Review

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Procalcitonin guidance in patients with lower respiratory tract infections: a systematic review and meta-analysis

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Abstract: Although effective for bacterial lower respiratory tract infections (LRTIs), antibiotic treatment is often incorrectly prescribed for non-bacterial LRTIs. Procalcitonin has emerged as a promising biomarker to diagnose bacterial infections and guide antibiotic treatment decisions. As part of a regulatory submission to the U.S. Food and Drug Administration, this systematic review and meta-analysis summarizes the effects of procalcitonin-guided antibiotic stewardship on antibiotic use and clinical outcomes in adult LRTI patients. PubMed and the Cochrane Database of Systematic Reviews were searched for English-language randomized controlled trials published between January 2004 and May 2016. Random and fixed effects meta-analyses were performed to study efficacy (initiation of antibiotics, antibiotic use) and safety (mortality, length of hospital stay). Eleven trials were retained, comprising 4090 patients. Procalcitonin-guided patients had lower odds of antibiotic initiation (odds ratio: 0.26; 95% confidence interval [CI]: 0.13–0.52) and shorter mean antibiotic use (weighted mean difference: –2.15 days; 95% CI: –3.30

to –0.99) compared to patients treated with standard care. Procalcitonin use had no adverse impact on mortality (relative risk: 0.94; 95% CI: 0.69–1.28) and length of hospital stay (weighted mean difference: –0.15 days; 95% CI: –0.60 to 0.30). Procalcitonin guidance reduces antibiotic initiation and use among adults with LRTIs with no apparent adverse impact on length of hospital stay or mortality.

Keywords: antibiotics; biomarker; bronchitis; calcitonin; pneumonia; procalcitonin.

Introduction

Lower respiratory tract infections (LRTIs), which include acute bronchitis, exacerbations of chronic obstructive pulmonary disease (COPD) and pneumonia, are an important cause of morbidity and mortality among all age groups [1, 2]. Antibiotics (ABs) are an effective treatment for bacterial LRTIs but are commonly prescribed for non-bacterial LRTIs or when there is uncertainty regarding whether the infection is bacterial or not [3].

Incorrect use and overuse of ABs is associated with an increase in antimicrobial resistance, mortality and health-care costs [4]. Unnecessary exposure to ABs also increases the risks of allergic reactions and *Clostridium difficile* infections [5, 6]. The World Health Organization recently declared antimicrobial resistance “one of the biggest threats to global health, food security, and development today” [7]. In the United States, the Centers for Disease Control and Prevention (CDC) estimate there are at least 37,000 deaths (including deaths related to *Clostridium difficile*) directly related to AB use and resistance, costing as much as \$55 billion in direct and indirect healthcare costs annually [8]. Early classification of LRTIs as bacterial or non-bacterial could curtail the number of unnecessary AB prescriptions, thereby reducing antimicrobial resistance as well as AB-related adverse events.

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A commonly used biomarker to assess whether an LRTI is bacterial or viral is C-reactive protein. However, evidence suggests that C-reactive protein lacks sensitivity and specificity and should not be used alone to guide AB initiation [9–11]. An alternative biomarker, procalcitonin (PCT), could help decision making for both initiation and cessation of ABs in patients with LRTIs [12]. PCT is already recognized as an effective biomarker for infection [12, 13]. In normal physiologic conditions, PCT is made and converted to calcitonin by the C cells of the thyroid gland [14]. However, in systemic bacterial infections, PCT is rapidly synthesized in various extrathyroidal tissues, resulting in elevated serum PCT levels [4, 14].

It has been several years since a systematic review of the literature has been performed to evaluate the effectiveness and safety of PCT in guiding AB therapy in LRTI [12, 15–17]. Although some American guidelines recommend PCT as an infectious disease marker for sepsis [18], and for hospital-acquired and ventilator-associated pneumonia [19], there are currently no guidelines in the United States that recommend measuring PCT as an aid to decision making for AB prescribing in LRTI. Therefore, this study sought to summarize the current state of the clinical evidence around the effectiveness and safety of PCT guidance compared to standard of care in adults with LRTIs in a clinical setting. Effectiveness and safety were measured by four outcomes: AB initiation, AB use, hospital length of stay (LOS) and mortality.

This study was conducted as part of a regulatory submission to the U.S. Food and Drug Administration [20].

