC

Diagnosis	Direct microscopy examination for yeast detection from purulent and necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration is recommended in all patients with nonappendicular abdominal infections including secondary and tertiary peritonitis	All
	Samples obtained from drainage tubes are not valuable except for study of colonization	DIII
	Blood cultures should be taken through peripheral vein punctures upon diagnosis or suspicion of intra-abdominal infections and tertiary peritonitis, and specific media for fungi are recommended, if available	All
	Antifungal susceptibility test should be performed on yeast isolates from blood, sterile sites, and other appropriate specimens. MICs should be reported to the clinicians, specifying the reference method used (CLSI versus EUCAST)	BIII
Culture interpretation	Systemic antifungal treatment should be considered when adequate intra-abdominal specimens (obtained surgically or within 24 h from external drainage) are positive for <i>Candida</i> , irrespective of the fungal concentration and the associated bacterial growth	All
	Positive cultures from drains should not be treated, especially if the drains are in place for more than 24 h	DIII
Nonculture test	When available, mannan and antimannan tests and BDG should be performed in patients with secondary or tertiary peritonitis and at least one specific risk factor for IAC	BII

Therapy of IAC

Prophylaxis	Patients with recent abdominal surgery and recurrent gastrointestinal perforation or anastomotic leakage should receive treatment with fluconazole	BII
	An echinocandin should be considered if there is a high likelihood of azole resistance	CII
Empirical therapy	Empirical antifungal treatment may be considered in patients with a diagnosis of intra-abdominal infection and at least one specific risk factor for <i>Candida</i> infection (Table 2)	CIII
	In patients with intra-abdominal infection with or without specific risk factor for <i>Candida</i> infection, empirical antifungal treatment should be administered if a positive mannan/antimannan or BDG or PCR test result is present	BII
	Fungicidal antifungal agents (i.e., echinocandins or lipid formulation of amphotericin B) should be prescribed for the empirical therapy of all critically ill patients or patients with previous exposure to azoles	AII
	Azoles can be adopted for the empirical therapy of non-critically ill patients without previous exposure to azoles unless they are known to be colonized with a <i>Candida</i> strain with reduced susceptibility to azoles	BII
Targeted therapy	Fungicidal agents such as echinocandins or lipid formulations of amphotericin B should be used for targeted therapy of all critically ill patients or patients with previous exposure to azoles	BII
	For the subgroup of patients infected with <i>C. parapsilosis</i> , lipid formulations of amphotericin B or fluconazole should be preferred	BII
	Azoles (fluconazole) can be used for targeted therapy of non-critically ill patients without previous exposure to azoles unless there is evidence of multisite colonization with a <i>Candida</i> strain characterized by reduced susceptibility to azoles	BII

