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Procalcitonin: a valuable marker for assessment of the success of antimicrobial therapy for severe sepsis

An analysis using routine clinical data

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Abstract:

Introduction

Severe sepsis is a live-threatening disease despite enormous progress in medical treatment. This study evaluated the survival of patients due to procalcitonin (PCT) reduction within 12 days from first pathological PCT measurement. PCT is a well evaluated biomarker not only able to differentiate between bacterial and non-bacterial infections, but also to assess the effectiveness of antibiotic therapy.

Materials and methods

Out of 358.763 clinical cases from 7 German hospitals in 2012 and 2013, 3.854 cases had an ICD-10 code representing sepsis. 2.101 cases showed at least one pathologic PCT value and 1.778 cases had exactly one episode of infection. An episode of infection was defined as initial PCT > 0.5 ng/ml and final value reduced by at least 80% of the highest value or < 0.25 ng/ml. Of the 1.778 cases 671 showed a series of measures that was suitable to assess treatment success using PCT-reduction. To avoid bias from covariates propensity score matching was used to create two comparable groups with a group size of 211 patients each.

Results:

The group with PCT-reduction within 12 days showed a highly significant better proportion of survival (146/211 vs. 17/211; $p < 0.0001$). The odds ratio for death according to PCT-reduction vs. non-reduction is 25.64 ($p < 0.0001$; 95%-CI: 14.49-45.45). The risk to die if PCT is not reduced within the first 12 days of treatment is therefore 25.64 times higher than in the PCT-reduction group. The literature recommends to stop antibiotic therapy, as soon as PCT is normalized. In this study this point was reached in average after 6.2 days.

Discussion:

The remarkable difference in survival implicates that PCT-reduction is a suitable surrogate parameter to indicate successful antimicrobial therapy. This is concordant to other analyses. Successful antibiotic therapy is a proven predictor for survival in sepsis. This study also showed concordant results in the often criticized group of patients with sepsis after abdominal surgery. Subgroup analyses

were undertaken to analyze possible bias derived from the definition of suitable measures. The results confirm the initial findings. The downside of routine data is that the actual antimicrobial therapy was not available electronically. Thus success was measured using the reduction of initially pathologic PCT.

Conclusion:
This analysis of clinical routine data underpins the evidence to use PCT for monitoring of antimicrobial therapy derived from clinical studies. However, the data also show that the overall use of PCT to monitor sepsis therapy is far from 'routine'. Only 671 of 3.584 patients showed suitable measures. Hospitals should establish algorithms for sepsis treatment that include PCT for the assessment of adequacy and the monitoring of success of the antimicrobial therapy.

Introduction and Objectives

Procalcitonin (PCT), a precursor of the hormone calcitonin, is produced by C cells in the thyroid. PCT is consistently produced during severe bacterial infections, causing its levels to increase [1,2]. However, increased PCT levels are also characteristic of other disease states, such as calcitonin-producing tumors, medullary C-cell carcinoma of the thyroid, acute respiratory distress syndrome, and invasive fungal infections. In particular, extensive clinical evidence indicates that PCT is a biomarker for both follow-up and evaluation of the effectiveness of antibiotic therapy for severe respiratory infections and sepsis; in all relevant guidelines, the use of PCT in this context is categorized as evidence class 2B or 2C [3,4]. For example, PCT levels differentiate more effectively between sepsis and systemic inflammatory response syndrome (SIRS) than those of IL-6, IL-8, or CRP [5,6]. A meta-analysis of several clinical studies of various infections demonstrated that PCT-guided antibiotic therapy reduced both therapy duration and the length of stay in intensive care [7]. Based on this broad evidence, another meta-analysis focused on sepsis was conducted, the results of which indicated that antibiotic therapy can be curtailed by a mean of four days, and length of ICU stay reduced by a mean of 1.8 days. Based on existing algorithms, a sequence of PCT measurements appropriate to guide the use of antibiotic therapy was determined. In addition, rules for when therapy should commence and end, and cut off values to evaluate successful treatment have been established. Implementation of this system may introduce savings for the German diagnosis-related group (G-DRG) system [8].

A fall in PCT levels by 80% compared with the highest value, or to 0.25 ng/ml, indicate successful antibiotic therapy. Hochreiter and Schröder showed that, in the case of adequate antibiotic therapy, PCT levels decrease significantly after 4 days [9]. In addition, Charles et al. demonstrated that a lack of PCT reduction on day 3, compared with day 2 of antibiotic therapy, is a resilient indicator of inadequate treatment (OR = 10.29) [10].

