Procalcitonin: Is This the Promised Biomarker for Critically Ill Patients?

Patricia S. Fontela^{1,2} Jacques Lacroix³

¹Department of Pediatrics, McGill University, Montreal, Quebec, Canada

²Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

³Department of Pediatrics, Université de Montréal, Montreal, Quebec, Canada

Address for correspondence Patricia S. Fontela, MD, PhD, Division of Pediatric Critical Care, The Montreal Children's Hospital, 1001 Boulevard Décarie, B06.3822.3, Montreal, QC H4A 3J1, Canada (e-mail: patricia.fontela@mcgill.ca).

J Pediatr Intensive Care 2016;5:162–171.

Abstract

Objective Procalcitonin (PCT) has been increasingly used in the critical care setting to determine the presence of bacterial infection and also to guide antibiotic therapy. We reviewed PCT's physiologic role, as well as its clinical utility for the management of pediatric critically ill patients.

Findings PCT is a precursor of the hormone calcitonin. Its production is induced by inflammatory conditions, especially bacterial infections. Literature shows that PCT is a moderately reliable diagnostic test for severe bacterial infection in children. Synthesis of available adult studies suggests that the use of PCT-based algorithms to support medical decision making reduces antibiotic exposure without compromising safety in critically ill patients. However, no study has addressed the usefulness and safety of PCT to guide antibiotic therapy in severely ill children. In pediatric patients with acute lower respiratory tract infections, the use of PCT-based algorithms also led to a safe decrease in antibiotic treatment duration.

Conclusion PCT has demonstrated clinical utility in the pediatric critical care setting when used for the diagnosis of bacterial infections and to guide antibiotic use in children with acute lower respiratory tract infections. However, more research is needed in critically ill children to determine the utility of PCT-driven antibiotic therapy in this population.

Keywords

- procalcitonin
- infection
- children
- critical care
- antibiotics
- medical decision making

Introduction

Over the last few decades, studies have shown procalcitonin (PCT) to be a potentially useful biomarker in the critical care setting. Initially used to diagnose severe bacterial infections, PCT has also been proposed to improve the appropriateness of antibiotic choice in bacterial infections and to guide the duration of antibiotic treatment in adult and pediatric patients.

Antibiotic overuse in intensive care units (ICUs) is a major problem. Between 40 and 72% of patients admitted to pediatric intensive care units (PICUs) receive antibiotics as part of

an empiric treatment and in 9 to 33% of cases, inappropriately.^{1–7} As current recommendations about the optimal duration of antibiotic treatment in empiric situations and/or proven severe bacterial infections are vague and frequently based on expert opinion, ICU physicians must rely on their clinical judgment to decide when to stop antibiotics. In the last few years, the use of PCT-based algorithms has been successfully proposed to objectively guide antibiotic use in critically ill patients. In this article, we review the physiologic role of PCT, as well as its clinical utility for the management of adult and pediatric critically ill patients.

received
August 28, 2015
accepted after revision
November 19, 2015
published online
May 9, 2016

Issue Theme Endocrinology in Pediatric Critical Care; Guest Editors: Kusum Menon, MSc, MD, and Dayre McNally, MSc, PhD

Copyright © 2016 by Georg Thieme Verlag KG, Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0036-1583279>.
ISSN 2146-4618.

Biochemistry of Procalcitonin

PCT is a 116-AA polypeptide precursor of the hormone calcitonin, which is responsible for reducing calcium levels in response to hypercalcemia.⁸ PCT is a composite of three sections (►Fig. 1): (1) the N-terminal sequence (N-PCT), (2) immature calcitonin, and (3) calcitonin carboxyl-terminus peptide 1 (CCP-1).⁸ The CALC-1 gene, present in chromosome 11, governs PCT production. CALC-1 is translated into pre-PCT, which then moves to an endoplasmic reticulum compartment where its N-terminal sequence is cleaved to generate PCT.^{9,10} PCT then translocates to the Golgi apparatus where it is cleaved to generate mature calcitonin.^{10,11}

In healthy individuals, PCT is produced by the thyroid C-cells with extremely low concentrations being detected in the blood (~ 0.19 fmol/mL), as practically all PCT is converted into calcitonin.^{9,12,13} Increased levels of PCT are observed in medullary thyroid cancer and other neuroendocrine tumors, such as small cell lung cancer and pheochromocytoma.^{9,14} Furthermore, inflammatory and bacterial infectious stimuli, especially sepsis, upregulate the expression of the CALC-1 gene. This induces the production of PCT in not only thyroidal, but also extrathyroidal tissues, such as adrenals, spleen, spinal cord, brain, liver, kidney, pancreas, colon, lungs, and fat.^{9,11,15–19} However, these organs are incapable of biosynthesizing mature calcitonin. It is possible that cytokines block the proteolysis of PCT to calcitonin in the endoplasmic reticulum, but this hypothesis has yet to be confirmed.¹³ This tissue-wide secretion explains the important elevations of PCT with concomitant low serum levels of calcitonin in septic patients.²⁰

Physiological Role of Procalcitonin

It is still not clear if PCT is a surrogate biomarker of bacterial infection and “poor prognosis” or if it actually plays a causative role in the inflammatory response. Multiple animal studies have attempted to address this question. Whang et al showed that the injection of PCT in healthy hamsters did not increase interleukin-1 β (IL-1 β) or tumor necrosis factor- α (TNF- α) levels (i.e., it did not induce sepsis) and had no effect on mortality.²¹ Based on these findings, the authors hypothesized that PCT acts as a secondary mediator requiring a primary inflammatory insult to exert its toxicity in sepsis.²¹

