Intensive Care Med (2000) 26: S165–S169
© Springer-Verlag 2000

ORIGINAL

H.B. Reith
U. Mittelkötter
R. Wagner
A. Thiede

Procalcitonin (PCT) in patients with abdominal sepsis

H. B. Reith (✉) · U. Mittelkötter · R. Wagner · A. Thiede
Department of Surgery,
University of Würzburg,
Josef-Schneider Str. 2, D-97080 Würzburg, Germany
e-mail: Hans-Bernd.Reith@mail.uni-wuerzburg.de
Tel.: + 49-931-201-32 46/32 71
Fax: + 49-931-201-32 25

H. B. Reith · U. Mittelkötter
Department of Surgery,
University of Bochum,
In der Schornau 23,
D-44892 Bochum, Germany

Abstract *Background:* To assess the accuracy of procalcitonin as a measure of severity in patients with septic abdominal illnesses and the sepsis syndrome, to compare measurements with those of other inflammatory mediators, and to predict outcome.
Methods: We carried out a prospective clinical study from 246 patients with infective or septic episodes confirmed at laparotomy and 66 patients undergoing elective operations who acted as controls. Specimens of blood for measurement of cytokine concentrations determination were obtained daily from septic patients. In the control group specimens were obtained before operation, at the end of operation, and on each of the following days until normal recovery (day 10). Every two weeks up to 3 months for patients with metastases, who were being followed up.
Results: Compared with other cytokines such as tumor necrosis factor αa and interleukin 6 procalcitonin was closely related to the development of infective and septic complications. 59 of 246 patients (24%) with sepsis died. Procalcitonin concentrations preoperatively [median 2.05 compared with 4.2 ng/ml ($p = 0.08$)] (Mann-Whitney U-test) did not differ, but those on the days 1, 4 and at the end differed significantly [day 1: 4.9 compared with 13.8 ng/ml ($p < 0.01$); day 4: 4.8 compared with 13.0 ng/ml ($p < 0.01$) and 0.4 compared with 13.25 ng/ml ($p < 0.01$) at the end of the study]. In the control group only 7 (1.6%) of all blood samples, were detected outside the normal range (up to 0.8 ng/ml).
Conclusions: Procalcitonin is a new indicator of infection and sepsis. TNF and IL-6 concentrations always rise after major operations and fall in the absence of infection, indicating operative trauma. Procalcitonin is sensitive in detecting infective complications. Under routine conditions the procalcitonin concentrations seems to be valid, reproducible and detectable.

Key words Peritonitis · Sepsis · Septic courses · Diagnosis · Cytokines · Procalcitonin

Introduction

Sepsis is primarily a clinical diagnosis and is correlated with objective clinical data. Different scoring systems and other measurement have been developed to monitor the septic course, but they have limitations in predicting individual outcomes.

Most mediators (for example endotoxin and cytokines) are not yet suitable for use in routine diagnosis, though they do correlate with clinical outcome in controlled clinical and experimental studies [1, 2].

Concentrations of C-reactive protein (CRP), an acute phase protein, have been used to follow up septic patients, but are unable to predict the outcome of dis-

Table 1 Diagnosis in patients who developed abdominal infection and SIRS

Diagnosis	Total No	No (%) who died
Pancreatitis	24	5 (21)
Colon perforation	99	16 (16)
Postoperative peritonitis		
Anastomotic breakdown	33	15 (45)
Abscess	26	4 (15)
Biliary peritonitis	4	1 (25)
Traumatic peritonitis	19	3 (16)
Mesenterial infarction	40	14 (35)
Others	1	1 (100)
Total	246	59 (24)

ease or its severity. CRP has also failed to be of immediate diagnostic and prognostic help because of the time taken to produce a reaction and the duration of increased serum concentrations [3, 4, 5].