Once guidelines and algorithms have been established for some time, the question of how well they are implemented in practice in the clinic arises.

Objectives of this work:
- Evaluation of the application of PCT measurement in a routine clinical setting
- Review of how often the algorithm published in 2011 is applied (adherence)
- Development of a process to determine an "appropriate measurement sequence" (since only when a minimum sequence of PCT measurements are performed the success of antibiotic therapy can be assessed)

The primary endpoint in this study was the survival of patients whose PCT levels felt according to described “PCT reduction” within 12 days of the first pathological PCT measurement and who had undergone an "appropriate measurement sequence".

Materials and Methods

Data types and data transmission
Participating DRG hospitals submitted relevant data, including ICD codes, German operation codes (OPS), ventilation hours, age, gender, admission and discharge dates and the results of PCT tests. These data, collected during 2012 and 2013, were verified by peer group-based random audits at each hospital.

After examination of the study protocol, along with data from a methodologically identical study, the ethics committee of the Bavarian Chamber of Physicians (BLÄK) declared that this type of investigation required neither ethical approval nor the consent of individual patients.

Participating hospitals
Seven hospitals in Germany, including one university hospital, three maximum care clinics, and three priority clinics, were

included in this study.

Definitions for evaluating routine data

Pathological PCT value:
A PCT value > 0.5 ng/ml measured in patients with sepsis requiring initiation of calculated antibiotic therapy [16,17].

Episode:
An episode was defined as the period between the measurement of a pathological PCT value and the date of PCT reduction, according to previously described cut-off values. Incidents of pathological PCT values recorded after "PCT reduction" were defined as new episodes. Only patients with exactly one episode were included in this study, as a relapse after PCT reduction may occur for many reasons (e.g., superinfection and sepsis, among others).

PCT Reduction: PCT reduction within 12 days of the first pathological PCT measurement
PCT reduction was considered to have occurred when the PCT value was 80% lower than the highest value recorded, or 0.25 ng/ml; these definitions have been used in various scientific publications and ensure practical limits to evaluate the effect of an antibiotic [7,11].

Adherence to the algorithm published in 2011:
The number of patients with sepsis, at least one pathological PCT value, and a series of measurements consistent with the algorithm published in 2011 (Figure 1).