Dandona et al demonstrated that levels of PCT rise rapidly after the injection of endotoxin.¹² The same findings were observed after the administration of TNF- α , IL-1, IL-2, and IL-6.^{13,22} Studies also showed that the injection of PCT in septic animals further stimulates the release of proinflammatory cytokines (IL-6, IL-1 β , and TNF- α) and activates macrophages, leading to the amplification of the initial inflammatory response and increasing mortality.^{23–26} Similar to IL-8, PCT also induces an increase in the concentration of intracellular calcium in granulocytes.¹⁷ Finally, PCT may be associated with the vasodilation seen in septic shock, as it increased the expression of nitric oxide synthase and, consequently, its production in rat aortic vascular smooth muscle cells prestimulated using lipopolysaccharide and TNF- α .²⁷

Supporting the hypothesis that PCT has immunomodulatory abilities, Nylen et al showed that the neutralization of PCT using a PCT-reactive antiserum significantly reduced the mortality of septic hamsters from 82 to 54% ($p = 0.045$).²⁸ Furthermore, Wagner et al and Martinez et al also reported improvement of physiologic and metabolic parameters and

Fig. 1 Procalcitonin structure.

an increased survival of septic pigs and dogs, respectively, after PCT suppression.^{29,30} The mechanism through which PCT may cause deleterious effects includes the targeting of hematopoietic cells with consequent decrease in phagocytosis, directed neutrophil migration, chemotaxis of monocytes, and microbial activities.^{23,25,31}

Procalcitonin Kinetics

Experimental Studies

Dandona et al described the kinetics of PCT after the injection of *Escherichia coli* toxin in seven healthy human subjects.¹² PCT was first detected in the participants' plasma 4 hours after the exposure to the toxin. Its blood level peaked at 6 hours. A plateau in the plasma concentration was observed between 8 and 24 hours. Finally, the plasma levels of PCT returned to baseline after 48 to 72 hours. Brunkhorst et al reported the evolution of PCT levels in a patient who accidentally received blood contaminated by *Acinetobacter baumannii* (a "natural" experiment).³² In this case, a rise in PCT levels was observed 2.5 hours after the exposure, with a peak reached after 13.5 hours and a plateau observed as of 24 hours. Based on the findings of the aforementioned studies, PCT seems to follow first-order elimination kinetics with a half-life of 22.5 hours.³²

Clinical Setting: Infectious Processes

The evolution of PCT demonstrates a rise and fall pattern most consistent with infection resolution in several studies that included adults diagnosed with sepsis and septic shock (►Table 1).^{33–37} However, PCT levels were also observed to vary significantly between studies on similar populations, probably due to the moment in the infectious process at which levels are drawn and also due to the use of different assays.

In general, PCT levels are positively associated with the severity of the infectious process and clinical picture (i.e., PCT levels in sepsis are lower than levels observed in septic shock). The meta-analysis of Liu et al showed that high levels of PCT are strongly associated with mortality in adult patients with sepsis, severe sepsis, and septic shock (pooled relative risk [RR], 2.60; 95% confidence interval [CI], 2.05–3.30).³⁸ Furthermore, the absence of PCT clearance during antibiotic treatment was associated with an even higher mortality risk (RR, 3.05; 95% CI, 2.35–3.95).

The kinetics of PCT in children with different severe bacterial infections has also been described, but most authors limited the monitoring of PCT to the first 24 to 72 hours after initiation of treatment (►Table 1).^{39–46} Consequently, most pediatric studies do not provide the full portrait of PCT evolution during bacterial infections. One exception is the Van der Kaay et al study, which included 64 children with meningococcemia. PCT was measured on days 0, 2, and 8 of treatment; on day 0, its level was 300 to 350 ng/mL and decreased to virtually zero on day 8.⁴⁴ In contrast, Zurek and Vavrina did not observe a similar fall over the first 5 days of antibiotic therapy in 62 septic children, with mean PCT levels remaining between

15.6 ± 34.3 and 23.8 ± 87.1 ng/mL.⁴⁶ As no information regarding the clinical response to antibiotic treatment was provided, it is possible that the persistent elevation in PCT was due to antibiotic treatment failure. Another possible explanation is that the 5-day follow-up period was not long enough to capture the fall in the PCT levels. From these studies, we can conclude that PCT levels are higher in children with severe bacterial infections, but we cannot yet properly describe its trajectory once antibiotics are initiated and define the thresholds associated with treatment success.

Clinical Setting: Inflammatory Processes

The presence of high PCT levels is not perfectly specific to bacterial infections. PCT levels are also elevated in the presence of systemic inflammatory response syndrome (SIRS) caused by major surgery/trauma, severe burns, cardiogenic shock, and exposure to cardiopulmonary bypass (CPB). Similarly to what is observed in patients with bacterial infections, PCT levels in inflammatory conditions present a rise and fall pattern in adults and children with good clinical evolution.^{35,36,45,47,48} Furthermore, PCT levels tend to increase proportionally to the severity of the clinical picture, but, when compared with levels observed in sepsis and septic shock, PCT levels for SIRS (related or not to CPB exposure) and nonseptic shock are significantly lower.

Difference in Kinetics between Procalcitonin and Other Infection Markers

The kinetics of PCT and those of other infection markers have been compared in adult and pediatric patients. Dandona et al and Brunkhorst et al observed that a rise in PCT levels occurs more rapidly after the insult than an increase in C-reactive protein (CRP), but slower than TNF-α and IL-6 (►Table 2).^{12,32} The same pattern is observed regarding the return to baseline levels, with TNF-α and IL-6 being the first markers to reach normal levels and CRP being the last. Moreover, Castelli et al compared the levels of PCT and CRP in 34 adult patients with sepsis from ICU admission to day 8 of evolution. They showed that, while CRP levels peaked on day 3 of treatment and remained high until day 8, PCT levels peaked on day 1 and declined thereafter.³³

As previously mentioned, studies comparing the evolution of PCT and other infection markers in pediatric patients mainly focused on the first 24 to 72 hours after diagnosis. In 20 children treated for bacterial meningitis, Alkholi et al demonstrated a fall in PCT from day 1 to day 3 for PCT (26.8 ± 12 vs. 10.8 ± 5.3 ng/mL; $p < 0.001$) and white blood cell count (18.4 ± 9.1 vs. 12.6 ± 5.8 mm³; $p < 0.05$), while CRP remained stable (24.4 ± 12.1 vs. 28.6 ± 12 mg/dL; $p > 0.05$).³⁹ Van der Kaay et al measured PCT, CRP, and IL-6 levels in 64 children treated for meningococcemia and reported that both PCT and IL-6 peaked at PICU admission with levels falling within 6 hours. In contrast, CRP peaked at 24 hours followed by a subsequent decline.⁴⁴ In this study, levels were also measured at day 8, showing a return to baseline for all markers.