Materials and methods

A systematic review and meta-analysis of randomized controlled trials (RCTs) published in peer-reviewed journals was performed to identify original articles on the use of PCT-guided therapy compared to standard of care among adult patients with suspected or confirmed LRTI. The review protocol was not registered.

Data source

The search strategy used a prospectively defined algorithm in PubMed and the Cochrane Database of Systematic Reviews and was conducted on May 4, 2016. The following keywords were used: [“procalcitonin” OR “PCT”] AND [“anti bacterial agents” OR “antibiotic” OR “antibiotics” OR “antibacterial agent” OR “antibacterial agents” OR “anti bacterial agent” OR “anti bacterial agents” OR

“antimicrobial agent” OR “antimicrobial agents” OR “anti microbial agent” OR “antimicrobial agents”] AND [“LRTI” OR “low respiratory tract infection”, OR “low respiratory tract infections” OR “pneumonia” OR “bronchitis” OR “COPD” OR “chronic obstructive pulmonary disease” OR “chronic obstructive pulmonary diseases”]. Full details on the search strategy are available in the Supplementary Materials.

Study selection

Articles published in English between 2004 (commercialization of the first automated [CE-IVD marked] PCT immunoassay) and 2016 were retained. Each article was screened by two independent reviewers. Articles were excluded if any of the following conditions was met: (1) population of interest was restricted to ventilator-associated pneumonia (VAP); (2) no original study data were presented; (3) the population of interest was not patients with LRTI; (4) PCT was not used to guide clinical AB decision making; (5) absence of control group; (6) PCT was not the focus of the trial; or (7) the article was not in English. Studies that were only available in abstract/poster formats or included pediatric patients were also excluded. Discrepancies between reviewers’ inclusion and exclusion decisions were resolved through discussion. In the event that an agreement between both reviewers could not be reached, the advice of a third adjudicator was used as a tie breaker. If multiple exclusions were identified, the highest-ranked exclusion was selected.

Data extraction and quality assessment

Prospectively defined variables were extracted from the identified studies in an extraction grid. Two reviewers independently extracted data elements from the publications identified. Any discrepancies between the two extractions were identified in a reconciliation process by a third reviewer and were subsequently reconciled among the extractors.

Bias was assessed using the Risk of Bias Assessment Tool for RCTs proposed by the Cochrane Collaboration [21]. The Risk of Bias Assessment Tool provides an overview of the quality of the RCTs by scoring each publication on seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting

(reporting bias), and other. Because of its ambiguity, the “other” category was not assessed in this study.

Analysis

In addition to the outcomes, other variables extracted from the articles included country of study, patient eligibility criteria, study setting, time to end point, and the PCT algorithm (i.e. the specific threshold of serum PCT that dictated whether or not ABs were appropriate). Aggregate-level demographic and clinical characteristics, such as age, race/ethnicity, previous use of AB medication and primary diagnosis of interest, were also extracted. The reviewers extracted data from the identified publications in a standardized Microsoft Excel form.

Dichotomous end points included AB initiation and mortality. AB initiation was expressed as an odds ratio (OR), and a weighted pooled OR was calculated among all studies that reported AB initiation. Mortality was expressed as a risk ratio (RR) and, similarly, a weighted pooled RR was computed. Continuous outcomes extracted included AB use and length of hospital stay. AB use was reported in one of two ways: exposure (the number of days during which a patient was prescribed ABs, including exposures of zero days when patients were not prescribed ABs) and duration (the number of days during which patients were treated, conditional on AB initiation). One article did not specify whether the trial evaluated exposure or duration, and the authors were contacted for clarification (this was the only instance where authors of the studies were contacted). No response was received. Continuous outcomes were summarized using weighted mean differences (WMD). All results were summarized in forest plots with both point estimates and 95% confidence intervals (CI) displayed. When the mean and standard deviation (SD) were not reported in a study, the median, interquartile range (IQR) and/or range were extracted to estimate the mean and SD [21, 22].

To evaluate the differences due to diagnosis (e.g. PCT guidance have the same effect in patient management in pneumonia patients vs. bronchitis patients), a stratification of the meta-analysis was conducted. The three strata consisted of (1) studies for which the main diagnosis was COPD, (2) studies for which the main diagnosis was community-acquired pneumonia and (3) studies that had a mix of LRTI diagnoses.