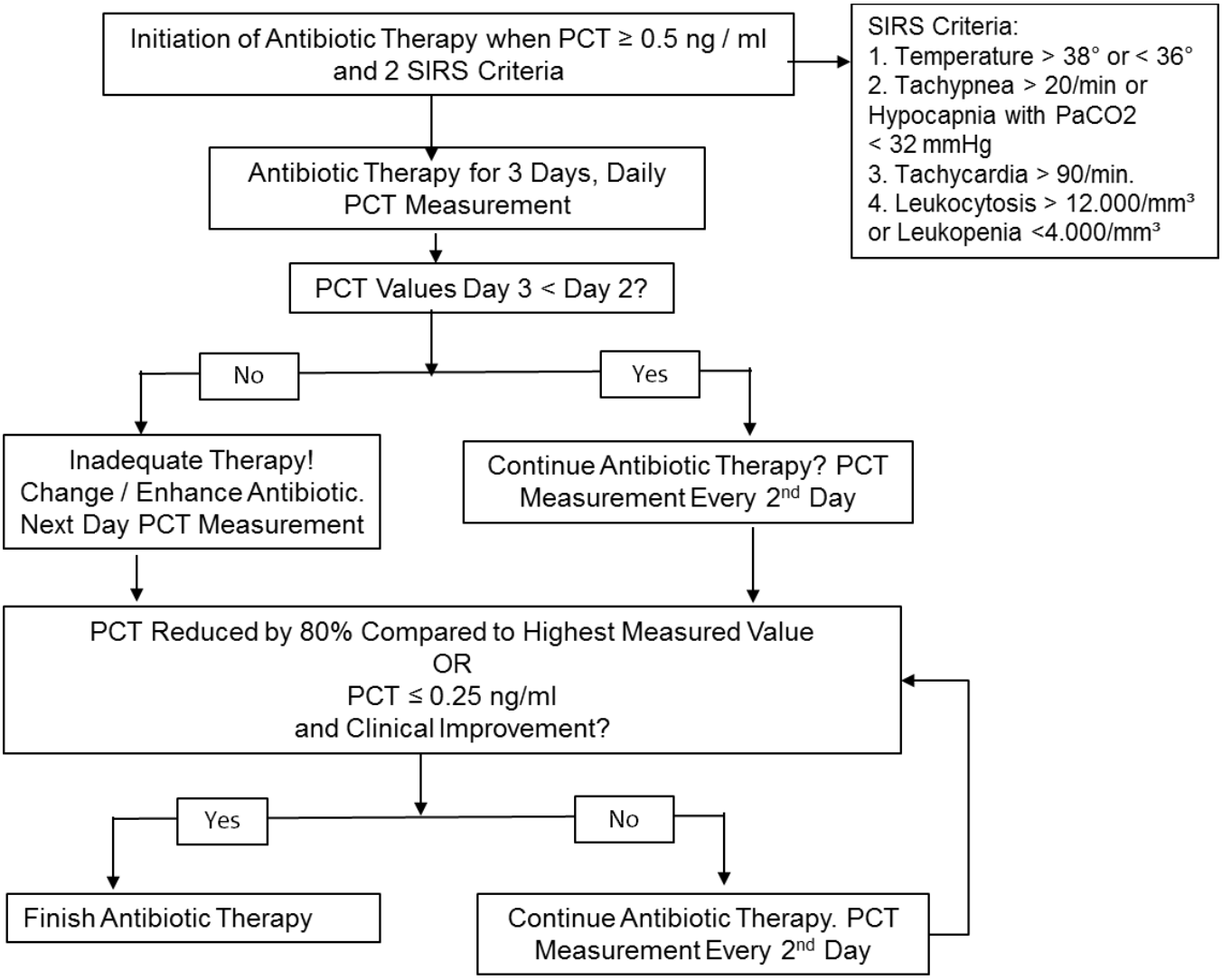

Figure 1: Published PCT algorithm for monitoring antibiotic therapy in sepsis (adapted from [8]).

A preliminary study showed that very few patients (116 of 1,778 patients with sepsis, pathological PCT, and one episode) had already undergone PCT measurements meeting the requirements of this algorithm.

"Appropriate measurement sequence" as a modified method to determine an appropriate sequence of PCT measurements

The "appropriate measurement *sequence* ", as defined in this study, reflects clinical experience and requirements for sufficient antibiotic therapy. In particular, the following information was incorporated:

- antibiotic or anti-infection therapies should be evaluated within at most 72 hours after initiation of therapy [12]
- In cases of sufficient and effective antibiotic treatment, PCT levels should decrease to those described in the definition of "PCT reduction" in less than 12 days
- Measurement of PCT should be performed at intervals of 72–96 h after the highest measured value to determine the success of therapy
- PCT is a valuable parameter when measurements are performed on several sequential occasions [13]

Figure 2 describes the process applied to identify appropriate measurement sequences from among those observed in the clinic.