Table 1 Kinetics of PCT in adult and pediatric patients with suspected/proven bacterial infection

Authors	N	PCT levels (ng/mL) according to length of antibiotic treatment (mean ± SD)										
		0 h	6 h	12 h	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 10
Adult patients												
Septic shock												
Reynolds et al 2012	270	–	–	–	31.7 ± 58.2	25.6 ± 46.4	17.5 ± 31.4	10.9 ± 17.1	8.3 ± 11.9	5.9 ± 8.1	4.4 ± 6.0	3.4 ± 4.2
Sepsis												
Miki and Iba 2015	30	10	–	–	10.5	–	2	–	–	–	1	–
Reynolds et al 2012	80	–	–	–	12.8 ± 44.2	12.1 ± 53.7	8.8 ± 52.9	8.0 ± 54.3	6.3 ± 42.8	5.9 ± 38.1	4.7 ± 27.0	2.3 ± 6.6
Charles et al 2009	180	–	–	–	27.2 ± 62.7	27.4 ± 45.1	24.4 ± 58.4	17.3 ± 45.8	–	–	–	–
Castelli et al 2004 ^a	34	–	–	–	1.6	1.2	0.95	0.6	0.5	0.35	0.25	0.25
Ugarte et al 1999	111	2.1	–	–	4.3	4.3	3.7	1.4	–	–	–	–
Nonseptic shock												
Reynolds et al 2012	48	–	–	–	11.4 ± 22.4	7.6 ± 13.5	4.9 ± 10.1	4.5 ± 8.2	2.4 ± 3.5	2.7 ± 3.2	1.8 ± 1.6	1.3 ± 1.3
Noninfected patients without shock												
Reynolds et al 2012	200	–	–	–	4.0 ± 21.7	4.5 ± 26.1	1.7 ± 4.0	0.9 ± 1.3	0.7 ± 1.0	0.6 ± 0.7	0.6 ± 0.8	0.6 ± 0.6
Ugarte et al 1999 ^a	79	0.8	–	–	1.2	1.6	1.3	0.8	–	–	–	–
Pediatric patients												
Sepsis												
Zurek and Vavrina 2015	62	–	–	–	16.3 ± 28.8	15.6 ± 34.3	18.4 ± 69.0	23.8 ± 87.1	16.2 ± 67.0	–	–	–
Garcia et al 2012	7	3.2 ± 1.9	–	–	6.6 ± 4.6	55.5 ± 90.9	–	–	–	–	–	–
Casado-Flores et al 2003 ^a	80	20.4	33.9	–	18.8	7	–	–	–	–	–	–
Han et al 2003 ^a	78	7.1 (0.9–44.8)	–	–	–	–	2.9 (0.1–32.4)	–	–	–	–	–
Van der Kaay 2002 ^a	64	315	440	275	180	100	±	–	–	0	–	–
Meningitis												
Alkholi et al 2011	20	26.8 ± 12	–	–	–	–	10.8 ± 5	–	–	–	–	–

Abbreviations: PCT, procalcitonin; SD, standard deviation.

^aMedian (interquartile range).

Table 2 Kinetics of PCT compared with other biomarkers

Biomarker	Start to rise (h)	Peak (h)	Plateau (h)	Return to baseline (h)
PCT	2.5 to 4	6 to 13.5	8 to 24	48 to 72
CRP	12 to 24	30	20 to 72	72 to 168
IL-6	1 to 1.5	3	1.5 to 14	–
TNF- α	1	2 to 2.5	–	6 to 9

Abbreviations: CRP, C-reactive protein; IL-6, interleukin 6; PCT, procalcitonin; TNF- α , tumor necrosis factor- α .

Procalcitonin Use in the Critical Care Setting

Use of Procalcitonin for the Diagnosis of Severe Bacterial Infections/Sepsis

PCT has been proposed as a biomarker capable of discriminating between bacterial infections and other inflammatory processes (including viral infection) based on the significantly higher increase in its levels in the presence of bacterial stimulus. Although two cutoffs are commonly used (≥ 0.5 and ≥ 2.0 ng/mL),^{8,49,50} other values have been proposed to adjust for the timing of measurement (if early in the infection, PCT levels may not have reached their peak) and different patient populations (e.g., patients in the emergency room vs. in the ICU). Importantly, studies have suggested that the use of anti-inflammatories, such as steroids, does not meaningfully affect PCT levels in the context of pneumonia and sepsis.^{51,52}

Tang et al performed a meta-analysis to estimate the accuracy of PCT to diagnose sepsis in critically ill adult patients.⁵³ The pooled results of 14 phase II diagnostic studies (i.e., studies evaluating the discriminatory ability of a test) showed positive and negative likelihood ratios of 3.03 (95% CI, 2.51–3.65) and 0.43 (95% CI, 0.37–0.48), respectively, and an area under the receiver operating characteristics curve (AUC ROC) of 0.73 (95% CI, 0.69–0.77). Wacker et al tried to answer the same question with a meta-analysis that included 26 adult and 4 pediatric studies, with PCT cutoffs ranging from 0.28 to 5.79 ng/mL.⁵⁴ The pooled results showed a sensitivity of 0.77 (95% CI, 0.72–0.81), specificity of 0.79 (95% CI, 0.74–0.84), and an AUC ROC of 0.85 (95% CI, 0.81–0.88). Importantly, despite the substantial heterogeneity between studies, the proportion of heterogeneity caused by different cutoffs was small (0.05) and the AUC ROCs for the pediatric and adult studies were identical (0.85 [95% CI, 0.82–0.88] vs. 0.85 [95% CI, 0.81–0.88]).

