Procalcitonin for reduced antibiotic exposure in the critical care setting: A systematic review and an economic evaluation*

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Objective: **Procalcitonin may be associated with reduced antibiotic usage compared to usual care. However, individual randomized controlled trials testing this hypothesis were too small to rule out harm, and the full cost–benefit of this strategy has not been evaluated. The purpose of this analysis was to evaluate the effect of a procalcitonin-guided antibiotic strategy on clinical and economic outcomes.**

Interventions: **The use of procalcitonin-guided antibiotic therapy.**

Methods and Main Results: **We searched computerized databases, reference lists of pertinent articles, and personal files. We included randomized controlled trials conducted in the intensive care unit that compared a procalcitonin-guided strategy to usual care and reported on antibiotic utilization and clinically important outcomes. Results were qualitatively and quantitatively summarized. On the basis of no effect in hospital mortality or hospital length of stay, a cost or cost-minimization analysis was conducted using the costs of procalcitonin testing and antibiotic acquisition and administration. Costs were determined from the literature and are reported in 2009 Canadian dollars. Five articles met the inclusion criteria. Procalcitonin-guided strategies were associated with a significant reduction in antibiotic use (weighted mean difference −2.14 days, 95% confidence interval −2.51 to −1.78, $p < .00001$). No effect was seen of a procalcitonin-guided strategy on hospital mortality (risk ratio 1.06, 95% confidence interval 0.86–1.30, $p = .59$; risk difference 0.01, 95% confidence interval −0.04 to +0.07, $p = .61$) and intensive care unit and hospital lengths of stay. The cost model revealed that, for the base case scenario (daily price of procalcitonin Can$49.42, 6 days of procalcitonin measurement, and 2-day difference in antibiotic treatment between procalcitonin-guided therapy and usual care), the point at which the cost of testing equals the cost of antibiotics saved is when daily antibiotics cost Can$148.26 (ranging between Can$59.30 and Can$296.52 on the basis of different assumptions in sensitivity analyses).**

Conclusions: **Procalcitonin-guided antibiotic therapy is associated with a reduction in antibiotic usage that, under certain assumptions, may reduce overall costs of care. However, the overall estimate cannot rule out a 7% increase in hospital mortality. (Crit Care Med 2011; 39:1792–1799)**

Key Words: infection; antibiotics; intensive care units; procalcitonin; biomarkers

In the past decade, the development of antimicrobial resistance in the intensive care unit (ICU) has emerged as a high-priority problem (1). The association between antibiotic exposure, the development of multidrug-resistant pathogens, and worse clinical outcomes have prompted the development of strategies to reduce antibiotic consumption (2). Recent randomized controlled trials (RCTs) of treatment for ventilator-associated pneumonia have demonstrated that shorter courses of antibiotic therapy are not associated with harm (3, 4). These have prompted reconsideration of the duration of appropriate antibiotic therapy for infections in the ICU. Several investigators have suggested that tailoring antibiotics to the resolution of clinical signs and symptoms augmented by biomarker evidence of the resolution of infection may be helpful in shortening antibiotic duration (5–7).

In this regard, the most promising and studied biomarker is procalcitonin (PCT), a prehormone of calcitonin. Since levels of PCT rise in response to infection, its utility for the diagnosis of infection has been extensively investigated with conflicting results depending on the setting and population studied (8–10). Adding to the variability in results is the lack of a reference standard for the diagnosis of infections in the critically ill. As a consequence, the focus has shifted to the ability of PCT to influence outcomes and antibiotic utilization.

Outside the ICU, several trials have shown that a PCT-guided strategy resulted in a prescription of less antibiotics with no apparent negative effects on outcome in ambulatory patients with community-acquired respiratory infections (11–14). However, these trials may not apply to ICU patients who experience higher levels of systemic inflammation, where noninfectious causes of systemic inflammation are common, where colonization as opposed to infection is frequently found, and where the clinician may be reluctant to discontinue antibiotics because of patient acuity. These factors may all impair the ability of PCT to guide antibiotic therapy.

Several RCTs have been performed in the ICU setting, but individually, these trials were too small to rule out a clinically important negative effect on out-

*See also p. 1849.

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comes. In fact, the largest study to date examining the impact of PCT-guided therapy on antibiotic utilization demonstrated that the upper limit of the 95% confidence limit suggested a possible 10% risk increase in 60-day mortality (15). Furthermore, the costs associated with using PCT have not been properly evaluated relative to the costs (savings) associated with the outcomes of this strategy.

The purpose of this systematic review was to evaluate the effect of a PCT-guided antibiotic reduction strategy on clinically important outcomes. Furthermore, the more precise estimates of safety and effectiveness derived from the statistical aggregation of pertinent end points allow an economic evaluation of the PCT-guided strategy from the hospital perspective.