Systemic infection may induce a cascade of cytokine secretion, which can damage the tight junctions that bind together the inner and outer portions of the cell membranes of neuroendocrine cells. Apical cell membranes usually secrete mature hormones, and basolateral membranes secrete incompletely processed prohormones. The loss of polarity of an epithelial cell converts is entire cell membrane into a basolateral membrane. The result is that the Golgi apparatus receives the message to produce predominantly non-processed or incompletely processed procalcitonin. Procalcitonin is a 116 amino acid peptide that contains a peptide termed nPCT (or PAS-57) at its aminoterminus, a dibasic amino acid cleavage site at the aminoterminus of calcitonin (a 32amino acid part of the prohormone) and katacalcin (another determed part of the prohormone). Only limited information is available on source and effect of procalcitonin in various diseases. Neuroendocrine cells that produce procalcitonin have been found in liver and lung tissue, but it seems possible that it depends on an increase in the endotoxin and also exotoxin concentrations [6, 7].

Patients and methods

In a prospective study we have measured procalcitonin in 246 patients with septic syndromes or infections after abdominal surgery for peritonitis [peritonitis was suspected as follows (local inflammation of the peritoneum, exsudate, GI-tract perforation) or ileus] (see Table 1). We defined sepsis according to Bone's criteria [8]. Criteria for inclusion in the study were clinical and objective diagnoses of sepsis and an APACHE II-score of 15 points or more. All patients required artificial ventilation. A votum of local ethic committee was confirmed. Exclusion criteria were pregnancy, breast feeding, treatment with any other investigational drug, progressive fatal disease, onset of pancreatitis and patients after planned relaparotomies.

Tumor necrosis factor α (TNF), interleukin 6 (Il-6), neopterin, CRP, and other standard laboratory variables were also measured to validate the procalcitonin values. TNF, IL-6, and neopterin were analysed with a specific enzyme-linked immunosorbent assay (ELISA, Medgenix Diagnostics, Ratingen, Germany or B.R.A.H.M.S Diagnostica GmbH, Berlin, Germany). CRP-concentrations were analysed with a nephelometric assay (Behring Diagnostics Marburg, Germany). Concentrations of procalcitonin were measured with a specific, ultrasensitive, immunoluminometric assay (LUMItest PCT assay, B.R.A.H.M.S Diagnostica, Berlin, Germany). The analytic sensitivity of the assay was 0.1 ng/ml, the reference range from 0.1–0.5 ng/ml, and for patients in hospital we found the range to be 0.1–0.8 ng/ml.

To predict the accuracy of procalcitonin we also studied a control group consisting of 56 patients undergoing elective surgery (open cholecystectomy, n = 11, laparoscopic cholecystectomy, n = 12, and resections for cancer, n = 33) and 10 patients who had developed metastases and were being followed up. These 10 also had increased TNF-α concentrations.

The measurements were made preoperatively, at the end of the operation, and daily for the first 10 days postoperatively; for the patients with metastases they were made every two weeks for three months.

The 246 patients with infective or septic episodes were assessed daily until they stay on the intensive care unit (ICU) to document the follow up of the infection, that means day of death or discharge. The first clinical classification was initially made using the APACHE II score and the follow up was monitored by the multiple organ failure (MOF)-score [9].

The significance of differences was assessed using the Mann-Whitney U test, and probabilities of less than 0.05 were accepted as significant. All values are expressed as mean (SD). The correlation among laboratory variables was accepted as significant when r was greater than 0.60.

Results

Patients in the control group who had no signs of postoperative infection or sepsis had procalcitonin concentrations within the reference range [0.1 ng/ml: 359/ 431 (83 %), 65 measurements were between 0.2 and 0.7 ng/ml (15 %) and only seven were between 0.8 and 1.2 ng/ml (2 %)] (Table 2).

