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Meta-Analysis and Systematic Review of Procalcitonin-Guided Therapy in Respiratory Tract Infections▽

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Circulating procalcitonin (PCT) is a biomarker that can be used in diagnosing bacterial infections. We performed a quantitative meta-analysis of available randomized controlled trials to determine whether antibiotic therapy based on PCT measurements alters clinical outcomes and antibiotic use in patients with lower respiratory tract infections. We identified studies through MEDLINE (1996 to 2010), the ISI Web of Knowledge (1996 to 2010), and Ovid. Studies that met our criteria were prospective, randomized controlled trials involving patients with respiratory tract infections. Outcomes of mortality, intensive care unit (ICU) admission, length of hospital stay, number of antibiotic prescriptions, and duration of antibiotic treatment were evaluated. Eight studies randomizing 3,431 patients met our criteria for inclusion. Pooled analysis showed a significant reduction in number of antibiotic prescriptions and duration of antibiotic use in patients with PCT-guided antibiotic treatment compared to standard therapy. In addition, the use of PCT-guided antibiotic therapy did not impact mortality, ICU admission, or length of hospital stay in these studies. A high degree of heterogeneity was identified in 3 of 5 outcomes that were evaluated, and sensitivity analysis indicated that heterogeneity was decreased among studies using the same PCT-based treatment algorithm. In conclusion, PCT-guided antibiotic therapy in patients with respiratory tract infections appears to reduce antibiotic use without affecting overall mortality or length of stay in the hospital.

The circulating procalcitonin (PCT) concentration has been investigated as a marker of systemic inflammation, infection, and sepsis in a number of studies (3). While levels of PCT are elevated in bacterial, fungal, and parasite infections, PCT exhibits slight or no elevation in viral infections and in severe inflammation without an infectious etiology (29). Furthermore, compared to traditional indicators of bacterial infection, i.e., white blood cell (WBC) counts and C-reactive protein (CRP) levels, PCT levels correlated with the CRB-65 score, which indicates the severity of community-acquired pneumonia (CAP) (21). According to recent data, antibiotics are most commonly prescribed for presumed respiratory tract infections (1), which vary from self-limited acute bronchitis to severe exacerbations of chronic obstructive pulmonary disease (COPD) and CAP (31). Despite many studies demonstrating marginal efficacy for antibiotic therapy in COPD, 85% of patients with COPD exacerbations are treated with antibiotics (22). In addition, despite the fact that lower respiratory tract infections (LTRI) are frequently due to viral infections, up to 75% of these patients seen in general medical practices are treated with antibiotics (24). Current guidelines recommend antibiotic therapy for most patients with CAP and acute exacerbation of COPD of 7 to 15 days and 3 to 7 days, respectively (12, 25). Thus, it is widely agreed that antibiotics are overprescribed. This misuse of antibiotics can be harmful in two ways: patient-specific side effects from treatment and population-based adverse events related to development of bacterial resistance (36). As a consequence, investigators have explored biological markers that can be quantitated in serum or bronchoalveolar lavage fluid for the purpose of guiding the antibiotic treatment. To date, several studies have indicated that PCT is a promising candidate biomarker for guiding physicians regarding antibiotic use during the treatment of patients with LRTI or sepsis (5–8, 15, 19, 26, 31, 33, 34). To provide a more robust estimate of the potential benefits and drawbacks of PCT-guided therapy in LTRI, we performed a meta-analysis from available clinical trials to evaluate the impact of PCT-guided therapy on all-cause mortality, antibiotic use, and length of hospital stay in patients with LTRI.

MATERIALS AND METHODS

Search strategy. We sought to identify all relevant clinical trials using searches of web-based databases (MEDLINE [1996 to 2010], ISI Web of Knowledge [1996 to 2010], The Cochrane Central Register of Controlled Trials [1996 to 2010], and EMBASE) with no language restrictions. The search was performed in November 2010. Search terms were "PCT," "Pro-CT," "procalcitonin," "antibiotic therapy," "antimicrobial therapy," "lower respiratory tract infection," "respiratory tract infection," "CAP," "community-acquired pneumonia," "COPD," and "chronic obstructive pulmonary disease." Potentially relevant studies were retrieved and reviewed by 2 reviewers.

Selection criteria. Studies were included in our analysis if they met the following criteria: (i) the design was a prospective, randomized controlled trial (RCT); (ii) the study was performed with adults who had an established or suspected diagnosis of respiratory tract infection; (iii) patients were randomized to a strategy of PCT-guided antibiotic therapy (based on the level of circulating PCT) compared to a parallel control group; and (iv) the study reported as an outcome either duration of antibiotic therapy, length of stay in the hospital, or mortality.