METHODS

Study Identification. We conducted a systematic review of the published literature to identify all relevant randomized trials. Using text word or Medical Subject Headings containing "randomized," "blind," "clinical trial," "procalcitonin," "intensive care unit patients," and "intensive care," we performed computerized searches for relevant articles on MEDLINE, EMBASE, BIIOSIS, and CINAHL electronic databases and the Cochrane Controlled Trials Register from 1990 to November 2009. We also searched our personal files and reference lists of review articles and original studies.

Study Selection Criteria. To select for studies with the greatest validity in relation to relative treatment effects, we included only RCTs. Further, we included studies only if they 1) studied adult critically ill patients, 2) compared a PCT-guided strategy to standard care, 3) evaluated the impact on antibiotic therapy, and 4) included clinically important outcomes, such as mortality, recurrent infectious complications, and length of stay (LOS). We excluded studies reporting on PCT strategies used outside the ICU as their findings may not generalize to the critical care setting.

Utilizing a scoring system that we have used in previous studies (16), we scored the methodologic quality of individual studies and abstracted necessary data in duplicate and independently. Disagreement was resolved by consensus. We attempted to contact the authors of included studies for required additional information not contained in the published articles.

Data Synthesis. The primary outcomes of interest in this study relate to patient safety. Accordingly, we examined 28-day mortality and the development of recurrent infections as our primary outcomes. We used definitions of recurrent infectious complications as defined by the original authors. Secondary outcomes included ICU and hospital LOSs, hospital mortality, acquisition of multidrug-resistant organisms, and antibiotic utilization data. We combined data from all studies to estimate the pooled risk ratio with 95% confidence intervals (CIs) for death and infectious complications and the overall weighted mean difference with 95% CIs for ICU and hospital LOSs. To avoid problems with bias and instability associated with risk ratio estimation in sparse mortality and infection data, one half was added to each cell. In the meta-analysis, we used the random effects model of combining risk ratios across all trials and examined the data for evidence of heterogeneity within groups. Heterogeneity was determined using the chi-square test and interclass correlation I (2). For the LOS and duration of antibiotic analysis, the weighted mean difference was used to describe the difference between treatment and control group means, respectively. We evaluated the influence of the methodologic trials by conducting subgroup analyses comparing treatment effects between studies of high quality and those of low quality. All analyses were conducted using Review Manager 5 (17). We considered a two-sided $p < .05$ without adjustment for multiplicity of outcomes to be statistically significant.

Economic Evaluation. The economic evaluation conducted examined PCT testing as an adjunct for antibiotic management in the treatment of ICU infections from a hospital perspective in 2009 Canadian dollars. Because the results of the meta-analysis demonstrate no difference in mortality, LOS, or recurrent infections, a cost-minimization analysis that considers only the acquisition costs of antibiotics, administration costs of intravenous antibiotics, and costs of the PCT test is justified. Estimates in the literature of the total cost of running a PCT measurement, including assay material, reagents, technician time, purchase, maintenance of a bench top analyzer, and overhead, are approximately Can$49.42 per test (12, 18, 19). We considered three approaches to model antibiotic costs in the ICU setting: 1) a less expensive option such as what might be used for an uncomplicated infection requiring monotherapy (ceftriaxone alone), 2) a more expensive option such as what might be used for complicated infections requiring combination antipseudomonal therapy and coverage for methicillin-resistant *Staphylococcus aureus* (meropenem, ciprofloxacin, and linezolid), and 3) a midpoint cost option comprising the midpoint cost for the prior strategies. Table 1 shows the cost of each antibiotic strategy and the average cost. The duration of antibiotics in each group is derived from the results of the meta-analysis. The incremental costs are the differences in the costs between the PCT-guided strategy and usual care. These costs represent the additional expenditure required per additional patient with ICU infection as a result of PCT testing. Multiway sensitivity analyses were performed, varying the estimates of daily costs of the PCT test (Can$25.88 to Can$69.29), duration of measurement of PCT (6 days, 12 days, or every other day as long as on antibiotics), and difference in the duration of antibiotic treatment between the PCT-guided strategy and usual care (1–5 days).

Table 1. Daily cost of antibiotics per patient for intensive care unit infection

Treatment Strategy	Antibiotic	Typical Antibiotic Therapy	Daily Antibiotic Costs (Can$)	Source	Daily Administration Costs[a] (Can$)	Daily Combination (Can$)	Midpoint Daily Treatment Cost for Intensive Care Unit Infection (Can$)
Expensive	Meropenem	1 g q 8 hrs	273.94	Kotapati et al (37), Edwards et al (38), Kuti et al (39)	51.21		383.57
	Ciprofloxacin	400 mg q 12 hrs	81.51	Bounthanvang et al (42), Walters et al (40)	37.00	715.69	
	Linezolid	600 mg q 12 hrs	235.03	Rosner et al (41), Bounthanvang et al (42)	37.00		
Cheap	Ceftriaxone	1 g q 24 hrs	28.66	Ontario Drug Benefit Formulary (43), Clay et al (44), Hotchies et al (45)	22.78	51.44	

q, every.