Several meta-analyses were performed to estimate the usefulness of PCT for the diagnosis of different severe bacterial infections in pediatric patient populations (►Table 3).^{50,55–59} The results for sepsis demonstrate that PCT is a moderately useful diagnostic test, with sensitivity between 0.59 and 0.89, and specificities between 0.74 and 0.81.^{55,57,59} The exception is meningococcal disease, for which an excellent AUC ROC was obtained (0.95; 95% CI, 0.93–0.97).⁵⁵ PCT was found to be a good diagnostic test for severe bacterial infections, with AUC ROC between 0.84 and 0.85.^{50,56,58}

Finally, in their systematic review, Simon et al demonstrated the ability of PCT to discriminate between bacterial and viral infections to be excellent, with positive and negative likelihood ratios of 6.05 (95% CI, 4.67–7.82) and 0.10 (95% CI,

0.06–0.15).⁵⁷ After the publication of this meta-analysis in 2004, Laham et al performed a retrospective cohort study to evaluate the usefulness of PCT for the diagnosis of bacterial coinfection in 40 PICU patients with bronchiolitis.⁶⁰ Using a cutoff of 1.5 ng/mL, they obtained a sensitivity of 0.80, a specificity of 1.0, and an AUC ROC of 0.88.

Utility of Procalcitonin to Guide Antibiotic Use

The rise in PCT levels observed in patients with bacterial infections and their decline in the ones who responded to antibiotic therapy led to the hypothesis that this biomarker could be used to tailor antibiotic use and duration. In the last decade, several randomized controlled trials (RCTs) evaluated the benefit of using PCT-based algorithms to drive medical decisions regarding antibiotic use (initiation and/or withdrawal) in adult critical care patients with suspected/proven severe bacterial infections, including sepsis, septic shock, and ventilator-associated pneumonia (►Table 4).^{61–68} Importantly, all aforementioned studies tested different PCT algorithms, with cutoffs for antibiotic initiation ranging from ≥ 0.5 to >1.0 ng/mL. Regarding antibiotic discontinuation, suggested cutoffs included absolute PCT values ranging from <1.0 to <0.1 ng/mL and PCT level reductions between ≥ 65 and $\geq 90\%$ of initial value (baseline).

Since 2010, six meta-analyses assessing the effect of using PCT algorithms to tailor antibiotic use in adult critical care have been published (►Table 4).^{69–74} They all showed a reduction in antibiotic treatment duration, with pooled mean differences from –2.05 days (95% CI, –2.59 to –1.52) to –3.17 days (95% CI, –4.35 to –1.95), with no difference in mortality and ICU/hospital length of stay between study groups. Regarding antibiotic treatment duration, it is important to mention that three RCTs failed to demonstrate a reduction in antibiotic use associated with PCT algorithms.^{63,66,67} Their results are discussed in depth in the next paragraphs. Importantly, the results of two of these trials were released in 2013 and 2014, which precluded their inclusion in the most recent meta-analyses (published in 2013).^{66,67}

In 2008, Nobre et al published the first RCT evaluating a PCT-based algorithm to tailor antibiotic use in adult ICUs.⁶³ In the intention-to-treat analysis, they observed a clinically relevant, but not statistically significant, mean difference in the antibiotic treatment duration between groups which was favorable to PCT (median of 6 days [range 2–33] vs. 9.5 days [range 3–34]; $p = 0.15$). Study results were significantly impacted by the fact that stopping rules in the PCT group were overruled by treating physicians in 19% of patients. In

Table 3 Meta-analyses evaluating the use of PCT to diagnose severe bacterial infections in pediatric patients

Authors	Subgroup	N (articles)	PCT cutoff range (ng/mL)	Pooled results (95% CI)				LR (+)	LR(-)	AUC ROC	DOR	RR
				Sens	Sp							
Sepsis												
Bell et al 2015	Meningococcal disease	6	0.2-2.0	0.89 (0.76-0.96)	0.74 (0.40-0.92)	-	-	0.95 (0.93-0.97)	-	-	-	-
Lin et al 2012	Neutropenic patients	10	0.12-7.0	0.59 (0.42-0.74)	0.76 (0.64-0.85)	1.97 (1.46-2.66)	-	-	4.82 (2.10-11)	-	-	-
Simon et al 2004	Adult, children, and neonates. Also other SBI	12	0.5-6.1	0.88 (0.80-0.93)	0.81 (0.67-0.90)	3.58 (2.99-4.28)	0.18 (0.15-0.23)	-	-	-	-	-
Severe bacterial infection												
England et al 2014	<91 d old	7	0.12-0.5	-	-	-	-	-	-	-	-	3.97 (3.41-4.62)
Yo et al 2012	7 d to 36 mo old	8	0.5-2.0	0.83 (0.70-0.91)	0.69 (0.59-0.85)	2.69 (1.87-3.87)	0.25 (0.15-0.40)	0.84 (0.80-0.87)	-	-	-	-
Jones et al 2007	-	7	0.5-2.0	-	-	-	-	0.85 (0.63-0.95)	-	-	-	-
Viral versus bacterial infection												
Simon et al 2004	Adult, children, and neonates. Also other SBI	12	0.5-6.1	0.92 (0.86-0.95)	0.73 (0.42-0.91)	6.05 (4.67-7.82)	0.10 (0.06-0.15)	-	-	-	-	-

Abbreviations: 95% CI, 95% confidence interval; AUC ROC, area under the receiver operating curve; DOR, diagnostic odds ratio; LR(+), positive likelihood ratio; LR(–), negative likelihood ratio; PCT, procalcitonin; RR, relative risk; SBI, severe bacterial infection; sens, sensitivity; sp, specificity.