Both inverse-variance fixed and random effects (DerSimonian and Laird method) analyses were conducted [23]. The I^2 statistic was used to describe heterogeneity across studies [21, 24, 25]. All analyses were conducted

using Stata IC version 14.2, and package `sbe24_3` was used to produce forest plots.

Results

Figure 1 presents the PRISMA diagram of the search strategy and study inclusion process [26]. The PubMed literature search initially identified 253 articles, whereas the Cochrane Database of Systematic Reviews identified 104 publications. From these, nine articles were excluded because they were published before PCT determinations were commercially available, and 40 were removed because they were not published in English. An additional 51 duplicates were removed from the 308 articles remaining. One expert from the U.S. Food and Drug Administration overseeing the search proposed an additional list of eight potentially relevant articles, two of which had already been identified [20]. These six additional articles brought the total of articles to 263. After applying the exclusion criteria, 240 articles were excluded: 20 articles were excluded because the population studied had VAP; 136 articles were excluded because the article did not present original data; 20 articles were excluded because the population was not patients with LRTI; 55 articles were excluded because PCT was not intended to guide clinical AB decision making; 1 article was excluded because there was no control group; 6 articles were excluded because PCT was not the focus of the publication; and 2 articles were excluded because they were not in English. A total of 23 articles were considered for final inclusion.

After excluding posters and meeting abstracts (four), non-RCTs and secondary analyses of RCTs (six) and pediatric studies (two), 11 studies remained and were included in the meta-analysis [2, 27–36].

Table 1 presents key characteristics and outcomes of the retained studies. Sample size of the RCTs included in the meta-analysis ranged between 120 and 1259 subjects per study. Among the studies included in the meta-analysis, six publications [2, 27, 32–36] occurred in a hospital setting compared to three in the emergency department (ED) [30, 31, 34] and two in primary care [28, 29]. Clinicians whose patients were in the PCT cohort were generally adherent to the PCT algorithm (64%–91%, among reported [27–33, 35]). All eleven studies reported AB initiation and mortality by cohort. Only one study [2] did not report AB duration and seven studies [2, 30–33, 35] reported hospital LOS.

All studies used 0.25 ng/mL as a cutoff, below which initial antibiotic treatment was discouraged, and multiple

Figure 1: Study selection process.

FDA, U.S. Food and Drug Administration; LRTI, lower respiratory tract infections; PCT, procalcitonin; RCT, randomized controlled trial; VAP, ventilator-associated pneumonia.

studies [2, 28, 30–35] supported the <0.1 and/or >0.5 ng/mL cutoffs corresponding, respectively, to strongly discouraged or strongly encouraged initial antibiotic use. In addition to these absolute cutoffs, discontinuation was also guided by relative reductions in subsequent PCT measurements. A PCT reduction of $\geq 80\%$ and/or 90% from the initial or peak PCT measure was used in the algorithms of three studies [31, 32, 35]. Physicians in the PCT-guided treatment arms were usually directed to consider their clinical judgment when making a decision about AB treatment, so the decision to initiate or discontinue AB was based on both PCT levels and clinical judgment.

Quality assessment

The Risk of Bias Assessment for the 11 studies retained is presented in the Supplementary Materials. Because the data extracted came from publications instead of clinical study reports, it was not possible to assess whether some outcomes were omitted from the publication, and all studies had an unclear risk of bias for selective reporting (reporting bias) (see Supplementary Materials). There was

no study which did not report the reasons for missing patients, so incomplete outcome data (attrition bias) were judged low risk in all studies. The type of bias with the most numerous high-risk studies was blinding of participants and personal (performance bias), which is due to the open-label nature of many of the trials.

Efficacy

Among the eleven studies reporting AB initiation, Verduri et al. [36] was the only study that was excluded for this outcome because all patients were prescribed ABs for some time. Among the 10 studies included in the meta-analysis for AB initiation, both the fixed and random effects model demonstrated a statistically significant reduction in the odds of AB initiation in the PCT-guided cohort compared to those treated with standard care (random effects OR = 0.26; 95% CI: 0.13–0.52; p-value <0.001 , Figure 2). Heterogeneity was considerable ($I^2 = 93.1\%$). Among the nine studies that reported AB use, both random effects and fixed effects models demonstrated a statistically significant reduction in AB treatment (random effects

Table 1: Study details and outcomes.

