Systematischer Review und Meta-Analyse zur Überlegenheit einer Procalcitonin-gesteuerten Therapie bei Patienten mit schwerer Sepsis und septischem Schock

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1 Abkürzungsverzeichnis

95%CI	95% confidence interval
df	degrees of freedom
h	hours
HR	Hazard Ratio
I^2	percentage of variation across studies that is due to heterogeneity rather than chance
ICU	intensive care unit
ICU-LOS	length of stay in the intensive care unit
IQR	interquartile range
MeSH	medical subject headings
PCT	procalcitonin
PRISMA	preferred reporting items for systematic reviews and meta-analyses
Q	heterogeneity statistic
RCT	randomized controlled clinical trial
RR	relative risk
SD	standard deviation
SE	standard error
SIRS	systemic inflammatory response syndrome
tau	square-root of between-study variance (moment estimator of DerSimonian-Laird)
W	weight of individual studies (in fixed and random effects model)
WMD	weighted mean difference

2 Zusammenfassung

2.1 Einleitung

Procalcitonin ist ein Prohormon des Calcitonins und findet als Sepsismarker bereits zunehmend Anwendung im klinischen Alltag. Im Gegensatz zu anderen Infektionsparametern steigt das Serum-Proclacitonin vor allem bei bakteriellen Infektionen deutlich an, wohingegen bei Pilz- oder Virusinfektionen nur ein geringer Anstieg zu verzeichnen ist. Eine weitere Besonderheit ist, dass der Anstieg des Procalcitonins sehr rasch erfolgt und eine adäquate Therapie wiederum einen schnellen Abfall der Procalcitoninwerte zur Folge hat. Daher wurden schon verschiedene Ansätze von Procalcitonin-gesteuerten Therapien in klinischen Studien untersucht, wobei die Procalcitonin-gesteuerte Therapie in unterschiedlichsten Settings (hausärztliche Grundversorgung, Notaufnahme, Intensivstation) erforscht wurde. Es fanden sich Hinweise darauf, dass die Procalcitonin-gesteuerte Therapie die Antibiotikaexposition verringern kann, ohne dass dies eine Erhöhung der Mortalitätsrate bedingt. Allerdings gibt es keine Angaben über Effizienz und Sicherheit dieser Vorgehensweise in der am stärksten gefährdeten Patientenpopulation: Kritisch kranke Patienten mit schwerer Sepsis und septischem Schock.

2.2 Methode

Der systematische Review inklusive der Meta-Analyse wurde gemäß den aktuellen Richtlinien und Empfehlungen des „PRISMA statement“ durchgeführt. Um möglichst alle geeigneten Studien zu finden, welche in die Metaanalyse eingeschlossen werden können, wurde eine umfangreiche systematische Suche in mehreren Datenbanken durchgeführt. Dabei durchsuchten zwei Reviewer (Anna Prkno und Christina Wacker) unabhängig voneinander folgende Datenbanken: PubMed, Embase, ISI Web of Knowledge, BioMed Central, ScienceDirect, Cochrane Central Register of Controlled Trials, sowie die Websites http://www.ClinicalTrials.gov und http://www.ISRCTN.org. Bei der Suche kamen sowohl folgende Stichworte als auch MeSH-Termini zum Einsatz: „Procalcitonin” oder „PCT” in Kombination mit „Sepsis” oder „SIRS” oder „systemic inflammatory response syndrome” oder „bacterial infection”. Die Einschlusskriterien wurden vor Studienbeginn festgelegt und konstant beibehalten. Geeignete Studien zum Einschluss in die Meta-Analyse waren randomisierte, kontrollierte, klinische Studien oder Kohortenstudien, welche die Procalcitonin-gesteuerte Therapie mit einer Standardtherapie in der Population von Patienten mit

schwerer Sepsis oder septischem Schock vergleichen. Zudem musste in den Studien mindestens einer der folgenden Endpunkte berichtet werden: Krankenhausmortalität, 28-Tage-Mortalität, Dauer der antimikrobiellen Therapie, Länge des Aufenthaltes in der Intensivstation oder Länge des Krankenhausaufenthaltes. Das Risiko von Bias wurde mittels des „Cochrane Collaboration tool for assessing risk of bias“ ermittelt. Bei Differenzen der beiden Reviewer bezüglich des Einschlusses von Studien oder der Beurteilung von Bias wurde eine gemeinsame Lösung gefunden. Wurden zusätzliche Informationen oder Daten benötigt, kontaktierten wir die Autoren der entsprechenden Studien per E-Mail. Die statistischen Berechnungen wurden mit der frei erhältlichen Software „R“ und dem Paket „meta“ realisiert. Die Ergebnisse wurden graphisch als Forest plots dargestellt. Zudem wurden Bias und Heterogenität statistisch untersucht.

2.3 Ergebnisse

Letztendlich konnten wir sieben Studien, welche insgesamt eine Anzahl von 1,075 Patienten mit schwerer Sepsis oder septischen Schock umfassen, in die Meta-Analyse einschliessen. Sowohl die Krankenhausmortalität (RR: 0.91, 95%CI: 0.61; 1.36) als auch die 28-Tage-Mortalität (RR: 1.02, 95%CI: 0.85; 1.23) waren nicht unterschiedlich in der Procalcitonin-gesteuerten Therapiegruppe verglichen mit der Standardtherapiegruppe. Die Dauer der antimikrobiellen Therapie war zugunsten der Procalcitonin-gesteuerten Therapie signifikant reduziert (HR: 1.27, 95%CI: 1.01; 1.53). Dagegen ergab sich für die Endpunkte Aufenthaltslänge in der Intensivstation und Krankenhausaufenthaltslänge kein signifikanter Unterschied zwischen den beiden Therapiegruppen.

2.4 Schlussfolgerungen

Die Procalcitonin-gesteuerte Therapie ist eine hilfreiche Vorgehensweise um sowohl die Antibiotikatherapie als auch chirurgische Interventionen zu steuern. Sie scheint nach aktueller Studienlage jedoch keinen positiven Effekt auf die Mortalität zu haben. Der bedeutendste Vorteil einer Procalcitonin-gesteuerten Therapie, verglichen mit der Standardbehandlung, liegt in der verkürzten Dauer der antibiotischen Therapie.
Um den Effekt der Procalcitonin-gesteuerten Therapie auf Mortalität, Länge des Aufenthaltes in der Intensivstation und Länge des Krankenhausaufenthaltes bei Patienten mit schwerer Sepsis und septischem Schock zu klären, ist die Durchführung weiterer klinischer Studien nötig.

3 Einleitung

Die Definitionen von Sepsis, schwerer Sepsis und septischem Schock wurden erstmals im Jahr 1992 einheitlich von der American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Conference (Bone et al. 1992) festgelegt und fanden auch Einzug in die Richtlinien der Deutschen Sepsis-Gesellschaft e.V. und der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin (Reinhart et al. 2010).

Dabei wurden folgende Kriterien zur Definition der Sepsis festgesetzt:

I. Die Infektion muss entweder über einen mikrobiologischen Nachweis oder durch klinische Kriterien nachgewiesen werden. II. Für den Nachweis eines SIRS müssen mindestens zwei der folgenden Kriterien zutreffen: Fieber (≥38 °C) oder Hypothermie (≤36 °C); Tachykardie (Herzfrequenz ≥90/min); Tachypnoe (Atemfrequenz ≥20/min); Hyperventilation (PaCO2 ≤4.3 kPa/ ≤33 mmHg); Leukozytose (≥12000/mm³) oder Leukopenie (≤4000/mm³) oder ≥10% unreife Neutrophile im Differentialblutbild.

Um eine schwere Sepsis diagnostizieren zu können, muss zusätzlich zu den Sepsiskriterien I und II eine akute Organdysfunktion bestehen. Dies ist der Fall, wenn mindestens eines der folgenden Merkmale zutrifft: Akute Enzephalopathie (eingeschränkte Vigilanz, Desorientiertheit, Unruhe, Delirium); relative oder absolute Thrombozytopenie (Abfall der Thrombozyten um mehr als 30% innerhalb von 24 Stunden oder Thrombozytenzahl ≤100.000/mm³, eine Thrombozytopenie durch akute Blutung oder immunologische Ursachen muss dabei ausgeschlossen sein); arterielle Hypoxämie (PaO2 ≤10 kPa/ ≤75 mmHg) unter Raumluft oder ein PaO2/FiO2-Verhältnis von ≤33 kPa/ ≤250 mmHg unter Sauerstoffapplikation (eine manifeste Herz- oder Lungenerkrankung muss als Ursache der Hypoxämie ausgeschlossen sein); renale Dysfunktion (eine Diurese von ≤0.5 ml/kg/h für wenigstens zwei Stunden trotz ausreichender Volumensubstitution und/oder ein Anstieg des Serumkreatinins um mehr als das zweifache oberhalb des lokal üblichen Referenzbereiches); metabolische Azidose (Base Excess ≤-5 mmol/l oder eine Laktatkonzentration über dem anderthalbfachen oberhalb des lokal üblichen Referenzbereiches).

Bei einem septischen Schock müssen außer den Sepsiskriterien I und II noch für wenigstens eine Stunde ein systolischer arterieller Blutdruck unter 90 mmHg bzw. ein mittlerer arterieller Blutdruck unter 65 mmHg oder ein notwendiger Vasopressoreinsatz, um den systolischen arteriellen Blutdruck über 90 mmHg bzw.

den arteriellen Mitteldruck gleich 65mmHg zu halten, zu verzeichnen sein. Die Hypotonie bei einem septischen Schock besteht dabei trotz adäquater Volumengabe und ist nicht durch andere Ursachen zu erklären.

Schwere Sepsis und septischer Schock sind Krankheiten, welche häufig im Krankenhausalltag vorkommen und hohe Mortalitätsraten in Intensivstationen bedingen (Engel et al. 2007, Brunbuisson et al. 1995). Laut aktuellen Daten des Statistischen Bundesamtes erkrankten im Jahr 2011 in deutschen Krankenhäusern 88,000 Menschen an schwerer Sepsis oder septischem Schock. Die entsprechenden Krankenhausmortalitätsraten betrugen für schwere Sepsis 43% und für septischen Schock 60% (Heublein et al. 2013). Um diese hohen Mortalitätsraten zu senken, ist eine frühzeitige und adäquate Antibiotikatherapie zwingend notwendig. Zur Steuerung einer derartigen Therapie scheinen Plasmaspiegel von Procalcitonin die vielversprechendsten Parameter zu sein (Carrol et al. 2002). PCT ist ein aus 116 Aminosäuren bestehendes Polypeptid und Prohormon des Calcitonins. Es wird bei bakteriellen Entzündungen vermehrt ausgeschüttet und kann bei der Differenzierung zwischen Sepsis und systemischem inflammatorischen Response-Syndrom helfen (Wacker et al. 2013). Im letzten Jahrzehnt erreichte kein anderer Sepsis-Biomarker außer Proclacitonin eine solch breite Anwendung in den verschiedenen medizinischen Versorgungseinrichtungen in Deutschland und den benachbarten europäischen Staaten. Hohe Procalcitonin-Serumspiegel treten üblicherweise bei bakteriellen Infektionen auf, wohingegen bei Virusinfektionen in der Regel niedrigere PCT-Spiegel und bei Patienten ohne Infektion PCT-Spiegel unter 0.1 ng/mL gemessen werden (Assicot et al. 1993). Zudem weisen Procalcitonin-Spiegel im Serum eine positive Korrelation mit der Schwere der Infektion auf. Auch zur Überprüfung einer eingeleiteten Therapie scheint die Messung der Procalcitonin-Serumspiegel geeignet zu sein, da eine adäquate Antibiotikatherapie zu sinkenden PCT-Spiegeln führt (Assicot et al. 1993).
Aktuelle Reviews zu PCT-basierten Algorithmen konzentrierten sich auf Patienten mit Infektionen im Allgemeinen (Schuetz et al. 2011, Tang et al. 2009), Patienten mit Infektionen des Atemweges (Schuetz et al. 2012, Zhang et al. 2012), oder auf Patienten, die in Intensivstationen behandelt wurden (Heyland et al. 2011, Kopterides et al. 2010, Matthaiou et al. 2012, Agarwal und Schwartz 2011). Dabei wurden heterogene Patientengruppen zusammenfassend untersucht. Oft wurden dabei in den statistischen Berechnungen die unterschiedlichen Einrichtungen und verschiedenen Be-

handlungsalgorithmen nicht differenziert analysiert, sondern in einer gemeinsamen Meta-Analyse ohne Untergruppenanalysen vereint. Zumeist wurden kritisch kranke Patienten mit unterschiedlichen Krankheitsschweregraden, das heißt von vermuteter Infektion, über Pneumonie, bis hin zu Sepsis, in einem Review eingeschlossen und zusammenfassend analysiert (Heyland et al. 2011, Kopterides et al. 2010, Matthaiou et al. 2012, Agarwal und Schwartz 2011). Andere Reviews enthielten extrem heterogene Patientengruppen aus den unterschiedlichsten Umfeldern und Einrichtungen (wie Allgemeinarztpraxis, Notaufnahme, Intensivstation und Normalstation). Dabei reichten die Krankheitsbilder der eingeschlossenen Patienten von unkomplizierten Atemwegsinfektionen bis hin zur Sepsis (Schuetz et al. 2011, Tang et al. 2009). In zwei Reviews wurden nur Patienten mit Atemwegsinfektionen eingeschlossen (Schuetz et al. 2012, Zhang et al. 2012).

Es gibt jedoch aktuell keinen Review, der sich exklusiv mit der Population von in der Intensivstation behandelten Patienten mit schwerer Sepsis und septischen Schock beschäftigt. Nachfolgend werden die beiden Begriffe schwere Sepsis und septischer Schock unter dem Terminus „schwere Sepsis“ zusammengefasst.

Unsere Meta-Analyse thematisiert zudem zwei grundlegende und aktuelle Forschungsfragen: 1. Verringert ein PCT-gesteuerter Therapiealgorithmus, der zur Festlegung der Dauer der Antibiotikatherapie verwendet wird, den Antibiotikaverbrauch, verglichen mit einer Behandlungsstrategie, die nicht auf PCT basiert? 2. Verbessert eine solche PCT-gesteuerte Therapiestrategie gesundheitsspezifische Endpunkte im Vergleich zu einer Strategie, die nicht auf PCT basiert? (Noorani et al. 2013).

Da es bisher keine Meta-Analyse gibt, die den Effekt der PCT-gesteuerten Therapie bei schwerer Sepsis thematisiert, untersuchten wir den Effekt der PCT-gesteuerten Therapie im Vergleich zur Standardbehandlung bei Patienten mit schwerer Sepsis.