Patients with peritonitis and pancreatitis, and sepsis always had increased concentrations of procalcitonin. A reduction in the procalcitonin concentration correlated with improvement in the infection and sepsis, and was found in all surviving patients. The 59 patients, who died, had initial procalcitonin values of 4.2 (1.3) ng/ml rising to a mean (SD) of 13.8 ng/ml (8.9) on day 1, 13.0 (7.5) ng/ml on day 4 and 13.2 ng/ml (5.8) at the time of death. The 187 patients, who survived, sepsis or infections had a initial concentration of 2.1 (0.7) ng/ml, 4.9 (2.8) ng/ml on day 1, 4.8 (3.1) ng/ml on day 4, and than a reduction to the mean reference range of 0.4 (0.1) ng/ml (Table 3). Compared with the values for CRP, PCT showed significant differences between survi-

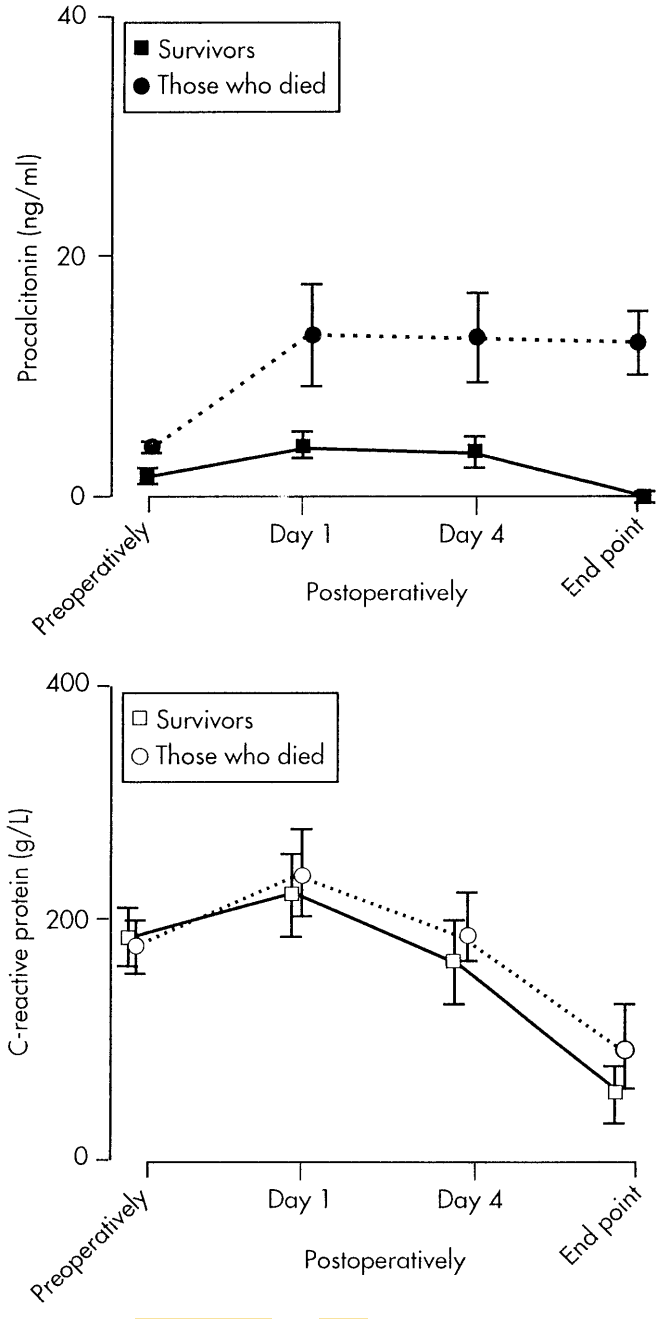


Fig. 1 Mean procalcitionin and CRP values preoperatively and on days 1 and 4 and at the endpoint of sepsis differentiated for survivors and those who died. Procalcitonin values were significantly different for both groups on day 1, 4, and at the endpoint ($p < 0.05$)

vors and patients who died ($p < 0.05$ on days 1 and 4 and at the endpoint); CRP did not (Fig. 1).

Of particular interest were results from patients who developed infection or sepsis during the observation period. In these cases an increase in procalcitonin concentrations was seen at the same time as that in the TNF concentration and before the IL-6 concentration began to rise. There was a good correlation with the MOF score ($r = 0.83$). Only leucocytes and blood urea showed a similar pattern.

The APACHE II score for patients who died [20.9 (3.3) points] and those who survived [20.1 (3.6) points] was initially similar. The MOF score for those who died ranged from 5–12 points [mean 9.6 (3.7) points] and for the survivors it ranged from 0–9 [mean 2.8 (1.8) points]. The mortality (59/246) was 24 % and this corresponds to rates reported by other authors.

