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Original article

A PCT algorithm for discontinuation of antibiotic therapy is a cost-effective way to reduce antibiotic exposure in adult intensive care patients with sepsis

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Abstract

Objective:
Procalcitonin (PCT) is a specific marker for differentiating bacterial from non-infective causes of inflammation. It can be used to guide initiation and duration of antibiotic therapy in intensive care unit (ICU) patients with suspected sepsis, and might reduce the duration of hospital stay. Limiting antibiotic treatment duration is highly important because antibiotic over-use may cause patient harm, prolonged hospital stay, and resistance development. Several systematic reviews show that a PCT algorithm for antibiotic discontinuation is safe, but upfront investment required for PCT remains an important barrier against implementation. The current study investigates to what extent this PCT algorithm is a cost-effective use of scarce healthcare resources in ICU patients with sepsis compared to current practice.

Methods:
A decision tree was developed to estimate the health economic consequences of the PCT algorithm for antibiotic discontinuation from a Dutch hospital perspective. Input data were obtained from a systematic literature review. When necessary, additional information was gathered from open interviews with clinical chemists and intensivists. The primary effectiveness measure is defined as the number of antibiotic days, and cost-effectiveness is expressed as incremental costs per antibiotic day avoided.

Results:
The PCT algorithm for antibiotic discontinuation is expected to reduce hospital spending by circa €3503 per patient, indicating savings of 9.2%. Savings are mainly due to reductions in length of hospital stay, number of blood cultures performed, and, importantly, days on antibiotic therapy. Probabilistic and one-way sensitivity analyses showed the model outcome to be robust against changes in model inputs.

Conclusion:
Proven safe, a PCT algorithm for antibiotic discontinuation is a cost-effective means of reducing antibiotic exposure in adult ICU patients with sepsis, compared to current practice. Additional resources required for PCT are more than offset by downstream cost savings. This finding is highly important given the aim of preventing widespread antibiotic resistance.

Abbreviations:
CAP, community acquired pneumonia; ICU, intensive care unit; IQR, interquartile range; NZA, Nederlandse Zorg Autoriteit (Dutch Healthcare Authority); PCT, procalcitonin; PSA, probabilistic sensitivity analysis; RCT, randomized controlled trial; SD, standard deviation

Background

Despite advances in medical technology and clinical care, sepsis remains a common cause of morbidity and mortality among hospitalized patients[1]. Diagnosing patients with sepsis is challenging, due to the often non-specific presentation[2]. Yet, early diagnosis of infection and rapid initiation of adequate antimicrobial therapy are critical for successful treatment outcome[3]. While the use of antibiotics has led to great reductions in mortality and morbidity rates among sepsis patients, antibiotic over-use should be avoided as this may cause patient harm and prolonged hospital stay, and plays a role in the development of widespread antibiotic resistance[4,5].

A biomarker that might improve the efficient and more judicious use of antibiotic therapy by monitoring the progression and prognosis of bacterial infections and sepsis is procalcitonin (PCT), a precursor of calcitonin. PCT elevation occurs within 2–4 h after onset of the inflammatory disorder, typically peaks in the second day, and falls rapidly during clinical recovery. The magnitude and duration of PCT elevation correlate with injury severity and prognosis. While PCT may also be elevated in viral and fungal infections (e.g., candidemia), this is generally much less so than with bacterial infections[6].

Several studies have assessed the added value of using PCT to monitor and manage antibiotic therapy in septic intensive care unit (ICU) patients, as well as in reducing the duration of hospital stay[7–9]. A number of systematic reviews have shown that a PCT discontinuation algorithm is safe and may even improve clinical outcomes[10–12]. Yet, the upfront investment for PCT testing compared to other laboratory assays remains a barrier against implementation. Therefore, analysis of the impact of PCT testing on in-hospital mortality, number of antibiotic days, duration of hospitalization, and total costs of sepsis care is warranted.

The goal of the current study is to investigate to what extent this PCT algorithm is a cost-effective use of scarce healthcare resources in ICU patients with sepsis compared to current practice. A model-based analysis was performed based on a systematic review of the literature published until mid-2014.

In addition to previously published cost-effectiveness analyses in this patient population[13,14], this study explicitly considers the impact of PCT testing on hospital length of stay and on specific clinical outcomes, and reports costs from a non-US perspective.

Methods

A decision tree was developed to estimate the health economic consequences of a PCT algorithm for antibiotic discontinuation in a hypothetical population of adult ICU patients with sepsis. The analysis was performed from a Dutch hospital perspective. The time horizon of the model covers the duration of a patient's hospital stay. All relevant health economic impacts of hospital stay and accompanying treatment were incorporated, and compared to current practice. The primary effectiveness measure was defined as the number of antibiotic days in both the PCT strategy and current practice. In this analysis, the total direct hospital costs were balanced against the number of antibiotic days avoided. The Incremental Cost Effectiveness Ratio (ICER) was expressed as incremental costs per antibiotic day avoided and calculated as the difference in direct healthcare costs, between the PCT strategy and current practice, divided by number of antibiotic days avoided by the PCT strategy.