Table 4 Evidence regarding the use of PCT to tailor initiation/duration of antibiotics in adult critical care patients

Authors	N	Infection type	Antibiotic duration (mean $\pm$ SD), d	Mortality (%)	ICU LOS (mean $\pm$ SD; d)	Hospital LOS (mean $\pm$ SD), d
Individual RCTs						
Shehabi et al 2014	400	Suspected severe bacterial infection	9 (6–20) versus 11 (6–22) ^a HR, 1.01 (95% CI, 0.80–1.26)	90-d mortality, 35 (18) versus 31 (16) ^a ($p = 0.60$)	6 (3–9.5) versus 6 (4–10) ^a ($p = 0.87$)	15 (9–29) versus 17 (10–32) ^a ($p = 0.19$)
Annane et al 2013	62	Suspected severe sepsis and septic shock	5 (2–5) versus 5 (3–5) ^a ($p = 0.52$)	Hospital mortality, 23 versus 33% RR, 0.68 (95% CI, 0.30–1.55)	22 (8–42) versus 23 (10–60) ^a ($p = 0.58$)	27 (9–49) versus 33 (11–69) ^a ($p = 0.22$)
Jensen et al 2011	1,200	Suspected severe bacterial infection	6 (3–11) versus 4 (3–10) ^a	28-d mortality, RR, 0.98 (95% CI, 0.83–1.16)	6 (3–12) versus 5 (3–11) ^a ($p = 0.004$)	–
Bouadma et al 2010	630	Suspected severe bacterial infections	10.3 $\pm$ 7.7 versus 13.3 $\pm$ 7.6 ($p < 0.0001$)	28-d mortality, 21.2 versus 20.4% MD, 0.8% (95% CI, –4.6 to 6.2)	15.9 $\pm$ 16.1 versus 14.4 $\pm$ 14.1 MD, 1.5 (95% CI, –0.9 to 3.9)	26.1 $\pm$ 19.3 versus 26.4 $\pm$ 18.3 MD, –0.3 (95% CI, –3.2 to 2.7)
Hochreiter et al 2009	110	Suspected/confirmed severe bacterial infection	5.9 $\pm$ 1.7 versus 7.9 $\pm$ 0.5 ($p < 0.001$)	Hospital mortality, 21.4 versus 23%	15.5 $\pm$ 12.5 versus 17.7 $\pm$ 10.1 ($p = 0.046$)	–
Schroeder et al 2009	27	Suspected severe sepsis	6.6 $\pm$ 1.1 versus 8.3 $\pm$ 0.7 ($p < 0.001$)	Hospital mortality, 26.3 versus 26.4% ($p > 0.05$)	16.4 $\pm$ 8.3 versus 16.7 $\pm$ 5.6 ($p > 0.05$)	–
Stolz et al 2009	101	Suspected VAP	10 (6–16) versus 15 (10–23) ^a ($p = 0.038$)	28-d mortality, 16 versus 24% ($p = 0.33$)	–	26 (7–21) versus 26 (16.8–22.3) ^a
Nobre et al 2008	79	Severe sepsis or septic shock	6 (2–33) versus 9.5 (3–34) ^b MD, 2.6 (95% CI, –0.3 to 5.5)	28-d mortality, 20.5 versus 20% ($p = 0.82$) RR, 0.9 (95% CI, 0.9–1.3)	7.7 $\pm$ 5.7 versus 12.3 $\pm$ 9.7 ($p = 0.02$) MD, 4.6 (95% CI, 1.0–8.2)	20.9 $\pm$ 17 versus 28.1 $\pm$ 20 ($p = 0.85$) MD, 2.5 (95% CI, –1.5 to 6.5)
Meta-analyses						
Soni et al 2013	5 RCTs	Suspected severe bacterial infection	MD, –2.05 (95% CI, –2.59 to 1.52)	Short-term mortality (hospital + 28-d) MD, 0.00 (95% CI, –0.06 to 0.05)	MD, 0.33 (95% CI, –1.88 to 2.53)	–
Prkno et al 2013	7 RCTs	Severe sepsis and septic shock	HR, 1.27 (95% CI, 1.01–1.53)	28-d mortality RR, 1.02 (95% CI 0.85–1.23)	HR, 1.05 (95% CI, 0.82–1.29)	HR, 1.03 (95% CI, 0.82–1.24)
Schuetz et al 2012	5 RCTs	Acute respiratory infection	MD, –3.17 (95% CI, –4.28 to –2.06)		MD, 1.01 (95% CI, –1.26 to 3.28)	MD, –1.36 (95% CI, –4.55 to 1.77)

Table 4 (Continued)

Authors	N	Infection type	Antibiotic duration (mean $\pm$ SD), d	Mortality (%)	ICU LOS (mean $\pm$ SD; d)	Hospital LOS (mean $\pm$ SD), d
Meta-analyses						
Matthaiou et al 2012	7 RCTs	Severe bacterial infection	MD, -3.15 (95% CI, -4.35 to -1.95)	30-d mortality OR, 0.79 (95% CI, 0.53-1.17)	MD, -0.36 (95% CI, -1.97 to 1.26)	MD, -0.12 (95% CI, -1.09 to 0.85)
Heyland et al 2011	5 RCTs	Severe bacterial infection	MD, -2.14 (95% CI, -2.51 to -1.78)	Hospital mortality OR, 1.06 (95% CI, 0.86-1.30)	-	-
Kopterides et al 2010	5 RCTs	Severe bacterial infection	MD, -2.36 (95% CI, -3.11 to -1.61)	28-d mortality OR, 0.93 (95% CI, 0.69-1.26)	MD, -0.57 (95% CI, -1.90 to 0.76)	MD, -0.13 (95% CI, -1.10 to 0.84)

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay; MD, mean difference; OR, odds ratio; RCTs, randomized controlled trials; RR, relative risk; SD, standard deviation; VAP, ventilator-associated pneumonia.