[a]Daily administration costs are based on the literature (39, 45, 46) and include the cost of preparation/reconstitution (minibag, saline lock, sodium chloride, needles, syringes, labels, nursing time), antibiotic administration (saline flushes, changing intravenous tubing), and waste disposal.

RESULTS

We found 17 potentially eligible trials. We excluded 12 for the following reasons: not ICU patients, (11–14, 20–22), a duplicate study (23), a meta-analysis (24), nonrandomized (25), and did not report on antibiotic utilization (26). Five trials (15, 27–30) met the inclusion criteria and were included in this review. Tables 2, 3, and 4 summarize the details of each of the individual studies.

Review of Individual Studies

Nobre et al (27) studied the duration of antibiotic therapy in 79 patients with severe sepsis and septic shock. PCT levels were measured at baseline and daily for 7 days in all study patients. In the intervention group, patients who had a baseline PCT level ≥1 μg/L were reevaluated at day 5, and clinicians were encouraged to discontinue antibiotics when PCT dropped >90% from baseline or the absolute value was <0.25 μg/L. Patients with a PCT level <1 μg/L at baseline were reevaluated at day 3, and treating physicians were encouraged to discontinue antibiotics when the PCT level was <0.1 μg/L. In the control group, antibiotic duration was at the discretion of the treating physician. In the intention to treat analysis, there was a trend toward reduced antibiotic duration in the PCT-guided group (median 6.0 days, range 3–34 days vs. 9.5 days, 2–33 days, $p = .15$). There was no difference in clinical outcomes with the exception that ICU LOS was reduced in the PCT-guided group (4 days, 1–21 days vs. 7 days, 1–91 days, $p = .02$). Compliance with the PCT algorithm in the intervention group was not reported.

Hochreiter et al (28) studied the influence of PCT measurements on the duration of antibiotic therapy in 110 surgical ICU patients. Patients were randomized to either PCT-guided antibiotic discontinuation or a standard of 8 days of antibiotic therapy. In the PCT-guided group, antibiotics were discontinued if the clinical signs and symptoms of infection improved and PCT decreased to <1 ng/mL or if the PCT value was >1 ng/mL but had dropped by 25% to 35% of the initial value. Compliance with the study decision rule was not reported. The duration of antibiotic treatment in the PCT-guided group was significantly shorter than in the control group (5.9 ± 1.7 days vs. 7.9 ± 0.5 days, $p < .001$). ICU LOS was also significantly shorter in the PCT-guided group (15.5 ± 12.5 days vs. 17.7 ± 10.1 days, $p = .046$). There was no difference in survival.

Schroeder et al (29) studied the duration of antibiotic therapy in 27 surgical patients with severe sepsis. PCT was done daily, and antibiotic therapy was stopped if PCT was <1 ng/L or if PCT was >1 ng/mL but had dropped at least 25% to 35% less than the baseline value. In the control group, antibiotics were discontinued according to clinical signs and symptoms, and C-reactive protein levels were followed in this group. No comment was made by the authors on compliance with the PCT-guided antibiotic discontinuation policy. Nevertheless, the length of antibiotic treatment was significantly shortened in the PCT-guided group (6.6 ± 1.1 days vs. 8.3 ± 0.7 days, $p < .0001$). There was no difference in clinical outcomes, including mortality.

Bouadma et al (15) studied the use of PCT as a decision tool for the initiation and cessation of antibiotics in a mixed medical/surgical cohort (n = 630). Patients were randomized to either a PCT-directed algorithm for antibiotic initiation and cessation or the control group, where all antibiotic decisions were at the discretion of the managing physician with no adjunctive biomarker information. PCT levels were drawn 7 days per week and communicated to the managing physician with a recommendation based on a prescribed algorithm. It is important to note that in the PCT group the algorithms were suggestions and were disregarded by the clinician 53% of the time. Mortalities between the PCT group and control were not significantly different at 28 days (21.2% vs. 20.4%, respectively) or 60 days (30.0% vs. 26.1%, respectively). The PCT group had significantly more days without antibiotics (14.3 ± 9.1 days vs. 11.6 ± 8.2 days, $p < .0001$) largely due to the effect of the PCT algorithm on early discontinuation. There was no difference in rates of relapse, superinfection, LOS in the ICU, or number of mechanical-ventilator-free days.