Literature review

A systematic literature review was performed to determine to what extent a PCT algorithm affects the number of antibiotics days, ICU length of stay, total duration of hospital stay, number of days on mechanical ventilation and/ or dialysis, number of blood cultures and other lab analyses performed, as well as patient safety which is expressed as in-hospital mortality rates. The PubMed database was searched for relevant articles that reported outcomes on at least one of those parameters. The following combinations of terms were searched in all fields: (*algorithm* OR *guide* OR *guided* OR *based*) AND (*sepsis* OR *septic shock* OR *critically ill*) AND (*PCT* or *procalcitonin*) AND (*antibiotic* OR *antibiotics*). The search was limited to articles published in English or Dutch, and was restricted to randomized controlled trials (RCTs), meta-analyses, and systematic reviews. Articles were excluded when they did not focus on: (1) adult patients, (2) sepsis or critically ill patients on the ICU, and (3) the added value of a PCT algorithm for antibiotic discontinuation. Relevant articles were initially selected based on title and abstract. After that, full texts were reviewed to assess whether the papers met the inclusion criteria. The literature search was performed in July 2014. Mean values and standard deviations (SDs) were obtained from each of the individual studies where possible. For studies in which no mean or SDs could be obtained, estimates of mean and SDs were calculated according to Hozo *et al.*[15]. Following this, weighted mean differences were calculated using Review Manager version 5.1, combining the sample sizes of the studies included with the mean and standard deviations of each parameter (see Supplementary Additional file 1) using a random effects model[16].

Resource use

Data concerning the length of a patient's hospital stay (both on the ICU and on the general ward), as well as the duration of antibiotic treatment in both the PCT strategy and in current practice, have been derived from the systematic literature review, as described above. In addition, the change in the duration of mechanical ventilation has also been derived from this review. The percentage of patients with sepsis that are treated with

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mechanical ventilation and/or dialysis, as well as the duration of each, were derived from a retrospective database analysis of ICU patients (age > 16 years) performed by Adrie *et al.*[17]. The percentage of patients in whom a blood culture is performed and who are finally diagnosed as having sepsis was derived from an observational cohort study by Shapiro *et al.*[18]. A prospective cohort study by Müller *et al.*[19] found that PCT measurement is an accurate parameter for predicting bacteraemia in patients with community acquired pneumonia (CAP), and that it has the potential to reduce the number of blood cultures drawn from hospitalized patients with suspected CAP. Because pneumonia is a common site of infection for sepsis[17], the percentage of patients with suspected sepsis in whom a blood culture was performed (both with and without PCT) as well as the number of sets of blood cultures taken per patient, were derived from Müller *et al.*[19]. The number of PCT measurements performed in ICU patients with sepsis was estimated based on RCTs by Stocker *et al.*[20] and Schuetz *et al.*[21]. For the percentage of patients treated with antibiotics, and the frequency at which laboratory tests (other than the PCT test) are ordered in ICU patients with sepsis, no single estimate could be obtained from the literature. Therefore, those were estimated based on qualitative interviews with intensivists ($n = 2$) and clinical chemists ($n = 5$). An overview of the resource use parameters, the data sources, and assumptions that served as input for the model is provided in Table 1.

Unit costs

The model incorporates costs of diagnostic testing (i.e., blood cultures, PCT testing, and other routinely performed laboratory tests), hospital stay on ICU and general ward, antibiotic therapy, mechanical ventilation, and dialysis. Unit costs of blood cultures performed were derived from publications by Müller *et al.*[19] and Van Nieuwkoop *et al.*[22]. Tariffs for laboratory tests were derived from the Dutch Healthcare Authority (Nederlandse Zorgautoriteit, NZA)[23]. Because no such tariff currently exists for PCT, those costs were based on interviews with clinical chemists and intensivists. Unit costs of hospital stay, separate for ICU stay and stay on a general ward, mechanical ventilation, and dialysis were derived from the Dutch Healthcare Authority[24] and the costing manual by Hakkaart-van Roijen *et al.*[25]. Mean daily costs for antibiotic treatment were obtained from Vandijck *et al.*[26]. All costs were converted to 2013 Euros, using Dutch consumer price index levels[27]. Because the time horizon of the model concerns the duration of a patient's hospital stay, lasting shorter than 1 year, discounting is not required. A summary of all cost inputs used in the model is provided in Table 2. Direct hospital costs are calculated by multiplying resource use with the accompanying unit costs.

Sensitivity analyses

To determine the joint decision uncertainty, a probabilistic sensitivity analysis (PSA) was performed with 10,000 model runs, in which random samples are drawn from all input parameters simultaneously based on pre-defined parameter distributions. Distributions were parameterized based on the observed parameter mean and on the observed or assumed standard error[28]. Beta distributions were fitted to the probability parameters, and Gamma distributions to the resource use parameters[28].

To identify which individual parameters drive the model outcome we conducted a one-way sensitivity analysis. For each parameter, the impact of a change in the base case value across a pre-determined range on the ICER (i.e., costs per antibiotic day avoided) was analysed. Parameters concerning resource use that were obtained

Table 1. Resource use. Overview of resource use in the model, showing the values used in the model, and the values applied in the one-way sensitivity analysis in brackets. The right column shows the references used to obtain an estimate for each parameter.

