Chapter 7

Limited diagnostic value of procalcitonin for proven infection in patients admitted on the ICU with SIRS.

Evelien de Jong, Hans Kemperman, Jozef Kesecioglu, Dylan W. de Lange

Submitted

Abstract

Introduction

This study investigated whether the biomarker procalcitonin (PCT) is a better and more useful predictor of proven infection than C-reactive protein (CRP) in consecutive patients with a systemic inflammatory response syndrome (SIRS) who are admitted on the intensive care unit (ICU).

Methods

In this observational cohort study patients with SIRS on admission and an anticipated stay > 24 hours were included. Clinical data and blood was collected in order to measure PCT and CRP.

Results

In total 191 out of 481 consecutive admissions had SIRS on admission, 27/191 had a "probable" infection, and only 70/191 had a "proven infection". PCT showed a limited diagnostic value in discriminating between patients with a "proven" or "probable infection" or "without infection" (1.7, 0.8 and 1.0 ug/L respectively, p=0.12). Furthermore both PCT and CRP had low positive predictive values for the prediction of "proven infection" in this ICU cohort (31-38% depending upon the cut-off values). PCT was higher on admission in non-survivors than survivors (2.3 [0.5-7.6] vs 1.0 [0.3-4.1] ; p=0.03)

Conclusion

Both PCT and CRP are not able to discern patients with a proven (or even probable) infection in an ICU-population with SIRS . However, PCT showed a substantially higher PCT on admission in non-survivors.

Introduction:

Sepsis is frequently encountered in the ICU and remains a common cause of death over the years. Recent estimates suggest that, at any given day on the ICU, half of the patients is suspected of or having an infection.[1] The mortality of patients with an infection in the ICU is high and, depending on the severity of illness, mortality rates of 25-60% are reported.[1,2] To counter these high mortality rate most contemporary guidelines advocate swift recognition of infected patients and a rapid, adequate treatment for all such patients.[2] However, how do you recognize infected patients? All patients with a systemic inflammatory response syndrome (SIRS) are at risk of having an infection. Unfortunately, SIRS is not a very specific condition and can be seen in many other non-infectious conditions as well: ischemia, trauma, after surgery or with conjunction with inflammatory processes.[3] Only when SIRS is due to infection the condition is called sepsis.[4] Of course, patients with sepsis should have early and appropriate antimicrobial treatment. So, whenever a patient has SIRS and is suspected of having an infection antimicrobial treatment should be instigated immediately. Conversely, due to the low specificity of SIRS many patients will be unnecessarily treated with antimicrobials. Differentiation between SIRS and sepsis is thus of great importance. Unfortunately, to this day, there still is no fast clinical test that provides quick and accurate answer whether an infection is present or not. Procalcitonin (PCT) is a serum peptide which is elevated in patients with bacterial infection. Such elevated PCT levels are not seen in patients with merely an inflammatory response.[5] Normally, serum values are below 0.5 µg/ml and patients with values over 1 to 2 µg/ml are supposed to carry an increased risk of infection. Although some studies showed promising predictive values for infection other studies were not able to show that PCT was associated with infection.[6-8] In other words, it is still doubtful whether the elevated levels of PCT in patients with SIRS can predict the presence of infection. In contrast, C-reactive protein (CRP) is nowadays routinely monitored in ICU patients. However, this protein is not at all specific for infection or sepsis; CRP is known to be elevated in both infectious as non infectious conditions.[9]

The purpose of this observational cohort study is to evaluate whether PCT-measurements are more useful than CRP in predicting the presence of an infection in patients with SIRS who are admitted on the ICU.

Methods

Study design and setting

This prospective cohort study was performed during a 6-month period was executed in the intensive care unit (ICU) of the University Medical Center Utrecht (UMCU) in the Netherlands, an academic hospital with 1042 beds. The mixed ICUs received admissions from all specialties (surgery, medical, transplant, cardio surgical, neurosurgical, trauma, etc.) except burns. The entire ICU consists of 30 beds and receives over 2200 admissions annually. The study was approved by the Institutional Review

Board of the University Medical Center Utrecht and it waived the need for informed consent (UMC Utrecht IRB research protocol 108-188).