Stolz et al (30) randomized 101 patients with ventilator-associated pneumonia to an antibiotic discontinuation strategy according to accepted guidelines or a PCT-based algorithm. In both groups the ultimate decision regarding discontinuation of antibiotics was with the managing clinicians. PCT levels were measured daily until day 10 and communicated to the managing physician in the context of predetermined antibiotic cessation recommendations. The PCT group was found to have significantly higher antibiotic-free days alive (13 days, range 2–21 days vs. 9.5 days, range 1.5–17 days). Antibiotics were continued beyond 7 days in 82% of the patients in the control group and 65% in the PCT group, suggesting poor guideline adherence in the control group. There was no difference between the two groups in 28-day mortality, ICU-free days, LOS, or ventilator-associated-pneumonia-related clinical deterioration.

Aggregated Results

Effect on Antibiotic Duration. We aggregated the four trials that reported the mean and SD of antibiotic duration and found a significant reduction in antibiotic use associated with the PCT-guided strategy (weighted mean difference −2.14 days, 95% CI −2.51 to −1.78, $p < .00001$) (Fig. 1).

Mortality. When the results of the five studies were statistically aggregated, no effect was seen of a PCT-guided strategy on hospital mortality (risk ratio 1.06, 95% CI 0.86–1.30, $p = .59$; risk difference 0.01, 95% CI −0.04 to +0.07, $p = .61$] (Fig. 2). No effect was seen for 28-day mortality; the risk ratio was 0.98 (95% CI 0.75–1.29, $p = .91$) and the risk difference 0.00 (95% CI −0.06 to +0.05, $p = .88$).

LOS. There was no overall effect of a PCT-guided therapy on ICU or hospital LOS. The weighted mean difference for ICU LOS was −1.50 (95% CI −4.50 to +1.05, $p = .25$), and that for hospital LOS was −1.86 (95% CI −4.75 to +1.04, $p = .21$).

Infections. In the two studies that reported recurrent or relapsing infections, there was no evidence of an increase in such infection with a PCT-guided strategy (risk ratio 1.26, 95% CI 0.68–2.35; $p = .46$).

Subgroup Analysis. When studies with high methodologic quality scores (15, 27, 30) were compared to studies with low quality scores (28, 29), there were no differences in antibiotic utilization, mortality, or LOS (data not shown).

Economic Evaluation

Table 5 demonstrates that the cost of a per patient treatment episode using an average antibiotic cost is lower under the PCT-guided strategy (Can$470.62 cost savings) in comparison to the cost associated with the usual care in the base

Table 2. Description and methodologic quality of included trials

Trial Number	Author, Year (Reference)	Population (n)	Specific Details of Population Studied	Method, Score	Intervention	
					PCT	Control
1	Nobre et al, 2008 (27)	Sepsis and septic shock (79)	Positive culture, 50%	Concealed, yes; ITT, yes	PCT daily × 7 days	Antibiotics given on standard starting/stoppage regimen; no tapering on the basis of resolution of clinical signs and symptoms
			ICU-acquired infection, 33%	Score, 11	Baseline PCT ≥1.0 μg/L re-evaluated at day 5; discontinue antibiotics if PCT down by 90% or <0.25; baseline PCT ≤1.0 μg/L re-evaluated at day 3 and discontinue if <0.1 μg/L	
			Prior antibiotics, 0% (excluded if 48 hrs prior)			
			Surgical, 24%			
2	Hochreiter et al, 2009 (28)	Surgical ICU patients requiring antibiotics and two systemic antibiotic syndrome (110)	Positive culture, NR	Concealed, yes; ITT, yes	PCT done daily; antibiotic therapy stopped if PCT <1 ng/L or if PCT >1 ng/mL but had dropped at least 25% to 35% less than the baseline value	Antibiotics given on standard regimen for 8 days
			ICU-acquired infection, NR	Score, 7		
			Prior antibiotics, 0% (excluded if on prior)			
			Surgical, 100%			
3	Schroeder et al, 2009 (29)	Abdominal surgery with severe sepsis (27)	Positive culture, 65%	Concealed, yes; ITT, yes	PCT done daily; antibiotic therapy stopped if PCT <1 ng/L or if PCT >1 ng/mL but had dropped at least 25% to 35% less than the baseline value	According to clinical signs and empirical rules, C-reactive protein available
			ICU-acquired infection, NR	Score, 7		
			Prior antibiotics, 0% (excluded if on prior)			
			Surgical, 100%			
4	Stolz et al, 2009 (30)	Mechanically ventilated patients with ventilator-associated pneumonia (101)	Positive culture, 73%	Concealed, yes; ITT, yes	PCT done daily for up to 10 days	Antibiotics given on standard starting/stoppage regimen; no tapering on the basis of resolution of clinical signs and symptoms
			ICU-acquired infection, 100%	Score, 9	1. Antibiotic therapy stopped if PCT <0.25 μg/L	
			Prior antibiotics, 75%		2. Antibiotic therapy encouraged to be stopped if PCT between 0.25 and 0.5 μg/L or a decrease by ≥80% from baseline	
			Medical, 90%		3. Antibiotic therapy continued if PCT ≥0.5 μg/L or decrease of <80% from baseline	
					4. Antibiotic therapy strongly suggested to continue if PCT >1 μg/L	
5	Bouadma et al, 2010 (15)	ICU patients with suspected bacterial infection (630)	Positive culture, 70%	Concealed, yes; ITT, yes	PCT done daily until treatment finished	Antibiotics given on standard starting/stoppage regimen; no tapering on the basis of resolution of clinical signs and symptoms
			ICU-acquired infection, 33%	Score, 8	Starting guidelines:	
			Prior antibiotics, 23% (excluded if >24 hrs)		1. Antibiotics strongly discouraged if PCT <0.25 μg/L	
			Medical, 90%; surgical, 10%		2. Antibiotics discouraged if PCT ≥0.25 and <0.5 μg/L	
					3. Antibiotics encouraged if PCT ≥0.5 and <1 μg/L	
					4. Antibiotics strongly encouraged if PCT ≥1 μg/L	
					Stopping Guidelines:	
					1. Antibiotics strongly encouraged to stop if PCT <0.25 μg/L	
					2. Antibiotics encouraged to stop if PCT decreases by ≥80% from peak concentration or PCT ≥0.25 and <0.5 μg/L	
					3. Antibiotics encouraged if PCT decreases by <80% from peak concentration or PCT ≥0.5 μg/L	
					4. Changing of antibiotics strongly encouraged if PCT increases from peak concentration and PCT ≥0.5 μg/L	