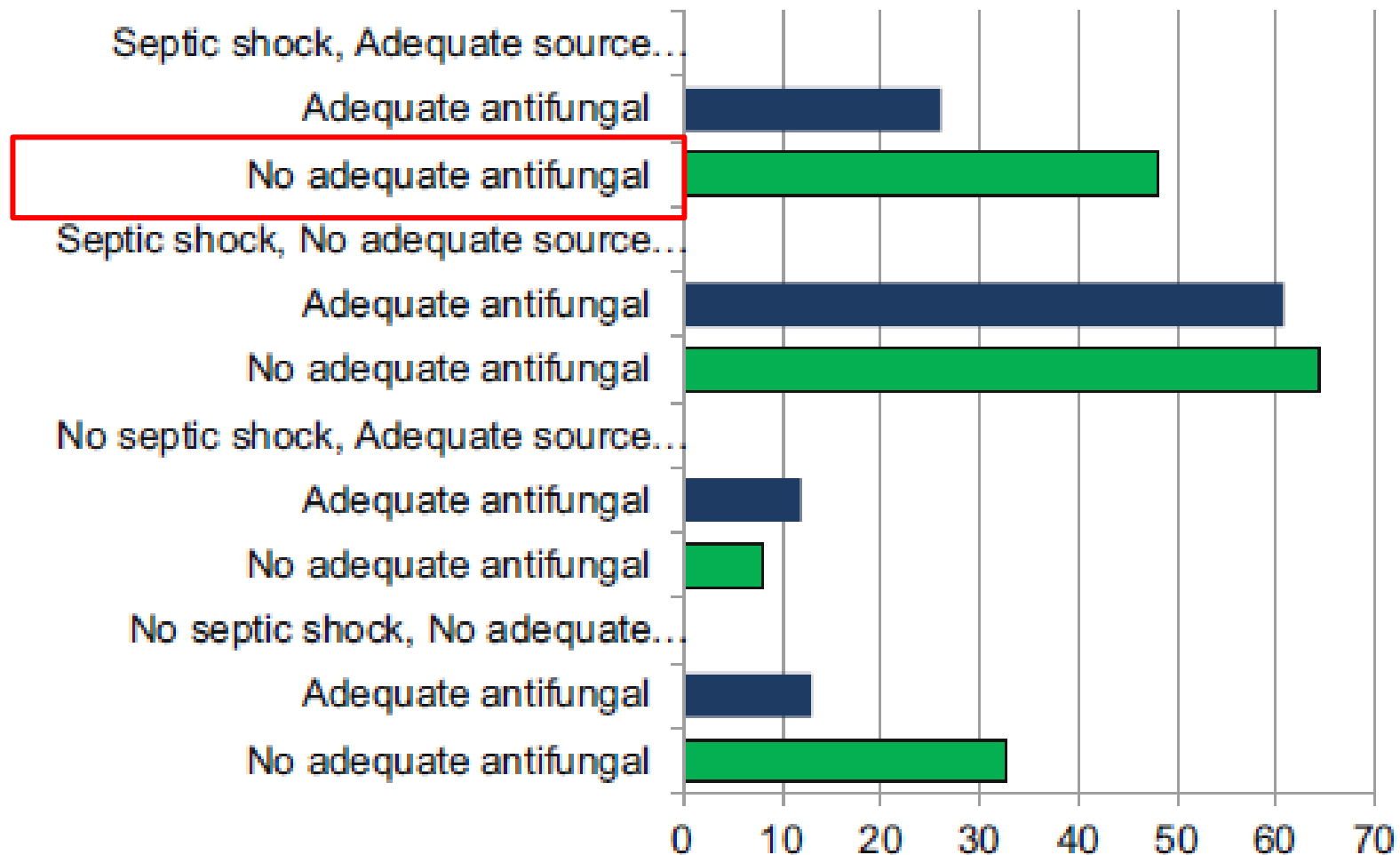


Fig. 1 Thirty-day hospital mortality in patients with or without septic shock and adequate antifungal therapy and/or source control

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,¹ Carol A. Kauffman,² David R. Andes,³ Cornelius J. Clancy,⁴ Kieren A. Marr,⁵ Luis Ostrosky-Zeichner,⁶ Annette C. Reboli,⁷ Mindy G. Schuster, Jose A. Vazquez,⁹ Thomas J. Walsh,¹⁰ Theoklis E. Zaoutis,¹¹ and Jack D. Sobel¹²

VIII. What Is the Treatment for Intra-abdominal Candidiasis?

Recommendations

54. Empiric antifungal therapy should be considered for patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis (*strong recommendation; moderate-quality evidence*).
55. Treatment of intra-abdominal candidiasis should include source control with appropriate drainage and/or debridement (*strong recommendation; moderate-quality evidence*).

IAC

- **Candida peritonitis is life-threatening complication of surgical patients**
- **With poor prognosis**
- **Patients with IA catastrophe are at high risk of IAC**
- **Colonisation vs infection??????**

León C, Ostrosky-Zeichner L, Schuster M. What's new in the clinical and diagnostic management of invasive candidiasis in critically ill patients. *Intensive Care Med* 2014; 40:808-19

Montravers P, Dupont H, Gauzit R, Veber B, Auboyer C, Blin P, et al. *Candida as a risk factor for mortality in peritonitis. Crit Care Med* 2006; 34:646-52.

Montravers P, Dupont H, Eggimann P. Intra-abdominal candidiasis: the guidelines-forgotten non-candidemic invasive candidiasis. *Intensive Care Med* 2013; 39:2226-30.

Zaragoza R, Ferrer R, Maseda E, Llinares P, Rodríguez A; EPICO PROJECT GROUP. EPICO 2.0 PROJECT: Development of educational therapeutic recommendations using the DELPHI technique on invasive candidiasis in critically ill adult patients in special situations. *Rev Esp Quimioter* 2014; 27:196-212.