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Data extraction. Two reviewers (H.L. and Y.-F.L.) independently extracted the following data from each study: first author, year of publication, country where trial was executed, study design, number of initially enrolled individuals, number of evaluated participants, type of PCT assay used, details of PCT-based antibiotic use, number of patients managed with versus without a PCT-based algorithms, subgroup of COPD and/or CAP in the evaluated patients, and intensive care unit (ICU) admission. Data on mortality, number of antibiotic-treated patients with versus without PCT-based algorithms, duration of antibiotic use, and length of hospital stay were also extracted. In assessing the methodological quality of the RCTs included in our analysis, we followed the recommendations in the Cochrane handbook for systematic reviews of interventions. We summarized the following components in a domain-based evaluation: randomization, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias (14). If the study provided medians and interquartile ranges instead of means and standard deviations (SDs), we imputed the means and SDs as described by Hozo et al. (16) and Liu et al. (23).

Outcome. Our primary outcomes were all-cause mortality, ICU admission during study course, and length of hospital stay. Our secondary outcome was use of antibiotics, including number of antibiotic prescriptions and duration of antibiotic use.

Statistical analysis. We assessed heterogeneity between trials using the χ^2 and I^2 tests. The I^2 statistic approximates the proportion of total variation in the effect size estimates that is due to heterogeneity rather than sampling error. I^2 values of above 25%, 50%, and 75% were taken as indicators of mild, modest, and high heterogeneities, respectively, and a P value lower than 0.10 was considered statistically significant. We assessed publication bias using the funnel plot method and Egger's test (10). We calculated pooled risk ratios (RR) and 95% confidence intervals (CI) for all primary and secondary outcomes using both the Mantel-Haenszel fixed-effect and the DerSimonian-Laird random-effect models. For all analyses, the results from the fixed-effect model are presented only when there was no heterogeneity between trials; otherwise, the results from the random-effect model are presented.

Sensitivity analysis. We performed multiple sensitivity analyses to evaluate the impact of study design variability on our results. Our evaluation included the following alternative schemes: (i) excluding the studies by Briel et al. (5) and Burkhardt et al. (6) (since they enrolled patients with acute respiratory tract infection without considering upper or lower), (ii) excluding the study by Kristoffersen et al. (19) (since it has no posthospital follow-up), and (iii) including the study by Schuetz et al. (31) and the two studies by Christ-Crain et al. (7, 8) (since they used the same level of PCT to guide antibiotic therapy).

RESULTS

Study selection. As a result of our literature search, 66 studies were identified. By reviewing the titles and abstracts of articles, review articles ($n = 17$), editorials, letters or author replies ($n = 6$), and irrelevant papers ($n = 29$) were excluded. After full review, an additional 5 articles that did not meet our criteria were excluded. Eventually, we identified 8 randomized, controlled studies that met our criteria (5–8, 19, 31, 33, 34).

Study methodology and quality. All 8 clinical trials included in our analysis were prospective randomized controlled trials (Table 1). All studies randomized patients on a 1:1 basis to either a PCT-guided antibiotic treatment group or a control group. Six studies used intention-to-treat analysis to evaluate endpoints. Because treatment algorithms were based on PCT values, blinding the treating doctors was difficult. Only 2 studies used a single-blind method for blinding patients, while the others were unblinded. All 8 studies used the same method of TRACE to quantify the serum PCT level. Three of eight studies used the same PCT-guided algorithm in their PCT-guided groups. All trials treated control groups using published guidelines for antibiotic treatment or standard clinical practice. In the intervention groups from these studies, antibiotic treatment recommendations varied based on PCT levels but could be overruled by the treating physicians.

Patient population. Eight studies enrolled a total of 3,431 patients with suspected respiratory tract infections. A summary of the characteristics of each analyzed study is shown in Table 2. The first study by Stolz et al. (33) enrolled patients with COPD, that by Christ-Crain et al. (8) enrolled patients with CAP, and those by Briel et al. (5) and Burkhardt et al. (6) included patients with either upper or lower acute respiratory tract infections. The second study by Stolz et al. (34) enrolled patients with ventilator-associated pneumonia (VAP). The remaining studies (7, 19, 31) enrolled patients with suspected LRTI. The studies by Briel et al. and Burkhardt et al., which included patients with acute upper and lower respiratory tract infections, enrolled populations with younger mean ages.