PCT, procalcitonin; ICU, intensive care unit; ITT, intention to treat; NR, not reported.

Table 3. Clinical outcomes of included trials

Trial Number	Author, Year (Reference)	Mortality (%)			Infections (%)			Length of Stay (days), Mean (SD)			Length of Ventilation (days), Mean (SD)		
		PCT-Guided	Control	*p*	PCT-Guided	Control	*p*	PCT-Guided	Control	*p*	PCT-Guided	Control	*P*
1	Nobre et al, 2008 (27)	Hospital	Hospital		Recurrent	Recurrent		ICU	ICU				
		9 of 39 (23)	9 of 40 (23)	.83	1 of 39 (3)	1 of 40 (3)	.74	7.7 (5.7)	12.3 (9.7)	.02	NR	NR	NR
		28 day	28 day					Hospital	Hospital				
		8 of 39 (21)	8 of 40 (20)	.82				20.9 (16.8)	28.1 (19.7)	.85			
2	Hochreiter et al, 2009, (28)	Hospital	Hospital					ICU	ICU				
		15 of 57 (26)	14 of 53 (26)	>.05	NR	NR	NR	15.5 (12.5)	17.7 (10.1)	.046	NR	NR	NR
3	Schroeder et al, 2009 (29)	Hospital	Hospital					ICU	ICU				
		3 of 14 (21)	3 of 13 (23)	>.05	NR	NR		16.4 (8.3)	16.7 (5.6)	>.05	NR	NR	NR
4	Stolz et al, 2009 (30)	Hospital	Hospital					ICU	ICU				
		10 of 51 (20)	14 of 50 (28)	.32	NR	NR	NR	14.7 (8.2)	17.3 (12.9)		9.4 (8.7)	9.8 (7.6)	NR
		28 day	28 day					Hospital	Hospital				
		8 of 51 (16)	12 of 50 (24)	.32				17.1 (9.2)	19.5 (11.2)				
5	Bouadma et al, 2010 (15)	28 day	28 day		Recurrent	Recurrent		ICU	ICU				
		65 of 307 (21)	64 of 314 (20)	NR	20 of 307 (7)	16 of 314 (5)	.45	15.9 (16.1)	14.4 (14.1)	.23	8 (9.0)	8 (9.0)	NR
		Hospital	Hospital		Acquisition multidrug resistant	Acquisition multidrug resistant		Hospital	Hospital				
		98 of 307 (31.9)	89 of 314 (29.3)	NR	55 of 307 (18)	52 of 314 (17)		26.1 (19.3)	26.4 (18.3)	.87			
		60 day	60 day	NR									
		92 of 307 (30)	82 of 314 (26)										

PCT, procalcitonin; ICU, intensive care unit; NR, not reported.