Discussion

Deaths of patients with sepsis often results from septic shock with coexisting hypotension, tissue damage, and organ failure. It has been shown in animals that increases in concentrations of TNFα and interleukin-1 (Il-1) were triggered by trauma and or infection.

When patients with intra-abdominal sepsis and the sepsis syndrome are being monitored, measurements of these mediators should be made routinely. This may increase the chance of modulating the inflammatory response in sepsis [8].

TNF, Il-1, and Il-6 are valid and sensitive indicators [10], but they are not yet available for routine diagnosis. Procalcitonin (a precursor protein of calcitonin and katacalcin), the position of which in the sepsis cascade is not yet known, may be a new indicator of microbial infections and sepsis that can be measured routinely in the clinical laboratory [7, 11].

According to our results the measurement of procalcitonin is not too expensive (one test cost less than US$ 10, costs including standard curve and calibration are less than US$ 30) and it is a clinical marker of sepsis and infection, that is more sensitive than leucocytes and blood urea concentration.

In the meta-analysis of results from other clinical research groups Beier convincingly verified the prognostic value of procalcitonin [11]. Our results are in agreement with other studies in burns and adult respiratory distress syndrome, which reported that an increase or a constant rise in procalcitonin concentrations predicted a lethal outcome [12, 13]; (the sensitivity was 84 % and the specificity 91 %).

New data comparing PCT and CRP in the inflammatory response after trauma, demonstrated an early production of PCT related to tissue damage and the magnitude of hypovolemic challenge [14], yet unrelated to an infection.

The comparison with the results in the control group (in which procalcitonin concentrations did not rise) showed no association between procalcitonin concentrations and operative trauma. TNF and IL-6 values, however, did correlate with operative trauma [15, 16].

Table 2 Distribution of individual measurements of procalcitonin concentrations in the control group ($n=66$)

Procalcitonin concentrations (ng/ml)	Laparoscopic cholecystectomy ($n=12$)	Open cholecystectomy ($n=11$)	Resections for cancer ($n=33$)	Operations for metastatic disease ($n=10$)
0.09	66	67	132	39
0.1	9	14	28	4
0.2	5	9	19	5
0.3	1	4	10	4
0.4	0	0	2	0
0.6	0	1	2	0
0.7	0	2	1	0
0.8	0	1	2	0
1.0	0	0	2	0
1.2	0	1	1	0

Table 3 Mean (SD) values for patients who survived ($n=187$) and those who died ($n=59$) at the four measuring points

	Day 0		Day 1		Day 4		Endpoint	
	Lived	Died	Lived	Died	Lived	Died	Lived	Died
APACHE II score	20.1 (3.6)	20.9 (3.3)						
MOF score	2.8 (1.8)	9.6 (3.7)	3.2 (2.1)	8.4 (3.1)	3.1 (1.9)	8.6 (2.1)	1.2 (0.4)	10.1 (3.1)
PCT (ng/ml)	2.1 (0.7)	4.2 (1.3)	4.9 (2.8)	13.8 (8.9)	4.8 (3.1)	13.0 (7.5)	0.4 (0.1)	13.2 (5.8)
CRP (g/L)	180 (45)	178 (41)	223 (65)	245 (72)	167 (66)	188 (56)	56 (42)	94 (69)
TNF α (pg/ml)	45 (23)	34 (33)	38 (16)	42 (21)	28 (44)	26 (33)	29 (28)	31 (24)
Il-6 (pg/ml)	567 (278)	672 (299)	434 (198)	443 (178)	342 (237)	387 (265)	68 (145)	121 (134)
WBC ($\times 10^9$/L)	14.6 (3.1)	17.2 (4.6)	16.3 (4.9)	14.1 (4.6)	15.2 (3.9)	16.5 (6.4)	11.4 (6.4)	12.4 (9.1)
Urea (mmol/L)	78 (34)	72 (44)	88 (24)	84 (28)	66 (38)	67 (45)	56 (14)	63 (34)
Neopterin (nmol/ml)	26 (14)	28 (22)	34 (16)	33 (19)	28 (19)	34 (23)	36 (22)	44 (18)