Effect of PCT-guided therapy on mortality, ICU admission, and length of hospital stay. All studies reported the number of patients who died during therapy and the subsequent follow-up period. No patient died in the study by Burkhardt et al. (6). In the study by Briel et al. (5), zero patients and one patient were reported dead in the PCT group and the control group, respectively. Hence, we ruled out both studies for pooled mortality analysis. The odds ratio (OR) and 95% CI for all-cause mortality in each of the remaining 6 studies are shown in Fig. 1. The profile test for homogeneity by $\chi^2$and I^2 demonstrated $P = 0.912$ and $I^2 = 0\%$, suggesting that there was no statistical evidence for heterogeneity among the studies included in the analysis. Using the Mantel-Haenszel fixed-effect model, the overall RR for mortality was 0.998 (95% CI, 0.977 to 1.018). There was no difference in mortality between patients receiving PCT-guided therapy or standard therapy.

Five studies reported data for ICU admissions. Because Stolz et al. (34) reported on VAP patients collected from the ICU, this study was ruled out for analysis. There was no heterogeneity found among the remaining 4 studies ($P = 0.727$ for χ^2 test; $I^2 = 0\%$). Using the Mantel-Haenszel fixed-effect model, the RR for ICU admission for patients treated with PCT-guided therapy compared to standard therapy was 0.785 (95% CI, 0.57 to 1.076). There was no significant difference in ICU admissions between the two groups ($P = 0.132$) (Fig. 2).

To evaluate the effects of PCT-guided therapy on length of hospital stay, we first analyzed the heterogeneity in this parameter among the 6 studies that included this information and concluded that significant heterogeneity existed ($\chi^2 = 100.20$; $P < 0.001$; $I^2 = 95.0\%$). Accordingly, we used a random-effect model to analyze the weighted mean difference in length of hospital stay. This analysis indicated that there was no significant difference in length of hospital stay among treatment groups in studies included in the analysis ($P = 0.097$); however, there was a trend toward reduced length of stay in the groups with PCT-guided therapy (Fig. 3).

Effect of PCT-guided therapy on antibiotic use. To analyze the effects of PCT-guided therapy on antibiotic use, we evaluated two outcomes: number of patients with antibiotic prescriptions and duration of antibiotic use in the different groups. While all 8 studies reported the number of patients receiving antibiotic prescriptions, 1 study (34) was excluded from this analysis because all patients in this study received antibiotics. Data regarding the duration of antibiotic use were available from 7 studies.

For the outcome of number of patients with antibiotic prescriptions, we found significant heterogeneity among the 7

TABLE 1. Summary of analyzed studies

Parameter	Schuetz et al. (31)	Christ-Crain et al. (7)	Briel et al. (5)	Christ-Crain et al. (8)	Stolz et al. (33)	Kristoffersen et al. (19)	Stolz et al. (34)	Burkhardt et al. (6)
No. of patients	1,359	243	458	302	208	210	101	550
Location	Multicenter; Switzerland	Single center; Switzerland	Multicenter; Switzerland	Single center; Switzerland	Single center; Switzerland	Multicenter; Denmark	Multicenter; Switzerland, USA	Multicenter; Germany
Randomization	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blinding	No	Single blind	No	No	No	No	No	Yes
Allocation concealment	Yes	Not mentioned	Yes	Not mentioned	Not mentioned	Yes	Yes	Yes
Follow-up	30 days	10–14 days/4–6 mo	28 days	6 wk	14–21 days/6 months	No	28 days	14 days and 28 days
Primary endpoint	Adverse event	Use of antibiotic	Patient's daily restricted activity	Antibiotic use and duration	Antibiotic use and antibiotic exposure	Antibiotic use and hospital stay length	No. of antibiotic-free days	Patient's daily restricted activity
Antibiotic use strategy in PCT group	PCT $\leq$ 0.1 μg/liter, strongly discourage; 0.1 μg/liter $<$ PCT $\leq$ 0.25 μg/liter, discourage; 0.25 μg/liter $<$ PCT $\leq$ 0.5 μg/liter, encourage; PCT $>$ 0.5 μg/liter, strongly encourage	PCT $\leq$ 0.1 μg/liter, strongly discourage; 0.1 μg/liter $<$ PCT $\leq$ 0.25 μg/liter, discourage; 0.25 μg/liter $<$ PCT $\leq$ 0.5 μg/liter, encourage; PCT $>$ 0.5 μg/liter, strongly encourage	PCT $\leq$ 0.1 μg/liter, discourage; 0.1 μg/liter $<$ PCT $\leq$ 0.25 μg/liter, do not recommend; PCT $>$ 0.25 μg/liter, encourage	PCT $\leq$ 0.1 μg/liter, strongly discourage; 0.1 μg/liter $<$ PCT $\leq$ 0.25 μg/liter, discourage; 0.25 μg/liter $<$ PCT $\leq$ 0.5 μg/liter, encourage; PCT $>$ 0.5 μg/liter, strongly encourage	PCT $<$ 0.1 μg/liter, discourage; 0.1 μg/liter $\leq$ PCT $\leq$ 0.25 μg/liter, discourage or encourage; PCT $>$ 0.25 μg/liter, encourage	PCT $<$ 0.25 μg/liter, discourage; 0.25 μg/liter $\leq$ PCT $<$ 0.5 μg/liter, encourage; PCT $\geq$ 0.5 μg/liter, strongly encourage	PCT $<$ 0.25 mg/liter, strongly discourage; 0.25 $\leq$ PCT $<$ 0.5 mg/liter or a decrease of 80% compared with day 0, discourage; PCT $\geq$ 0.5 mg/liter or a decrease of 80% compared with day 0, encourage; PCT $>$ 1 mg/liter, strongly encourage	PCT $<$ 0.25 μg/liter, no antibiotics; PCT $\geq$ 0.25 μg/liter, with antibiotics
Strategy in control group	Up-to-date guideline	Standard	Current guideline	Usual practice guideline	Up-to-date guideline	Standard	Standard	Standard
Intention-to-treat analysis	Yes	Yes	Yes	Yes	No	No	Yes	Yes