Dieser systematische Review mit Meta-Analyse wurde nach einheitlichen internationalen Standards für systematische Übersichtsarbeiten und Meta-Analysen durchgeführt (Liberati et al. 2009, Moher et al. 2009, Kunz et al. 2009).

4 Ziele der Arbeit

Mit diesem systematischen Review untersuchten wir den Effekt der Procalcitonin-gesteuerten Therapie bei Patienten mit schwerer Sepsis und septischem Schock. Durch eine umfassende systematische Suche in unterschiedlichen Datenbanken sollten alle geeigneten randomisierten kontrollierten klinischen Studien oder prospektiven Kohortenstudien, welche die PCT-gesteuerte Therapie im Vergleich zu einer Standardtherapie evaluieren, erfasst werden.

Folgende Ergebnisse wurden dabei mittels einer Meta-Analyse für alle Studien übergreifend als Gesamtschätzer kalkuliert: Die Krankenhausmortalität, die 28-Tage-Mortalität, die Dauer der antimikrobiellen Therapie, die Länge des Aufenthaltes in der Intensivstation und die Länge des gesamten Krankenhausaufenthaltes.

5 Publizierte Originalarbeit

Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock – a systematic review and meta-analysis

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Abstract

Introduction: Procalcitonin (PCT) algorithms for antibiotic treatment decisions have been studied in adult patients from primary care, emergency department, and intensive care unit (ICU) settings, suggesting that procalcitonin-guided therapy may reduce antibiotic exposure without increasing the mortality rate. However, information on the efficacy and safety of this approach in the most vulnerable population of critically ill patients with severe sepsis and septic shock is missing.

Method: Two reviewers independently performed a systematic search in PubMed, Embase, ISI Web of Knowledge, BioMed Central, ScienceDirect, Cochrane Central Register of Controlled Trials, http://www.ClinicalTrials.gov and http://www.ISRCTN.org.
Eligible studies had to be randomized controlled clinical trials or cohort studies which compare procalcitonin-guided therapy with standard care in severe sepsis patients and report at least one of the following outcomes: hospital mortality, 28-day mortality, duration of antimicrobial therapy, length of stay in the intensive care unit or length of hospital stay. Disagreements about inclusion of studies and judgment of bias were solved by consensus.

Results: Finally seven studies comprising a total of 1,075 patients with severe sepsis or septic shock were included in the meta-analysis.
Both hospital mortality (RR [relative risk]: 0.91, 95%CI [confidence interval]: 0.61; 1.36) and 28-day mortality (RR: 1.02, 95%CI: 0.85; 1.23) were not different between procalcitonin-guided therapy and standard treatment groups.
Duration of antimicrobial therapy was significantly reduced in favor of procalcitonin-guided therapy (HR [hazard ratio]: 1.27, 95%CI: 1.01; 1.53). Combined estimates of the length of stay in the ICU and in hospital did not differ between groups.

Conclusion: Procalcitonin-guided therapy is a helpful approach to guide antibiotic therapy and surgical interventions without a beneficial effect on mortality. The major benefit of PCT-guided therapy consists of a shorter duration of antibiotic treatment compared to standard care.
Trials are needed to investigate the effect of PCT-guided therapy on mortality, length of ICU and in-hospital stay in severe sepsis patients.

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Introduction

Severe sepsis and septic shock are common diseases in ICUs, with high mortality rates [1,2]. According to more recent data from the Statistical Federal Office in Germany, there were 88,000 patients with severe sepsis or septic shock in 2011 in German hospitals, with associated hospital mortality rates of 43% for severe sepsis and 60% for septic shock, respectively [3]. To overcome this high mortality, an adequate antimicrobial therapy starting at an early stage is mandatory. To guide such a therapy, the most promising parameters appear to be plasma levels of procalcitonin (PCT) [4]. Besides PCT, no other sepsis biomarker has achieved universal use throughout different healthcare settings in Germany and neighboring Europe in the last decade. High PCT concentrations are typically found in bacterial infection, in contrast to lower levels in viral infection and levels below 0.1 ng/mL in patients without infection [5]. Furthermore, serum PCT concentrations are positively correlated with the severity of infection. Thus, adequate antibiotic treatment leads to decreasing PCT levels [5].

Recent reviews focused on PCT-based algorithms in patients with infections in general [6,7], respiratory tract infections [8,9], or patients treated in the ICU [10-13]. These reviews focused on different patients in different settings with different treatment algorithms. Most of them included critically ill patients with different disease severity ranging from suspected infection to pneumonia or sepsis [10-13]. The others comprised even more patients of different settings: patients with various diseases such as sepsis, bronchitis, and respiratory tract infection, in various settings (primary care, emergency department, ICU, and inpatient wards) were combined in one review [6,7]. Two reviews focused only on patients with respiratory tract infection [8,9]. However there is no review exclusively including the population of ICU patients with severe sepsis or septic shock: both entities are hereinafter collectively referred to severe sepsis. Our meta-analysis addresses two essential research questions: 1) does a PCT-guided strategy to determine the duration of antimicrobial therapy reduce antibiotic use compared with a strategy not based on PCT? 2) Does such a PCT-guided strategy improve health outcomes compared with a strategy not based on PCT? [14]. As evidence for the effect of PCT-guided therapy in severe sepsis is missing, we investigated the effect of PCT-guided therapy compared to standard care.

Materials and methods

The systematic review was performed following current guidelines and is reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [15,16].

Literature search and data extraction

Two reviewers (AP, CW) independently performed a systematic search in the databases Medline via PubMed, Excerpta Medica database (Embase), ISI Web of Knowledge including the databases Web of Science, Journal Citation Reports and Science Citation Index (SCI). Furthermore, searches in BioMed Central, ScienceDirect and the Cochrane Central Register of Controlled Trials were continued. To identify unpublished or ongoing studies and to obtain the study protocols we searched two further websites (http://www.ClinicalTrials.gov and http://www.ISRCTN.org). The following keywords or medical subject headings (MeSH) were used: "procalcitonin" or "PCT" combined with "sepsis" or "SIRS" or "systemic inflammatory response syndrome" or "bacterial infection". All databases had been searched up to 14 June 2013.

All primary intervention studies were included that compared PCT-guided therapy with standard care according to current guidelines that met the following inclusion criteria: 1) studies that assessed the efficacy of a treatment algorithm based on procalcitonin; 2) studies that had a well-defined standard for the target condition (severe sepsis), which included the use of definitions according to the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Conference [17] and the German Sepsis Society [18]; and 3) studies that provided sufficient information to calculate the relative risk (RR) together with 95% CI or the hazard ratio (HR) together with 95% CI respectively.

Eligible studies had to be randomized controlled clinical trials (RCTs) or prospective cohort studies. Studies dealing with neonates were excluded, because of considerable differences in diagnosis, course and therapy of sepsis compared to adults. The published language was not restricted. Disagreements of judgment and inclusion of studies were solved by consensus.

Data were extracted using a structured data collection sheet including the following items: authors and year of study, design, setting, diagnosis, procalcitonin test, randomization, number and characteristics of participants, interventions, outcomes, duration, availability of study protocol, and country. Primary outcomes of this meta-analysis were 28-day mortality and hospital mortality. Secondary outcomes were duration of antimicrobial therapy, length of stay in the ICU and length of stay in the hospital. If additional information was needed, the authors of the studies were contacted by Email. Eligible studies with insufficient data for calculation or missing replies from the authors were excluded.

Risk of bias

For assessing risk of bias, we applied the Cochrane Collaboration tool for assessing risk of bias by judging

seven items representing sources of risk of bias [19]. The following items were evaluated: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The classification of the assessment was: low risk of bias, high risk of bias, or uncertain risk of bias. The assessment was done independently by two reviewers (AP, CW). Disagreements were resolved by consensus.

Statistical analysis

The statistical calculations were done with the freely available software R [20] using the R package meta [21]. Results were presented graphically using forest plots. As a meta-analysis is an observational study, the statistical analysis covered the investigation of bias and heterogeneity. A formal analysis of publication bias was based on Egger's test [22]. For dichotomous outcomes (for example, hospital mortality) RRs were calculated for every single study by means of 2×2 contingency tables. The calculation of combined estimates was performed using the Mantel-Haenszel method. For continuous outcomes (for example, length of antibiotic treatment) HRs based on the exponential distribution were calculated together with their variances [23]. This approach was chosen because the necessary information for the calculation of standardized mean differences was not available. Thus, the length of stay and antibiotic therapy were modeled using the exponential distribution. This approach was chosen rather than the standardized differences because it can be used if only the mean duration is reported in the respective study. Summary estimates were obtained using the inverse variance method.

Heterogeneity was assessed using the Cochran Q-test and the I^2 measure [24]. The heterogeneity variance tau^2 was calculated using the moment estimator of DerSimonian-Laird [25]. For all outcomes the fixed effect model as well as the random effects model was applied. Outliers and influential studies were investigated using case-deletion techniques analysis in order to identify studies with great impact on the overall results.

Results

Literature search

We identified 9,071 records by searching the databases PubMed, Embase, ISI Web of Knowledge, BioMed Central, ScienceDirect and the Cochrane Central Register of Controlled Trials. After removing 5,602 duplicates, the titles and abstracts of the remaining 3,469 records were screened. Therefore 3,360 records could be excluded. By assessing the full-text articles of the remaining 109 records, 7 studies [26-32] fulfilled the inclusion criteria and were thus eligible for our meta-analysis (Figure 1). Furthermore, we identified 7 ongoing studies registered at http://www.ClinicalTrials.gov that might deliver important results for future meta-analyses.

We excluded two studies due to insufficient information and missing replies [33,34].

The study from Bagnenko *et al*. [34] was excluded because of missing data and deficits in quality: the inclusion of patients was not clearly described, the exact number of patients treated in each group was not given, for hospital mortality only percentages without absolute numbers were reported, and finally the treatment regimen for the control group was not specified. The authors did not respond to clarify these questions. Another study had to be excluded, because information of a subgroup of 25 patients with sepsis was missing [33]. Again, the authors did not respond to clarify these questions. In particular we tried to obtain the data for all septic patients included in two trials [27,29]. In one case, further information was provided [29], in another the authors did not pass on any further information, so we could only include the patients with septic shock from this study [27].

Publication bias

As only seven studies were included in the meta-analysis, assessment of publication bias using a funnel plot, followed by a linear regression test of funnel plot asymmetry (Egger's test) [22], was not possible.

Study characteristics

All eligible studies were published in the English language. Because no cohort study met the inclusion criteria, the meta-analysis only consists of RCTs. All studies were conducted in Europe between 2003 [32] and 2009 [26]. Four studies were conducted in mixed surgical/medical ICUs [26,27,29,30], and three studies were conducted in surgical ICUs without medical patients [28,31,32]. The number of included patients from each study ranged from 27 [31] to 459 [29] with a total number of 1,075 patients. In two studies the subgroup of septic patients was included [27,29].

For PCT measurements three different PCT tests were used: Brahms PCT Kryptor [26,27,29,30], Brahms PCT LIA [28,31] and Brahms PCT-Q [32]. The main focus in the PCT-guided therapy was on de-escalation in three studies [28,30,31], on de-escalation as well as escalation in two studies [26,27], and mainly on escalation in two studies [29,32]. A summary of study characteristics and treatment algorithms of the eligible studies is shown in Tables 1 and 2.

Risk of bias

The overall risk of bias was moderate according to the Cochrane Collaboration tool for assessing risk of bias of all included studies. Two studies achieved low overall

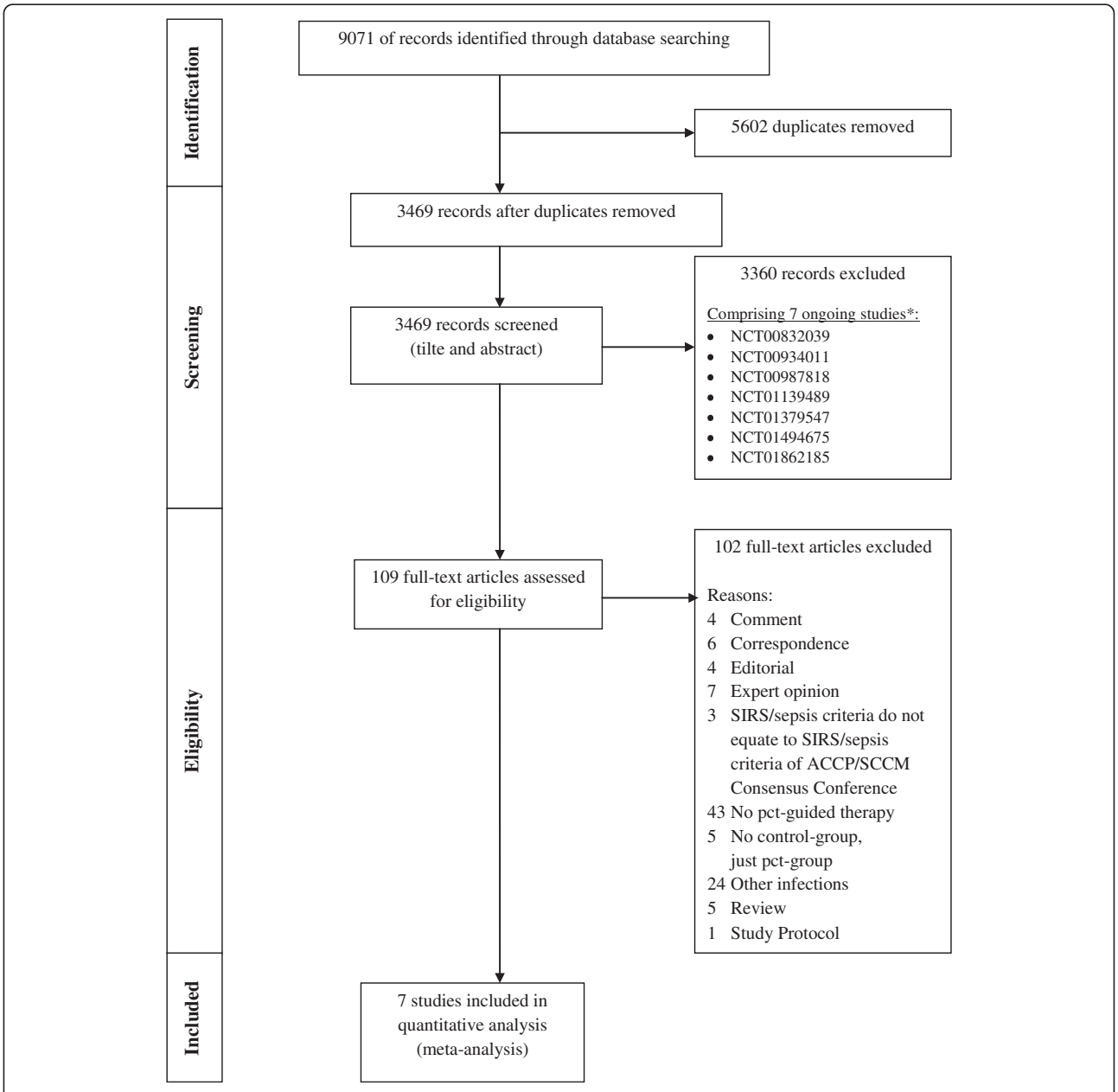

Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram. Study identification and selection process. SIRS, systemic inflammatory response syndrome; ACCP, American College of Chest Physicians; SCCM, Society of Critical Care Medicine; PCT, procalcitonin. *, available online at http://www.ClinicalTrials.gov.

risk of bias [27,32], whereas the remaining studies had moderate overall risk of bias [26,28-31]. Two items had low risk of bias in all studies: "incomplete outcome data" and "other bias". Oftentimes the risk of bias remained unclear due to insufficient information given in each study.