The diagnosis of a septic complication is therefore not possible with these two cytokines, though high Il-6 concentrations (cut-off point > 500 pg/ml) correlate with the sepsis syndrome. Procalcitonin might become an important marker for the monitoring of septic conditions or courses. Further investigations must be started to obtain more knowledge about this remarkable new marker, further studies are warranted to identify the site of production and the role of PCT as a predictor of forthcoming multiple organ failure with or without sepsis.

References

1. Haupt W, Fritsche H, Hohenberger W, Zirngibl H (1996) Selective cytokine release induced by serum and separated plasma from septic patients. Eur J Surg 162, p 769
2. Reith HB, Dittrich H, Haarmann W, Smektala R, Dohle J, Kozuschek W (1996) Adjuvante Therapie der Peritonitis und ihrer septischer Verlaufsformen mit Taurolidin – eine prospektive randomisierte Untersuchung. Chir. Gastroenterologie 12, p 358
3. Heney D, Lewis IJ, Evans SW, Banks R, Bailey CC, Whicher JT (1992) Interleukin-6 and its relationship to C-reactive protein and fever in children with febrile neutropenia. J Infect Dis 165, p 886
4. Heuer HO, Darius H, Lohmann HF, Meyer J, Schierenberg M, Treese N (1991) Platelet-activating factor type activity in plasma from patients with septicemia and other diseases. Lipids 26, p 1381
5. Rosman C, Grond J, Buurman WA, et al (1993) Fish oil increases the release of tumour necrosis factor and interleukin-6 and has no effect on the incidence of multiple organ failure in rats with peritonitis. Eur J Surg 159, p 563
6. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C (1993) High serum procalcitonin concentration in patients with sepsis and infection. Lancet 341, p 515
7. Becker KL, Nash DR, Silva OL, Snider RH, Moore CF (1981) Increased serum and urinary calcitonin levels in patients with pulmonary disease. Chest 79, p 211
8. Bone RC (1991) The pathogenesis of sepsis. Ann Intern Med 115, p 457
9. Goris RJA, Boekhorst TPA, Nuytinck JKS (1985) Multiple organ failure. Arch Surg 118, p 1109
10. Ertel W, Kremer JP, Kenney J, Steckholzer U, Jarrar D, Trentz O, Schildberg FW (1995) Downregulation of proinflammatory cytokine release in whole blood from septic patients. Blood 85, p 1341
11. Beier W (1994) Procalcitonin (ProCt) – ein innovativer Inflammationsparameter mit prognostischen Eigenschaften (editorial). Anästh Intensivmed 36: 18

12. Huttemeier PC, Ritter EF, Benveniste H (1993) Calcitonin gene-related peptide mediates hypotension and tachycardia in endotoxin rats. Am J Physiol 265, p 4767
13. Joyce CD, Fiscus RR, Wang X, Dries DJ, Morris RC, Prinz RA (1990) Calcitonin related peptide levels are elevated in patients with sepsis. Surgery 108, p 1097
14. Mimos O, Benoist JF, Edouard AR, Assicot M, Bohoun C, Samii K (1998) Procalcitonin and C-reactive protein during the early posttraumatic systemic inflammatory response syndrome. Intensive Care Med 24: 185–188
15. Brunkhorst FM, Forycki ZF, Beier W, Wagner J (1993) Discrimination of infectious and non-infectious etiologies of the adult respiratory distress syndrome (ARDS) with procalcitonin immunoreactivity. Clin Intensive Care 3, p 12
16. Nylen ES, O'Neill WO, Jordan MH, et al (1992) Serum procalcitonin as an index of inhalation injury in burns. Horm Metab Res 24, p 439