TABLE 2. Data extracted from included studies

Parameter	Group	Value in study by:							
		Schuetz et al. (31)	Christ-Crain et al. (7)	Briel et al. (5)	Christ-Crain et al. (8)	Stolz et al. (33)	Kristoffersen et al. (19)	Stolz et al. (34)	Burkhardt et al. (6)
Age, yr (mean ± SD)	PCT	73 (59–82)	65.3 ± 17.3	48 ± 18	70 ± 17	69.5	67.2 ± 17.6	53 (21–88)	41.4 ± 15.3
	Control	72 (59–82)	62.8 ± 19.8	48 ± 18	70 ± 17	69.5	67 ± 15.6	59 (18–83)	43.4 ± 15.5
Male gender, *n* (%)	PCT	402 (59.9)	61 (51)	98 (42)	94 (62)	50 (49)	54 (52)	38 (75)	111 (40.4)
	Control	380 (55.2)	67 (54)	87 (38)	93 (62)	44 (41.5)	58 (54)	37 (74)	114 (41.5)
Patients, *n*	PCT	671	124	232	151	102	103	51	275
	Control	688	119	226	151	106	107	50	275
Antibiotic use, *n* (%)	PCT	506 (75.4)	55 (44.3)	58 (25)	128 (84.8)	41 (40.2)	88 (85.4)	51 (100)	84 (30.5)
	Control	603 (87.6)	99 (83.2)	219 (96.9)	149 (98.7)	76 (71.7)	85 (79.4)	50 (100)	89 (32.4)
COPD subgroup, *n*	PCT	115	29	12	44	102	28	8	2
	Control	113	31	9	32	106	32	11	4
CAP subgroup, *n*	PCT	460	42	38	151	0	47	0	0
	Control	465	45	31	151	0	50	0	3
Died, *n*	PCT	34	4	0	18	7	2	12	0
	Control	33	4	1	20	9	1	8	0
Loss of follow-up, *n*	PCT	1	8	2	2	0		0	1
	Control	0	5	2	0	0		0	3
ICU admission, *n*	PCT	43	5			8	7	51	0
	Control	60	6			11	5	50	0
Hospital stay, days (mean ± SD)	PCT	9.4 ± 6.0	10.7 ± 8.9		12.0 ± 9.1	9 ± 2.3	5.9 ± 0.5	26 ± 2.3	0
	Control	9.2 ± 6.0	11.2 ± 10.6		13.0 ± 9.0	10 ± 2.3	6.7 ± 0.5	26 ± 0.92	0
Duration of antibiotic use, days (mean ± SD)	PCT	5.7 ± 5.3	10.9 ± 3.6	6.2 ± 2.5	5.8 ± 5.3		5.2 ± 0.4	10 ± 1.7	7.7 ± 3.3
	Control	8.7 ± 3.8	12.8 ± 5.5	7.1 ± 2.2	12.9 ± 6.5		6.8 ± 0.4	15 ± 2.2	7.8 ± 2.8

analyzed studies ($\chi^2 = 192.34$; $P < 0.001$, $I^2 = 96.9\%$). By using a random-effect analyzer, we found significant differences between PCT-guided antibiotic treatment and standard antibiotic treatment. Not surprisingly, antibiotic prescriptions were reduced in the PCT-guided antibiotic treatment groups ($P = 0.03$) (Fig. 4).