Figure 2 summarizes the risk of bias of included studies. Detailed information about risk of bias, support for judgment of bias and graphically summarized information on risk of bias are given in the online supplement (Additional files 1 and 2).

Combined estimates

Primary outcomes

Hospital mortality in severe sepsis patients was reported in four studies [26,28,30,31]. The combined estimate of the RR based on the fixed-effect model for hospital mortality is 0.91 (95% CI: 0.61; 1.36) (Figure 3), with no differences between the PCT-guided therapy and standard-care group. The test of heterogeneity showed no significant heterogeneity between these studies ($Q = 0.66$; df = 3; $I^2 = 0\%$; $tau^2 = 0$; $P = 0.8835$).

Table 1 Characteristics of included studies

Study	Annane *et al.* 2013 [26]	Bouadma *et al.* 2010 [27]	Hochreiter *et al.* 2009 [28]	Jensen *et al.* 2011 [29]	Nobre *et al.* 2008 [30]	Schroeder *et al.* 2009 [31]	Svoboda *et al.* 2007 [32]
Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Setting	Surgical and medical ICU	Surgical and medical ICU	Surgical ICU	Surgical and medical ICU	Surgical and medical ICU	Surgical ICU	Surgical ICU
Condition	Severe sepsis and septic shock	Septic shock	Severe sepsis	Severe sepsis and septic shock	Severe sepsis and septic shock	Severe sepsis	Severe sepsis
Total number of included patients	61	267	110	459	79	27	72
Number of patients							
PCT group/control group	31/30	138/129 (septic shock)	57/53	247/212	39/40	14/13	38/34
		55/53 (positive blood culture)					
Hospital mortality							
Relative risk (95% CI)	0.68 (0.30; 1.55)	NA	1.00 (0.53; 1.86)	NA	1.03 (0.46; 2.31)	0.93 (0.23; 3.81)	NA
Events PCT group/events control group	7/10		15/14		9/9	3/3	
28-day mortality							
Relative risk (95% CI)	NA	1.15 (0.81; 1.63)	NA	1.02 (0.80; 1.30)	1.03 (0.43; 2.46)	NA	0.69 (0.35; 1.36)
Events PCT group/events control group		48/39 (septic shock)		90/76	8/8		10/13
Duration of antibiotic treatment, days							
PCT group/control group	5/5 (median)	9.8/12.8 (mean) (only positive blood culture)	5.9/7.9 (mean)	NA	6.0/9.5 (median)	6.6/8.3 (mean)	NA
Length of ICU stay, days							
PCT group/control group	22/23 (median)	NA	15.5/17.7 (mean)	6.0/5.0 (median)	4.0/7.0 (median)	16.4/16.7 (mean)	16.1/19.4 (mean)
Length of hospital stay, days							
PCT group/control group	27/33 (median)	NA	NA	23.0/22.0 (median)	17.0/23.5 (median)	NA	NA
SOFA score							
PCT group/control group	9.5/10 (median)	NA	6.7/7.0 (mean)	NA	6.4/6.6 (mean)	7.3/8.3 (mean)	7.9/9.3 (mean)
	8.5 to 11/8 to 11 (IQR)		3.68/3.62 (SD)		3.3/3.0 (SD)	3.5/4.2 (SD)	2.8/3.3 (SD)
Medical patients, %*	97%	89%	0%	59%	NA	0%	0%
Subgroup of study	No	Yes	No	Yes	No	No	No
Duration of study, months	36	12	15	29	15	7	29
Study protocol available	Yes	Yes	Yes	Yes	Yes	No	No
Country	France	France	Germany	Denmark	Switzerland	Germany	Czech Republic

PCT, procalcitonin; RCT, randomized controlled clinical trial; SOFA, sequential organ failure assessment; NA, data were not available; *data were stated in study or calculated from information given in study.

Table 2 PCT assays and algorithms used for procalcitonin (PCT)-guided treatment in the included studies

Study	PCT test	Regimen in the PCT group	Regimen in the control group
Annane *et al.* 2013 [26]	Brahms PCT Kryptor	**Medical patients:** PCT <0.25 ng/mL: antibiotics not initiated or stopped PCT ≥ 0.25 and < 0.5 ng/mL: Antibiotics strongly discouraged PCT ≥0.5 and <5 ng/mL: antibiotics recommended PCT ≥5 ng/mL: antibiotics strongly recommended **Surgical patients:** PCT <4 ng/mL: antibiotics not initiated or stopped PCT ≥4 and <9 ng/mL: antibiotics recommended PCT ≥9 ng/mL: antibiotics strongly recommended	Antibiotic treatment at the discretion of the patient's physician
Bouadma *et al.* 2010 [27]	Brahms PCT Kryptor	**Guidelines for starting of antibiotics:** PCT <0.25 ng/mL: antibiotics strongly discouraged PCT ≥0.25 and <0.5 ng/mL: antibiotics discouraged PCT ≥0.5 and <1 ng/mL: antibiotics encouraged PCT ≥1 ng/mL: antibiotics strongly encouraged **Guidelines for continuing or stopping of antibiotics:** PCT <0.25 ng/mL: stopping of antibiotics strongly encouraged. Decrease by ≥80% from peak concentration, or concentration ≥0.25 and <0.5 ng/mL: stopping of antibiotics encouraged Decrease by <80% from peak concentration and concentration ≥0.5 ng/mL: continuing of antibiotics encouraged Increase of concentration compared with peak concentration and concentration ≥0.5 ng/mL: changing of antibiotics strongly encouraged	Treatment according to international and local guidelines
Hochreiter *et al.* 2009 [28]	Brahms PCT LIA	PCT < 1 ng/mL: Antibiotics discontinued. PCT >1 ng/mL and dropped to 25 to 35% of the initial value over 3 days: antibiotics discontinued Additionally the infection had to improve clinically	Antibiotic treatment according to standard regimen over 8 days
Jensen *et al.* 2011 [29]	Brahms PCT Kryptor	Single baseline measurement of PCT ≥1.00 ng/mL or PCT ≥1.00 ng/mL and not decreased at least 10% from the previous day: 1) increasing the antimicrobial spectrum covered 2) intensifying the diagnostic effort to find uncontrolled sources of infection PCT <1.00 ng/mL for at least 3 days: de-escalation possible	Antibiotic treatment according to current guidelines
Nobre *et al.* 2008 [30]	Brahms PCT Kryptor	Patients with PCT <1 ng/mL re-evaluated at day 3: antibiotics discontinued if PCT <0.1 ng/mL Patients with PCT ≥1 ng/mL re-evaluated at day 5: antibiotics discontinued if PCT dropped >90% from the baseline peak level or if PCT <0,25 ng/mL	Antibiotic treatment based on empirical rules
Schroeder *et al.* 2009 [31]	Brahms PCT LIA	PCT <1 ng/mL and clinical signs of infection improved: antibiotics discontinued PCT dropped to <35% of the initial concentration within 3 days and clinical signs of infection improved: antibiotics discontinued	Antibiotic treatment according to clinical signs and empiric rules
Svoboda *et al.* 2007 [32]	Brahms PCT-Q	PCT >2 ng/mL: change of antibiotics and catheters PCT ≤2 ng/mL: ultrasonography and/or computer tomography followed by repeated surgical treatment if localized infection was confirmed	Treatment according to contemporary treatment protocol of the institute

PCT, procalcitonin.

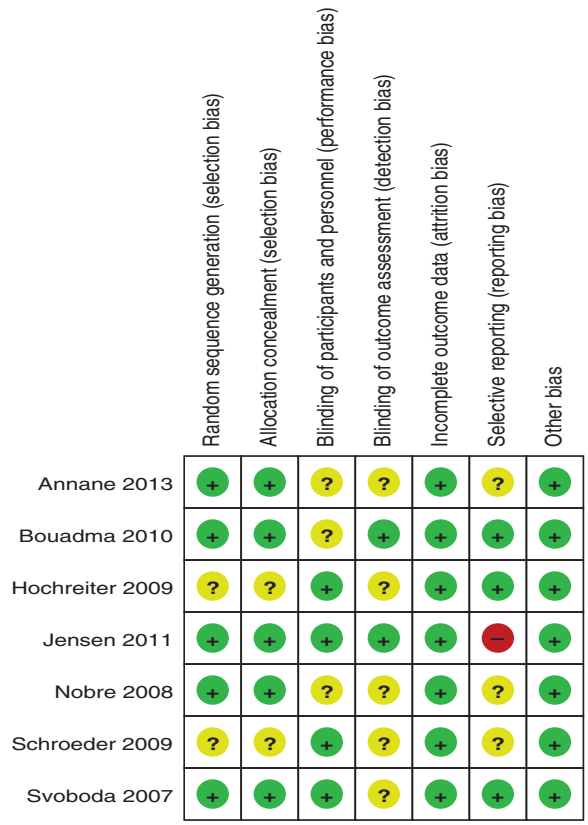

Figure 2 Risk of bias summary. Cochrane Collaboration tool for assessing risk of bias. Review authors' judgments about each risk of bias item for each included study. +, low risk of bias; –, high risk of bias; ?, unclear risk of bias.

The 28-day mortality was covered in four studies [27,29,30,32]. The combined estimate of the RR based on the fixed-effect model for 28-day mortality is 1.02 (95% CI: 0.85; 1.23) (Figure 4), again, with no difference between the PCT-guided therapy and standard care group. The test of heterogeneity showed no significant heterogeneity between these studies ($Q = 1.74$; df = 3; $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.6287$).

The influential analysis using both the fixed-effect model and the random-effects model showed that no study had great impact on the overall results of hospital mortality and 28-day mortality, respectively.

Secondary outcomes

The duration of antimicrobial therapy in severe sepsis patients was documented in five studies [26-28,30,31]. In one study we could only include the subgroup of septic patients with positive blood cultures for assessment of this outcome [27]. The combined estimate for the duration of antimicrobial therapy assessed as the HR and based on the fixed-effect model amounted to 1.27 (95% CI: 1.01; 1.53) (Figure 5). These results indicate a significantly shorter median duration of antimicrobial therapy with PCT-guided therapy compared to standard therapy. No significant heterogeneity could be detected between these studies ($Q = 1.92$; df = 4; $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.7499$).

The length of stay in the ICU (ICU-LOS) was documented in five studies [26,28,30-32]. Additionally, information on ICU-LOS for the subgroup of patients with severe sepsis of the study from Jensen *et al.* [29] was available by correspondence (median ICU-LOS of 6 days in the PCT group versus 5 days in the control group). The combined estimate for ICU-LOS assessed as the HR and based on the fixed-effect model is 0.93 (95% CI: 0.80; 1.06) (Figure 6). No significant heterogeneity was detected between these studies ($Q = 7.98$; df = 5; $I^2 = 37.3\%$; $\tau^2 = 0.0227$; $P = 0.1575$).

The length of hospital stay was reported in two studies [26,30]. In addition we obtained the median hospital stay for the subgroup of patients with severe sepsis of the study from Jensen *et al.* [29] by correspondence with the author (23 days in the PCT group versus 22 days in the control group). The combined estimate assessed by the HR and fixed-effect model amounted 1.00 (95% CI: 0.84; 1.17) (Figure 7). No significant heterogeneity was detected between these studies ($Q = 2.22$; df = 2; $I^2 = 10\%$; $\tau^2 = 0.0069$; $P = 0.3292$).

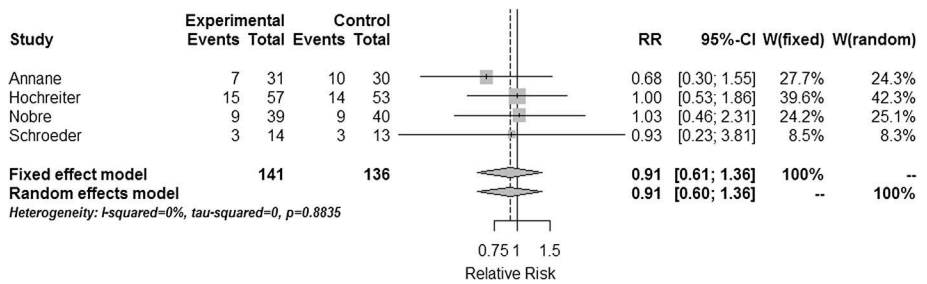

Figure 3 Forest plot - hospital mortality. The forest plot represents the relative risk (RR) together with the 95% CI comparing patients treated in the procalcitonin (PCT) and the control groups (Control). Events, number of deceased patients in group; Experimental, PCT group; Total, number of all patients in group; W, weight of individual studies (in fixed- and random-effects model).

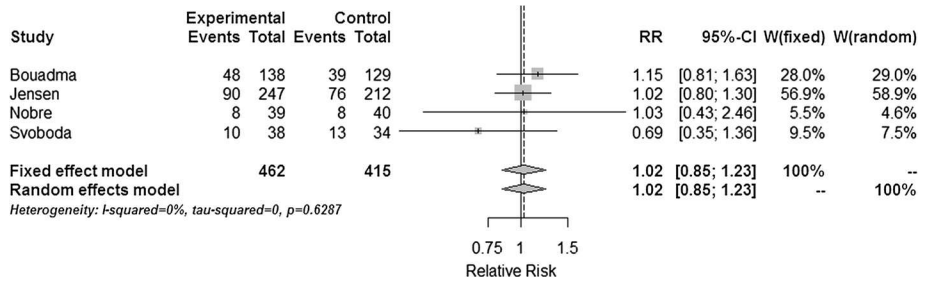

Figure 4 Forest plot - 28-day mortality. The forest plot represents the relative risk (RR) together with the 95% CI comparing patients treated in the procalcitonin (PCT) and the control groups (Control). Events, number of deceased patients in group; Experimental, PCT group; Total, number of all patients in group; W, weight of individual studies (in fixed- and random-effects model).