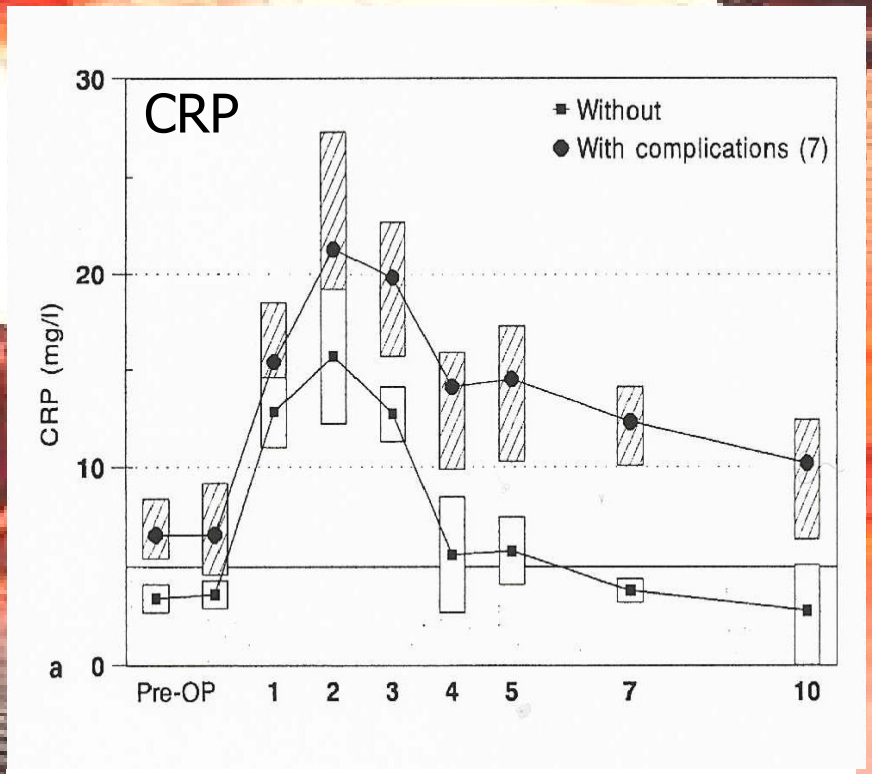
UNCONTROLLED INFECTION ?

PCT and Surgery

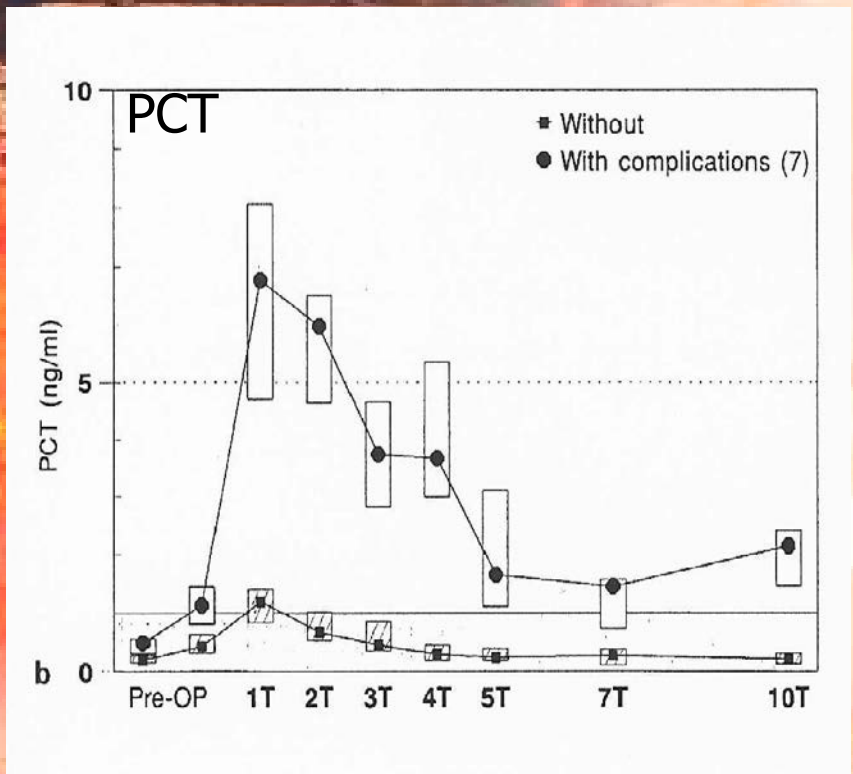
H.B. Reith
U. Mittelkötter
R. Wagner
A. Thiede

Procalcitonin (PCT) in patients with abdominal sepsis

Intensive Care Med (2000) 26: S165–S169



p < 0,05: post OP 7 – 10 giorni



p < 0,001: post OP 1-10 giorni

UNCONTROLLED INFECTION ?