Table 4. Effect of procalcitonin-guided therapy on antibiotic utilization

Trial Number	Author, Year (Reference)	Duration of Antibiotic Use (days)			Total Antibiotic Exposure Days/1000 days			Days Alive Without Antibiotics		
		PCT-Guided	Control	*p*	PCT-Guided	Control	*p*	PCT-guided	Control	*p*
1	Nobre et al, 2008 (27)	8.6 (6.0)[a]	10.5 (5.7)[a]	.15	541	644	.07	15.3 (8.9)[a]	13.3 (8.2)[a]	.28
2	Hochreiter et al, 2009, (28)	5.9 (1.7)[a]	7.9 (0.5)[a]	<.001	NR	NR		NR	NR	
3	Schroeder et al, 2009 (29)	6.6 (1.1)[a]	8.3 (0.7)[a]	<.001	NR	NR		NR	NR	
4	Stolz et al, 2009 (30)	10 (6-16)^	15 (10-23)[b]	.038	NR	NR		13 (2-21)[b]	9.5 (1.5-17)[b]	.049
5	Bouadma et al, 2010 (15)	10.3 (7.7)[a]	13.3 (7.6)[a]	<.0001	653	812	.001	14.3 (9.1)[a]	11.6 (8.2)[a]	.001

PCT, procalcitonin; NR, not reported.
[a]Mean (SD); [b]the median (range).

case. Using the more expensive antibiotics, the cost savings per case rise to Can$1134.86. If cheaper antibiotics are used, costs would increase by Can$193.64 per patient. Table 6 shows the results of the sensitivity analysis. When all inputs are varied at once (multiway sensitivity analysis) to a "best case scenario" or more favorable results (lowest cost of PCT test, Can$25.88; smallest duration of measurement of PCT, every 2 days [3 days/8 vs. 6 days]; largest difference in duration of antibiotic treatment, 2 days [8 vs. 6 days]; most expensive treatment, Can$715.69), cost savings equal Can$1353.74. Meanwhile, a "worst case" or less favorable scenario (highest cost of PCT test, Can$69.29; largest duration of measurement of PCT, 14 vs. 13 days; smallest difference in duration of antibiotic treatment, 1 day [14 vs. 13 days]; least expensive treatment, Can$51.44) results in higher costs under the PCT-guided strategy (Can$849.33) compared with usual care. For the base case scenario (daily price of PCT, Can$49.42, 6-day duration of measurement of PCT, and 2-day difference in antibiotic treatment), the point at which the cost of testing equals the cost of antibiotics saved is when the daily cost for antibiotics is Can$148.26 (and it ranges from Can$37.07 to Can$296.52 on the basis of more and less favorable results, respectively).

DISCUSSION

We have systematically reviewed the literature and summarized the findings of five randomized studies evaluating the impact of a PCT-guided strategy on antibiotic utilization and clinical outcomes.

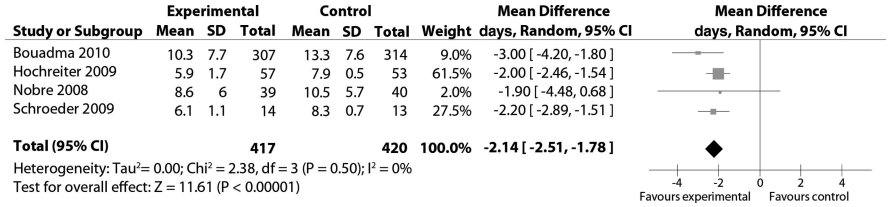

Figure 1. Effect of procalcitonin-guided therapy on duration of antibiotic utilization. *Gray squares* represent the point estimate and 95% confidence intervals (*CIs*) around the treatment effect of each individual study. The *black diamond* is the summary or overall combined estimate of treatment effect. *df*, degrees of freedom.

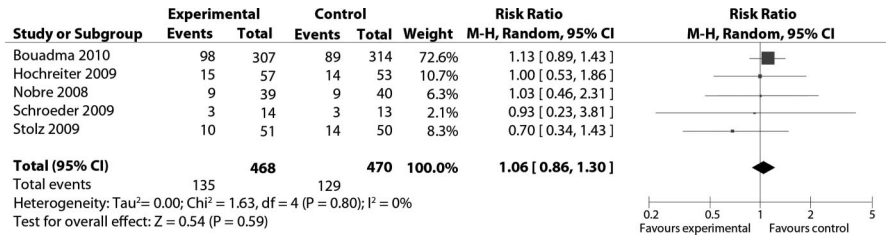

Figure 2. Effect of procalcitonin-guided therapy on hospital mortality. *Gray squares* represent the point estimate and 95% confidence intervals (*CIs*) around the treatment effect of each individual study. The *black diamond* is the summary or overall combined estimate of treatment effect. *M-H*, Mantel-Hanzel; *df*, degrees of freedom.