For duration of antibiotic use, heterogeneity also existed among the 7 studies included in our analysis ($\chi^2 = 327.75$; $P < 0.001$; $I^2 = 98.2\%$). We found a significant difference between PCT-guided therapy and standard therapy in duration of antibiotic use by analyzing the weighted mean difference using a random-effect analyzer. The duration of antibiotic use in the PCT-guided groups was greatly reduced compared to that in the standard therapy groups ($P < 0.001$) (Fig. 5).

Sensitivity analysis. Because we found heterogeneity in 3 of 5 outcomes investigated, we conducted multiple sensitivity analyses to investigate whether variations in the design of the included studies influenced our results. The results of sensitivity analysis are shown in Table 3. By analyzing the I^2 values exhibited in the subgroup of studies using the same PCT algorithm to guide therapy (7, 8, 31), we found that a source of heterogeneity could be related to the PCT levels used in guiding antibiotic treatment. However, we could not identify all the causes of heterogeneity across these studies by simply excluding studies in which the posthospital follow-up group was absent or in which both upper and lower respiratory tract infections were included. In general, patients with LRTI frequently have comorbid diseases. Differences in comorbidities in patients enrolled in individual studies could influence the results.

DISCUSSION

PCT is the prohormone of calcitonin but lacks hormonal activity (13). Elevated serum concentrations of PCT were ini-

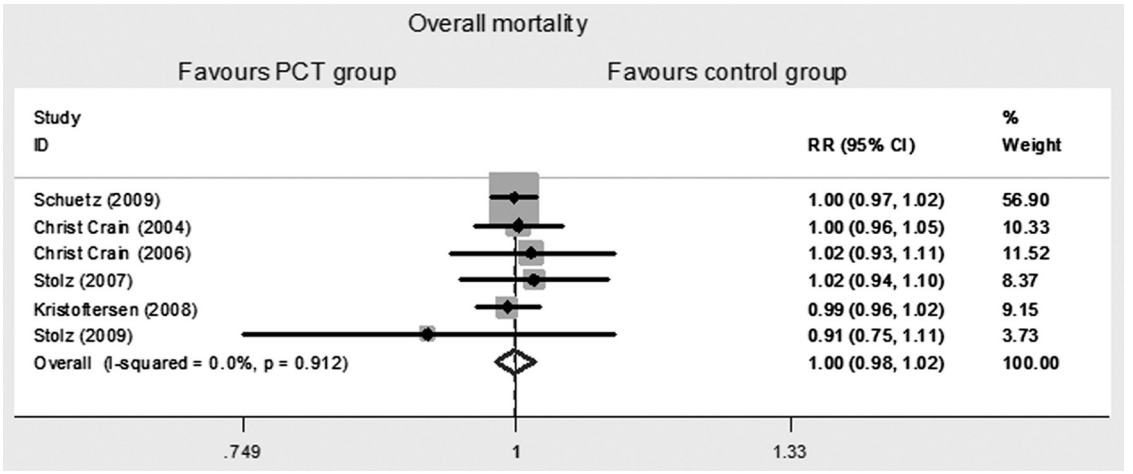

FIG. 1. Comparison of all-cause mortality between the PCT-guided antibiotic group and the control group. Test for heterogeneity: $\chi^2 = 1.51$, $P = 0.912$, and $I^2 = 0.0\%$. Test for overall effect: RR = 0.998, $z = 0.24$, and $P = 0.809$.