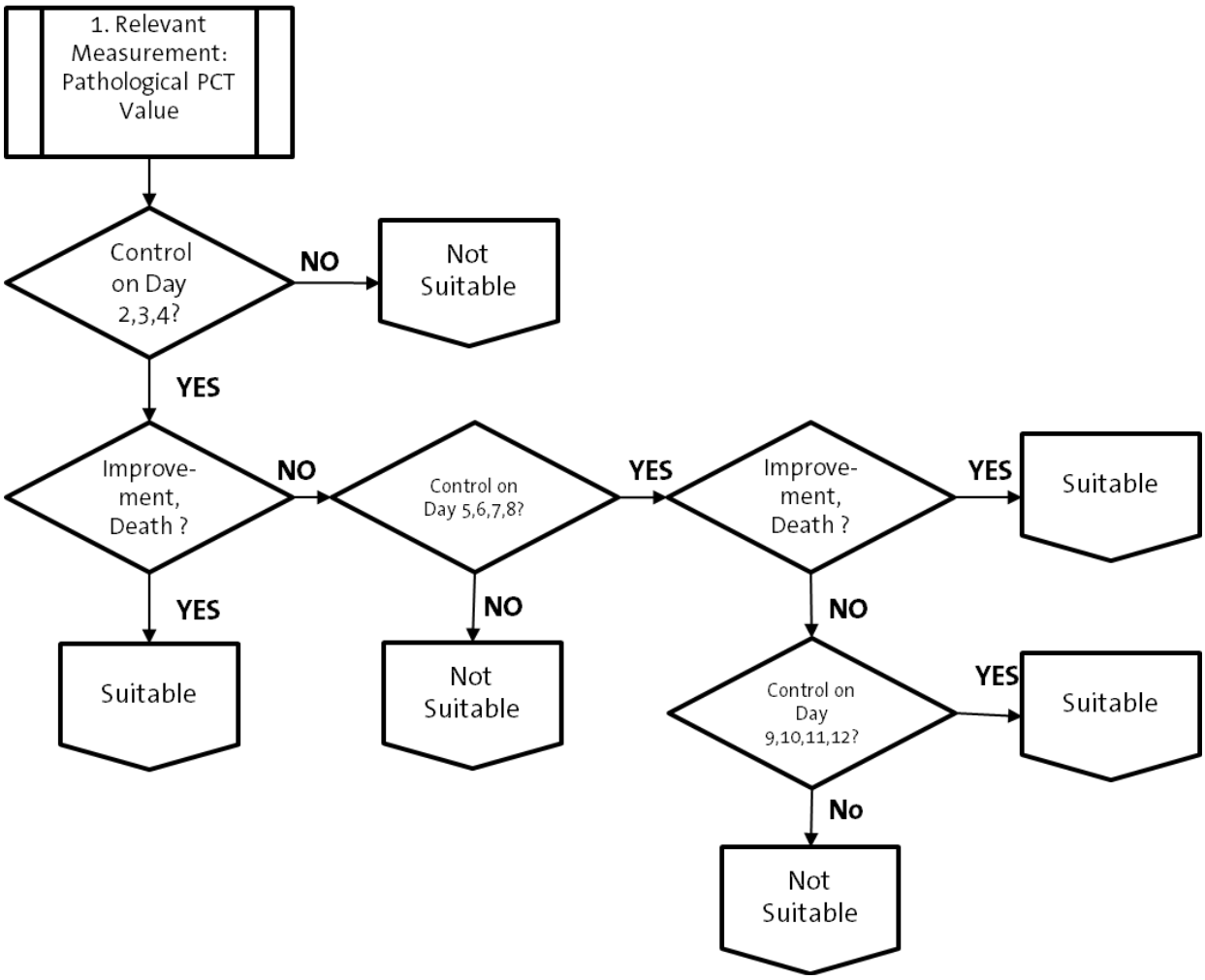

Figure 2: Decision tree to identify whether an "appropriate measurement sequence" had been applied.

In this study, cases with ≥ 2 measurements were considered to have undergone an "appropriate measurement sequence".

Patient population

Patients with an ICD-10-GM code for sepsis, a recorded pathological PCT value, AND an "appropriate measurement sequence" as described above were included in this study. Patients with more than one episode were excluded. ICD-10-GM codes for sepsis are listed in the Annex.

Statistical analyses

Data analysis was performed using SPSS version 19 and propensity score matching was carried out using a module in R. The statistical evaluation of the primary endpoint, namely the survival of patients, was performed using a chi-square test, according to Pearson, and odds ratios and 95% confidence intervals (CIs) were calculated.

Propensity score matching is a commonly used statistical method to achieve a good

balance between observed covariates in retrospective cohorts [14,15]. The method enables effective bias reduction in routine data [16].

To enable the comparison of treated sepsis cases, despite the heterogeneous disease pattern among patients, factors were identified which defined the severity of each case. We used accumulated CCL values of secondary diagnoses (sum CCL), the DRG partition (surgical, other, medical) and organ failure; all items derived from the coding and DRG grouping process.

As the number of failing organs predicts survival in sepsis, we identified cases with circulation, kidney, respiratory, and coagulation failure due to ICD-10-GM and German operation codes (OPS) [17,18].

The ICD-10-GM and German operation codes (OPS) used are listed in the Annex. After linear regression analysis of additional severity criteria at the endpoint "survival" the parameters listed in Table 1 were selected.

Factor	Adjusted coefficient of determination (R^2)	Significance (P)
Circulation failure	0.144	< 0.0001
Respiratory failure	0.090	< 0.0001
Kidney failure	0.061	< 0.0001
Age	0.042	< 0.0001
Total CCL	0.034	< 0.0001
Coagulation failure	0.001	0.195
Partition	-0.001	0.792
Gender	-0.001	0.563

Table 1: Overview of relevant confounders of the endpoint “survival” determined by linear regression analysis.

In conducted propensity score matching the "nearest neighbor" method with calipers of 0.2 [19,20] was used to minimized the influence of significant confounders listed in Table 1.

Our data pool included anonymized patient data from seven different hospitals. So called §21 SGB V data (ICD and procedure codes) from a total of 358.763 treated cases and PCT values with date, time, and measured value in ng/ml (if measured) were available.

Results

After selection according to the scheme in Table 2, there were 422 cases available for statistical analysis.