Inclusion and exclusion criteria

Patients with an age of over 18 years and with SIRS on admission were included. SIRS was defined as two or more of the following symptoms: fever (> 38.0 °C or < 36.0 °C), leucocytosis (> 12 x 10*9/L or > 4 x 10*9/L), tachypnoea (respiratory rate > 20 per minute or P_aCO_2< 4.3 kPa) and/or tachycardia (heart frequency > 90 beats per minute). Patients who were anticipated to stay less than 24 hours on the ICU (e.g. elective surgery, uncomplicated surgical patients) were excluded.

Procedures and definitions

During the period of research each newly admitted patient on the ICU was either in- or excluded based on the above mentioned criteria. When included, research nurses collected data and results on a daily basis of clinical diagnostics of the patient during a maximum period of ten days, or until discharge or death. This enabled us to identify infections that were not yet clear on the day of admission. Blood samples of each included patient were collected for determining the values of PCT (in heparin plasma on Kryptor, Brahms GmbH, Berlin, Germany), CRP (in heparin plasma on a DxC 800 routine chemistry system, Beckman Coulter, Brea, California) and leukocytes (in EDTA-blood on a CD-Saphire routine hematology analyzer, Abbott, Santa Clara, California, USA). PCT values were not part of the normal clinical routine and were not made available for attending physicians during the study, and, therefore, they did not influence decision making. Whenever multiple measurements were performed during one day, the highest PCT-level or CRP-level of that day was used. Afterwards, when all data were collected, two researchers (EdJ and DWL) adjudicated which patients had a "proven infection", a "probable infection" or "no infection". The Centers of Disease Control (CDC) have published algorithms for "proven infection" of health care-associated infection and criteria for specific types of infections in the acute care setting.[9] We adhered to these definitions, but placed patients into the "probable infection"-category when they did not have a culture proven infection or had positive cultures with microorganisms that are considered colonization. For example, a patient with SIRS, dysuria, urgency for whom a physician has instituted appropriate antimicrobial therapy has a urinary tract infection according to the CDC-criteria. We, however, placed such patients in the "probable infection"-group. The same is true for patients that had "clinically defined pneumonia" according to the CDC-criteria. Absence of positive cultures made us decide to place such patients into the "probable infection" group. The same is true for patients with suspicion of endocarditis and mediastinitis but no positive cultures and no abnormalities on radiological examinations. Vice versa, a patient with a positive blood culture, drawn from an arterial line, with coagulase negative staphylococci (in the absence of other positive blood cultures) would clinically be categorized as colonization. We placed such patients in the "probable infection" group.

We calculated the likelihood ratios (LR) and diagnostic odds ratio (DOR). Basically the DOR represents the relationship between the LRs (DOR = LR+/LR-). The DOR ranges from 0 to infinity and gives information about the usefulness of a test. A higher value indicates a better performance. A DOR of greater than 25 means a test is useful, a DOR of greater than 100 makes it a good test.[7,9] Another way to represent these test characteristics is in a receiver operating curve (ROC) in which the relationship between sensitivity and specificity is depicted. An area under the ROC (AUROC) of 0.5 means that the test is useless for the prediction of proven infection while an AUROC of 1.0 means perfect test characteristics.

Statistical analysis

When data were distributed non-normally (Kolmogorov-Smirnov test $P<0.05$) data were expressed as median (with interquartile range, IQR) or as number of patients (percentage) where appropriate. Patient characteristics and outcomes according to the presence of a virus were compared using chi square test, Fisher exact chi square test, or Mann-Whitney U test as appropriate. The primary analyses compares detection of viral infection versus no detection of a viral infection. All tests were two-sided and a P-value <0.05 was considered statistically significant. All data were analyzed using a statistical software package (SPSS Inc., Chicago, IL, USA).

Results

During the half-year-period 499 patients with an anticipated stay longer than 24 hours were admitted, in which 191 fulfilled criteria for SIRS and a PCT-measurement performed on the day of inclusion. Demographic and clinical characteristics are shown in Table 1. Patients with SIRS were divided into those with a “proven infection”, “probable infection” and those with SIRS but “without a proven infection”. The groups were quite comparable except for the amount of ventilated patients 49/ 70 patients (71%) for patients with a proven infection, 11/27 (41%) for “possible” and 64 out of 94 (68%) for a patients without infection with SIRS (p=0.03). More patients with pneumonia were seen in the ‘proven’ en ‘possible’ group than in patients with only SIRS (36%, 56%, 20 % respectively; p=0.01) In 27/191 patients (14%) patients a infection was considered “possible”, (n=70/191, 37%) “probable” and (n=94/191, 49%) “proven” according to the CDC definitions for infection.[9] On admission to the ICU 176/191 (92%) patients received antimicrobial therapy. Sixty-nine patients (37%) patients used antibiotics prophylactic reasons only (either perioperative prophylaxis or selective decontamination of the digestive tract [SDD]. SDD is applied on our ICU whenever a length of stay on the ICU longer than 48 hours is anticipated).