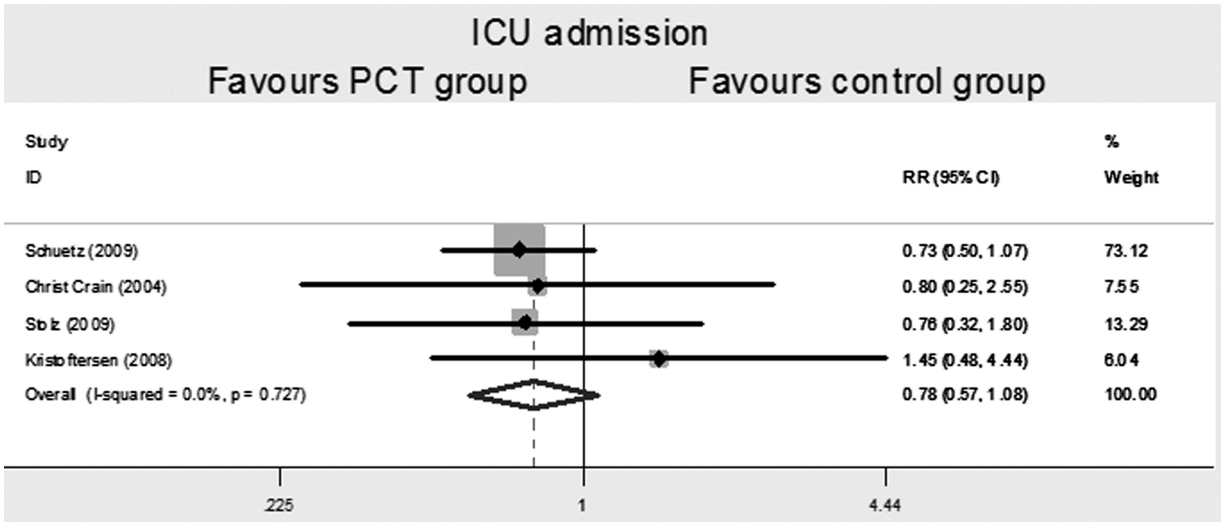

FIG. 2. Comparison of overall ICU admissions between patients receiving PCT-guided antibiotic therapy and those receiving standard antibiotic therapy. Test for heterogeneity: $\chi^2 = 1.31$, $P = 0.727$, and $I^2 = 0.0\%$. Test for overall effect: RR = 0.785, $z = 1.50$, and $P = 0.132$.

tially detected in patients with sepsis and infection (2). Hyperprocalcitonemia appears within 2 to 4 h in patients with infection, often reaches peak values in 8 to 24 h, and then persists as long as the inflammatory process continues. With recovery, PCT levels return to normal (3). This information led researchers to hypothesize that PCT might be a promising indicator for guidance of antibiotic therapy and judgment of antibiotic therapeutic efficiency in patients with infections. A variety of studies have shown that PCT levels are effective for diagnosis, outcome prediction, and efficacy of therapy for various populations, including infants, adults, and elderly patients with different sites of infections (4, 11, 18, 30). However, a recent report assessed the value of PCT and CRP and found that in COPD patients PCT levels are not associated with bacterial presence and that benefit from antibiotic therapy is more likely with low PCT levels (9). In addition, PCT may not be the best predictor of outcomes in CAP (20). In CAP, initial PCT levels appear to provide only moderate prognostic information regarding mortality risk and do not improve clinical risk scores (32). Hence, it puzzled us whether PCT is safe enough for guidance of antibiotic therapy in LTRI. During the past decade, several prospective randomized controlled trials have been conducted to investigate this issue. The aim of this meta-analysis was to evaluate pooled data regarding clinical outcomes between PCT-guided antibiotic therapy and standard therapy in patients with respiratory tract infections. Tang et al. performed a meta-analysis regarding PCT-guided therapy in patients with different types of infections. In their study, they enrolled 7 randomized controlled studies (35). Significant heterogeneities were found in several outcomes, including duration of antibiotic use, antibiotic exposure, and number of antibiotic prescriptions. This finding may have been due to patient heterogeneity (patients had postsurgical infections, sepsis, and LRTI) and different methods used in PCT mea-

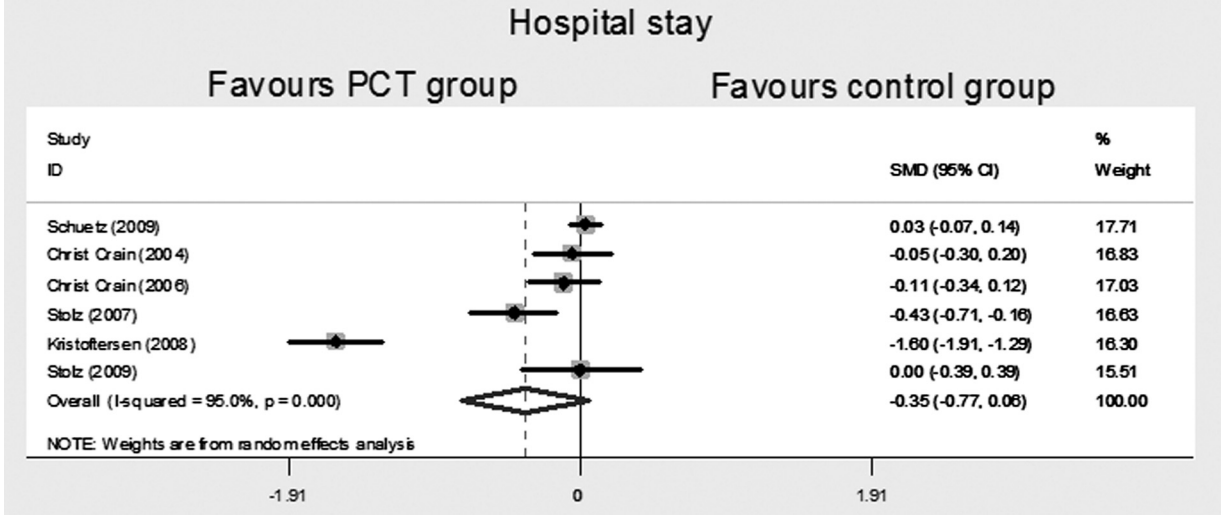

FIG. 3. Forest plot for the weighted mean difference in length of hospital stay. Test for heterogeneity: $\chi^2 = 100.20$, $P < 0.001$, and $I^2 = 95\%$. Test for overall effect: standardized mean difference (SMD) = -0.355, $z = 1.66$, and $P = 0.097$.