The influential analysis using the fixed-effect model showed no predominant influence on the combined HR of duration of antimicrobial therapy in any study. As shown in the influential analyses based on the fixed-effect model, the study from Jensen *et al*. had great influence on the combined estimates of ICU-LOS and length of hospital stay, respectively. When omitting this study, the results show a trend towards shorter ICU-LOS (HR: 1.19; 95% CI: 0.93; 1.44) and hospital stay (HR: 1.30; 95% CI: 0.87; 1.74) with PCT-guided therapy.

We did not detect significant heterogeneity among these studies and therefore did not perform a meta-regression analysis. Furthermore, the data basis for a meta-regression is rather small.

Discussion

Our meta-analysis aimed to investigate the impact of a PCT-guided therapy compared to standard treatment administered to severe sepsis patients treated in an ICU. Contrary to previous reviews that analyzed patients in various settings with different disease severities, we focused on patients with severe sepsis, a population in which clinical decision-making to stop antibiotic treatment is challenging. In view of the high mortality rate in severe sepsis, clinicians believe themselves to "be on the safer side" with more prolonged courses of antimicrobial treatment. Current evidence to limit duration of antibiotic treatment to 7 to 10 days is rather low and has been included only as a grade-2C recommendation in the recent guidelines of the Surviving Sepsis Campaign [35], in which the authors state that "decisions to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment and clinical information". Variance of treatment regimens in the control groups of our meta-analysis might therefore reflect the current way of treatment of patients with severe sepsis.

Our findings do not show a significant difference between a PCT-guided therapy and standard care treatment regarding 28-day or hospital mortality, respectively. Furthermore, length of stay in the ICU and in-hospital stay were not different between both groups. However, we found a significant reduction of the length of antibiotic therapy in favor of a PCT-guided therapy strategy. Our calculations, based on the exponential model, indicate a median length of antibiotic treatment of 6 days in the PCT-guided group compared to 8 days in the control group, resulting in a median reduction of approximately 2 days. A reduction of antimicrobial therapy using

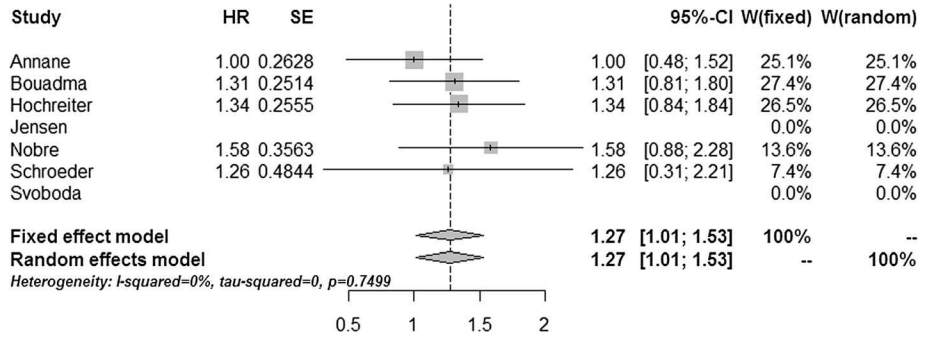

Figure 5 Forest plot - duration of antimicrobial therapy. The forest plot represents the hazard ratios (HRs) together with the 95% CIs comparing patients treated in the procalcitonin (PCT) and the control groups. SE, standard error; W, weight of individual studies (in fixed- and random-effects model).

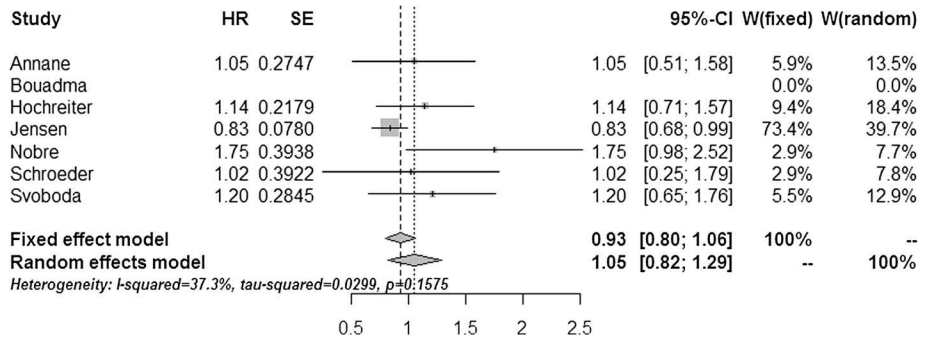

Figure 6 Forest plot - length of stay in the ICU. The forest plot represents the hazard ratios (HRs) together with the 95% CIs comparing patients treated in the procalcitonin (PCT) and the control groups. SE, standard error; W, weight of individual studies (in fixed- and random-effects model).

biomarkers for clinical decision-making may have certain advantages, as antimicrobial resistance becomes more prevalent by using prolonged courses of broad-spectrum antimicrobial agents for treatment of severe sepsis patients [36,37]. Moreover, antibiotic consumption and acquired antimicrobial resistance had been shown to be associated with increased mortality, morbidity, length of hospitalization, and health care costs [38,39].

Currently, no treatment algorithms for guidance of severe sepsis treatment using PCT levels are well established in this high-risk population. To establish a PCT-guided treatment algorithm in severe sepsis patients, it is important to distinguish between escalation and de-escalation of therapeutic interventions. Reliable cut-off values of PCT levels to guide therapeutic decisions need to be defined in future studies, since treatment algorithms varied substantially between the studies included in our systematic review. For instance, Annane *et al*. and Bouadma *et al*. [26,27] encouraged a prolongation of antibiotic treatment if PCT levels were above 0.5 ng/mL, and discouraged antibiotic treatment if levels dropped below 0.5 ng/mL. Furthermore, Annane *et al*. distinguished between medical and surgical patients. In surgical patients a different algorithm was applied with a recommendation to stop antibiotics when PCT levels were below 4 ng/mL. Bouadma *et al*. recommended stopping antibiotics at PCT levels below 0.25 ng/mL. If PCT levels were between 0.5 ng/mL and 0.25 ng/mL, antibiotics were stopped if there was a decrease of at least 80% of the peak concentration of PCT levels. Four studies recommended a PCT level of 1.0 ng/mL as the cutoff [28-31]. Hochreiter *et al*. and Schroeder *et al*. recommended discontinuing antibiotics if PCT was below 1.0 ng/mL. Both recommended to discontinue antibiotics if PCT levels dropped by 35% of the initial level within 3 days. Nobre *et al*. recommended discontinuing antibiotics in patients with PCT levels below 0.1 ng/mL after 3 days. In patients with PCT levels above 1.0 ng/mL antibiotics were discontinued if PCT levels dropped more than 90% from the baseline peak level or if PCT levels were below 0.25 ng/mL after 5 days.

In contrast to all other studies, Jensen *et al*. tested a rigorous escalation strategy [29]. In the case of PCT levels above 1.0 ng/mL an intensified antibiotic treatment strategy was recommended. De-escalation was only possible if

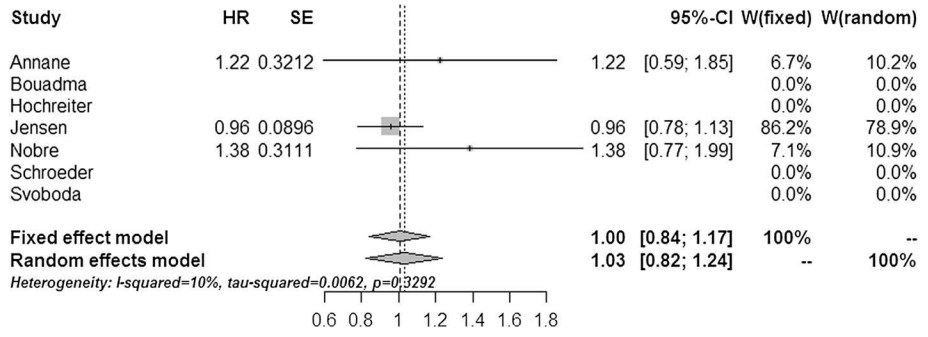

Figure 7 Forest plot - length of stay in the hospital. The forest plot represents the hazard ratios (HRs) together with the 95% CIs comparing patients treated in the procalcitonin (PCT) and the control groups. SE, standard error; W, weight of individual studies (in fixed- and random-effects model).

PCT levels dropped below 1.0 ng/mL for at least 3 days. This treatment algorithm led to a prolonged length of stay in the ICU and substantially higher use of broad-spectrum antimicrobials. A different cut-off level of 2.0 ng/mL was used by Svoboda *et al.* in surgical patients [32].

This meta-analysis has several limitations. First, studies included in our meta-analysis varied substantially in study design and objectives. Two studies provided rules for starting or continuing as well as discontinuing antibiotic treatment [26,27]. Three studies focused on de-escalation of antibiotic therapy [28,30,31], whereas two studies placed the focus on escalation of antibiotic treatment and diagnostic efforts [29,32] and surgical treatment [32]. Second, a limited number of patients is included, third, a combined analysis of medical and surgical patients is problematic, since there are substantial differences in outcomes regarding surgical patients, where surgical source-control measures play a dominant role.

In order to explore knowledge on a PCT-guided treatment in severe sepsis patients in more detail, we await the results of seven ongoing studies registered at http://www.ClinicalTrials.gov that might deliver important results for future systematic reviews.

Conclusion

An approach along a biomarker-guided treatment algorithm using procalcitonin levels may be helpful to guide antimicrobial treatment in severe sepsis patients, treated in ICUs and reduces the duration of antimicrobial therapy without an obvious increase in mortality. However, more research is urgently needed to investigate the safety and effectiveness in subgroups of surgical and medical severe sepsis patients, treated in ICUs. Most importantly, treatment algorithms differ substantially and have to be clarified in future studies.

Key messages

- A PCT-guided treatment reduces the duration of antimicrobial therapy in severe sepsis patients, without increasing 28-day and in-hospital mortality rates
- Recommendations for PCT-guided treatment algorithms for treatment of severe sepsis patients differ substantially among published studies
- Future studies have to show which PCT-guided treatment algorithms could be recommended in severe sepsis patients

Additional files

Additional file 1: Risk of bias table. Cochrane Collaboration tool for assessing risk of bias. Detailed information about risk of bias and support for judgment of bias.

Additional file 2: Risk of bias graph. Cochrane Collaboration tool for assessing risk of bias. Review authors' judgments about each risk of bias item presented as percentages across all included studies.

Abbreviations

Df: Degrees of freedom; HR: Hazard ratio; I^2: Percentage of variation across studies that is due to heterogeneity rather than chance; ICU-LOS: Length of stay in the ICU; PCT: Procalcitonin; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; Q: Heterogeneity statistic; RCT: Randomized controlled clinical trial; RR: Relative risk; SE: Standard error; SIRS: Systemic inflammatory response syndrome; tau: Square-root of between-study variance (moment estimator of DerSimonian-Laird); W: Weight of individual studies (in fixed- and random-effects model); WMD: Weighted mean difference.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AP conceived and designed the study, did the literature search and the acquisition of data, analyzed and interpreted data, drafted and critically revised the manuscript for important intellectual content. CW did the literature search and the acquisition of data, drafted and critically revised the manuscript for important intellectual content. FMB conceived and designed the study, drafted and critically revised the manuscript for important intellectual content, supervised the study and gave administrative, technical or material support. PS conceived and designed the study, statistically analyzed and interpreted the data, drafted and critically revised the manuscript for important intellectual content, supervised the study and gave administrative, technical or material support. All authors read and approved the final version of the manuscript.

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References

1. Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, Gruendling M, Huhle G, Jaschinski U, John S, Mayer K, Oppert M, Olthoff D, Quintel M, Ragaller M, Rossaint R, Stuber F, Weiler N, Welte T, Bogatsch H, Hartog C, Loeffler M, Reinhart K: **Epidemiology of sepsis in Germany: results from a national prospective multicenter study.** *Intensive Care Med* 2007, **33:**606–618.
2. Brunbuisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Regnier B: **Incidence, risk-factors, and outcome of severe sepsis and septic shock in adults - a multicenter prospective-study in intensive-care units.** *JAMA* 1995, **274:**968–974.
3. Heublein S, Hartmann M, Hagel S, Hutagalung R, Brunkhorst FM: **Epidemiology of sepsis in German hospitals derived from administrative databases.** *Infection* 2013, **41:**S71.
4. Carrol ED, Thomson AP, Hart CA: **Procalcitonin as a marker of sepsis.** *Int J Antimicrob Agents* 2002, **20:**1–9.
5. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C: **High serum procalcitonin concentrations in patients with sepsis and infection.** *Lancet* 1993, **341:**515–518.