Candida score

- >7 d at ICU

- Surgery (1 pt)
 - Multifocal Candida colonization (1 pt)
 - Parenteral nutrition (1 pt)
 - Severe sepsis (2 pt)
-
- Cut off ≥ 3 = at high risk for IC
 - Sensitivity 81 %, specificity 74 %

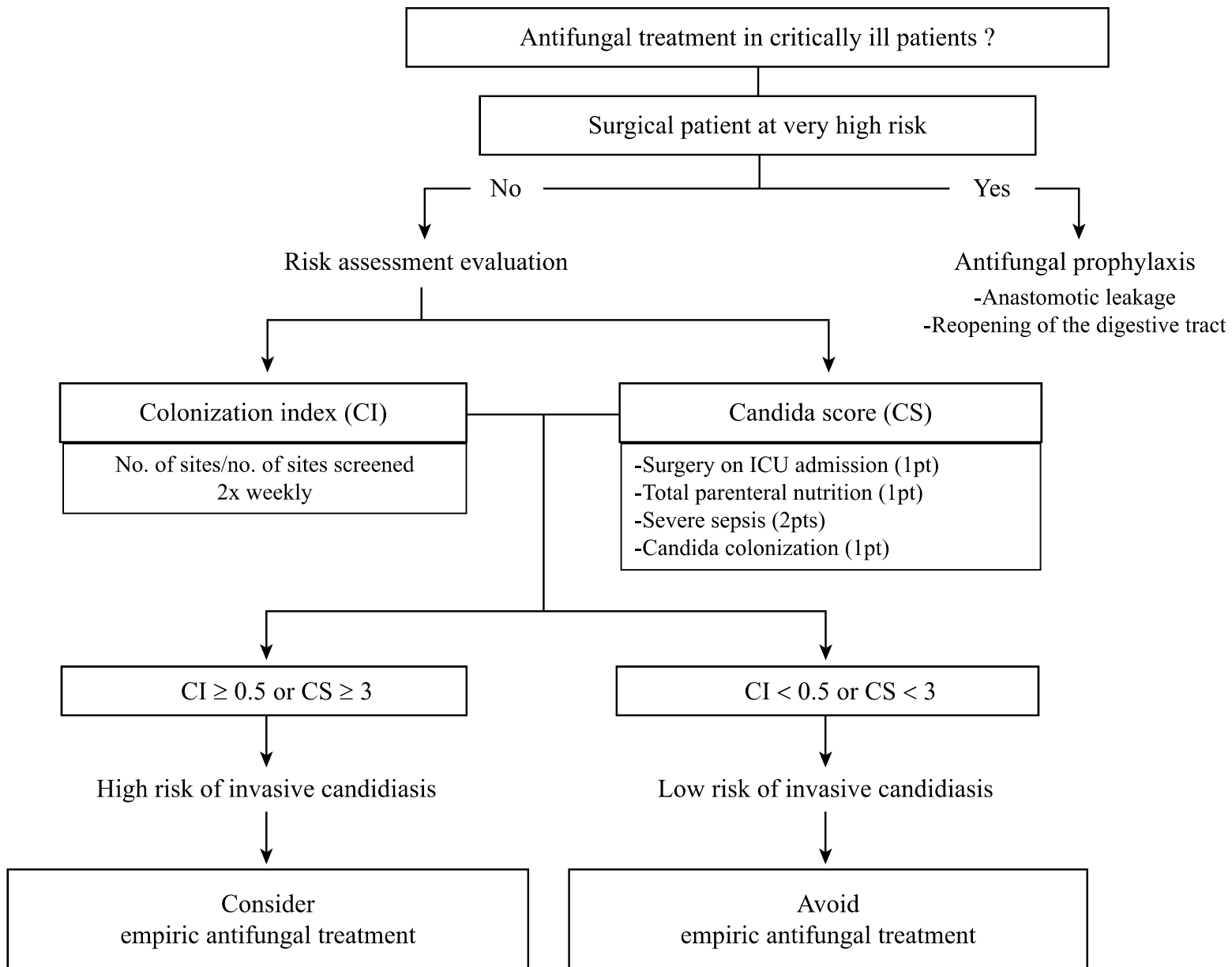


Figure 1. Risk assessment strategies for antifungal treatment.

Conclusion

- Endogenous source, no exogenous
- 7 – 10 days interval between exposition to risk factors and development of IAC
- **Enough time for evaluation of risk factors and consideration of AF prophylaxis/empirical therapy**

A microscopic image of a filamentous cyanobacterium. The filament is composed of elongated, rod-shaped cells. Interspersed along the filament are numerous heterocysts, which are specialized cells for nitrogen fixation. These heterocysts are characterized by a thick, multi-layered cell wall and a distinct internal structure, including a large, clear central vacuole and a dense, greenish-blue cytoplasm. The background is a light, uniform color, typical of a microscope slide.

Thank you.