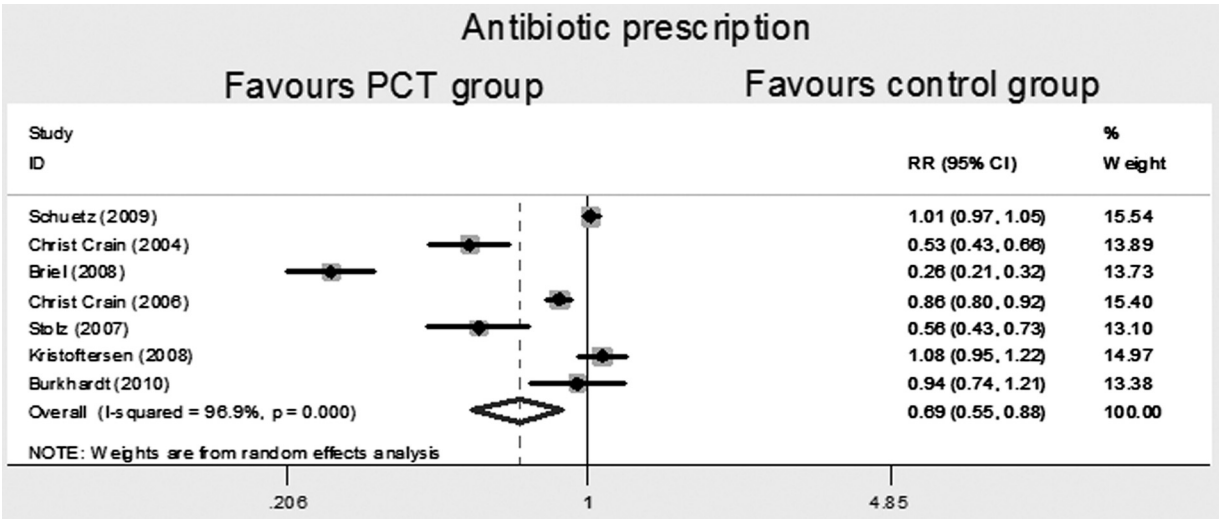

FIG. 4. Forest plot for odds ratio of antibiotic prescriptions in PCT-guided antibiotic treatment groups and control groups. Test for heterogeneity: $\chi^2 = 192.34$, $P < 0.001$, and $I^2 = 96.9\%$. Test for overall effect: RR = 0.692, $z = 3.01$, and $P = 0.03$.

surement. In our analysis of studies involving patients with respiratory tract infections, we focused on outcomes of safety and antibiotic use. Overall, PCT-guided antibiotic treatment reduced the number of antibiotic prescriptions and duration of antibiotic use in patients with respiratory tract infections without increasing mortality and duration of hospital stay compared to standard recommended therapy. Although 8 randomized controlled trials that focused only on respiratory tract infections were enrolled in our study, heterogeneity was also found during the analysis for hospital stay duration, antibiotic use duration, and number of antibiotic prescriptions. Since the trials that we evaluated enrolled patients with respiratory tract infections ranging from acute bronchitis to ventilation-associated pneumonia, differences in disease severity and variability in comorbidities in enrolled patients might partly explain the heterogeneity, along with differences in the PCT-guided treatment algorithms. In addition to our study and the report by Tang et al. (35), another recently reported meta-analysis regarding PCT-guided antibiotic therapy in the ICU also showed a high degree of heterogeneity (17).

Similar to the pooled analysis of PCT-guided antibiotic therapy among ICU patients (17), the pooled data in our analysis indicate that PCT-guided therapy is safe without compromising clinical outcomes. Interestingly, we found a trend toward reduction in the length of hospital stay in the PCT-guided therapy group (mean reduction from 0.5 to 1 day). Without a negative impact on clinical outcome, PCT-guided antibiotic therapy may allow patients not requiring antibiotics to be discharged from the hospital sooner.