Table 5. Base case cost-minimization analyses

Treatment Strategy	Procalcitonin-Guided Therapy Costs[a] (Can$)	Standard Therapy Costs[b] (Can$)	Incremental Costs[c] (Can$)
Average	2597.94	3068.56	−470.62
Cheap	605.16	411.52	193.64
Expensive	4590.66	5725.52	−1134.86

[a]Procalcitonin-guided therapy costs = costs based on 6 days of antibiotic therapy per results of meta-analysis + 6 days of procalcitonin testing (Can$49.42 per test, base case); [b]standard therapy costs = costs based on 8 days of antibiotic therapy per results of meta-analysis; [c]procalcitonin-guided therapy costs = standard therapy costs.

We have shown that the daily use of PCT to guide antibiotic duration is associated with approximately 2 days of reduction in antibiotic usage and no difference in clinical outcomes in critically ill patients treated for infections. The reduction in antibiotic use comes from early discontinuation rather than less initiation of empirical antibiotics. It is important to point out that while just under 1,000 patients have been studied in these five RCTs, we cannot exclude a 7% risk increase (or smaller) in hospital mortality. For a clinically important increase in mortality to be ruled out, more studies and/or larger studies are still required. Furthermore, there are even fewer patients who contribute to the aggregated estimate of recurrent infections or superinfections as a consequence of premature antibiotic discontinuation. Notwithstanding, the results of the meta-analysis and the individual studies indicate that PCT-guided antibiotic therapy does not influence LOS in the ICU or in the hospital. Accordingly, we conducted an economic evaluation and found that daily PCT-guided therapy is associated, on average, with a cost savings of approximately Can$470 per treatment course. Given the high prevalence of infections in the ICU (31), at a system level over 1 yr, this could translate into significant cost savings.

Whereas prior reviews of PCT-guided therapy do exist (32, 33), one is outdated

Table 6. Sensitivity analysis

	Base Case Results		Less Favorable Results		More Favorable Results	
Variable	Value	Incremental Costs[a] (Can$)	Value	Incremental Costs[a] (Can$) (Deviation, %)[b]	Value	Incremental Costs[a] (Can$) (Deviation, %)[b]
Daily cost of procalcitonin test	49.42		69.29		25.88	
Average treatment		−470.62		−351.40 (25.3)		−611.860 (30.0)
Cheap treatment		193.64		312.86 (61.6)		52.40 (72.9)
Expensive treatment		−1134.86		−1015.64 (10.5)		−1276.10 (12.4)
Break-even treatment[c]	148.26		207.87		77.64	
Duration of measurement of procalcitonin	Every day (6 days)[d]		Every day (12 days)[e]		Every 2 days (3 days)[d]	
Average treatment		−470.62		−174.10 (63.0)		−618.88 (31.5)
Cheap treatment		193.64		490.16 (153.1)		45.38 (76.6)
Expensive treatment		−1134.86		−838.34 (26.1)		−1283.12 (13.1)
Break-even treatment[c]	148.26		296.52		37.07	
Difference in duration of antibiotic treatment[f]	2		1		5	
Average treatment		−470.62		258.89 (155.0)		−1473.07 (213.0)
Cheap treatment		193.64		591.02 (205.2)		187.58 (3.1)
Expensive treatment		−1134.86		−73.23 (93.5)		−3133.67 (176.1)
Break-even treatment[c]	148.26		296.52		59.30	

[a]Incremental costs (cost of procalcitonin-guided therapy − cost of standard therapy), in 2009 Canadian dollars. A negative number is associated with cost savings; [b]percentage by which the results of sensitivity analysis differ from the results of base case cost-minimization analysis; [c]point at which the daily cost of antibiotics is equal to the daily cost of procalcitonin testing; [d]antibiotic treatment based on 8 days for standard therapy versus 6 days for procalcitonin-guided therapy; [e]antibiotic treatment based on 14 days for standard therapy versus 12 days for procalcitonin-guided therapy; [f]antibiotic treatment based on 14 days for standard therapy versus 13 and 9 days for procalcitonin-guided therapy, respectively, based on less or more favorable results.

as it does not include recent trials (15, 29), both include trials of heterogeneous patients (trials with non-ICU hospitalized patients, outpatients, and neonates), and neither includes a formal economic evaluation. We believe the PCT response to infection to be very different across these disparate populations, and the focus of our review is on the adult ICU patient population. Our findings are consistent with both prior reviews (32, 33), in that PCT-guided therapy is associated with a 2–3-day reduction in antibiotic use and no overall effect on mortality.