358.763 cases in database
3.854 cases with coded sepsis
2.317 cases with at least one PCT measurement
2.101 cases with at least one pathological measurement
1.778 cases with exactly one episode
671 cases with one appropriate measurement sequence
422 cases after propensity score matching
211 cases each with and without PCT reduction

Table 2: Pathway of patient selection.

As shown in Table 3, propensity score matching delivered homogenous case to case mapping for all significant confounders with regard to the chosen primary endpoint (survival).

	PCT Reduction?	
	Yes	No
Number of cases	211	211
Gender (m/f)	133/78	124/87
Age (m/f)	67.4 / 65.9	70.1/73.3
SUM_CCL	25.04	22.50
Organ failure breathing	171	159
Organ failure coagulation	23	27
Organ failure circulation	113	113
Organ failure kidney	102	114
Average number of organ failure	1.94	1.96

Table 3: Distribution and characteristics of the groups studied. There were no significant differences between the two groups in parameters relevant to the primary endpoint.

Statistical analysis of cases who died, relative to those who survived (Table 4), demonstrated a significant survival benefit of PCT reduction.

	PCT reduction within 12 days after first pathological PCT measurement		
	Yes	No	P-value (Pearson's Chi-Square Test)
N	211	211	
survivor	146	17	< 0.0001
	(69.2%)	(8.1%)	

Table 4: Statistical evaluation of the primary endpoint (survival).

Of 211 patients with reduced PCT, 65 died and 146 survived, while among 211 patients without PCT reduction, 194 died and only 17 survived.
The odds ratio for survival with respect to "no PCT reduction vs. PCT reduction" was 0.039 (95% CI, 0.022–0.069; P < 0.0001). Hence, when no PCT reduction occurs, the risk of dying is 25.6 times higher than where PCT reduction is observed.

Discussion

The results presented here represent clinical routine data and are not extrapolated from other studies. The measurement of a series of PCT levels has consistently been described as useful for the evaluation of therapeutic success [7,21]. Hohn et al. demonstrated these effects, even among routine clinical populations [22]. In addition, numerous clinical studies have confirmed that antibiotic therapy can be stopped when PCT levels have normalized and clinical improvement has occurred, without risk of increased mortality. The initiation of antibiotic therapy is typically driven by a range of clinical assessments, whereas increased PCT is only used to confirm a likely bacterial infection. A report published in 2015 demonstrated that the density of antibiotic use in antibiotic stewardship programs was significantly reduced when PCT was measured [23].

Our study proves that failure of PCT levels to fall is accompanied by a dramatic increase in mortality. This is certainly not due to whether measurements were regular. Even when data regarding the actual antibiotic therapy used was not available, it must be assumed that the lack of PCT reduction indicates inadequate antibiotic therapy. Other studies, in which the relationship between inadequate antibiotic therapy in sepsis and survival was analyzed, reported death rates in inadequately treated groups became as high as 90% [24,25].

PCT is also a predictor of outcome in severe infections [26]. Jung et al. concluded in their paper in Critical Care in 2013 [27] that PCT is not an appropriate marker for assessment of therapeutic success in perioperative settings for patients with septic shock as a result of intra-abdominal infection. Unfortunately, this study had extensive methodical and content-related limitations. The conclusions made by the authors are not at all plausible, since PCT measurements were not performed after the fifth day. Nevertheless, the results of Jung's study do not contradict those of previously published reports. The critical problems with the Jung et al. publication [27] are the limitation of PCT measurements to day 5 and the definition of treatment failure. A subgroup analysis of the patients reported by Jung et al. in our study demonstrated no significant differences between those patients and the overall population. Linear regression analysis of our cohort revealed no significant influence of "abdominal surgery" on the outcome parameter "mortality". Similar results of mortality and survival rates unveiled no significant difference between our overall population of 422 persons and the subgroup of patients who underwent abdominal surgery.

Despite convincing results, our study has some limitations. Given the number of patients where "sepsis" was coded (see selection of ICD-10-GM codes in the Annex), it was notable that less than two thirds of these ever had their PCT levels measured (2.317 of 3.854

patients). For the majority (2.101 patients) of those who did have PCT measurements, pathological values (according to the literature) were recorded. From 1.778 patients with an “episode”, only 671 underwent an appropriate measurement sequence, and only 116 had a series of measurements consistent with the algorithm published in 2011. In addition, this study is largely based on the analysis of routine data. Peer reviews took place in every clinic (20 cases per clinic) and found that cases lacking PCT reduction also received inadequate antibiotic therapy. As the number of audited samples was small it is difficult to infer for all cases. The definition of “appropriate measurement sequence” could also have an inherent bias and over-frequently include deceased patients who were "appropriate" according to our algorithm before achieving PCT reduction. Our study reveals a dramatically high mortality rate among patients in the group "no PCT reduction". After linear regression and matching the two groups by propensity score analysis, enabled an equivalent distribution of factors influencing the endpoint "survival" between the groups. Comparisons between the groups revealed no significant difference in any relevant parameter, particularly organ failure and DRG Partition. All cases with an appropriate measurement sequence which were included in our patient group had similar risk profiles with respect to "mortality"; hence, "PCT reduction" can be considered a major influence on patient survival.