Table 1 Baseline characteristics of the study population with SIRS on admission (n=191)					
	Total (n=191)	Proven infection (n=70)	Probable infection (n=27)	Without proven infection (n=94)	P-value
Age*	62 (49-74)	62 (41-73)	66 (56-72)	61 (49-73)	0.52
Gender (male)	119 (62%)	49 (70%)	15 (56%)	55 (59%)	0.24
APACHE IV score*	75 (57-96)	80 (58-91)	71 (57-86)	73 (51-109)	0.60
MV at admission	124 (66%)	49 (71%)	11 (41%)	64 (68%)	0.03
Referring specialty					
Cardiology	16 (8%)	3 (4%)	1 (4%)	12 (13%)	0.10
Internal medicine	23 (12%)	9 (13%)	6(14%)	8 (9%)	0.15
Neurology	20 (11%)	7 (10%)	3 (13%)	10 (11%)	0.99
Neurosurgery	22 (12%)	9 (13%)	3 (11%)	10 (11%)	0.91
Heart lung surgery	16 (8%)	5 (7%)	2 (7%)	9 (10%)	0.84
Surgery	64 (34%)	30 (43%)	6 (30%)	28 (30%)	0.09
Other	29 (15%)	7 (10%)	6 (16%)	16 (17%)	0.22
Reason for antibiotics					
SDD	69 (37%)	21 (30%)	7 (26%)	41 (44%)	0.10
Infection	100 (52%)	42 (60%)	19 (70%)	39 (41%)	0.01
Otherreasons	5 (3%)	1 (1%)	1 (4%)	3 (3%)	0.73
No treatment	15 (8%)	6 (9%)	0	9 (10%)	0.26
Infection site					
Pneumonia	59 (31%)	25 (36%)	15 (56%)	19 (20%)	0.01
CR-BSI	5 (3%)	3 (4%)	0 (0%)	2 (2%)	0.46
UTI	7 (4%)	1 (1%)	0 (0%)	6 (6%)	0.14
Wound infection	10 (5%)	4 (6%)	3 (19%)	3 (3%)	0.26
Abdominal sepsis	25 (13%)	12 (17%)	3 (11%)	10 (11%)	0.45
Meningitis/CNS	9 (5%)	4 (6%)	0 (0%)	5 (5%)	0.46
Sepsis eci	24 (13%)	9 (13%)	4 (6%)	11 (12%)	0.91
Other sites***	63 (33%)	16 (23%)	3 (11%)	44 (47%)	0.00
Outcome					
Hospital LOS*	35 (20-51)	42 (29-73)	32 (22-44)	29 (18-45)	0.07
Hospital mortality	66 (21%)	23 (25%)	11 (21%)	32 (20%)	0.76

*Legend to table 1: Baseline characteristics of the entire study population and the patients with "proven infection", "probable infection" and those "without proven infection" according to the CDC definition. See method section for further explanation of definitions. Depicted are the numbers and percentages unless stated otherwise. *Median, interquartile range. *** Among others: Skin infection not due to wound infections, bacteremia unrelated to other infectious foci.*

In all patients PCT and CRP was measured on admission and every subsequent morning. Table 2a shows the analysis of clinical and diagnostic data of the patients with “proven infection”, “probable infection” versus those “without infection”. No difference was seen in median PCT level in patients with a “proven infection” ‘probable or ‘no infection’(1.7 ug/L,0.8 ug/L,1.0 ug/L, p=0.12). Leukocytes were quite comparable between the groups. CRP was highest in patients with a “possible infection” (195 mg/L, 223 mg/L, 147 mg/L, respectively; p=0.01). A difference was seen in temperature between the three groups, although not expected the lowest temperature in patients with proven infections. Table 2b shows the same diagnostic parameters divided by non-survivors (35%) in hospital and survivors (65%). PCT (µg/L) was higher in non-survivors versus survivors (2.3 [0.5-7.6] vs 1.0 [0.3-4.1]; p=0.03). Temperature was lower 38.0°C [37.3-38.7] vs 38.3 °C [37.8-38.9] respectively; p=0.03) and leukocytes higher in non-survivors 18.1 x10^9/L [14.1-24.4] vs survivors 15.5 x10^9/L [12.2-20.1]; p =0.02.