We consider the limitations of our meta-analysis to be the following: (i) there was a small number of available trials, as only 8 randomized controlled trials were available for review; (ii) not all the enrolled studies were blinded for allo-

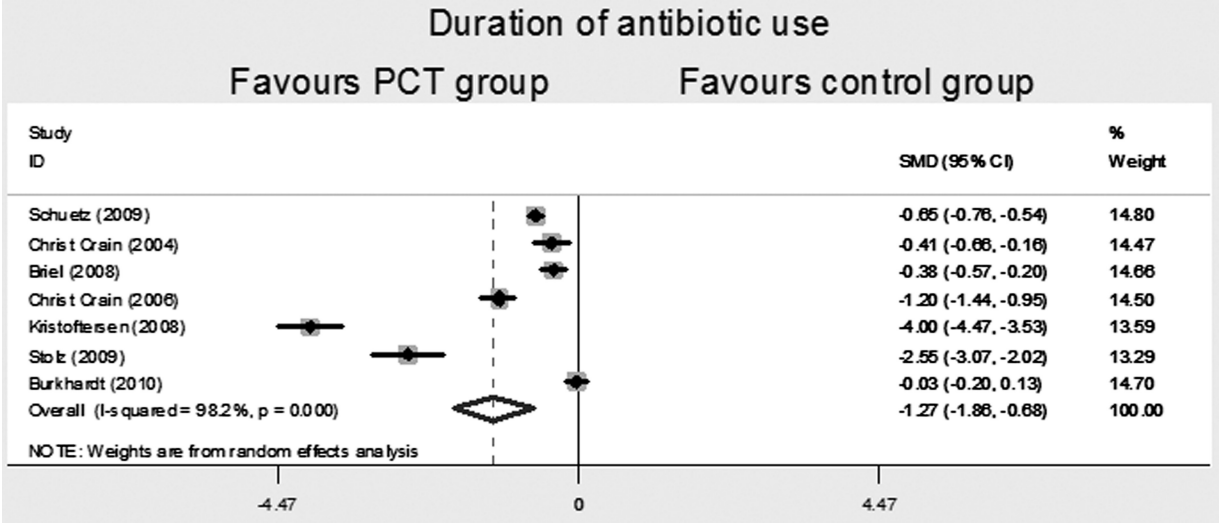

FIG. 5. Forest plot for the weighted mean difference of duration of antibiotic use. Test for heterogeneity: $\chi^2 = 327.75$, $P < 0.001$, and $I^2 = 98.2\%$. Test for overall effect: SMD = -1.272, $z = 4.23$, and $P < 0.001$.

TABLE 3. Sensitivity analysis

Studies used	Outcome	No. of studies (no. of patients) in subgroup	OR (CI) or SMD (CI)	*z*	*P* value	Heterogeneity		
						χ^2	*P*	I^2 (%)
Studies by Briel et al. (5) and Burkhardt et al. (6) excluded	Length of hospital stay[a]							
	No. of antibiotic prescriptions	5 (2,322)	0.453 (0.133 to 1.548)	1.26	<0.001	95.95	0.207	95.8
	Duration of antibiotics	5 (2,215)	−1.732 (−2.619 to −0.845)	3.83	<0.001	243.93	<0.001	98.4
Study by Kristoffersen et al. (19) excluded	Length of hospital stay	5 (2,213)	−0.099 (−0.261 to 0.063)	1.20	0.231	10.16	0.038	60.6
	No. of antibiotic prescriptions	6 (3,119)	0.175 (0.065 to 0.472)	3.44	<0.001	111.57	0.001	95.5
	Duration of antibiotics	6 (2,738)	−0.810 (−1.216 to −0.404)	3.91	<0.001	126.34	<0.001	96.0
Studies by Schuetz et al. (31) and Christ-Crain et al. (7, 8) included	Length of hospital stay	3 (1,904)	0 (−0.090 to 0.090)	0.01	0.996	1.46	0.483	0
	No. of antibiotic prescriptions	3 (1,904)	0.207 (0.081 to 0.530)	3.28	0.002	12.82	0.001	84.4
	Duration of antibiotics	3 (1,904)	−0.750 (−1.128 to −0.373)	3.89	<0.001	21.54	<0.001	90.7

[a] Data absent in the studies by Briel et al. and Burkhardt et al.

cation of treatment; and (iii) there was potential publication bias in the enrolled studies since positive results are more likely to be published than negative results. Nevertheless, we conclude that PCT-guided antibiotic therapy in patients with respiratory tract infections is likely to reduce antibiotic use and exposure without a detrimental effect on patient safety. Further randomized controlled studies to investigate PCT-guided antibiotic therapy in specific populations of patients with suspected respiratory tract infections could help to clarify the utility of this approach.

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