To check for possible bias, a subgroup analysis was performed, in which all patients who died on days 1, 2, or 3 were excluded, which resulted in a remaining cohort of 337 patients. The Kaplan-Meier survival analysis performed using these data again demonstrated a highly significant difference in survival between the “PCT reduction” and “no PCT reduction” groups (Figure 3 and Table 5).

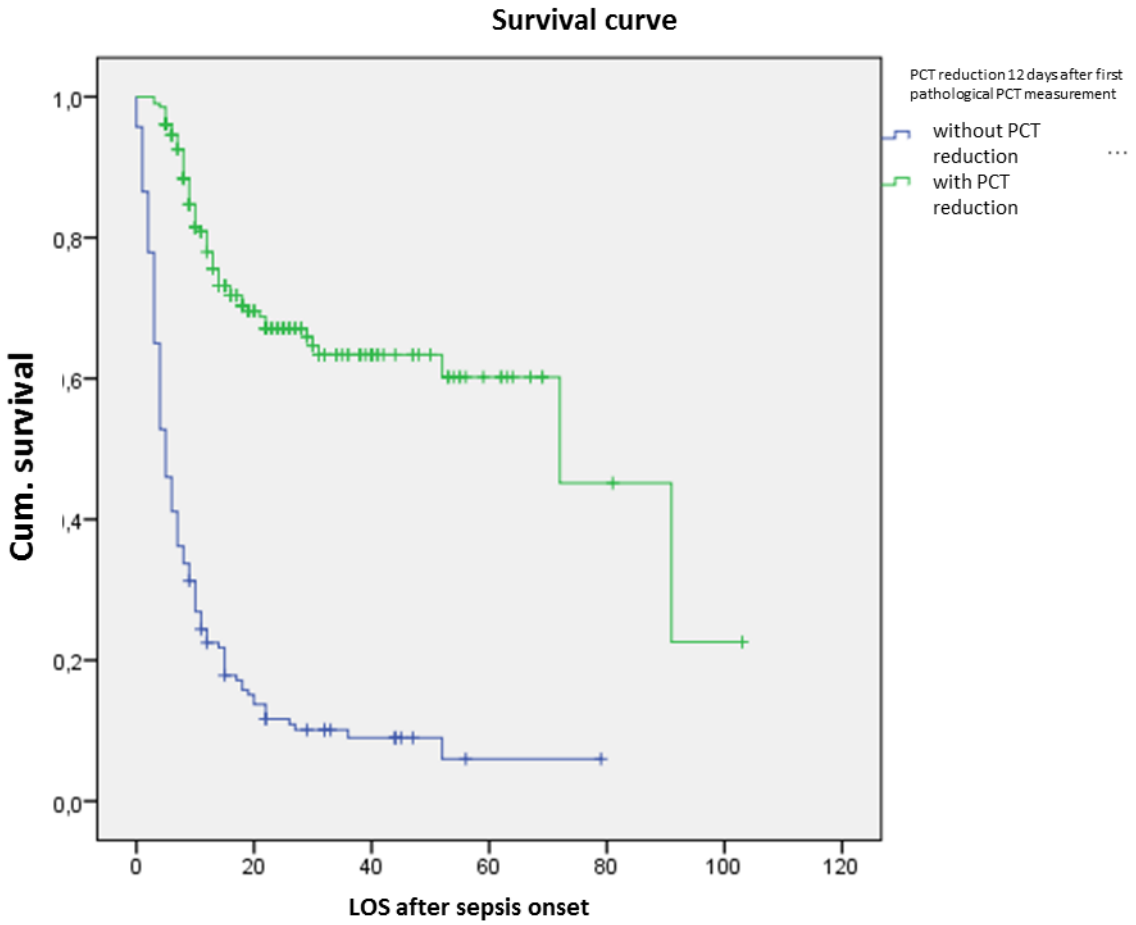

Figure 3: Survival curve (Kaplan-Meier) for the subgroup "length of stay > 3 days".