British Journal of Anaesthesia 94 (6): 767–73 (2005)
doi:10.1093/bja/aei143 Advance Access publication April 22, 2005

BJA

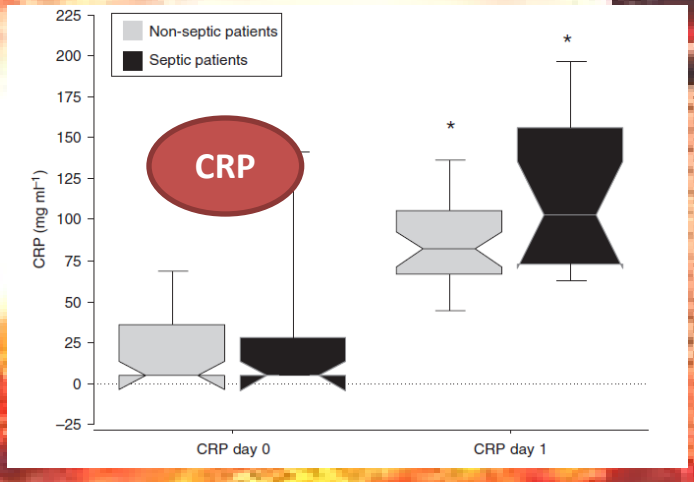
Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery

D. Mokart[1]*, M. Merlin[2], A. Sannini[1], J. P. Brun[1], J. R. Delpero[3], G. Houvenaeghel[3],

PCT and Surgery

Methods. Serial blood samples were collected from 50 consecutive patients for determination of IL-6, PCT and CRP serum levels. Blood samples were obtained on the morning of surgery and on the morning of the first postoperative day.

consent of patients and approval from our institutional ethics committee, 50 consecutive patients undergoing elective major surgical procedures were studied. The criteria for inclusion were major gastrointestinal or gynaecological tumour resection, with surgery expected to last >5 h. The



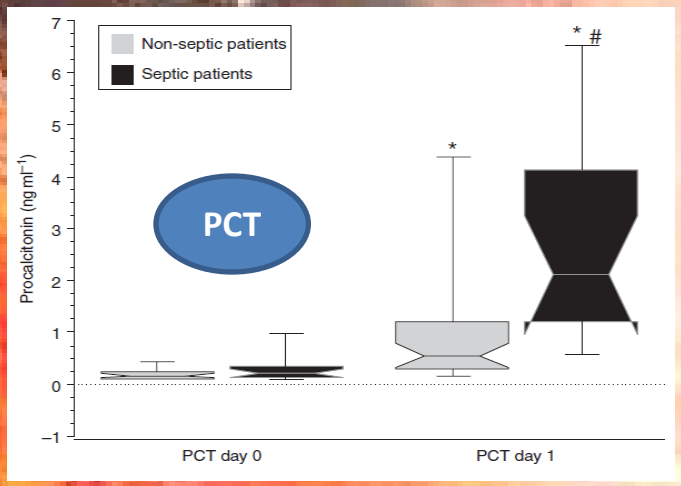


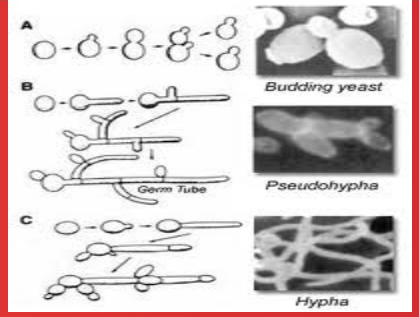
Table 2 Sensitivity, specificity, positive and negative predictive values, and areas under the curve (AUC) for C-reactive protein (CRP), procalcitonin (PCT) and IL-6 on day 1 in diagnosing septic complications during the first 5 postoperative days