Parameter	Value		Reference
	Without PCT	With PCT	
Percentage treated with antibiotics*	100.0%	100.0% (75–100.0%)	Expert opinion
Percentage treated with mechanical ventilation	77.0%	77.0% (57.8–96.3%)	Adrie *et al.*[17]
Percentage treated with dialysis	16.0%	16.0% (12–20%)	Adrie *et al.*[17]
Days on dialysis	5.0	5.0 (3.75–6.25)	Adrie *et al.*[17]
Percentage of patients with (suspected) sepsis in whom a blood culture is taken	97.5%	61.4% (79.5–43.4%)	Müller *et al.*[19]
Percentage of patients with blood culture performed, diagnosed as having sepsis	8.2%	8.2% (6.1–10.2%)	Shapiro *et al.*[18]
Sets of blood cultures taken per patient with (suspected) sepsis	2	2 (1.5–2.5)	Müller *et al.*[19]
Frequency of laboratory tests ordered per patient*	25.1	21.8 (23.4–20.1)	Expert opinion
Number of PCT measurements performed per patient**	0	5 (2.5–7.5)	Stocker *et al.*[20], Schuetz *et al.*[21]

*Expert opinions were obtained via interviews with intensivists ($n = 2$) and clinical chemists ($n = 5$).
**Because these publications both report that four-to-five PCT measurements are performed in neonates with suspected sepsis and patients with lower respiratory tract infections, respectively, an estimate of five PCT measurements is assumed to be a conservative estimate for adult ICU patients with sepsis.

Table 2. Cost parameters. Overview of cost parameters used in the model. The right column shows the references used.

Parameter	Value	Reference
Day on general ward	€500.96	Hakkaart-van Roijen *et al.*[25]
ICU admission	€485.23	NZA tariffs[23]
Day on ICU	€1811.79	NZA tariffs[23]
Day mechanical ventilation	€386.32	NZA tariffs[23]
Day dialysis treatment	€290.48	NZA tariffs[23]
Day of intravenous antibiotics	€126.66	Vandijck *et al.*[26]
Set of blood cultures performed	€57.84	Müller *et al.*[19], van Nieuwkoop *et al.*[22]
Order tariff for laboratory tests	€13.73	NZA tariffs[23]
PCT test	€15.00	Expert opinion*
Other laboratory tests	Varying	NZA tariffs[23]

*Expert opinions were obtained via interviews with intensivists ($n=2$) and clinical chemists ($n=5$).

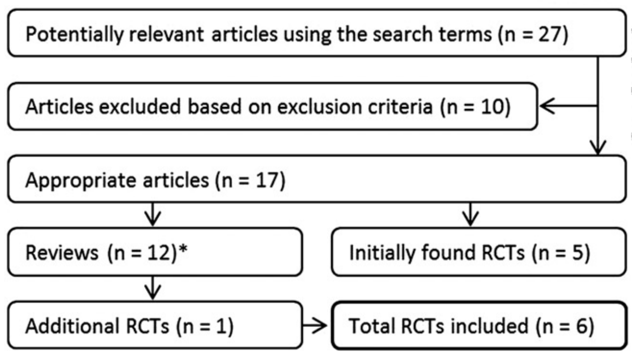

Figure 1. Overview of included and excluded articles. This figure shows an overview of the selection process of the studies included in the systematic review. *Consisting of 11 reviews (of which 8 meta-analyses), and 1 economic evaluation.

from the literature review (ICU days, general ward days, duration of antibiotics, and duration of mechanical ventilation) were all varied with 1 SD below and above the mean.

Parameters that are not directly affected by PCT implementation but which are to some extent uncertain in both strategies were varied, with 25% below and above the mean in the PCT strategy. In the remaining parameters for which an effect due to the PCT algorithm compared to current practice was expected, this effect was increased and decreased with 50% in the PCT strategy (Table 1). The results of this sensitivity analysis are shown in a tornado diagram, in which the impact of each parameter is sorted by decreasing impact on the ICER (i.e., costs per antibiotic day avoided).

Results

Systematic review

The search strategy initially resulted in 27 articles. Based on the exclusion criteria, five articles were excluded because they did not focus on sepsis or critically ill patients at the ICU, three articles were excluded because they focused on infants or new-borns instead of adults, and two articles were excluded because they either focused specifically on point-of care testing or on the comparison with another laboratory marker instead of focusing on current practice. Finally, this resulted in the identification of 11 reviews (of which eight meta-analyses), five original RCTs and one economic evaluation of PCT. As the summarized or pooled data from the reviews and economic evaluation did not exactly match the data specification as needed for our model, the reviews and the economic evaluation were hand searched to find the relevant original studies (RCTs) to directly obtain the relevant original data. In addition to five RCTs already identified, this hand search yielded one additional RCT, amounting to a total of six unique RCTs that were included[7–9,29–31]. Figure 1 shows a flow chart of the search strategy. Review Manager was used to calculate pooled estimates of the duration of ICU and general ward stay, duration of mechanical ventilation, duration of antibiotic treatment, and in-hospital mortality. Mean values and SDs were obtained from each of the individual studies where possible. In one study, no means or SDs were reported[29]. Because the sample size of this study was sufficiently

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Table 3. Result of systematic literature review, showing the values used in the model, and the values applied in the one-way sensitivity analysis (±1 SD) in brackets. The right column shows the references used.

Parameter	Value		Reference
	Without PCT	With PCT	
General ward days	11.3	9.0 (6.0–12.0)	Nobre *et al.*[9], Bouadma *et al.*[30], Annane *et al.*[31], Deliberato *et al.*[29]
ICU days	13.8	12.7 (11.5–13.9)	Nobre *et al.*[9], Hochreiter *et al.*[8], Schroeder *et al.*[7], Bouadma *et al.*[30], Annane *et al.*[31], Deliberato *et al.*[29]
Days on antibiotics	11.6	9.9 (9.4–10.3)	Nobre *et al.*[9], Hochreiter *et al.*[8], Schroeder *et al.*[7], Bouadma *et al.*[30], Annane *et al.*[31], Deliberato *et al.*[29]
Days on mechanical ventilation	10.0	10.6 (9.9–11.6)	Annane *et al.*[31], Bouadma *et al.*[30], Adrie *et al.*[17]

large, the median was assumed to be the best estimate of the mean according to Hozo *et al.*[15], who also state that the accompanying SD can be calculated by dividing the interquartile range (IQR) by a factor of 1.35 (SD = IQR/1.35)[15,16].