Table 2a CRP, PCT, leukocytes and temperature in patients with SIRS with or without proven infection on admission

	Total	Proven infection	Probable infection	without infection	P-value
CRP (mg/L)	181 (98-259)	195 (119-279)	223 (128-358)	147 (85-237)	0.01
PCT (µg/L)	1.3 (0.4-5.3)	1.7 (0.7-5.6)	0.8 (0.4-5.9)	1.0 (0.3-4.5)	0.12
Temperature (°C)	38.2 (37.7-38.9)	37.5 (37.5-39.0)	38.5 (37.9-39.3)	38.1 (38.1-38.6)	0.04
Leukocytes (x10^9/L)	16.1 (12.6-21.5)	16.1 (12.3-21.2)	17.9 (12.9-23.0)	15.9 (12.5-21.7)	0.86

Table 2b CRP, PCT, leukocytes and temperature on admission in survivors and non-survivors

	Survivors n=125	Non-survivors n= 66	P-value
CRP (mg/L)	181 (105-261)	162 (91-250)	0.60
PCT (µg/L)	1.0 (0.3-4.1)	2.3 (0.5-7.6)	0.03
Temperature (°C)	38.3 (37.8-38.9)	38.0 (37.3-38.7)	0.03
Leukocytes (x10^9/L)	15.5 (12.2-20.1)	18.1 (14.1-24.4)	0.02

All depicted numbers are median values with interquartile ranges. The Kruskall-Wallis test is used to compare these values

The positive and negative predictive abilities of various levels of PCT and CRP are shown intable 3. A PCT-level exceeding 0.5 µg/L had a positive predictive value (PPV) of 37% for subsequently "proven infection". Extremely high levels of PCT (>10 µg/L) had a PPV of 36% for "proven infection". The negative predictive values (NPV) of PCT ranged from 63 to 73% at different cut-off values. The same has been shown for CRP-levels. At a low cut-off level (CRP >50 mg/L) the PPV was 38%, but the NPV was 80%. At higher levels (CRP > 200 mg/L) the PPV decreased (31%), and the NPV decreased to 62%. The likelihood ratio (LR) depicts, for a given cut-off level of PCT or CRP, the probability that our patient comes from the group with "proven infection" versus "no infection". For example, if a patient has a PCT >5 µg/L the probability that this patient comes from the group with "proven infection" is 2.00 times larger than the probability that this patient has "no proven infection". Another way of expressing the likelihood ratio's is by calculating the DOR. We found DOR's ranging from 0.76 to 1.60 for PCT and 0.71 to 2.61 for CRP (see table 3).

Table 3 Test characteristics of PCT and CRP for patients with a "proven infection".

	Sensitivity	Specificity	PPV	NPV	LR+	LR-	DOR (95% CI)
PCT > 0.5 (µg/L)	82%	26%	37%	73%	1.11	0.69	1.60 (0.44-5.76)
PCT > 1 (µg/L)	68%	40%	38%	71%	1.13	0.80	1.41 (0.49-4.32)
PCT > 2 (µg/L)	50%	48%	33%	65%	0.96	1.04	0.92 (0.32-2.55)
PCT > 5 (µg/L)	32%	62%	30%	63%	0.84	1.10	0.76 (0.25-2.26)
PCT > 10 (µg/L)	23%	79%	36%	66%	1.10	0.97	1. 13(0.31-3.73)
CRP > 50 (mg/L)	96%	10%	38%	80%	1.07	0.4	2.68 (0.26-23.3)
CRP >100 (mg/L)	65%	28%	34%	58%	0.90	1.25	0.71 (0.24-2.14)
CRP > 150 (mg/L)	61%	43%	38%	65%	1.07	0.91	1.15 (0.40-3.27)
CRP > 200 (mg/L)	22%	73%	31%	62%	0.81	1.07	0.73 (0.29-2.46)

Sensitivity: percentage of SIRS patients and a "proven infection" with a positive test.
Specificity: percentage of SIRS patients and "no proven infection with a negative test.
PPV (positive predictive value): percentage of patients with a positive test and a proven infection.
NPV (negative predictive value): percentage of patients with a negative test and no proven infection.
LR+: Likelihood ratio positive: the probability of a patient with a "proven infection" testing positive divided by the probability of a patient without proven infection testing positive.
LR-: Likelihood ratio negative: the probability of a patient with "a proven infection"testing negative divided by the probability of a patient without a proven infection testing negative.