6. Schuetz P, Chiappa V, Briel M, Greenwald JL: **Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms.** *Arch Intern Med* 2011, **171:**1322–1331.
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. Schuetz P, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, Luyt CE, Chastre J, Tubach F, Kristoffersen KB, Wei L, Burkhardt O, Welte T, Schroeder S, Nobre V, Tamm M, Bhatnagar N, Bucher HC, Mueller B: **Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis.** *Clin Infect Dis* 2012, **55:**651–662.
9. Zhang L, Huang J, Xu T, Lin Y: **Procalcitonin-guided algorithms of antibiotic therapy in community-acquired lower respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials [article in Chinese].** *Zhonghua Jie He He Hu Xi Za Zhi* 2012, **35:**275–282.
10. Heyland DK, Johnson AP, Reynolds SC, Muscedere J: **Procalcitonin for reduced antibiotic exposure in the critical care setting: A systematic review and an economic evaluation.** *Crit Care Med* 2011, **39:**1792–1799.
11. Kopterides P, Siempos II, Tsangaris I, Tsantes A, Armaganidis A: **Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: A systematic review and meta-analysis of randomized controlled trials.** *Crit Care Med* 2010, **38:**2229–2241.
12. Matthaiou DK, Ntani G, Kontogiorgi M, Poulakou G, Armaganidis A, Dimopoulos G: **An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients.** *Intensive Care Med* 2012, **38:**940–949.
13. Agarwal R, Schwartz DN: **Procalcitonin to guide duration of antimicrobial therapy in intensive care units: a systematic review.** *Clin Infect Dis* 2011, **53:**379–387.
14. Noorani HZ, Adams E, Pitrak D, Belinson S, Aronson N: *Future Research Needs on Procalcitonin-Guided Antibiotic Therapy. Future Research Needs Paper No. 29.* http://www.effectivehealthcare.ahrq.gov/ehc/products/497/1377/FRN29_Procalcitonin_FinalReport_20130109.pdf.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.** *Ann Intern Med* 2009, **151:**W65–W94.
16. Moher D, Liberati A, Tetzlaff J, Altman DG: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.** *Ann Intern Med* 2009, **151:**264–269.
17. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: **Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis.** *Crit Care Med* 1992, **20:**864–874.
18. Reinhart K, Brunkhorst FM, Bone HG, Bardutzky J, Dempfle CE, Forst H, Gastmeier P, Gerlach H, Grundling M, John S, Kern W, Kreymann G, Kruger W, Kujath P, Marggraf G, Martin J, Mayer K, Meier-Hellmann A, Oppert M, Putensen C, Quintel M, Ragaller M, Rossaint R, Seifert H, Spies C, Stuber F, Weiler N, Weimann A, Werdan K, Welte T: **Prevention, diagnosis, treatment, and follow-up care of sepsis - First revision of the S2k Guidelines of the German Sepsis Society (DSG) and the German Interdisciplinary Association for Intensive and Emergency Care Medicine (DIVI).** *Anaesthesist* 2010, **59:**347–370.
19. Higgins JPT, Altman DG, Sterne JAC: **Chapter 8: Assessing risk of bias in included studies**. In *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* Edited by Higgins JPT, Green S. (updated March 2011) http://www.cochrane-handbook.org.
20. R Development Core Team: *R: A Language and Environment for Statistical Computing.* http://www.R-project.org/.
21. Schwarzer G: *Meta: Meta-Analysis with R, R Package Version: 1.6-1.* http://CRAN.R-project.org/package=meta.
22. Deeks JJ, Macaskill P, Irwig L: **The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed.** *J Clin Epidemiol* 2005, **58:**882–893.
23. Collet D: *Modelling Survival Data in Medical Research.* 2nd edition. Boca Raton (FL): CRC Press; 2003.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG: **Measuring inconsistency in meta-analyses.** *BMJ* 2003, **327:**557–560.
25. DerSimonian R, Laird N: **Meta-analysis in clinical trials.** *Control Clin Trials* 1986, **7:**177–188.
26. Annane D, Maxime V, Faller JP, Mezher C, Clec'h C, Martel P, Gonzales H, Feissel M, Cohen Y, Capellier G, Gharbi M, Nardi O: **Procalcitonin levels to guide antibiotic therapy in adults with non-microbiologically proven apparent severe sepsis: a randomised controlled trial.** *BMJ Open* 2013, **3:**e002186. doi:10.1136/bmjopen-2012-00218.
27. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B, Regnier B, Brun-Buisson C, Chastre J, Wolff M: **Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial.** *Lancet* 2010, **375:**463–474.
28. Hochreiter M, Koehler T, Schweiger AM, Keck FS, Bein B, von Spiegel T, Schroeder S: **Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial.** *Crit Care* 2009, **13:**R83.
29. Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, Thornberg KJ, Loken J, Steensen M, Fox Z, Tousi H, Soe-Jensen P, Lauritsen AO, Strange D, Petersen PL, Reiter N, Hestad S, Thormar K, Fjeldborg P, Larsen KM, Drenck NE, Ostergaard C, Kjaer J, Grarup J, Lundgren JD: **Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial.** *Crit Care Med* 2011, **39:**2048–2058.
30. Nobre V, Harbarth S, Graf L-D, Rohner P, Pugin J: **Use of procalcitonin to shorten antibiotic treatment duration in septic patients - A randomized trial.** *Am J Respir Crit Care Med* 2008, **177:**498–505.
31. Schroeder S, Hochreiter M, Koehler T, Schweiger AM, Bein B, Keck FS, von Spiegel T: **Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study.** *Langenbecks Arch Surg* 2009, **394:**221–226.
32. Svoboda P, Kantorova I, Scheer P, Radvanova J, Radvan M: **Can procalcitonin help us in timing of re-intervention in septic patients after multiple trauma or major surgery?** *Hepatogastroenterology* 2007, **54:**359–363.
33. Stolz D, Smyrnios N, Eggimann P, Pargger H, Thakkar N, Siegemund M, Marsch S, Azzola A, Rakic J, Mueller B, Tamm M: **Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study.** *Eur Respir J* 2009, **34:**1364–1375.
34. Bagnenko SF, Shliapnikov SA, Korol'kov AI: **Cholangitis and biliary sepsis: problem and ways of solution.** *Vestn Khir Im I I Grek* 2009, **168:**17–20.
35. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R: **Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012.** *Crit Care Med* 2013, **41:**580–637.
36. Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, Schlosser J, Martone WJ: **Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals - A challenge to hospital leadership.** *JAMA* 1996, **275:**234–240.
37. Goossens H: **Antibiotic consumption and link to resistance.** *Clin Microbiol Infect* 2009, **15:**12–15.
38. Cosgrove SE: **The relationship between antimicrobial resistance and patient outcomes: Mortality, length of hospital stay, and health care costs.** *Clin Infect Dis* 2006, **42:**S82–S89.
39. Roberts RR, Hota B, Ahmad I, Scott RD II, Foster SD, Abbasi F, Schabowski S, Kampe LM, Ciavarella GG, Supino M, Naples J, Cordell R, Levy SB, Weinstein RA: **Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship.** *Clin Infect Dis* 2009, **49:**1175–1184.

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6 Diskussion

Unsere Meta-Analyse untersuchte den Einfluss der PCT-gesteuerten Therapie im Vergleich zur Standardbehandlung in der Patientenpopulation mit schwerer Sepsis. Im Gegensatz zu vorausgegangenen Reviews, welche Patienten in diversen Einrichtungen und mit unterschiedlichen Krankheitsschweregraden untersuchten, konzentrierten wir uns nur auf Patienten mit schwerer Sepsis. Gerade bei dieser Patientenpopulation fehlen objektive Kriterien ob eine antibiotische Therapie beendet werden soll. Im Hinblick auf die hohen Mortalitätsraten bei schwerer Sepsis tendieren im Krankenhaus tätige Ärzte eher zu großzügigen Antibiotikatherapien, um auf der „sicheren Seite“ zu sein. In neuen Therapieansätzen wird hingegen vorgeschlagen, Antibiotikatherapien generell auf 7 bis 10 Tage zu begrenzen. Diese Auffassung ist jedoch aktuell kaum wissenschaftlich belegt und wurde nur als Grad 2C Empfehlung in die aktuellen Richtlinien der Surviving Sepsis Campaign aufgenommen (Dellinger et al. 2013). Da es somit keine einheitlichen Richtlinien für die Therapie der schweren Sepsis gibt, sind die derzeitigen Bahandlungsstrategien im klinischen Alltag sehr heterogen. Auch die Behandlungsregime der Kontrollgruppen in unserer Meta-Analyse unterscheiden sich deutlich voneinander und spiegeln damit den derzeitigen Klinikalltag gut wider.

Als primäre Endpunkte unserer Meta-Analyse setzten wir die 28-Tage-Mortalität und die Krankenhausmortalität fest. Jedoch konnten wir bezüglich beider Entitäten keinen signifikanten Unterschied zwischen einer PCT-gesteuerten Therapie und der Standardbehandlung feststellen.
Auch bei den beiden sekundären Endpunkten Länge des Aufenthaltes in der Intensivstation und Länge des Krankenhausaufenthaltes konnte in der Meta-Analyse kein signifikanter Unterschied zwischen beiden Therapiegruppen detektiert werden. Da diese vier Endpunkte kein signifikantes Ergebnis in der Meta-Analyse liefern, sind dringend weitere klinische Studien nötig, um die Sicherheit und Effektivität einer PCT-gesteuerten Therapie zu evaluieren.
Bei dem sekundären Endpunkt Dauer der Antibiotikatherapie konnten wir statistisch einen signifikanten Unterschied zugunsten der PCT-gesteuerten Therapie nachweisen. Um die Länge der Antibiotikatherapie abschätzen zu können, führten wir auf dem Exponentialmodell basierende Berechnungen durch. Daraus ergaben sich eine mittlere Dauer der Antibiotikatherapie von 6 Tagen in der PCT-gesteuerten Therapie-

gruppe und von 8 Tagen in der Kontrollgruppe. Demzufolge können wir von einer mittleren Reduktion der Therapiedauer von circa 2 Tagen infolge einer PCT-gesteuerten Therapie ausgehen. Somit können Biomarker wie Proclacitonin für die klinische Entscheidungsfindung hilfreich sein.
Ein weiterer Vorteil der auf PCT basierenden Therapiealgorithmen kann sich bei der Resistenzentwicklung von Mikroorganismen gegen Antibiotika zeigen. So ist bereits belegt, dass durch prolongierte Gaben von Breitspektrumantibiotika häufiger Resistenzen auftreten (Goldmann et al. 1996, Goossens 2009). Darüber hinaus wurde nachgewiesen, dass der Antibiotikaverbrauch und die damit verbundenen erworbenen antimikrobiellen Resistenzen sowohl mit einer Erhöhung von Mortalität und Morbidität, als auch mit einer Verlängerung des Krankenhausaufenthaltes und letztendlich mit steigenden Kosten für das Gesundheitssystem assoziiert sind (Cosgrove 2006, Roberts et al. 2009).

Zurzeit existieren noch keine etablierten Therapiealgorithmen, die auf Procalcitonin-Plasmaspiegeln basieren und zur Behandlung von Hochrisikopatienten mit schwerer Sepsis herangezogen werden könnten. Bei der Erstellung eines Therapiealgorithmus für Patienten mit schwerer Sepsis ist es wichtig, zwischen Eskalation und Deeskalation der therapeutischen Interventionen zu unterscheiden. So müssen geeignete Cut-off-Werte für PCT gefunden werden, um Antibiotikatherapien, chirurgische Interventionen oder weitere diagnostische Maßnahmen zu initiieren oder zu intensivieren. Zugleich darf die Deeskalation der diagnostischen und therapeutischen Maßnahmen nicht vernachlässigt werden, damit bei Abfall der PCT-Werte unter einem bestimmten Niveau zum Beispiel Antibiotikatherapien wieder beendet und nicht unnötig lang fortgeführt werden. Auch kann das Ansprechen der therapeutischen Maßnahmen mittels der PCT-Werte überprüft werden.
Annane et al. und Bouadma et al. befürworteten eine Fortführung der Antibiotikatherapie bei PCT-Werten über 0.5 ng/mL, und empfahlen die Beendigung der Antibiotikatherapie bei PCT-Werten unter 0.5 ng/mL (Annane et al. 2013, Bouadma et al. 2010). Zudem unterschieden Annane et al. zwischen medizinischen und chirurgischen Patienten. Bei chirurgischen Patienten wurde ein anderer Therapiealgorithmus angewandt: Hier wurde empfohlen, die Antibiotikatherapie bei PCT-Spiegeln unter 4ng/mL zu beenden. Bouadma et al. rieten zum Abbruch der Antibiotikatherapie bei PCT-Spiegeln unter 0.25 ng/mL. Bewegten sich die Spiegel

zwischen 0.5 ng/mL und 0.25 ng/mL, wurde die Antibiose in den Fällen gestoppt, bei denen eine Abnahme der PCT-Spiegel um mindestens 80% des Spitzenwertes zu verzeichnen war.
In vier Studien wurde ein PCT-Spiegel von 1.0 ng/mL als Cut-off-Wert empfohlen. (Hochreiter et al. 2009, Jensen et al. 2011, Nobre et al. 2008, Schroeder et al. 2009). Hochreiter et al. und Schroeder et al. rieten zum Abbruch der Antibiotikatherapie bei Werten unter 1.0 ng/mL, sowie bei einem Abfall der Spiegel innerhalb von 3 Tagen um 35% des Spitzenwertes.
Nobre et al. empfahlen die Antibiose zu beenden, wenn die PCT-Spiegel nach 3 Tagen unter 0.1 ng/mL gefallen waren. Waren die anfänglichen PCT-Spiegel über 1.0 ng/mL, so sollte die Antibiotikatherapie erst dann beendet werden, wenn die PCT-Spiegel um mehr als 90% des Spitzenwertes oder wenn sie unter 0.25 ng/mL innerhalb von 5 Tagen gefallen waren.
Im Gegensatz zu allen anderen Studien untersuchten Jensen et al. eine strikte Eskalationstrategie (Jensen et al. 2011). Bei PCT-Spiegeln über 1.0 ng/mL wurde eine intensivierte antibiotische Therapie empfohlen. Eine Deesskalation war nur möglich, wenn die PCT-Werte für mindestens 3 Tage unter 1.0 ng/mL gefallen waren. Dieser Therapiealgorithmus führte zu längeren Aufenthalten in der Intensivstation und einem erheblich gesteigerten Verbrauch an Breitspektrumantibiotika.
Svoboda et al. untersuchten nur chirurgische Patienten und verwendeten einen Schwellenwert für PCT von 2.0 ng/mL (Svoboda et al. 2007).
Demzufolge wird deutlich, dass die Therapiealgorithmen der in die Meta-Analyse eingeschlossenen Studien extrem heterogen sind. In Zukunft müssen daher weitere klinische Studien durchgeführt werden, um verlässliche Schwellenwerte für Procalcitonin zur Therapiesteuerung bei schwerer Sepsis zu finden.

Dieser systematische Review hat einige Einschränkungen, die es zu berücksichtigen gilt:
Die eingeschlossenen Studien variieren erheblich in Bezug auf Studiendesign und Studienziele. In zwei Studien wurden Richtlinien für den Beginn, die Fortführung, sowie den Abbruch der Antibiotikatherapie (Annane et al. 2013, Bouadma et al. 2010) angegeben. Bei drei Studien lag der Fokus auf der Deeskalation (Hochreiter et al. 2009, Nobre et al. 2008, Schroeder et al. 2009), bei zwei Studien sowohl auf der Eskalation der Antibiotikatherapie als auch der Intensivierung der Diagnostik (Jensen et

al. 2011, Svoboda et al. 2007). In einer Studie wurden zusätzlich chirurgische Interventionen als Therapieoption berücksichtigt (Svoboda et al. 2007).
Weiterhin ist die Aussagekraft des systematischen Reviews dadurch beschränkt, dass insgesamt nur 1,075 Patienten in die Meta-Analyse eingeschlossenen werden konnten.
Darüber hinaus ist eine kombinierte Analyse von internistischen und chirurgischen Patienten problematisch, da es wesentliche Unterschiede bezüglich der Studienergebnisse, der Interventionen und der Cut-off-Werte für PCT gibt. Denn gerade bei chirurgischen Patienten spielt die operative Sanierung neben einer adäquaten Antibiotikatherapie eine entscheidende Rolle.