Cost-effectiveness

Five studies reported in-hospital mortality rates and showed no statistically significant difference between the PCT strategy and current practice (OR = 0.83; 95% CI = 0.49–1.38)[7–9,29,31]. Therefore, equal in-hospital mortality rates of the PCT algorithm compared to current practice were applied.

The PCT algorithm applied varied between studies, using either a decrease in the peak PCT value (ranging from 20–90%), and/or a decrease in the absolute value of PCT (ranging from < 0.1 μg/L to < 1 μg/L)[7–9,29–31]. Regarding the primary effectiveness parameter, a statistically significant reduction in antibiotic days with a mean of 1.71 days (95% CI = −2.67, −0.74) was found[7–9,29–31]. Implementation of PCT testing showed a trend towards a decrease in overall hospital length of stay of on average 3.34 days (95% CI = −9.38, 2.69)[9,29–31] as well as a decrease in the duration of ICU stay of 1.08 days (95% CI = −3.52, 1.36)[7–9,29–31]. Therefore, a decreased length of stay on the general ward of 3.34–1.08 = 2.26 days is expected. Two studies reported the effect of the PCT algorithm on the duration of mechanical ventilation[30,31], with a weighted mean increase of 0.71 days (95% CI = −1.00, 2.42) per 12.0 days. Combined with the baseline number of 10.0 mechanical ventilation days as reported by Adrie *et al.*[17], the PCT strategy is associated with a weighted increase of 0.59 mechanical ventilation days. None of the included studies reported an effect of a PCT algorithm on the duration of dialysis. A summary of the parameter inputs based on the systematic review, as well as the range applied in the one-way sensitivity analysis (mean ± 1 SD) is provided in Table 3. The forest plots of these parameters are shown in Supplementary Additional file 1.

A PCT algorithm to guide antibiotic discontinuation is expected to reduce direct hospital costs per adult ICU patient with sepsis from €37,917 to €34,414, a decrease of €3503 (−9.2%). This cost reduction is achieved with a 1.7 day reduction in duration of antibiotic use, i.e. from 11.6 to 9.9 days, and this translates into an incremental cost saving of €2043 per antibiotic day avoided. On a national level it is estimated that ∼13,000 adult ICU patients in the Netherlands are diagnosed with sepsis each year, indicating a potential cost saving of almost 46 million Euros per year[32]. An overview of those results is shown in Table 4. Of the €3503 cost savings per patient, a decrease of €3132 is attributable to the reduced hospital length of stay. In the conservative scenario where the reduction of length of stay is fully ignored, as is the accompanying decrease in laboratory tests that are assumed to be performed once-daily (i.e., savings of €82), overall direct hospital costs are still estimated to decrease with €289 per patient (i.e. €3503 − €3132 − €82 = €289). Those cost savings are mainly achieved by a decrease in the number of blood cultures performed and the duration of antibiotic therapy.

The decision uncertainty surrounding the incremental cost-effectiveness ratio (ICER; point estimate €2043 per antibiotic day avoided), as depicted in Figure 2, is low, as 82% (i.e., 8167/10 000) of Monte Carlo simulations indicate that PCT reduces the duration of antibiotic treatment while saving costs compared to current practice. Only 18% (1771/10,000) of the simulations suggest that PCT would be more expensive while being more effective in reducing the number of antibiotic days.

One-way sensitivity analysis was performed to estimate the impact of changes in individual input parameters on the difference in costs of the PCT strategy compared to current practice. Results are summarized in a tornado diagram (Figure 3). This figure illustrates that the net change in ICU and general ward days have the largest impact on costs. An overview of all results of the

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Table 4. Model results. The costs per patient with sepsis at the ICU, split up for each of the aspects of the treatment. Overall costs are shown both per patient and for the estimated yearly number of ICU patients with sepsis in the Netherlands ($n = 13\,000$)[32]. Numbers may not add up due to rounding.

Parameter	Value		Difference
	Without PCT	With PCT	
Hospital stay	€31,214	€28,083	−€3132
General ward	€5666	€4555	−€1112
ICU admission and stay	€25,548	€23,528	−€2020
Treatment	€4672	€4637	−€35
Antibiotics	€1465	€1248	−€218
Mechanical ventilation	€2974	€3157	€182
Dialysis therapy	€232	€232	€0
Laboratory analyses	€2030	€1694	−€336
Blood cultures	€1392	€1063	−€329
PCT	€0	€75	€75
Other laboratory tests	€638	€556	−€82
Total costs per patient	€37,917	€34,414	−€3503
Total costs in the Netherlands ($n = 13\,000$)	€492,916,869	€447,379,610	−€45,537,259