	PCT reduction within 12 days after first pathogenic PCT measurement		
	Yes	No	P-value (Chi-Square Test of Pearson)
N	205	132	
Survivor	141	17	< 0.0001
	(68.8%)	(12.9%)	

Table 5: Survival rates of patients with a length of stay > 3 days, with or without PCT reduction

This subgroup analysis confirmed our results and excludes, or at least diminishes, the possibility of this type of bias.

The investigation of PCT reduction as a correlate of successful antibiotic therapy is almost tantamount to a study of PCT reduction over the entire length of stay. In the group with an "appropriate measurement sequence" (n = 671), 406 patients had PCT reduction within 12 days of the first pathological PCT measurement, while a total of 412 patients exhibited PCT reduction. These results indicate that PCT reduction signifies sufficient antibiotic therapy. In our study, PCT reduction occurred within the first 12 days of the initial pathological PCT measurement. Recent studies

even suggest that PCT reduction must occur after a treatment duration of 5–7 days to demonstrate sufficient antibiotic treatment [28,29].

The possibility of early termination of antibiotic therapy is one advantage of measuring PCT. In this study, PCT reduction occurred after an average of 6.2 days in the "PCT reduction" group.

Summary

On the basis of analyses of routine clinical data, it is to conclude that PCT is a suitable marker to monitor the success of antibiotic therapy in sepsis. However, it is clear that too few sepsis patients underwent sufficient PCT measurements at the correct frequency to allow precise PCT monitoring. Practical application of PCT measurements, following published algorithms, or at minimum the above-described "appropriate measurement sequence", is recommended. Clinics should define their own standards for PCT measurement (taking into account existing algorithms), evaluate adherence regularly and establish antibiotic therapy control in the context of antibiotic stewardship programs.

List of abbreviations

CC	Complication or Comorbidity
DRG	Diagnosis-related group
ICD-10-GM	ICD 10 German Modification
OPS	Operation- und Prozedurenschlüssel
PCCL	Patient Clinical Complexity Level
PCT	Procalcitonin
SIRS	Systemic Inflammatory Response Syndrome

Annex:

Overview of ICD codes used to define "sepsis"

A02.1	Salmonella sepsis
A20.7	Pestsepsis
A21.7	Generalized tularemia
A22.7	Anthrax sepsis
A26.7	Erysipelothrix sepsis
A32.7	Listerial sepsis
A39.2	Acute meningococcaemia
A39.3	Chronic meningococcaemia
A39.4	Meningococcaemia, unspecified
A40.0	Sepsis due to Streptococcus, group A
A40.1	Sepsis due to Streptococcus, group B
A40.2	Sepsis due to Streptococcus, group D
A40.3	Sepsis due to Streptococcus pneumoniae

A40.8	Other Streptococcal sepsis
A40.9	Designated Streptococcal sepsis, unspecified
A41.0	Sepsis due to Staphylococcus aureus
A41.1	Sepsis due to other specified Staphylococcus
A41.2	Sepsis due to unspecified Staphylococcus
A41.3	Sepsis due to Hemophilus influenzae
A41.4	Sepsis due to anaerobes
A41.51	Sepsis due to Escherichia coli [E. coli]
A41.52	Sepsis due to Pseudomonas
A41.58	Sepsis due to other Gram-negative pathogens
A41.8	Other specified septicemia
A41.9	Sepsis, unspecified organism
A42.7	Actinomycotic sepsis
B37.7	Candida sepsis
R57.2	Septic shock
R65.0	Systemic inflammatory response syndrome [SIRS] infectious etiology without organ complications
R65.1	Systemic inflammatory response syndrome [SIRS] infectious etiology with organ complications

Criteria for the definition of organ failure

	Organ failure kidney
N17.0	Acute renal failure with tubular necrosis
N17.1*	Acute renal failure with acute cortical necrosis
N17.2*	Acute kidney failure with medullary necrosis
N17.8*	Other acute kidney failure
N17.9*	Acute kidney failure, unspecified organ failure
	Organ failure breathing
Ventilation > 24 hours	
	Organ failure clotting
D65.1	Disseminated intravascular coagulation [DIG, DIC]
D69.5*	Secondary thrombocytopenia