Auf unseren Artikel gab es bisher folgende Reaktionen:
In einem Brief von Gu und Liu wurde noch einmal betont, dass alle in unsere Meta-Analyse eingeschlossenen Studien in Europa durchgeführt wurden (Gu und Liu 2014). Zudem merkten sie an, dass der fehlende günstige Effekt auf die Mortalität auch an anderen Faktoren wie Alter, Krankheitsschweregrad, Komorbiditäten etc. liegen könnte.
Ein Kommentar von Salluh et al. sieht einige zusätzliche Einschränkungen in der Verallgemeinerung unserer Ergebnisse (Salluh et al. 2014). So setzten sich die Ärzte oft über die Algorithmen hinweg, in der PRORATA Studie sogar in über 50% der Fälle (Bouadma et al. 2010). Auch sehen Salluh et al. die Heterogenität der Therapiestrategien in den Kontrollgruppen als problematisch an, sowie die Kosten, die durch die PCT-Messungen entstehen. Ihrer Meinung nach ist es zudem bereits bewiesen, dass eine antibiotische Therapie bei kritisch kranken Menschen sicher auf 6 bis 8 Tage reduziert werden kann.

Mittlerweile wurde eine weitere Studie, die wir im PRISMA flow diagram als damals noch nicht abgeschlossen erwähnten (registriert bei http://www.ClinicalTrials.gov unter der Nummer NCT01494675), veröffentlicht (Deliberato et al. 2013). Diese prospektive, randomisierte Studie trifft unsere Einschlusskriterien für die Meta-Analyse und liefert weitere wichtige Daten. Von insgesamt 81 eingeschlossenen Patienten wurden 42 der PCT-Gruppe und 39 der Kontrollgruppe randomisiert zugeteilt. In der Intention-to-treat-Analyse zeigte sich eine mittlere Dauer der Antibiotikartherapie von 10 Tagen in der PCT-Gruppe verglichen mit 11 Tagen in der Kontrollgruppe, aller-

dings ohne statistische Signifikanz. Auch die weiteren Endpunkte Krankenhausmortalität, Länge des Aufenthaltes in der Intensivstation und Länge des Krankenhausaufenthaltes blieben in der Intention-to-treat-Analyse ohne statistisch signifikanten Unterschied zwischen den beiden Therapiegruppen. Lediglich in der Per-protocol-Analyse konnte eine statistisch signifikante Reduktion der Antibiotikatherapiedauer zugunsten der PCT-Gruppe nachgewiesen werden (mittlere Dauer der Antibiotikatherapie von 9 Tagen in der PCT-Gruppe und von 13 Tagen in der Kontrollgruppe, p=0.008). Somit unterstützen diese Werte unsere Ergebnisse in der Meta-Analyse.

Ein weiterer interessanter Aspekt der Studie von Deliberato et al. ist die vorgenommene Kostenanalyse. Dabei wurden für beide Studiengruppen die Kosten für die Antibiotikatherapie und für die PCT-Messungen berücksichtigt. Demzufolge konnten mittels der PCT-gesteuerten Therapie annähernd 30% der Kosten pro Patient eingespart werden, verglichen mit der Kontrollgruppe.

Das zeigt, dass die Befürchtung steigender Kosten durch routinemäßige PCT-Messungen in Bezug auf die Reduktion des Antibiotikaverbrauchs weitgehend unbegründet erscheint. Auch ist der Einwand, dass eine sichere Reduktion der Antibiotikatherapie auf 6 bis 8 Tage bei kritisch kranken Patienten bereits etabliert ist, im Hinblick auf die oben erwähnte Studie von Deliberato et al. so nicht haltbar (Salluh et al. 2014).

In Zukunft muss ein geeigneter Algorithmus für die PCT-gesteuerte Therapie von Patienten mit schwerer Sepsis gefunden werden. Dieser sollte sowohl Eskalations- als auch Deeskalationsstrategien beinhalten, geeignete Cut-off-Werte für PCT festlegen und zwischen internistischen und chirurgischen Patienten unterscheiden.

Um die bestehenden Wissenslücken im Hinblick auf die PCT-gesteuerte Therapie von Patienten mit schwerer Sepsis zu schließen, erwarten wir die Ergebnisse von sechs bei http://www.ClinicalTrials.gov registrierten, laufenden Studien. Die Ergebnisse dieser Studien können wichtige Resultate für zukünftige systematische Reviews liefern.

7 Schlussfolgerung

Ein auf Biomarkern basierender Therapiealgorithmus, welcher Procalcitonin-Spiegel zur Entscheidungsfindung heranzieht, scheint bezüglich der Steuerung der Antibiotikatherapie bei der Behandlung von Patienten mit schwerer Sepsis in Intensivstationen hilfreich zu sein. Durch eine solche PCT-gesteuerte Therapie kann die Dauer der Antibiotikatherapie signifikant reduziert werden, ohne nach derzeitigem Kenntnisstand einen ersichtlichen Einfluss auf die Mortalität zu haben.

Jedoch sind weitere Forschungsarbeiten dringend nötig, um die Sicherheit und Effektivität der PCT-gesteuerten Therapie in den Untergruppen von chirurgischen und internistischen Patienten mit schwerer Sepsis zu untersuchen.

Für die Beurteilung zukünftiger Studien erscheint es wichtig, Behandlungsalgorithmen einheitlich zu definieren, da in den bisherigen Studien die Therapiealgorithmen erheblich variierten. Somit ist die Durchführung weiterer klinischer Studien essenziell, um einen geeigneten Algorithmus und geeignete Schwellenwerte für Procalcitonin bei der Behandlung von Patienten mit schwerer Sepsis in Intensivstationen zu finden.

8 Literatur- und Quellenverzeichnis

Agarwal R, Schwartz DN. 2011. Procalcitonin to Guide Duration of Antimicrobial Therapy in Intensive Care Units: A Systematic Review. Clin Infect Dis, 53 (4):379-387.

Annane D, Maxime V, Faller JP, Mezher C, Clec'h C, Martel P, Gonzales H, Feissel M, Cohen Y, Capellier G, Gharbi M, Nardi O. 2013. Procalcitonin levels to guide antibiotic therapy in adults with non-microbiologically proven apparent severe sepsis: a randomised controlled trial. BMJ Open, 3 (2).

Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. 1993. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet, 341 (8844):515-518.

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. 1992. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest, 101 (6):1644-1655.

Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B, Regnier B, Brun-Buisson C, Chastre J, Wolff M. 2010. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet, 375 (9713):463-474.

Brunbuisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Regnier B. 1995. Incidence, risk-factors, and outcome of severe sepsis and septic shock in adults - a multicenter prospective-study in intensive-care units. JAMA, 274 (12):968-974.

Carrol ED, Thomson AP, Hart CA. 2002. Procalcitonin as a marker of sepsis. Int J Antimicrob Agents, 20 (1):1-9.

Cosgrove SE. 2006. The relationship between antimicrobial resistance and patient outcomes: Mortality, length of hospital stay, and health care costs. Clin Infect Dis, 42:S82-S89.

Deliberato RO, Marra AR, Sanches PR, Martino MD, Ferreira CE, Pasternak J, Paes AT, Pinto LM, dos Santos OF, Edmond MB. 2013. Clinical and economic impact of procalcitonin to shorten antimicrobial therapy in septic patients with

proven bacterial infection in an intensive care setting. Diagn Microbiol Infect Dis, 76 (3):266-271.

Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R. 2013. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med, 41 (2):580-637.

Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, Gruendling M, Huhle G, Jaschinski U, John S, Mayer K, Oppert M, Olthoff D, Quintel M, Ragaller M, Rossaint R, Stuber F, Weiler N, Welte T, Bogatsch H, Hartog C, Loeffler M, Reinhart K. 2007. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. Intensive Care Med, 33 (4):606-618.

Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, Schlosser J, Martone WJ. 1996. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals - A challenge to hospital leadership. JAMA, 275 (3):234-240.

Goossens H. 2009. Antibiotic consumption and link to resistance. Clin Microbiol Infect, 15:12-15.

Gu WJ, Liu JC. 2014. Procalcitonin-guided therapy in severe sepsis and septic shock. Crit Care, 18 (3):427.

Heublein S, Hartmann M, Hagel S, Hutagalung R, Brunkhorst FM. 2013. Epidemiology of sepsis in German hospitals derived from administrative databases. Infection, 41 (Suppl 1):S71.

Heyland DK, Johnson AP, Reynolds SC, Muscedere J. 2011. Procalcitonin for reduced antibiotic exposure in the critical care setting: A systematic review and an economic evaluation. Crit Care Med, 39 (7):1792-1799.

Hochreiter M, Koehler T, Schweiger AM, Keck FS, Bein B, von Spiegel T, Schroeder S. 2009. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. Crit Care, 13 (3).

Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, Thornberg KJ, Loken J, Steensen M, Fox Z, Tousi H, Soe-Jensen P, Lauritsen AO, Strange D, Petersen PL, Reiter N, Hestad S, Thormar K, Fjeldborg P, Larsen KM, Drenck NE, Ostergaard C, Kjaer J, Grarup J, Lundgren JD, Procalcitonin

Survival Study P. 2011. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial. Crit Care Med, 39 (9):2048-2058.

Kopterides P, Siempos II, Tsangaris I, Tsantes A, Armaganidis A. 2010. Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: A systematic review and meta-analysis of randomized controlled trials. Crit Care Med, 38 (11):2229-2241.

Kunz R, Khan KS, Kleijnen J, Antes G. 2009. Systematische Übersichtsarbeiten und Meta-Analysen. Bern: Verlag Hans Huber.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med, 151 (4):W65-94.

Matthaiou DK, Ntani G, Kontogiorgi M, Poulakou G, Armaganidis A, Dimopoulos G. 2012. An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients. Intensive Care Med, 38 (6):940-949.

Moher D, Liberati A, Tetzlaff J, Altman DG. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med, 151 (4):264-269, W264.

Nobre V, Harbarth S, Graf L-D, Rohner P, Pugin J. 2008. Use of procalcitonin to shorten antibiotic treatment duration in septic patients - A randomized trial. Am J Respir Crit Care Med, 177 (5):498-505.

Noorani HZ, Adams E, Pitrak D, Belinson S, Aronson N. 2013. Future Research Needs on Procalcitonin-Guided Antibiotic Therapy. Future Research Needs Paper No. 29. [http://www.effectivehealthcare.ahrq.gov/ehc/products/497/1377/FRN29_Procalcitonin_FinalReport_20130109.pdf].

Reinhart K, Brunkhorst FM, Bone HG, Bardutzky J, Dempfle CE, Forst H, Gastmeier P, Gerlach H, Grundling M, John S, Kern W, Kreymann G, Kruger W, Kujath P, Marggraf G, Martin J, Mayer K, Meier-Hellmann A, Oppert M, Putensen C, Quintel M, Ragaller M, Rossaint R, Seifert H, Spies C, Stuber F, Weiler N, Weimann A, Werdan K, Welte T. 2010. Prevention, diagnosis, treatment, and follow-up care of sepsis - First revision of the S2k Guidelines of the German

Sepsis Society (DSG) and the German Interdisciplinary Association for Intensive and Emergency Care Medicine (DIVI). Anaesthesist, 59 (4):347-370.

Roberts RR, Hota B, Ahmad I, Scott RD, II, Foster SD, Abbasi F, Schabowski S, Kampe LM, Ciavarella GG, Supino M, Naples J, Cordell R, Levy SB, Weinstein RA. 2009. Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship. Clin Infect Dis, 49 (8):1175-1184.

Salluh JI, Nobre V, Povoa P. 2014. Using procalcitonin to guide antimicrobial duration in sepsis: asking the same questions will not bring different answers. Crit Care, 18 (3):142.

Schroeder S, Hochreiter M, Koehler T, Schweiger AM, Bein B, Keck FS, von Spiegel T. 2009. Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. Langenbecks Arch Surg, 394 (2):221-226.

Schuetz P, Chiappa V, Briel M, Greenwald JL. 2011. Procalcitonin Algorithms for Antibiotic Therapy Decisions A Systematic Review of Randomized Controlled Trials and Recommendations for Clinical Algorithms. Arch Intern Med, 171 (15):1322-1331.

Schuetz P, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, Luyt CE, Chastre J, Tubach F, Kristoffersen KB, Wei L, Burkhardt O, Welte T, Schroeder S, Nobre V, Tamm M, Bhatnagar N, Bucher HC, Mueller B. 2012. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis, 55 (5):651-662.

Svoboda P, Kantorova I, Scheer P, Radvanova J, Radvan M. 2007. Can procalcitonin help us in timing of re-intervention in septic patients after multiple trauma or major surgery? Hepatogastroenterology, 54 (74):359-363.

Tang H, Huang T, Jing J, Shen H, Cui W. 2009. Effect of Procalcitonin-Guided Treatment in Patients with Infections: a Systematic Review and Meta-Analysis. Infection, 37 (6):497-507.

Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. 2013. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis, 13 (5):426-435.

Zhang L, Huang J, Xu T, Lin Y. 2012. [Procalcitonin-guided algorithms of antibiotic therapy in community-acquired lower respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials]. Zhonghua Jie He He Hu Xi Za Zhi, 35 (4):275-282.