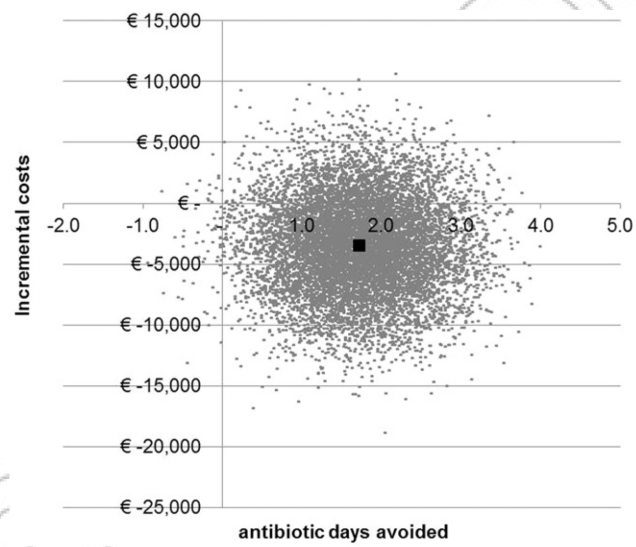

Figure 2. Scatterplot of the results of Probabilistic Sensitivity Analysis (PSA), showing the result of 10,000 simulations and the average value.

one-way sensitivity analysis is provided in Supplementary Additional file 2.

Discussion

This study shows that the upfront investments in PCT testing should not be considered in isolation, but as part of the whole pathway of care a patient receives. Our results indicate that, although PCT requires additional investments, those are more than offset against downstream cost savings due to a reduced duration of hospital stay and accompanying treatment. PCT to guide antibiotic discontinuation in adult ICU patients with sepsis is expected to reduce the number of antibiotic days and save costs without compromising patient outcomes. As such, this study adds new insights to the very recent evidence base regarding cost-effectiveness of PCT testing in different patient populations and settings. For example, Harrison and Collins (2015) found that the use of a PCT guided treatment algorithm dominated current practice with improved quality-of-life and decreased overall treatment costs in a US cohort of adult ICU patients with suspected bacterial infection and sepsis[14]. Notably, their analysis does not take the impact of PCT testing on hospital length of stay into account, which our study showed to be a very important driver of cost savings.

A couple of aspects of our analysis warrant further attention. First, none of the RCTs included showed a difference in in-hospital mortality for the PCT algorithm

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	Base case model input with PCT	Lower limit	Upper limit
Effect on ICU days	12.7	11.5	13.9
Effect on regular ward days	9.0	6.0	12.0
Effect on percentage mechanical ventilation	77%	58%	96%
Blood cultures performed in patients diagnosed as having sepsis	8.2%	6.1%	10.2%
Effect on percentage of patients in whom a blood culture is performed	61%	79%	43%
Effect on days mechanical ventilation	10.6	9.9	11.6
Sets of blood cultures performed per patient	2.0	1.5	2.5
Percentage receiving antibiotics	100%	75%	100%
Effect on antibiotic days	9.9	9.4	10.3
Number of days on dialysis therapy	5.0	3.8	6.3
Percentage of patients on dialysis therapy	16%	12%	20%
Number of times laboratory tests ordered	21.8	23.4	20.1
Number of times PCT test performed	5.0	2.5	7.5

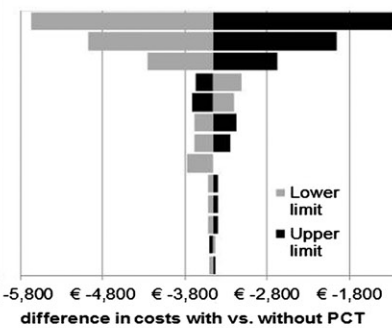

Figure 3. Tornado diagram showing the effect of varying input parameters on model outcome. The lower and upper limits used in the sensitivity analysis for each parameter are shown in the grey boxes. The parameters derived from the systematic review (duration of ICU stay, general ward stay, mechanical ventilation, and antibiotic therapy) are varied with one SD below and above the mean. For parameters that show an effect in the PCT strategy compared to current practice, the impact of changing this effect with 50% is shown (percentage of patients in whom a blood culture is performed). All input parameters for which no effect was found due to the PCT strategy, a variation of 25% was used as lower and upper limit.

compared to current practice. Actually, as the pooled estimate of the five RCTs reporting in-hospital mortality shows a trend towards decreased in-hospital mortality in the PCT group (odds ratio = 0.83), our model is conservative for using an equal mortality rate. Although one of the RCTs reported an absolute increase in 60-day mortality of 3.8% in the PCT group, which may potentially question the safety of that PCT algorithm, the authors of this study state that 'no patient in either group who died during days 29–60 had an infection relapse, and most deaths resulted from complications directly related to the severity of underlying disease'. Also, after controlling for potential confounders, the odds ratio for death by day 60 was not significantly different between the study groups[30].

Second, cost savings associated with a PCT algorithm were estimated to be €3503 per patient (−9.2%), while avoiding 1.7 antibiotic days (−14.8%), which indicates that the PCT algorithm dominates current practice. Those cost savings are achieved by a reduction in ICU and general ward length of stay, a reduction in the number of blood cultures performed, and, importantly, a reduction in the duration of antibiotic treatment. Although the results of the systematic review indicate a small (and non-significant) increase in mechanical ventilation days, this evidence is only based on two studies. Because one of these studies is very small, this increase cannot be considered conclusive. In addition, a retrospective study by Hohn *et al.*[33] shows a decrease in the duration of mechanical ventilation. This clearly indicates that further research about the effect of a PCT algorithm on the duration of mechanical ventilation is necessary.