The results of the economic evaluation have also demonstrated that the cost savings (or increase) associated with PCT-guided therapy are contingent upon the local costs of the PCT assay, the duration of measurement of PCT, the cost and duration of the antibiotics used, and the estimated difference in antibiotic utilization. Obviously, the lower the price of the PCT assay, the greater the cost savings. With an increase in the use of more expensive antibiotics and as the difference in antibiotic utilization between PCT-guided therapy and usual therapy increases, so do the cost savings attributable to PCT-guided therapies. These principles are supported by a cost analysis done alongside an RCT of PCT-guided therapy in the setting of community-acquired pneumonia (12). In our study, under the base case condition, PCT measurements would be cost neutral provided that the costs of PCT testing are less than Can$50 per test, the difference in antibiotic use realized is 2 days, and the average cost of the daily antibiotics is about Can$150. Although there is no empirical evidence to support this modeling, if PCT testing would be reduced to every 2 days and the same results applied, the break-even price point would be around Can$37.50 a day for antibiotics. To determine whether daily PCT measurements translate into a favorable economic situation at a local level, users will have to consider all these variables to develop an understanding of the impact of PCT on local budgets.

There are several limitations to the existing data that impact the generalizability of our study. First, the patient population studied in these five RCTs is quite narrow. The majority of studies excluded patients on prior antibiotics and focused on ICU-presenting infections, not ICU-acquired infections. We are less certain about PCT-guided therapy in the difficult to treat and diagnose infections that occur later in the ICU course in patients on previous antibiotics. Also, approximately 75% of studied patients had a medical, compared to a surgical, admission diagnosis. As the inflammatory cytokine response may be different in surgical vs. medical or ICU-presenting vs. ICU-acquired infections, the utility of PCT may be variable in these populations not well represented in these studies. Second, the degree of compliance with the PCT guidelines for discontinuing antibiotics in the PCT-guided group in these five studies was low. Compliance varied across the studies, but physician noncompliance was >50% in only two of the studies (14, 15). To the extent that compliance with PCT-guided recommendations was increased, we could increase the magnitude of cost savings considerably. With the exception of the two RCTs from the same group (28, 29), all the studies used different arbitrarily derived decision rules to guide antibiotic discontinuation. It remains to be seen if the arbitrariness of these rules is one important barrier in the uptake and adherence of the PCT-guided recommendations. A third limitation of the existing studies is that antibiotics in the usual care group were prescribed for fixed durations, usually 10–14 days. However, there is evidence that antibiotics can be safely discontinued in response to the resolution of clinical (not biochemical) signs and symptoms (5, 7). Ideally, to get a better understanding of the effect of PCT guidance on antibiotic therapy, both groups would have daily reminders to monitor the resolution of clinical signs and symptoms of infection with appropriate decision rules based on these signs and symptoms and only one group would get the PCT measurements as well. Alternatively, as was done in one study (29), C-reactive protein, a much cheaper and less specific biomarker commonly used in many ICUs worldwide, could be part of the information available to the patients in the usual care group. We hypothesize that the value of PCT measurements, both clinically and economically, would be less in the setting where physicians were using antibiotic discontinuation policies based on resolution of clinical signs or symptoms (and daily measurements of C-reactive protein). An additional limitation is that the meta-analysis is dominated by one large trial (n = 621) that accounts for about two thirds of the total sample size (n = 938). However, the results are remarkably consistent across the five studies, so the conclusions would remain similar even if the large study was removed. Finally, a limitation of the current analysis is that the economic evaluation did not include the costs of the analyzer, only the per test costs for PCT. For those hospitals that already have such an analyzer, there will be no additional incremental costs. For those hospitals that purchase the analyzer, it would be difficult to estimate the proportion of the fixed costs attributable to each PCT test given that the analyzer can measure a broad variety of other assays. Similarly, the additional costs savings associated with the beneficial effect of reduced antibiotics on patient adverse effects (such as *Clostridium difficile* colitis) and ICU microbiology are not included in our economic model.

CONCLUSIONS

While the literature on the value of PCT-guided antibiotic therapy will continue to evolve as the ongoing studies (34–36) of the same are completed and reported, we feel that the existing literature supports the position that PCT-guided therapy is associated with an average of 2 days of reduction in antibiotic use with no overall effect on clinical outcomes or LOS in the ICU or hospital. The magnitude of the cost savings (incurred) associated with PCT measurements will be a function of the costs of antibiotics commonly used, their prescribed duration, the frequency of use and cost of PCT, and the estimated difference in antibiotic utilization (in days). By considering these variables, local settings can determine the economic impact on local budgets of embracing this new technology to reduce unnecessary antibiotic exposure.

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