9 Anhang

9.1. Zusätzliche Materialien

9.1.1. Additional file 1. Risk of Bias Table

Judgment of bias via Cochrane Collaboration's tool for assessing risk of bias

Study: Annane et al. 2013

Bias	Authors´ Judgment	Support for Judgment
Random Sequence Generation (Selection Bias)	Low risk	**Quote:** "Patients were randomised in a 1:1 ratio according to a computer-generated list. Randomisation was centralised through a secured website and performed by an independent statistician, and was stratified by the centre and according to whether or not patients underwent surgery in the past 48 h, using permutation blocks, the size of which remained unknown to the investigators."
Allocation Concealment (Selection Bias)	Low risk	**Quote:** "Randomisation was centralised through a secured website and performed by an independent statistician, and was stratified by the centre and according to whether or not patients underwent surgery in the past 48 h, using permutation blocks, the size of which remained unknown to the investigators."
Blinding of Participants and Personnel (Performance Bias)	Unclear risk	**Quote:** "Masking of antibiotic therapy was not feasible in this study. In the control arm, patients, physicians, nurses, investigators, study coordinators, the statistician and the sponsor remained blinded to PCT levels throughout the study." **Quote:** "In the control arm, the decision to start or stop antibiotic therapy was at the discretion of the patient's physician, without knowledge of the patient's PCT concentrations." **Quote:** "In the experimental arm, both initiation and discontinuation of antibiotics were guided by a PCT-based algorithm, applied at 6 h and on day 3 and day 5 postrandomisation." **Quote:** "Investigators were strongly asked not to over-rule the algorithm every day up to the study day 5." **Quote:** "n the experimental arm, physicians were noncompliant with the PCT-based algorithm in 19% of patients at 6 h, 17% on day 3 and 37% on day 5." **Comment:** Patients treated according to a strict protocol but physicians were non-compliant with the algorithms in a notable amount of cases.
Blinding of Outcome Assessment (Detection Bias)	Unclear risk	**Comment:** No information given.
Incomplete Outcome Data (Attrition Bias)	Low risk	**Quote:** "From December 2006 to December 2009, of 1250 patients with the phenotype of severe sepsis or septic shock screened in the eight participating centres, only 62 patients were eligible." **Quote:** "Of the 62 were randomised patients, 31 to each arm, 4 (3 in the control arm and 1 in the

		experimental arm) later withdrew their consent. According to French regulations, vital status being public information, mortality data are given for all randomised patients." **Comment:** Just few exclusions in both groups. Same reason for missing outcome data across groups.
Selective Reporting (Reporting Bias)	Unclear risk	**Primary outcomes mentioned in protocol and mentioned in published article:** - rate of patients undergoing antibiotic treatment at day 5 postrandomisation **Secondary outcomes mentioned in protocol and mentioned in published article:** - evolution of the SOFA score between day 0, day 3 and day 5 **Secondary outcomes mentioned in published article and not mentioned in protocol:** - death at day 5, at ICU discharge and at hospital discharge - proportion of patients started on antibiotics postrandomisation - duration of antibiotic exposure - proportion of patients with infection acquired between randomisation and day 3, day 5 and ICU discharge - ICU length-of-stay - hospital length-of-stay **Comment:** In the published article there are many secondary outcomes mentioned which are not part of the protocol. **Registration of study:** http://www.Clinicaltrials.gov: NCT01025180
Other Bias	Low risk	**Quote:** "This work was partly funded by Thermo Fisher B.R.A.H.M.S. France, a subsidiary of the maker of the PCT assay used in this study. The sponsor has no input in study design, conduct and reporting. It helped with logistic support when organising investigators meeting." **Quote:** "Competing interests: None." **Quote:** "The two groups were well balanced for demographic and anthropometric characteristics, the prevalence and severity of co-morbidities and the severity of acute illness." **Comment:** No extreme baseline imbalance between groups.

Study: Bouadma et al. 2010

Bias	**Authors´ Judgment**	**Support for Judgment**
Random Sequence Generation (Selection Bias)	Low risk	**Quote:** "After baseline screening, an independent, centralised, computer-generated randomisation sequence (CleanWeb, Télémedecine, Technologies, Boulogne, France) was used to randomly assign patients in a 1:1 ratio to the procalcitonin or control groups. Patients were stratified by centre with random block sizes of 2, 4, or 6"
Allocation Concealment (Selection Bias)	Low risk	**Quote:** "Patients were stratified by centre with random block sizes of 2, 4, or 6; investigators were masked to assignment before, but not after, randomisation, as per our open-label design. This system

		was password protected and accessed by the principal investigator or study coordinator after the patient or surrogate gave consent and had met inclusion criteria. The patient's initials and date of birth were entered and then the patient's allocation was assigned."
Blinding of Participants and Personnel (Performance Bias)	Unclear risk	**Comment:** Patients treated according to a strict protocol, but final decision was up to the patient´s physician, irrespective of the procalcitonin concentration. **Quote:** "Investigators used predefined algorithms to guide physicians to start or discontinue antibiotics according to serum procalcitonin concentrations, using a modified version of a previously published algorithm." **Quote:** "Additionally, the final decision with respect to starting and continuing of antibiotics was at the discretion of the patients' physicians, irrespective of the procalcitonin concentration. " **Quote:** "For patients in the control group, before study onset all investigators received and approved a reminder including recommendations for duration of antimicrobial treatment for the most frequent infections (webappendix pp 1–3); these recommendations were derived from international and local guidelines." **Quote:** "Recommendations about duration of antimicrobial treatment for the procalcitonin group were not followed in 219 episodes." **Quote:** „Recommendations about duration of antimicrobial treatment for the control group were not heeded in 146 episodes" **Quote:** „53% of patients randomised to the procalcitonin group were not given algorithm-guided treatment, either because the algorithm was overruled (physicians refused to start or stop antibiotics, even though the algorithm recommended it), or because they were discharged from the intensive care unit, precluding serial serum procalcitonin measurements."
Blinding of Outcome Assessment (Detection Bias)	Low risk	**Quote:** "Although treatment assignments were not masked, all investigators were unaware of aggregate outcomes during the study, and primary endpoints were strictly defined and not patient-reported."
Incomplete Outcome Data (Attrition Bias)	Low risk	**Quote:** "Although not specified in the protocol, a worst-case imputation method was used for missing data to conform with the intention-to-treat analysis." **Quote:** "1315 patients with suspected infections were screened for eligibility, of whom 630 were enrolled and randomly assigned to the procalcitonin group (n=311 patients) or the control group (n=319; figure 2). Four patients in the procalcitonin group and five in the control group were subsequently excluded from the analysis." **Quote:** "Only two patients were lost to follow-up, one from each group. In the procalcitonin group, the patient died on day 25 but no information was available about antibiotic exposure for days 15–25. From worst-case imputation, this patient was judged to have received antibiotics until death. In the control group, the patient was lost to follow-up on day 22 but was judged to have survived until day 60, without receiving any antibiotics after day 22."

		Comment: Just few exclusions/attrition; mortality unlikely to be affected by this. Worst-case imputation method seems appropriate.
Selective Reporting (Reporting Bias)	Low risk	**Primary outcomes mentioned in protocol and mentioned in published article:** -Exposition to antibiotics, defined by antibiotic-free days -28-day mortality -60-day mortality **Secondary outcomes mentioned in protocol and mentioned in published article:** -Consumption of antibiotics expressed as the Defined Daily Dose/1000 ICU-days -The length of ICU and hospital stay -The evolution of SOFA score parameters -The number of mechanical ventilation-free days -The percentage of emerging multiresistant bacteria between D1 and D28, as assessed by microbiologic examination of all clinical samples -The percentages of relapses of infection **Secondary outcomes mentioned in protocol and not mentioned in published article:** -The acquisition cost of antibiotics **Secondary outcomes mentioned in published article and not mentioned in protocol:** -Percentage of patients with superinfection -Duration of first episode of antibiotic treatment -Duration of antibiotic treatment according to infectionsite **Quote:** "Although not prespecified in the protocol, we did several other exploratory subgroup analyses on the basis of age, sex, microbiologically documented infections, presence or absence of one or more positive blood cultures, septic shock, mechanical ventilation, and SOFA score at inclusion." **Comment:** These are no primary outcomes and just additional analysis. **Quote:** "Last, no formal cost-effectiveness evaluation was done." **Comment:** Judgment "low risk" because "the acquisition cost of antibiotics" (protocol) is not part of my meta-analysis. **Registration of study:** http://www.Clinicaltrials.gov: NCT00472667
Other Bias	Low risk	**Quote:** "The study sponsors did not participate in the study design, data collection, data analysis, data interpretation, or writing of the report." **Quote:** "C-EL has received lecture fees from Brahms, and Merck Sharp & Dohme-Chibret. BR has served as a consultant for AstraZeneca, Merck Sharp & Dohme-Chibret, and Lilly. JC has received consulting and lecture fees from Pfizer, Brahms, Wyeth, Johnson & Johnson, Nektar-Bayer, and Arpida. MW has received consulting and lectures fees from Merck Sharp & Dohme-Chibret, Janssen-Cilag, Gilead, and AstraZeneca. All other authors declare that they have no conflicts of interest." **Comment:** No extreme baseline imbalance between groups.

Study: Hochreiter et al. 2009

Bias	Authors´ Judgment	Support for Judgment
Random Sequence Generation (Selection Bias)	Unclear risk	**Quote:** "Patients were randomly assigned to either a PCT-guided (study group) or a standard (control group) antibiotic regimen." **Quote:** "Die Patienten wurden per Losverfahren entweder der PCT-gesteuerten Gruppe oder der Kontrollgruppe zugeteilt."
Allocation Concealment (Selection Bias)	Unclear risk	**Comment:** No information given.
Blinding of Participants and Personnel (Performance Bias)	Low risk	**Comment:** Patients treated according to a strict protocol. **Quote:** "Antibiotic therapy in the PCT-guided group was discontinued if clinical signs and symptoms of infection improved and PCT decreased to less than 1 ng/ml, or if the PCT value was more than 1 ng/ml, but had dropped to 25 to 35% of the initial value over three days. In the control group, antibiotic treatment was applied as standard regimen over eight days. Irrespective of the study group and at any time point, the physician in charge had the option to proceed with or adjust the antibiotic treatment, if there were clinical reasons to do so."
Blinding of Outcome Assessment (Detection Bias)	Unclear risk	**Comment:** No information given.
Incomplete Outcome Data (Attrition Bias)	Low risk	**Quote:** "Of 395 patients screened, a total of 110 patients fulfilling the inclusion criteria were entered in the study from January 2006 to March 2007." **Quote:** "Fifty-seven patients were randomly assigned to the PCT-guided group and 53 to the control group." **Comment:** No exclusion and attrition after inclusion of patients mentioned. No missing outcome data of all 110 included patients.
Selective Reporting (Reporting Bias)	Low risk	**Primary outcome was reported according to the study protocol:** -Duration of antibiotic therapy **Outcomes mentioned in published article and not mentioned in protocol:** -Length of intensive care treatment **Registration of study:** http://www.isrctn.org: ISRCTN10288268
Other Bias	Low risk	**Quote:** "In the present prospective, randomised open study, both treatment groups were comparable in terms of age, gender distribution, diagnoses, disease severity as reflected by SAPS II, and outcome (Table 1). The distribution of antibiotic classes used was comparable as well (Table 2)." **Comment:** No extreme baseline imbalance between groups.

		Quote: "SS has served as consultant and has received payments from BRAHMS AG for speaking engagements. All other authors declare no conflicts of interest."

Study: Jensen et al. 2011

Bias	**Authors´ Judgment**	**Support for Judgment**
Random Sequence Generation (Selection Bias)	Low risk	**Quote:** "Randomization was performed 1:1 using a computerized algorithm created by the database manager with concealed block size, prestratified for site of recruitment, initial Acute Physiology and Chronic Health Evaluation, and age (entered in an encrypted screening form in a passwordprotected Web site)"
Allocation Concealment (Selection Bias)	Low risk	**Quote:** "Randomization was performed 1:1 using a computerized algorithm created by the database manager with concealed block size, prestratified for site of recruitment, initial Acute Physiology and Chronic Health Evaluation, and age (entered in an encrypted screening form in a passwordprotected Web site); investigators were masked to assignment before randomization."
Blinding of Participants and Personnel (Performance Bias)	Low risk	**Comment:** Patients treated according to a strict protocol. **Quote:** "Patients were randomized either to the "standard-of-care-only arm," receiving treatment according to the current international guidelines and blinded to procalcitonin levels, or to the "procalcitonin arm," in which current guidelines were supplemented with a drug-escalation algorithm and intensified diagnostics based on daily procalcitonin measurements." **Quote:** "The interventional algorithm was available at all sites and all investigators were trained in it. Additionally, everyday, all sites were contacted by telephone (365 days/yr) to assure that interventions were conducted according to the algorithm." **Quote:** "The main principle in the intervention algorithm was whenever an "alert procalcitonin" occurred, 1) to substantially increase the antimicrobial spectrum covered and 2) to intensify the diagnostic effort to find uncontrolled sources of infection, in this way interpreting an "alert procalcitonin" as a warning of uncontrolled infection. "Alert procalcitonin" was defined as a procalcitonin >1.0 ng/mL that was not decreasing at least 10% from the previous day. At baseline, a single procalcitonin measurement of >1.0 ng/mL was considered to be "alert procalcitonin." Both arms received antimicrobial therapy according to current guidelines." **Quote:** "In the procalcitonin group, 256 of 312 (82.1%) of patients with baseline "alert procalcitonin" received antimicrobials according to the available procalcitonin measurement and the intervention algorithm" **Quote:** „Of patients in the standard-of-care-only arm, who were judged to have severe sepsis or septic shock at baseline, 172 of 209 (82.4%) received antimicrobials according to empiric "standard-of-care" principles"

Blinding of Outcome Assessment (Detection Bias)	Low risk	**Quote:** "Investigators, treating physicians and the coordinator were unaware of outcomes during the study as were all procalcitonin measurements in the standard-of-care- only (control) group."
Incomplete Outcome Data (Attrition Bias)	Low risk	**Quote:** "Good Clinical Practice was applied. As part of this, double-keying, monitoring, and correction of errors and missing data were done in collaboration between the investigator and a clinical monitor." **Quote:** "The primary analysis includes all patients who were randomized." **Quote:** "Follow-up for the primary end point was complete (100.0%) for all patients randomized (604 in the procalcitonin group, 596 in the standard-of-care-only group)." **Comment:** Regarding mortality no missing outcomes/exclusions/attrition.
Selective Reporting (Reporting Bias)	High risk	**Primary outcome was reported according to the study protocol:** -28-day mortality **Secondary outcomes mentioned in protocol and mentioned in published article:** -60-day mortality -Consumption of antimicrobial chemotherapy -Prevalence of complications to infection: 2) severe sepsis, 3) septic shock: data only for both outcomes together available **Secondary outcomes mentioned in protocol and not mentioned in published article:** -90 day mortality -120 day mortality -180 day mortality -Prevalence of complications to infection: 1)sepsis, 2)severe sepsis, 3) septic shock, 4)MODS, 5)DIC: data for severe sepsis/septic shock only in combination for both groups available. -Use of diagnostic imaging during admission to the ICU -Quality of life post-ICU **Quote:** "Patients in the procalcitonin group were more likely to have additional cultures performed within 24 hrs after an "alert procalcitonin" than patients in the standard-of-care-only group: 81.5% vs. 66.7% (p < .001) but no more likely to have imaging studies or surgical interventions (data not shown)." **Secondary outcomes mentioned in published article and not mentioned in protocol:** -Median intensive care unit admission length -Mean time to appropriate antimicrobials -Need for organ support (mechanical ventilation, vasopressors/inotropics, glomerular filtration rate <60 mL/1.73 m², dialysis) -Other organ failure measures (bilirubin>1.2 mg/dL, Glasgow Coma Score<13) -Rate of infection at the time of discharge or at day 28 -"alert procalcitonin" at baseline as predictor of 28-day all-cause mortality -Infection/host response by clinical assessment **Quote:** "the sensitivity of the procalcitonin test for infection estimated in this trial was as low as 59%"

		Quote: "In the present trial, the procalcitonin strategy increased costs substantially" **Registration of study:** http://Clinicaltrials.gov: NCT00271752
Other Bias	Low risk	**Comment:** No extreme baseline imbalance between groups. **Quote:** "Dr. Jensen received speaker fee and travel reimbursement from Brahms Diagnostica and received an unrestricted grant for the organization for sample transport and analysis. The remaining authors have not disclosed any potential conflicts of interest."