A conservative re-analysis of the model, assuming that the PCT strategy does not reduce ICU and general ward length of stay, further confirms the conclusion that the PCT algorithm to discontinue antibiotic treatment is cost-saving. Compared to current practice, €289 per ICU patient with sepsis are saved (compared to the €3503 in the base case scenario). These remaining cost savings are mainly attributable to the reduced duration of antibiotic treatment and the reduced number of blood cultures performed. As blood cultures are an important tool to confirm sepsis and because the amount of blood cultures required to do so is assumed to be affected by the PCT test, costs for all blood cultures performed in relation to sepsis were included to give the best estimate of the actual impact of PCT. An *ad hoc* two-way sensitivity analysis (data not shown) shows that, in fact, when the number of ICU days is kept equal between the strategies, the number of regular ward days may increase with 1 day in the PCT strategy, before this strategy becomes more costly than current practice. Clearly, when the cost-savings due to the length of stay reduction (i.e., €3132) would not accrue, the decision uncertainty surrounding the model outcomes will increase. The probabilistic sensitivity analysis performed under this conservative scenario shows a 53% probability that the PCT algorithm dominates current practice by saving €289 per patient (compared to 82% under the base case scenario), while there is a 46% probability that the PCT strategy is more expensive while reducing the number of antibiotic days.

Third, the reduction in number of antibiotic days that can be achieved by a PCT algorithm for antibiotic discontinuation is highly important, not only for its impact on total direct healthcare costs, but notably so given the rise in antibiotic resistance. Indeed, prolonged antibiotic duration impacts the incidence of antibiotic resistance and *Clostridium difficile* infections, which in this population amounts to 4.7% and 4.6% per hospital episode, respectively[34–36]. While not the focus of the current paper, one could make a rough estimation of the additional indirect

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cost savings of PCT testing by considering the excess length of stay due to antibiotic resistance and C. *difficile*, reportedly circa 4.6 days and 0.9 days per patient, respectively[37–39]. As shorter duration of antibiotic therapy is shown to decrease the incidence of antibiotic resistance and C. *difficile* infections to 4.5% and 3.9%, respectively[36,40,41], this accrues additional cost savings, leading to a new estimate of total costs per ICU patient with sepsis of roughly €35 235 in the PCT strategy (compared to €34 414 in the PCT base case analysis), i.e., additional savings of €821 per patient.

Fourth, adherence to the PCT algorithm is shown to affect its cost-effectiveness. For example, Harrison and Collins[14] showed that adherence of at least 42.3% was needed to render their specific PCT testing strategy cost-effective. Although we did not perform a sensitivity analysis on adherence rate, the data used in our model do reflect sub-optimal adherence to some extent, as the studies of Bouadma *et al.*[30] and Annane *et al.*[31] report that adherence in their studies was low. Explicit consideration of adherence is recommended for further work in this area.

The results of this analysis are in line with other reviews such as Tang *et al.*[12], Agarwal *et al.*[11], and Heyland *et al.*[42], who conclude that PCT guided antibiotic therapy is associated with a reduction in antibiotic usage that may reduce overall costs of care, under certain assumptions. The latter is important for transferring results to a specific country, as one has to consider to what extent the current model assumptions and inputs are representative for that country. Because relative treatment effects are typically more transferable between developed Western countries than costs are (due to large differences in resource use and unit costs), ideally the model should be populated with country-specific data as much as possible to make valid per country estimations. For example, the duration of hospital stay and the duration of antibiotic treatment is relatively short in the Netherlands compared to other European countries[43], thus more benefit might be expected of the PCT assay in other European countries. Analyses for Germany and the UK are currently ongoing, but preliminary results suggest that the conclusions are robust across the different countries.

Furthermore, the reduction in the duration of antibiotic use as found in our review (1.7 days) can be considered as consistent yet conservative compared to other studies. Heyland *et al.*[42] reported a weighted average decrease in antibiotic duration of 2.14 days, and a study by Wilke *et al.*[13] reports an average reduction of 4 days. Interestingly, the expected cost savings as reported in our study are higher than those reported by Wilke *et al.*, which can, amongst others, be explained by the fact that Wilke *et al.* considered the effect of PCT on ICU length of stay and on the duration of antibiotic therapy, while our study considered the effect of PCT on the entire hospitalization episode. Also, in the study by Wilke *et al.*, the costs were derived from the German DRG calculation and applied to a real-life patient population, which might explain the differences in reported cost savings. Despite differences in the magnitude of cost savings, both studies suggest that substantial cost savings can be achieved following PCT implementation[13,42].

This study considered the use of PCT as a biomarker for antibiotic discontinuation, not as a biomarker that guides initiation of antibiotic therapy. Although other studies, notably the one of Saeed *et al.*[44], report that PCT testing can support the decision of whether or not to start using antibiotics in situations where there is a clinical suspicion of infection, we conservatively did not consider this option in our model. Interviews with intensivists and clinical chemists in the Netherlands revealed that PCT is unlikely to be accepted as a marker to decide on starting antibiotics, because of the rapid increase in mortality associated with delayed antibiotic therapy in sepsis patients. However, it seems reasonable to argue that PCT might support the decision to withhold antibiotics if a sub-group of patients can be identified that only have a minor suspicion of sepsis. If possible, this may further improve the added value of the PCT test as a means for fighting antibiotic resistance.

An additional recommendation for further cost-effectiveness studies in this field is to consider the costs of implementing a PCT algorithm. Although the test is available for most routinely used laboratory analysers, other additional resources may be needed to implement a PCT algorithm (e.g., costs of educating laboratory staff to perform the test), which will affect its incremental cost-effectiveness, particularly in the early stages of implementation.