D69.6*	Thrombocytopenia, unspecified
R57.2	Septic shock

Asterix (*): valid for subcodes

Literature

1. Schuetz P, Aujesky D, Müller C, Müller B. Biomarker-guided personalised emergency medicine for all - hope for another hype? Swiss medical weekly 2015;145:w14079.
2. Muller B, White JC, Nylen ES, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-i gene in multiple tissues in response to sepsis. The Journal of clinical endocrinology and metabolism 2001;86:396–404.
3. Surviving Sepsis Campaign. International Guidelines for Managment of Severe Sepsis and Septic Shock: 2012.
4. AWMF. S3 Leitlinie zur Behandlung der tiefen Atemwegsinfektionen.
5. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. American Journal of Respiratory and Critical Care Medicine 2001;164:396–402.
6. 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. Critical Care Research and Practice 2011;2011:594645.
7. 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.
8. Wilke MH, Grube RF, Bodmann KF. The use of a standardized PCT-algorithm reduces costs in intensive care in septic patients - a DRG-based simulation model. European Journal of Medical Research 2011; 16:543–548.
9. Hochreiter M, Köhler T, Schweiger A, Keck FS, Bein B, Spiegel T von, et al. Antibiotikatherapie bei operativen Intensivpatienten. Anaesthesist 2008;57:571–577.
10. Charles PE, Tinel C, Barbar S, Aho S, Prin S, Doise J, et al. Procalcitonin kinetics within the first days of sepsis: relationship with the appropriateness of antibiotic therapy and the outcome. Crit Care 2009;13:R38.
11. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Medicine 2011;9:107.
12. Schuetz P, Maurer P, Punjabi V, Desai A, Amin DN, Gluck E. Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients. Critical Care 2013;17:R115.
13. Bodmann K. Diagnostische Marker und Effektivitätsbewertung in der antibakteriellen Therapie. Medizinische Klinik, Intensivmedizin und Notfallmedizin 2014;109:187–190.
14. Thoemmes FJ, Kim ES. A Systematic Review of Propensity Score Methods in the Social Sciences. Multivariate Behavioral Research 2011;46:90–118.
15. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.
16. Austin PC. The performance of different propensity-score methods for estimating relative risks. Journal of clinical epidemiology 2008;61:537–545.
17. Blanco J, Muriel-Bombin A, Sagredo V, Taboada F, Gandia F, Tamayo L, et al. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. Critical Care 2008;12:R158.
18. de Montmollin E, Annane D. Year in review 2010: Critical Care-Multiple organ dysfunction and sepsis. Critical Care 2011;15:236.
19. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharmaceutical Statistics 2011;10:150–161.
20. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biometrical journal. Biometrische Zeitschrift 2009;51:171–184.

21. Bouadma L, Luyt C, 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 multicentre randomised controlled trial. The Lancet 2010;375:463–474.
22.Hohn A, Schroeder S, Gehrt A, Bernhardt K, Bein B, Wegscheider K, et al. Procalcitonin-guided algorithm to reduce length of antibiotic therapy in patients with severe sepsis and septic shock. BMC Infect Dis 2013;13:158.
23. Hohn A, Heising B, Hertel S, Baumgarten G, Hochreiter M, Schroeder S. Antibiotic consumption after implementation of a procalcitonin-guided antimicrobial stewardship programme in surgical patients admitted to an intensive care unit: a retrospective before-and-after analysis. Infection 2015;43:405–412.
24. Kumar K, Mohindra S, Raj M, Choudhuri G. Procalcitonin as a marker of sepsis in alcoholic hepatitis. Hepatology international 2014;8:436–442.
25. Frakking FNJ, Rottier WC, Dorigo-Zetsma JW, Jarne M. van Hattem, Babette C. van Hees, Jan A. J. W. Kluytmans, et al. Appropriateness of Empirical Treatment and Outcome in Bacteremia Caused by Extended-Spectrum-β-Lactamase-Producing Bacteria; 2013. http://aac.asm.org/content/57/7/3092 (accessed 21. August 2015).
26. Wilhelm J, Hettwer S, Hammer D, Schürmann M, Christoph A, Amoury M, et al. Outcome prediction using clinical scores and biomarkers in patients with presumed severe infection in the emergency department. Medizinische Klinik, Intensivmedizin und Notfallmedizin 2012;107:558–563.
27. Jung B, Molinari N, Nasri M, Hajjej Z, Chanques G, Jean-Pierre H, et al. Procalcitonin biomarker kinetics fails to predict treatment response in perioperative abdominal infection with septic shock. Critical care (London, England) 2013;17:R255.
28. Albrich WC, Harbarth S. Pros and cons of using biomarkers versus clinical decisions in start and stop decisions for antibiotics in the critical care setting. Intensive care medicine 2015.
29. Timsit J, Soubirou J, Voiriot G, Chemam S, Neuville M, Mourvillier B, et al. Treatment of bloodstream infections in ICUs. BMC infectious diseases 2014;14:489.