	CRP (cut-off 93 mg ml^{-1})	PCT (cut-off 1.1 ng ml^{-1})	IL-6 (cut-off 310 pg ml^{-1})
Sensitivity (%)	63	81	90
Specificity (%)	72	72	58
Positive predictive value (%)	53	59	53
Negative predictive value (%)	79	89	92
AUC (% [95% CI])	66.4 (49.3–83.5)	74.9 (60.2–89.6)	82.1 (66.1–98.2)

Table 3 Sensitivity, specificity, positive and negative predictive values for C-reactive protein (CRP), procalcitonin (PCT) and IL-6 when associated with occurrence of SIRS on day 1 in diagnosing septic complications during the first 5 postoperative days

+ SIRS	CRP (cut-off 93 mg ml^{-1})	PCT (cut-off 1.1 ng ml^{-1})	IL-6 (cut-off 310 pg ml^{-1})
Sensitivity (%)	100	100	100
Specificity (%)	80	86	79
Positive predictive value (%)	67	81	75
Negative predictive value (%)	100	100	100

UNCONTROLLED INFECTION ?



DIAGNOSIS
Type of infection
PCT and Fungi

Procalcitonin levels in surgical patients at risk of candidemia

Journal of Infection (2010) 60, 425–430

Alvise Martini [a], Leonardo Gottin [a], Nicola Menestrina [a], Vittorio Schweiger [a], Davide Simion [a], Jean-Louis Vincent [b,*]

Table 4 Markers of sepsis and organ dysfunction at time of blood culture. Data are expressed as median [interquartile range].

	Bacterial sepsis	Candida sepsis	*p* value
n	16	17	
CRP (mg/L)	190 [115–316]	94 [66–129]	0.002
PCT (ng/ml)	12.9 [2.6–81.2]	0.71 [0.5–1.1]	0.001
SOFA	8 [7–13]	5 [3–8]	0.010
WBC ($\times 10^6$/ml)	14.3 [10.6–16.4]	11.6 [8.4–15.7]	0.336
T (°C)	38.0 [37.0–38.4]	37.8 [37.0–38.3]	0.493

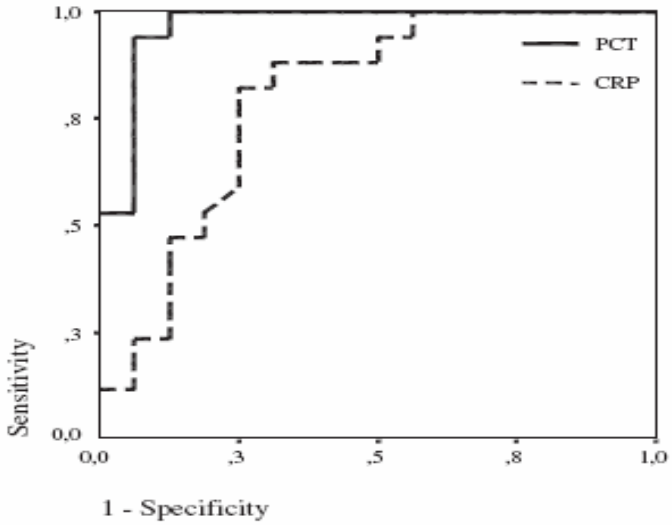


Figure 2 ROC-curves representing the sensitivity and specificity of PCT (solid line) and CRP (dashed line) for a diagnosis of candidemia.

sis (chi^2 = 0.016). A PCT cut-off value of 2 ng/mL separated *Candida* sepsis from bacterial sepsis with a sensitivity of 92%, a specificity of 93%, and positive and negative predictive values of 94%. The best cut-off value for CRP to separate bacterial sepsis from *Candida* sepsis was 100 mg/L, with a sensitivity of 82% and a specificity of 53%. The com-