Conclusions

Proven safe, we conclude that a PCT algorithm for antibiotic discontinuation is a cost-effective testing strategy in adult intensive care patients with sepsis compared to current practice. The PCT strategy as studied in this analysis effectively reduces the duration of antibiotic therapy, while the cost of testing is more than recouped by downstream cost-savings that accrue from shorter hospital length of stay, shorter duration of antibiotic therapy, and reduced number of blood cultures. Further research is needed to explore the potential impact of PCT algorithms on reducing antibiotic resistance.

Transparency

Declaration of funding
PANAXEA b.v. received funding from BRAHMS GmbH, part of Thermo Fisher Scientific, Hennigsdorf, Germany, for developing

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and analysing the model. The funding party has reviewed draft and final versions of the manuscript. The views expressed in this paper are solely the authors'.

Declaration of financial/other relationships

LMGS and MJI report stock ownership of Panaxea bv, Enschede, The Netherlands, which received funding from BRAHMS GmbH, part of Thermo Fisher Scientific, Hennigsdorf, Germany

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Additional file 1: results of literature review

Title: A PCT algorithm for discontinuation of antibiotic therapy is a safe and cost-effective intervention to reduce antibiotic exposure in adult intensive care patients with sepsis.
Journal: Journal of Medical Economics
Authors: Michelle MA Kip, Ron Kusters, Maarten J IJzerman, Lotte MG Steuten
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The following figures show the results of the literature review concerning the safety and effectiveness of a PCT algorithm for antibiotic discontinuation in adult ICU patients with sepsis. Pooled estimates for each parameter were obtained using Review Manager. A random effects model was applied. An overall estimate of the treatment effect is visualized in a forest plot for each parameter, including the 95% confidence interval.

Study or Subgroup	PCT Events	PCT Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Annane 2013	7	31	10	30	24.8%	0.58 [0.19, 1.81]
Deliberato 2013	2	42	4	39	12.4%	0.44 [0.08, 2.54]
Hochreiter 2009	15	57	14	53	33.6%	0.99 [0.43, 2.32]
Nobre 2008	9	39	9	40	21.5%	1.03 [0.36, 2.96]
Schroeder 2009	3	14	3	13	7.7%	0.91 [0.15, 5.58]
Total (95% CI)		**183**		**175**	**100.0%**	**0.83 [0.49, 1.38]**
Total events	36		40			

Heterogeneity: $Chi^2 = 1.23$, df = 4 (P = 0.87); $I^2 = 0\%$
Test for overall effect: Z = 0.73 (P = 0.47)

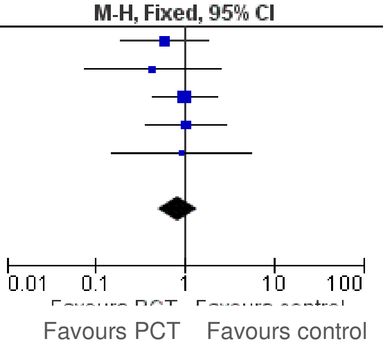

Figure Ia – in-hospital mortality. This table shows the impact of a PCT algorithm for antibiotic discontinuation on in-hospital mortality.

Study or Subgroup	PCT Mean	PCT SD	PCT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Annane 2013	32.3	26.8	30	55.5	79.5	28	3.6%	-23.20 [-54.17, 7.77]
Bouadma 2010	26.1	19.3	307	26.4	18.3	314	63.7%	-0.30 [-3.26, 2.66]
Deliberato 2013	11	136	14	11	56.5	13	0.6%	0.00 [-77.58, 77.58]
Nobre 2008	20.9	16.8	39	28.1	19.7	40	32.1%	-7.20 [-15.27, 0.87]
Total (95% CI)			**390**			**395**	**100.0%**	**-3.34 [-9.38, 2.69]**

Heterogeneity: $Tau^2 = 12.60$; $Chi^2 = 4.42$, df = 3 (P = 0.22); $I^2 = 32\%$
Test for overall effect: Z = 1.08 (P = 0.28)

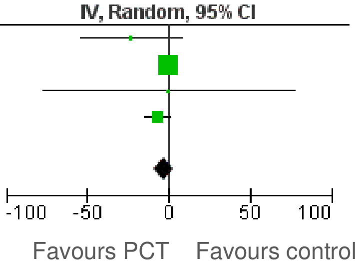

Figure Ib – hospital length of stay. Impact of a PCT algorithm for antibiotic discontinuation on hospital length of stay.

Study or Subgroup	PCT Mean	PCT SD	PCT Total	Standard of care Mean	Standard of care SD	Standard of care Total	Weight	Mean Difference IV, Random, 95% CI
Annane 2013	29	25	30	35.6	34.2	28	2.3%	-6.60 [-22.11, 8.91]
Bouadma 2010	15.9	16.1	307	14.4	14.1	314	28.5%	1.50 [-0.88, 3.88]
Deliberato 2013	3.5	14	42	3	6.75	39	15.8%	0.50 [-4.23, 5.23]
Hochreiter 2009	15.5	12.5	57	17.7	10.1	53	18.0%	-2.20 [-6.43, 2.03]
Nobre 2008	7.7	5.7	39	12.3	9.7	40	21.7%	-4.60 [-8.10, -1.10]
Schroeder 2009	16.4	8.3	14	16.7	5.6	13	13.7%	-0.30 [-5.61, 5.01]
Total (95% CI)			**489**			**487**	**100.0%**	**-1.08 [-3.52, 1.36]**

Heterogeneity: Tau² = 3.94; Chi² = 9.35, df = 5 (P = 0.10); I² = 47%
Test for overall effect: Z = 0.87 (P = 0.38)

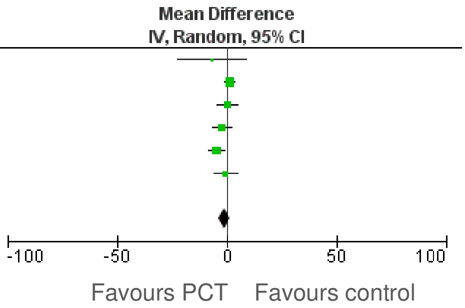

Figure Ic – ICU length of stay. Impact of a PCT algorithm for antibiotic discontinuation on ICU length of stay.