DOR (diagnostic odds ratio): [sensitivity/(1-sensitivity)]/[(1-specificity)/specificity]: ratio between the odds of a condition with a positive test and the odds of a condition with a negative test. The DOR is therefore a mathematical representation of the likelihood ratios (DOR = LR(+)/LR(-)) and a DOR of 2 means that the chances of a positive test (PCT > 5 µg/L) are twice as high a patients with a proven infection than in patients without a proven infection.

The ROC (see figure 1) shows an AUROC for PCT of 0.58 (95% confidence interval 0.48-0.67) and AUROC for CRP of 0.57 (95% confidence interval 0.49-0.67).

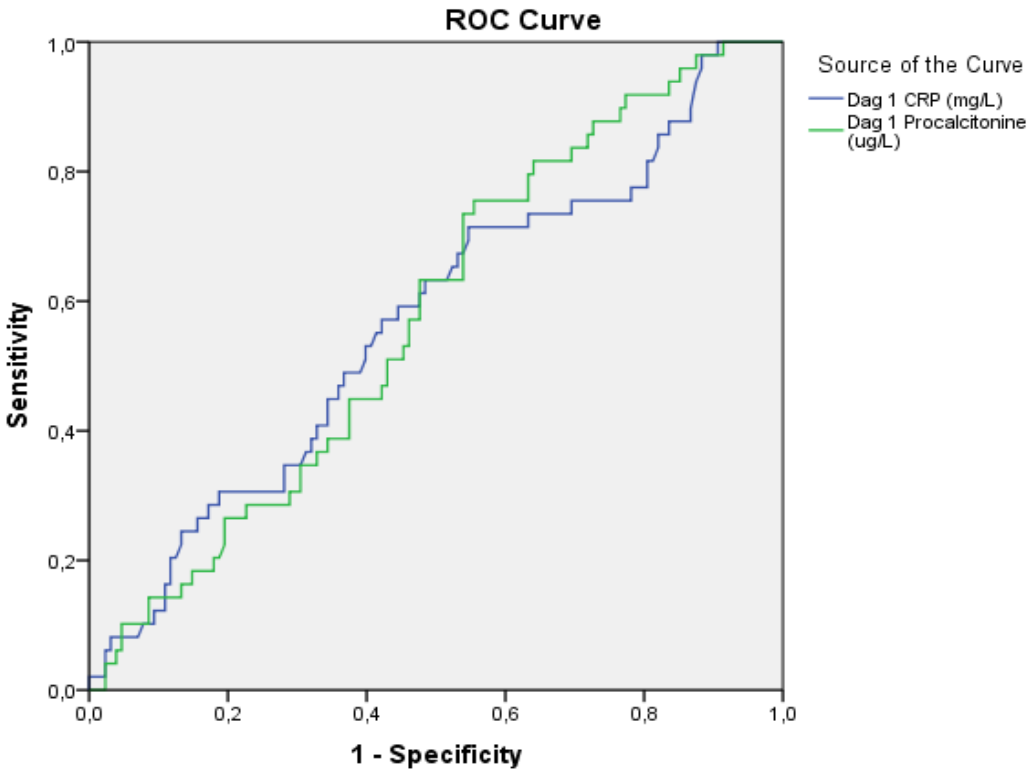

Figure 1: Receiver Operating Curve for PCT and CRP

Discussion

The goal of this study was to analyse whether PCT can be used as a fast and accurate test for predicting the presence of ”proven infection” in a patient who presents with SIRS in the ICU setting. This is crucial for the diagnosis of sepsis, a dangerous condition with a high mortality rate. Fast and accurate treatment of the infection and other supportive therapy is essential to ensure the survival of the patient.[10] Unfortunately, the performance of PCT to correctly identify patients with ”proven infection” was poor (positive predictive values of 30-38%, diagnostic odds ratio of only 0.76-1.60 and

an area under the ROC of 0.58). Vice versa, the negative predictive value (NPV) of PCT was insufficient to exclude patients who did not have a "proven infection". The ability of CRP to identify or exclude patients with a "proven infection" was equally poor.