^aMedian and interquartile range (IQR).

^bMedian and range.

their per-protocol analysis, a clinically and statistically significant difference between groups was calculated (median of 6 days [range 4-16] vs. 12.5 days [range 8-16]; $p = 0.0002$). Furthermore, the probability of having antibiotics stopped earlier was estimated to be twofold higher in the PCT group (hazard ratio [HR], 1.9; 95% CI, 1.2-3.2).

In their 2013 publication, Annane et al evaluated the benefit of using a PCT-based algorithm in 62 adults with suspected septic shock, but without a clear source of infection or positive cultures at study enrolment.⁶⁶ Due to the low incidence of eligible patients, this trial was prematurely stopped. Data up to this point showed no difference between groups regarding antibiotic use on day 5 after randomization (median of 5 days [interquartile range, IQR, 2-5] vs. 5 days [IQR 3-5]; $p = 0.52$). The authors proposed that the low number of patients whose PCT levels were <0.25 ng/mL (cutoff to not initiate or to stop antibiotics) throughout the study probably explained the lack of difference between groups. Moreover, the noncompliance with the PCT algorithm ranged from 17 to 37% at the three study time points (6 hours, 3 days, and 5 days). Finally, it is likely that the 5-day interval used was not long enough for PCT levels to decrease below the <0.25 ng/mL threshold in patients who were more severely ill, making it impossible for the proposed algorithm to show clinical benefit.

In 2014, Shehabi et al also reported the findings of their RCT, which failed to show a reduction in antibiotic treatment duration for adult ICU patients with suspected sepsis with the use of a PCT algorithm (HR, 1.01; 95% CI, 0.80-1.26).⁶⁷ Possible reasons for this negative result include a much lower PCT cutoff to stop antibiotics (0.1 ng/mL instead of 0.25-0.5 ng/mL) and the use of the algorithm only while patients were in the ICU (i.e., ward medical teams had no access to PCT levels, thus having to use their clinical judgment to make decisions about treatment duration for patients in both arms of the study).

Currently, only two RCTs evaluated the use of PCT to tailor antibiotic use in children and neither included critically ill pediatric patients. The open-label, parallel RCT of Esposito et al included 310 children (1 month to 18 years old) admitted to a pediatric ward for community-acquired pneumonia.⁷⁵ The use of an algorithm that encouraged to not start and/or to stop antibiotics when PCT level was <0.25 ng/mL led to a 5-day decrease in antimicrobial duration (5.37 days vs. 10.96 days; $p < 0.05$), as well as a reduction in antibiotic-related adverse events (3.9 vs. 25.2%; $p < 0.05$) and infection recurrence (0.007 vs. 0.04%; p -value not calculated). In the RCT by Baer et al, a cutoff of <0.25 ng/mL was used to decide upon both antibiotic initiation and termination for children with lower respiratory tract infection.⁷⁶ They also observed a reduction in antibiotic use (mean difference, -1.8 days; 95% CI, -3.1 to -0.5) with no increase in serious adverse events.

Conclusion

PCT is clinically useful in critically ill patients. Specifically for the pediatric population, PCT is a moderately helpful diagnostic test, except for the diagnosis of meningococcal disease, where it may be highly accurate. Regarding its use to tailor antibiotic therapy, pediatric studies suggest that the use of PCT-based algorithms

may safely decrease antibiotic treatment duration in patients with acute lower respiratory tract infection. In addition, adult studies including severely ill patients have showed that PCT-guided therapy leads to a decrease of antibiotic exposure without compromising infection cure and patient safety. At this point, the same cannot be said for critically ill children, as no studies have yet been performed to determine the utility of PCT-driven antibiotic therapy in this patient population. Before such studies can be performed, it is imperative to determine PCT kinetics during antibiotic treatment in PICU patients with severe bacterial infections and to define the PCT thresholds associated with infection cure.

Acknowledgment

The authors thank Dr. Jesse Papenburg for his critical review of this manuscript.