Study: Nobre et al. 2008

Bias	**Authors´ Judgment**	**Support for Judgment**
Random Sequence Generation (Selection Bias)	Low risk	**Quote:** "The randomization was performed using a computer-based random number generation."
Allocation Concealment (Selection Bias)	Low risk	**Quote:** "Allocation was issued using opaque, sealed, numbered envelopes."
Blinding of Participants and Personnel (Performance Bias)	Unclear risk	**Quote:** "We conducted a randomized, controlled, open interventional trial" **Comment:** Patients treated according to a strict protocol. **Quote:** "All patients received initial antibiotic therapy based on local guidelines and susceptibility patterns, according to the decision of the treating physician, who was unaware of the patient's initial PCT levels." **Quote:** "In patients randomly assigned to the intervention group, antibiotics were stopped when PCT levels had decreased 90% or more from the initial value (if clinicians agreed) but not before Day 3 (if baseline PCT levels were >1 mg/L) or Day 5 (if baseline PCT levels were >1 mg/L). In control patients, clinicians decided on the duration of antibiotic therapy based on empirical rules." **Quote:** "Of note, the final decision concerning the antibiotic therapy duration was always left to the discretion of the physician in charge." **Quote:** " "Algorithm overruling" ' in the PCT group (i.e., treating physician refused to stop the antibiotics, although the stopping rules allowed this) occurred in 6 of 31 (19%) patients of the PCT group." **Quote:** "It is worthy to stress that in 19% of patients allocated to the PCT group, treating physicians refused to stop the antibiotics, although the stopping rules allowed this (Table E4). We can consider protocol overruling (i.e., prolongation of the antibiotic therapy by the treating physician beyond the stopping rule) as a ''conservative bias.''" **Quote:** "In no case assigned to the PCT group did the treating physicians stop antibiotics before the time when patients had reached the criteria for discontinuation based on the algorithm."

Blinding of Outcome Assessment (Detection Bias)	Unclear risk	**Comment:** No information given.
Incomplete Outcome Data (Attrition Bias)	Low risk	**Quote:** "Seventy-nine of the 282 patients screened for eligibility were randomized; 39 in the PCT group and 40 in the control group (Figure 1)." **Quote:** "Primary endpoints were first analyzed on the basis of an intention-to-treat analysis, including all randomized patients." **Quote***:* "Because of dropouts (early deaths and newly discovered complicated infections), 68 patients (control group, n=37, and PCT group, n=31) reached a time when a decision to stop antibiotics could be taken (PCT group) or potentially be taken (control group) based on the relative decrease of daily measured PCT levels (per-protocol analysis, Figure 1)." **Quote:** "the number of dropouts observed in this trial was imbalanced between the two groups (8 patients in the PCT group vs. 3 patients in the control group, P=0.197)." **Comment:** In the meta-analysis we consider only the intention-to-treat-analysis. Therefore there are no missing data. However, it remains unclear how dropouts have been included in the intention-to-treat-analysis.
Selective Reporting (Reporting Bias)	Unclear risk	**Primary outcome was reported according to the study protocol:** -Duration of antibiotic treatment -Total antibiotic exposure **Primary outcomes not mentioned in protocol and mentioned in published article:** -Days alive without antibiotics **Secondary outcomes mentioned in protocol and mentioned in published article:** -Clinical cure -28-day mortality -Length of hospital stay -Rate of nosocomial super-infection **Secondary outcomes mentioned in protocol and not mentioned in published article:** -Costs of antimicrobial therapy (in CHF) -Isolation of multi-resitant microorganisms (in clinical isolates per 100 patient-days) **Secondary outcomes mentioned in published article and not mentioned in protocol:** -In-hospital mortality -Sepsis-related death -Primary infection relapse rate -Length of ICU stay **Registration of study:** http://Clinicaltrials.gov: NCT00250666
Other Bias	Low risk	**Quote:** "The reasons for exclusion were as follows: (1) microbiologically documented infections caused by Pseudomonas aeruginosa, Acinetobacter baumanni, Listeria spp., Legionella

		pneumophila, Pneumocystis jiroveci, or Mycobacterium tuberculosis, for which a prolonged duration of antibiotic therapy is standard-of-care (17); […] or (8) absence of antimicrobial treatment despite clinical suspicion of sepsis." **Quote:** "For security, we excluded difficult-to-treat microorganisms, infections that are known to require prolonged antibiotic therapy, and severely immunocompromised and neutropenic patients." **Comment:** No extreme baseline imbalance between groups. **Quote:** "V.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.H. and J.P. received a research grant from BRAHMS AG ($50,000). BRAHMS AG had no influence on study design, data analysis, or final preparation of this manuscript. S.H. received speaker honoraria ($1,500) from BRAHMS AG. J.-D.G. does not have a financial relationship with a commerical entity that has an interest in the subject of this manuscript. P.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.P. received speaking honoraria from BRAHMS AG (less than $1,000 in 2006 and 2007)."

Study: Schroeder et al. 2009

Bias	**Authors´ Judgment**	**Support for Judgment**
Random Sequence Generation (Selection Bias)	Unclear risk	**Quote:** "Thereafter, patients were randomly assigned to either PCT-guided antibiotic treatment or a control group receiving standard antibiotic therapy."
Allocation Concealment (Selection Bias)	Unclear risk	**Comment:** No information given.
Blinding of Participants and Personnel (Performance Bias)	Low risk	**Comment:** Patients treated according to a strict protocol. **Quote:** "For either group, a calculated antibiotic regimen according to the underlying infectious pathology was applied." **Quote:** "In the PCT-guided group, antibiotic therapy was discontinued if clinical signs and symptoms of sepsis improved and PCT values either had decreased to 1 ng/ml or less or had dropped to 25–35% of the initial PCT concentration over three consecutive days. In the control group, antibiotic treatment was discontinued according to clinical signs and empiric rules. Independent from the study protocol, the physician in charge was always free to decide to continue or change the antibiotic regimen upon clinical judgement."
Blinding of Outcome Assessment (Detection Bias)	Unclear risk	**Comment:** No information given.
Incomplete Outcome Data (Attrition Bias)	Low risk	**Quote:** "27 of 125 screened patients met the inclusion criteria" **Quote:** "Finally, 14 patients were randomly assigned to the PCT-guided treatment group and

		13 patients to the control group." **Comment:** No missing outcome data.
Selective Reporting (Reporting Bias)	Unclear risk	**Outcomes reported in the methods section and in the results section of the article:** -Length of ICU stay -Duration of antibiotic treatment -Hospital mortality -SOFA -SAPS II **Outcomes reported in the methods section but not in the results section of the article:** -Length of hospital stay **Outcomes reported in the results section but not in the methods section of the article:** -Cost of antibiotic treatment **Comment:** No study protocol published. Trial not registered at http://www.clinicaltrials.gov or at http://www.isrctn.org
Other Bias	Low risk	**Comment:** No extreme baseline imbalance between groups. **Quote:** "The corresponding author declares speaking engagements for BRAHMS AG. All other authors declare no conflict of interest."

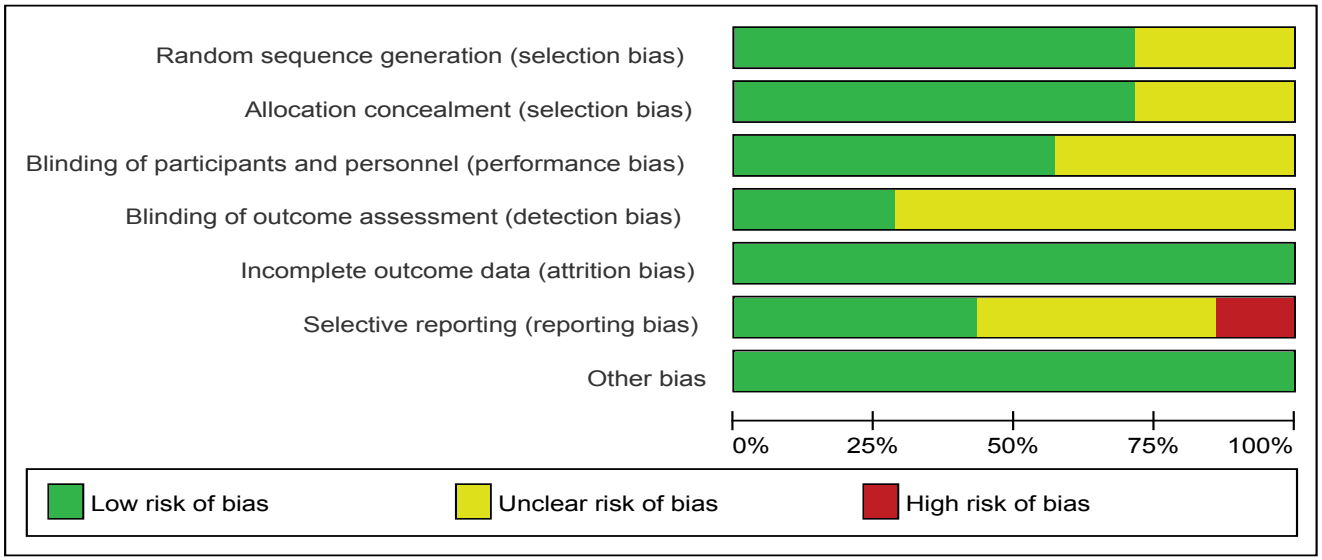
Study: Svoboda et al. 2007

Bias	**Authors´ Judgment**	**Support for Judgment**
Random Sequence Generation (Selection Bias)	Low risk	**Quote:** "Patients were randomly assigned to study groups by means of a computer generated random number table to generate a random treatment list."
Allocation Concealment (Selection Bias)	Low risk	**Quote:** "Treatment regimens were included in opaque sealed numbered envelopes and envelope with the lowest number was always used for consecutive patients."
Blinding of Participants and Personnel (Performance Bias)	Low risk	**Comment:** Patients treated according to a strict protocol. **Quote:** "Of 453 screened patients, 72 patients fulfilled the inclusion criteria and were randomized into 2 study groups: in the first group (PCT, n=38), more important role in the treatment decision was given to PCT level (severe sepsis with PCT >2ng/mL signalized bacteremia and pushed us to change antibiotics and catheters; severe sepsis with PCT <2ng/mL prompted to ultrasonography and/or CT, followed by repeated surgical treatment – drainage, re-operation - if localized infection was confirmed). The control group (CON, n=34) was treated by standard evaluation of all parameters by consultant surgeon according to contemporary treatment protocol of our institute."

Blinding of Outcome Assessment (Detection Bias)	Unclear risk	**Comment:** No information given.
Incomplete Outcome Data (Attrition Bias)	Low risk	**Quote:** "Of 453 screened patients, 72 patients fulfilled the inclusion criteria and were randomized into 2 study groups" **Quote:** "Seventy-two patients with severe sepsis after abdominal surgery or after surgery for multiple trauma were randomly allocated in group PCT (n=38) or CON (n=34)." **Comment:** no missing outcome data.
Selective Reporting (Reporting Bias)	Low risk	**Same outcomes reported in the methods section and the results section of the article:** -28-day mortality -Duration of stay in the ICU -Days of mechanical ventilation -SOFA score **Comment:** No study protocol published. Trial not registered at http://www.clinicaltrials.gov or at htpp://www.isrctn.org Trial registered at http://www.sukl.eu
Other Bias	Low risk	**Comment:** No extreme baseline imbalance between groups. **Quote:** "The study was supported by Grant of IGA MZ CR ND 7676-3."

9.1.2 Additional File 2. Risk of Bias Graph

Judgment of bias via Cochrane Collaboration's tool for assessing risk of bias



9.2 Lebenslauf

Name, Vorname	Anna Prkno
Geburtsdatum	10.04.1988
Geburtsort	Pirna

Schulbesuche

1998 bis 2000	Friedrich-Schiller-Gymnasium, Pirna
2000 bis 2006	Götzinger-Gymnasium, Neustadt in Sachsen

Schulabschluss

2006	Abitur

Hochschulstudium

2006 bis 2014	Friedrich-Schiller-Universität, Jena Studiengang Humanmedizin
2008	Erster Abschnitt der Ärztlichen Prüfung Mit der Note - Gut - bestanden
2011 bis 2012	Beurlaubung zwecks Promotion Promotionsstipendium des CSCC (Center for Sepsis Control and Care) Jena
2014	Zweiter Abschnitt der Ärztlichen Prüfung Mit der Note - Sehr gut – bestanden

Hochschulabschluss

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Assistenzarztausbildung

Seit 2014	Assistenzärztin an der Zürcher Höhenklinik Davos

Publikationen

2013 Prkno A, Wacker C, Brunkhorst FM, Schlattmann P: Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock – a systematic review and meta-analysis. Critical Care, 17 (6):R291

2013 Wacker C, Prkno A, Brunkhorst FM, Schlattmann P: Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Diseases, 13 (5):426-435

Davos, 27.10.2014

9.3 Ehrenwörtliche Erklärung

Hiermit erkläre ich, dass mir die Promotionsordnung der Medizinischen Fakultät der Friedrich-Schiller-Universität bekannt ist,
ich die Dissertation selbst angefertigt habe und alle von mir benutzten Hilfsmittel, persönlichen Mitteilungen und Quellen in meiner Arbeit angegeben sind,
mich folgende Personen bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskripts unterstützt haben: Prof. Schlattmann, Prof. Brunkhorst, Christina Wacker,
die Hilfe eines Promotionsberaters nicht in Anspruch genommen wurde und dass Dritte weder unmittelbar noch mittelbar geldwerte Leistungen von mir für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen,
dass ich die Dissertation noch nicht als Prüfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung eingereicht habe und
dass ich die gleiche, eine in wesentlichen Teilen ähnliche oder eine andere Abhandlung nicht bei einer anderen Hochschule als Dissertation eingereicht habe.

Davos, 27.10.2014 Unterschrift des Verfassers