Most patients who are admitted on our ICU with SIRS are treated with antimicrobials (85%). However, many used these antimicrobials as peri-operative prophylaxis or as SDD. Only 100/191 of the patients with SIRS were suspected of having an infection. The combination SIRS with suspicion of infection is called "sepsis" and often is the starting point of antimicrobial treatment as advocated by current guidelines.[2] Eventually, only a minority of the patients (70/190) had a "proven infection". Yet, the true infection rate will probably lie somewhere between 70/191 (37%) and 100/191 (52%). Not all patients that are clinically suspected of having a sepsis will have an infection and not all cultures will become positive (false negative cultures).[10] The CDC definitions of infections in acute settings depend heavily upon positive cultures.[9] False negative cultures or cultures that are just not done will result in an underestimation of the true infection rate. Still, the discrepancy between the amount of patients with SIRS and patients with a "proven" (or even "probable") infections illustrates that better ways to discriminate between just SIRS from true infection are needed.

Several biomarkers have been proposed which would correctly identify patients that truly have a bacterial infection and would thus benefit from antimicrobial therapy.[7] One of the most studied biomarkers is PCT and its performance to correctly identify infectious from non-infectious states is sometimes reported to be impressive.[8] However, most of the times PCT was used in homogenous patient groups or in patients that did have a high a priori chance of infection. For example, in one of the early publications on PCT Brunkhorst and coworkers recruited 185 patients.[5] Out of these 185 only 17 did have solely SIRS. The others had sepsis, severe sepsis or septic shock. If 90% of the population has more than just uncomplicated SIRS then any biomarker will correctly predict sepsis, severe sepsis or septic shock. Indeed, the AUROC in that study showed that PCT almost perfectly predicted severe sepsis. However, that is not the question to answer! The question actually is which part of suspected sepsis is truly caused by bacterial infection. In our study the prevalence of "proven infection" was low, but PCT did not improve the diagnostics. More studies have looked at the predictive abilities of PCT in subpopulations and shown impressive results.[12] However, whether PCT will be able to discriminate true infection from SIRS in a non-selected ICU population with a lower a priori chance of infection was not known. Our study shows that the ability of PCT to detect "proven infection" is very low (PPV 30-38% depending on which cut off values were being used). Indeed, likelihood ratio's ranging from 0.5-2.0 will rarely give a large shift from pre-test probability to post-test probability of a disease. In this study this means that measuring a PCT or CRP will not influence the probability of a patient having a "proven infection".

Some limitations of our study need to be addressed. Previous studies have shown that there might be a large inter-observer variability of SIRS. Depending on how restrictive or liberal the SIRS-criteria are applied, the incidence of SIRS ranges from 49 to 99% in a general ICU population.[3,13] On admission to the ICU we found 191 patients with SIRS out of 499 eligible patients (38%) suggesting that we used a rather restrictive way to adjudicate SIRS to patients. A more liberal way of adjudicating SIRS to patients would have resulted in more inclusions and possibly an even lower fraction of "true infection". Second, the term "proven infection" as used in Table 1 and 2 was determined according to the CDC criteria for infectious diagnosis in acute setting.[9] These criteria rely heavily on positive cultures. False negative cultures or cultures that were not properly or not timely performed might result in an underestimation of the true fraction of "proven infection". The majority of patients was using antimicrobial therapy on admission and this might have interfered with cultures becoming positive. Again, this will result in an underestimation of the true amount of infection. However, if we applied the CDC criteria to a higher-risk patient group; those that clinically had sepsis, severe sepsis or septic shock and were thus clinically suspected of having an infection (n=122) then the predictive abilities of PCT and CRP improved minimally. Than the DOR's ranged from 1.01 to 2.31. However, a DOR > 25 is considered a useful test. This shows that, even with more liberal end points, PCT and CRP are still not useful for the identification of infection. A third limitation might be that some of the patients came from other departments in our hospital, where they could have developed sepsis and were treated with antimicrobial therapy before being admitted on the ICU. Again, cultures taken on admission to the ICU might remain negative due to previous antimicrobial treatment.