References

- Audry-Degardin E, Dubos F, Leteurtre S, Beaucaire G, Leclerc F. Evaluation de la prescription antibiotique dans un service de réanimation pédiatrique [in French]. *Arch Pediatr* 2007;14(2):157–163
- Blinova E, Lau E, Bitnun A, et al. Point prevalence survey of antimicrobial utilization in the cardiac and pediatric critical care unit. *Pediatr Crit Care Med* 2013;14(6):e280–e288
- Ceyhan M, Yildirim I, Ecevit C, et al. Inappropriate antimicrobial use in Turkish pediatric hospitals: a multicenter point prevalence survey. *Int J Infect Dis* 2010;14(1):e55–e61
- Ciofi Degli Atti ML, Raponi M, Tozzi AE, Ciliento G, Ceradini J, Langiano T. Point prevalence study of antibiotic use in a paediatric hospital in Italy. *Euro Surveill* 2008;13(41):12–15
- Ding H, Yang Y, Chen Y, Wang Y, Fan S, Shen X. Antimicrobial usage in paediatric intensive care units in China. *Acta Paediatr* 2008;97(1):100–104
- Ding H, Yang Y, Lu Q, et al. Five-year surveillance of antimicrobial use in Chinese pediatric intensive care units. *J Trop Pediatr* 2008;54(4):238–242
- Fischer JE, Ramser M, Fanconi S. Use of antibiotics in pediatric intensive care and potential savings. *Intensive Care Med* 2000;26(7):959–966
- Schneider HG, Lam QT. Procalcitonin for the clinical laboratory: a review. *Pathology* 2007;39(4):383–390
- Becker KL, Nylén ES, White JC, Müller B, Snider RH Jr. Clinical review 167: procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. *J Clin Endocrinol Metab* 2004;89(4):1512–1525
- Matwiyoff GN, Pahl JD, Miller RJ, et al. Immune regulation of procalcitonin: a biomarker and mediator of infection. *Inflamm Res* 2012;61(5):401–409
- Müller B, White JC, Nylén ES, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-receptor-like receptor 1 gene in multiple tissues in response to sepsis. *J Clin Endocrinol Metab* 2001;86(1):396–404
- Dandona P, Nix D, Wilson MF, et al. Procalcitonin increase after endotoxin injection in normal subjects. *J Clin Endocrinol Metab* 1994;79(6):1605–1608
- Maruna P, Nedelínková K, Gürlich R. Physiology and genetics of procalcitonin. *Physiol Res* 2000;49(Suppl 1):S57–S61
- Bihan H, Becker KL, Snider RH, et al. Calcitonin precursor levels in human medullary thyroid carcinoma. *Thyroid* 2003;13(8):819–822
- Reinhart K, Meisner M. Biomarkers in the critically ill patient: procalcitonin. *Crit Care Clin* 2011;27(2):253–263
- Russwurm S, Wiederhold M, Oberhoffer M, Stonans I, Zipfel PF, Reinhart K. Molecular aspects and natural source of procalcitonin. *Clin Chem Lab Med* 1999;37(8):789–797
- Morgenthaler NG, Struck J, Chancellerie Y, et al. Production of procalcitonin (PCT) in non-thyroidal tissue after LPS injection. *Horm Metab Res* 2003;35(5):290–295
- Domenech VS, Nylén ES, White JC, et al. Calcitonin gene-related peptide expression in sepsis: postulation of microbial infection-specific response elements within the calcitonin I gene promoter. *J Invest Med* 2001;49(6):514–521
- Picariello C, Lazzeri C, Valente S, Chiostrì M, Attanà P, Gensini GF. Kinetics of procalcitonin in cardiogenic shock and in septic shock. Preliminary data. *Acute Card Care* 2010;12(3):96–101
- Becker KL, Snider R, Nylén ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. *Crit Care Med* 2008;36(3):941–952
- Whang KT, Vath SD, Becker KL, et al. Procalcitonin and proinflammatory cytokine interactions in sepsis. *Shock* 2000;14(1):73–78
- Nijsten MW, Olinga P, The TH, et al. Procalcitonin behaves as a fast responding acute phase protein in vivo and in vitro. *Crit Care Med* 2000;28(2):458–461
- Liappis AP, Gibbs KW, Nylén ES, et al. Exogenous procalcitonin evokes a pro-inflammatory cytokine response. *Inflamm Res* 2011;60(2):203–207
- Wei JX, Verity A, Garle M, Mahajan R, Wilson V. Examination of the effect of procalcitonin on human leucocytes and the porcine isolated coronary artery. *Br J Anaesth* 2008;100(5):612–621
- Wiedermann FJ, Kaneider N, Egger P, et al. Migration of human monocytes in response to procalcitonin. *Crit Care Med* 2002;30(5):1112–1117
- Steinwald PM, Whang KT, Becker KL, Snider RH, Nylén ES, White JC. Elevated calcitonin precursor levels are related to mortality in an animal model of sepsis. *Crit Care* 1999;3(1):11–16
- Hoffmann G, Czechowski M, Schloesser M, Schobersberger W. Procalcitonin amplifies inducible nitric oxide synthase gene expression and nitric oxide production in vascular smooth muscle cells. *Crit Care Med* 2002;30(9):2091–2095
- Nylén ES, Whang KT, Snider RH Jr, Steinwald PM, White JC, Becker KL. Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis. *Crit Care Med* 1998;26(6):1001–1006
- Wagner KE, Martinez JM, Vath SD, et al. Early immunoneutralization of calcitonin precursors attenuates the adverse physiologic response to sepsis in pigs. *Crit Care Med* 2002;30(10):2313–2321
- Martinez JM, Wagner KE, Snider RH, et al. Late immunoneutralization of procalcitonin arrests the progression of lethal porcine sepsis. *Surg Infect (Larchmt)* 2001;2(3):193–202, discussion 202–203
- Serezani CH, Ballinger MN, Aronoff DM, Peters-Golden M. Cyclic AMP: master regulator of innate immune cell function. *Am J Respir Cell Mol Biol* 2008;39(2):127–132
- Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic sepsis. *Intensive Care Med* 1998;24(8):888–889
- Castelli GP, Pognani C, Meisner M, Stüani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Crit Care* 2004;8(4):R234–R242
- Miki T, Iba T. Kinetics of circulating damage-associated molecular patterns in sepsis. *J Immunol Res* 2015;2015:424575
- Reynolds SC, Shorr AF, Muscedere J, Jiang X, Heyland DK. Longitudinal changes in procalcitonin in a heterogeneous group of critically ill patients. *Crit Care Med* 2012;40(10):2781–2787
- Ugarte H, Silva E, Mercan D, De Mendonça A, Vincent JL. Procalcitonin used as a marker of infection in the intensive care unit. *Crit Care Med* 1999;27(3):498–504
- Charles PE, Tinel C, Barbar S, et al. Procalcitonin kinetics within the first days of sepsis: relationship with the appropriateness of antibiotic therapy and the outcome. *Crit Care* 2009;13(2):R38