Study or Subgroup	PCT Mean	PCT SD	PCT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Annane 2013	4.3	1.4	30	4.5	1.2	28	24.5%	-0.20 [-0.87, 0.47]
Bouadma 2010	10.3	7.7	307	13.3	7.6	314	19.4%	-3.00 [-4.20, -1.80]
Deliberato 2013	10	9	42	11	10.75	39	4.2%	-1.00 [-5.33, 3.33]
Hochreiter 2009	5.9	1.7	57	7.9	0.5	52	26.1%	-2.00 [-2.46, -1.54]
Nobre 2008	20.9	16.8	39	28.1	19.7	40	1.4%	-7.20 [-15.27, 0.87]
Schroeder 2009	6.6	1.1	14	8.3	0.7	13	24.3%	-1.70 [-2.39, -1.01]
Total (95% CI)			**489**			**486**	**100.0%**	**-1.71 [-2.67, -0.74]**

Heterogeneity: Tau² = 0.87; Chi² = 26.87, df = 5 (P < 0.0001); I² = 81%
Test for overall effect: Z = 3.47 (P = 0.0005)

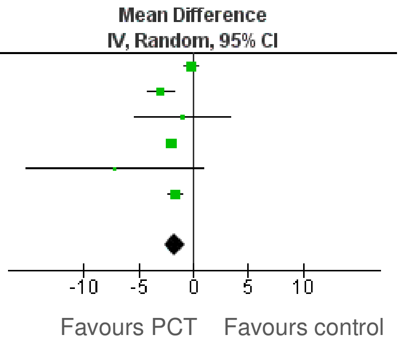

Figure Id – antibiotic use. Impact of a PCT algorithm for antibiotic discontinuation on duration of antibiotic treatment.

Study or Subgroup	PCT Mean	PCT SD	PCT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Annane 2013	21.5	25.1	30	20.3	18.6	28	2.3%	1.20 [-10.12, 12.52]
Bouadma 2010	11.8	11.1	307	11.1	10.9	314	97.7%	0.70 [-1.03, 2.43]
Total (95% CI)			**337**			**342**	**100.0%**	**0.71 [-1.00, 2.42]**

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.42)

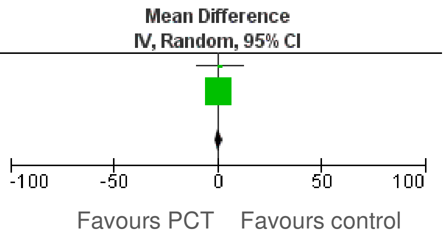

Figure Ie – mechanical ventilation. Impact of a PCT algorithm for antibiotic discontinuation on duration of mechanical ventilation.

Additional file 2: results of sensitivity analysis

Title: A PCT algorithm for discontinuation of antibiotic therapy is a safe and cost-effective intervention to reduce antibiotic exposure in adult intensive care patients with sepsis.
Journal: Journal of Medical Economics
Authors: Michelle MA Kip, Ron Kusters, Maarten J IJzerman, Lotte MG Steuten
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Table I – one-way sensitivity analysis results. This table shows the result of the one-way sensitivity analysis. Both the base case input parameter as well as the lower and upper limit, and the effect on direct hospital costs are shown for each parameter.

Parameter	Current model input with PCT	Lower and upper limit	Effect on costs
Base case		-	€ - 3,462
Effect on regular ward days	9.0	6.0 12.0	€ - 4,975 € - 1,951
Effect on ICU days	12.7	11.5 13.9	€ - 5,672 € - 1,251
Percentage receiving antibiotics	100.0%	75.0%	€ - 3,774
Effect on antibiotic days	9.9	9.4 10.3	€ - 3,523 € - 3,400
Effect on percentage mechanical ventilation	77.0%	57.8% 96.3%	€ - 4,249 € - 2,674
Effect on days mechanical ventilation	10.6	9.9 11.6	€ - 3,681 € - 3,172
Percentage of patients on dialysis therapy	16.0%	12.0% 20.0%	€ - 3,520 € - 3,404
Number of days on dialysis therapy	5.00	3.75 6.25	€ - 3,520 € - 3,404
Effect on percentage of patients in whom a blood culture is performed	61.4%	79.5% 43.4%	€ - 3,207 € - 3,717
Sets of blood cultures performed per patient	2.0	1.5 2.5	€ - 3,679 € - 3,244
Blood cultures performed in patients diagnosed as having sepsis	8.2%	6.1% 10.2%	€ - 3,111 € - 3,672
Number of times laboratory tests ordered	21.8	23.4 20.1	€ - 3,421 € - 3,502
Number of times PCT test performed	5.0	2.5 7.5	€ - 3,499 € - 3,424