However, a strong feature of this analysis is that it one of the few studies in which PCT was tested in a mixed surgical and medical ICU on consecutive patients with SIRS but with a low prevalence of sepsis and "proven infection". A real life situation!

Conclusion

A swift and accurate tool to discern patients with a true infection from those who only have SIRS is needed. We do not want to postpone antimicrobial therapy in patients that really need it, but we do not want to treat those who do not need it. The ubiquitously used CRP is not a good biomarker to distinguish SIRS from sepsis.[8] However, PCT does not perform better than CRP. The high predictive values of PCT as shown in previous studies could not be repeated in our heterogeneous ICU population with a low prevalence of "proven infection". Is PCT completely useless then? Several randomised controlled ICU trials have shown that PCT is a good biomarker for the individualisation of duration of antibiotic therapy.[14-17] However, in this population PCT fails to discriminate between SIRS and sepsis and apparently to guide in whether to start or withhold of antibiotics in the critically ill.

References

1. Vincent JL, Rello J, Marshall J, Silva E., Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323-2329
2. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327
3. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015 Apr 23;372(17):1629-38
4. Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. Chest 1992;101:1481-1483
5. Brunkhorst FM, Wegscheider K, Forycki ZF, Brunkhorst R. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. Intensive Care Med 2000;26 Suppl 2:S148-S152
6. Tang H, Huang T, Jing J, Shen H, Cui W. Effect of procalcitonin-guided treatment in patients with infections: a systematic review and meta-analysis. Infection 2009;37:497-507
7. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. Crit Care 2010;14:, R15
8. Meynaar IA, Droog W, Batstra M, Vreede R, Herbrink P. In Critically Ill Patients, Serum Procalcitonin Is More Useful in Differentiating between Sepsis and SIRS than CRP, Il-6, or LBP. Crit Care Res Pract 2011;2011:594645
9. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309-332
10. van Nieuwkoop C, Bonten TN, van't Wout JW, Kuijper EJ, Groeneveld GH, Becker MJ, Koster T, Wattel-Louis GH, Delfos NM, Ablij HC, Leyten EM, van Dissel JT. Procalcitonin reflects bacteremia and bacterial load in urosepsis syndrome: a prospective observational study. Crit Care. 2010;14(6):R206
11. Pepe S. Limitations of the Odds Ratio in Gauging the Performance of a Diagnostic, Prognostic, or Screening Marker. Am J Epidemiol 2004;159:882-89

12. Horie M, Ugajin M, Suzuki M, Noguchi S, Tanaka W, Yoshihara H, et al. Diagnostic and prognostic value of procalcitonin in community-acquired pneumonia. Am J Med Sci 2012;343:30-35
13. Sprung CL, Sakr Y, Vincent JL, Le Gall JR, Reinhart K, Ranieri MV, et al. An evaluation of systemic inflammatory response syndrome signs in the Sepsis Occurrence In Acutely Ill Patients (SOAP) study. Intensive Care Med 2006;32:421-427
14. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentrerandomised controlled trial. Lancet 2010;375:463-474
15. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. Am J RespirCrit Care Med 2008;177:498-505
16. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect ofprocalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet 2004;363:600-607
17. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect ofprocalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tractinfections: the ProHOSP randomized controlled trial. JAMA. 2009;302(10):1059-66
18. Deliberato RO, Marra AR, Sanches PR, et al. Clinical and economic impact of procalcitonin to shorten antimicrobial therapy in septic patients with proven bacterial infection in an intensive care setting. DiagnMicrobiol Infect Dis. 2013;76:266-71
19. Shehabi Y, Sterba M, Garrett PM, et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J RespirCrit Care Med. 2014;190:1102-10
20. Assink-de Jong E, de Lange DW, van Oers JA, Nijsten MW, Twisk JW, Beishuizen A. Stop Antibiotics on guidance of Procalcitonin Study (SAPS): a randomised prospective multicenterinvestigator-initiated trial to analyse whether daily measurements of procalcitonin versus a standard of-care approach can safely shorten antibiotic duration in intensive care unit patients—calculated sample size: 1816 patients. BMC Infect Dis. 2013;13:178