- 38 Liu D, Su L, Han G, Yan P, Xie L. Prognostic value of procalcitonin in adult patients with sepsis: a systematic review and meta-analysis. *PLoS ONE* 2015;10(6):e0129450
- 39 Alkholi UM, Abd Al-Monem N, Abd El-Azim AA, Sultan MH. Serum procalcitonin in viral and bacterial meningitis. *J Glob Infect Dis* 2011;3(1):14–18
- 40 Arkader R, Troster EJ, Lopes MR, et al. Procalcitonin does discriminate between sepsis and systemic inflammatory response syndrome. *Arch Dis Child* 2006;91(2):117–120
- 41 Casado-Flores J, Blanco-Quirós A, Asensio J, Arranz E, Garrote JA, Nieto M. Serum procalcitonin in children with suspected sepsis: a comparison with C-reactive protein and neutrophil count. *Pediatr Crit Care Med* 2003;4(2):190–195
- 42 Han YY, Doughty LA, Kofos D, Sasser H, Carcillo JA. Procalcitonin is persistently increased among children with poor outcome from bacterial sepsis. *Pediatr Crit Care Med* 2003;4(1):21–25
- 43 Secmeer G, Devrim I, Kara A, et al. Role of procalcitonin and CRP in differentiating a stable from a deteriorating clinical course in pediatric febrile neutropenia. *J Pediatr Hematol Oncol* 2007;29(2):107–111
- 44 Van der Kaay DCM, De Kleijn ED, De Rijke YB, Hop WCJ, De Groot R, Hazelzet JA. Procalcitonin as a prognostic marker in meningococcal disease. *Intensive Care Med* 2002;28(11):1606–1612
- 45 Garcia JJ, Gargallo MB, Torné EE, et al. Procalcitonin: a useful biomarker to discriminate infection after cardiopulmonary bypass in children. *Pediatr Crit Care Med* 2012;13(4):441–445
- 46 Zurek J, Vavrina M. Procalcitonin biomarker kinetics to predict multi-organ dysfunction syndrome in children with sepsis and systemic inflammatory response syndrome. *Iran J Pediatr* 2015;25(1):e324
- 47 Arkader R, Troster EJ, Abellan DM, et al. Procalcitonin and C-reactive protein kinetics in postoperative pediatric cardiac surgical patients. *J Cardiothorac Vasc Anesth* 2004;18(2):160–165
- 48 Beghetti M, Rimensberger PC, Kalangos A, Habre W, Gervais A. Kinetics of procalcitonin, interleukin 6 and C-reactive protein after cardiopulmonary-bypass in children. *Cardiol Young* 2003;13(2):161–167
- 49 Hatherill M, Tibby SM, Sykes K, Turner C, Murdoch IA. Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leucocyte count. *Arch Dis Child* 1999;81(5):417–421
- 50 Jones AE, Fiechtl JF, Brown MD, Ballew JJ, Kline JA. Procalcitonin test in the diagnosis of bacteremia: a meta-analysis. *Ann Emerg Med* 2007;50(1):34–41
- 51 de Kruif MD, Lemaire LC, Giebelen IA, et al. The influence of corticosteroids on the release of novel biomarkers in human endotoxemia. *Intensive Care Med* 2008;34(3):518–522
- 52 Perren A, Cerutti B, Lepori M, et al. Influence of steroids on procalcitonin and C-reactive protein in patients with COPD and community-acquired pneumonia. *Infection* 2008;36(2):163–166
- 53 Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis* 2007;7(3):210–217
- 54 Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013;13(5):426–435
- 55 Bell JM, Shields MD, Agus A, et al. Clinical and cost-effectiveness of procalcitonin test for prodromal meningococcal disease—a meta-analysis. *PLoS ONE* 2015;10(6):e0128993
- 56 England JT, Del Vecchio MT, Aronoff SC. Use of serum procalcitonin in evaluation of febrile infants: a meta-analysis of 2317 patients. *J Emerg Med* 2014;47(6):682–688
- 57 Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004;39(2):206–217
- 58 Yo C-H, Hsieh P-S, Lee S-H, et al. Comparison of the test characteristics of procalcitonin to C-reactive protein and leukocytosis for the detection of serious bacterial infections in children presenting with fever without source: a systematic review and meta-analysis. *Ann Emerg Med* 2012;60(5):591–600
- 59 Lin SG, Hou TY, Huang DH, et al. Role of procalcitonin in the diagnosis of severe infection in pediatric patients with fever and neutropenia—a systemic review and meta-analysis. *Pediatr Infect Dis J* 2012;31(10):e182–e188
- 60 Laham JL, Breheny PJ, Gardner BM, Bada H. Procalcitonin to predict bacterial coinfection in infants with acute bronchiolitis: a preliminary analysis. *Pediatr Emerg Care* 2014;30(1):11–15
- 61 Hochreiter M, Köhler T, Schweiger AM, et al. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. *Crit Care* 2009;13(3):R83
- 62 Jensen JU, Hein L, Lundgren B, et al; Procalcitonin And Survival Study (PASS) Group. 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(9):2048–2058
- 63 Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med* 2008;177(5):498–505
- 64 Schroeder S, Hochreiter M, Koehler T, et al. 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(2):221–226
- 65 Stolz D, Smyrniotis N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. *Eur Respir J* 2009;34(6):1364–1375
- 66 Annane D, Maxime V, Faller JP, et al. Procalcitonin levels to guide antibiotic therapy in adults with non-microbiologically proven apparent severe sepsis: a randomised controlled trial. *BMJ Open* 2013;3(2):3
- 67 Shehabi Y, Sterba M, Garrett PM, et al; ProGUARD Study Investigators; ANZICS Clinical Trials Group. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. *Am J Respir Crit Care Med* 2014;190(10):1102–1110
- 68 Bouadma L, Luyt C-E, Tubach F, et al; PRORATA trial group. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010;375(9713):463–474
- 69 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(7):1792–1799
- 70 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(6):940–949
- 71 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. *Crit Care* 2013;17(6):R291
- 72 Schuetz P, Müller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* 2012;9:CD007498
- 73 Soni NJ, Samson DJ, Galaydick JL, et al. Procalcitonin-guided antibiotic therapy: a systematic review and meta-analysis. *J Hosp Med* 2013;8(9):530–540
- 74 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(11):2229–2241
- 75 Esposito S, Tagliabue C, Piccioli I, et al. Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia. *Respir Med* 2011;105(12):1939–1945
- 76 Baer G, Baumann P, Buettcher M, et al. Procalcitonin guidance to reduce antibiotic treatment of lower respiratory tract infection in children and adolescents (ProPAED): a randomized controlled trial. *PLoS ONE* 2013;8(8):e68419