First author (year)	Time to end point	Diagnosis(es) of interest	Study setting	PCT	Controls	AB initiation	Mean AB days of use	Mean LOS in hospital, days	Mortality
Branche et al. (2015) [27]	30 days	Nonpneumonic LRTI	Hospital	151	149	46% (PCT)	3.7 (PCT)	Not reported	4% (PCT)
Briel et al. (2008) [28]	28 days	Acute respiratory tract infections (upper and lower)	Primary care	232	226	25% (PCT)	6.2 (PCT)	Not reported	5% (control)
Burkhardt et al. (2010) [29]	28 days	Acute respiratory tract infections (upper and lower)	Primary care	275	275	97% (control)	7.1 (control)	Not reported	0% (PCT)
Christ-Crain et al. (2004) [30]	10–14 days; mortality at 6 months	Various, including CAP, AECOPD, bronchitis, asthma	ED	124	119	13% (PCT)	7.8 (PCT)	Not reported	0.4% (control)
Christ-Crain et al. (2006) [31]	6 weeks		ED	151	151	32% (control)	7.7 (control)	Not reported	0% (PCT)
Corti et al. (2016) [32]	28 days	AECOPD	Hospital	62	58	44% (PCT)	10.9 (PCT)	10.7 (PCT)	0% (control)
Kristoffersen et al. (2009) [33]	Until hospital discharge	Various (suspected LRTI)	Hospital	103	107	83% (control)	12.8 (control)	11.2 (control)	3% (PCT)
Long et al. (2011) [34]	28 days	CAP	ED	81	81	85% (PCT)	5.8 (PCT)	12.0 (PCT)	3% (control)
Schuetz et al. (2009) [35]	30 days	ECOPD, CAP, acute bronchitis	Hospital	671	688	99% (control)	12.9 (control)	13.0 (control)	12% (PCT)
Stolz et al. (2007) [2]	14–21 days; 6 months	ECOPD	Hospital	102	106	58% (PCT)	6.1 (PCT)	4.5 (PCT)	2% (PCT)
Verduri et al. (2015) [36]	6 months	ECOPD	Hospital	88	90	74% (control)	9.0 (control)	5.1 (control)	3% (control)
						85% (PCT)	5.1 (PCT)	5.9 (PCT)	2% (PCT)
						79% (control)	6.8 (control)	6.7 (control)	1% (control)
						85% (PCT)	4.8 (PCT)	Not reported	0% (PCT)
						98% (control)	7.0 (control)	Not reported	0% (control)
						75% (PCT)	5.7 (PCT)	9.4 (PCT)	5% (PCT)
						88% (control)	8.7 (control)	9.2 (control)	5% (control)
						40% (PCT)	Not reported	8.3 (PCT)	5% (PCT)
						72% (control)		8.7 (control)	9% (control)
						20% (PCT)	6.6 (PCT)	5.7 (PCT)	3% (PCT)
						13% (control)	10.0 (control)	5.8 (control)	2% (control)

AB, antibiotic; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; ECOPD, exacerbation of chronic obstructive pulmonary disease; ED, emergency department; LOS, length of stay; LRTI, lower respiratory tract infection; PCT, procalcitonin.

Figure 2: Odds of antibiotic initiation in PCT-guided cohort vs. standard care. AB, antibiotic; CI, confidence interval; OR, odds ratio; PCT, procalcitonin.

WMD = −2.15 days; 95% CI: −3.30 to −0.99; p-value < 0.001, Figure 3 exposure and duration pooled). Heterogeneity was considerable ($I^2 = 94.9\%$).

Safety

Among the seven studies [2, 30–33, 35, 36] that reported hospital LOS, the overall mean LOS using the weights from the random effects model was 8.02 days in the treatment arms and 8.17 days in the control arms. There was no statistically significant difference in hospital LOS between the treatment arms (WMD = −0.15 days; 95% CI: −0.60 to 0.30; p-value = 0.507, Figure 4). Nine studies [2, 27, 28, 30–33, 35, 36] were included in the meta-analysis

assessing all-cause mortality, whereas two studies [29, 34] were excluded from the meta-analysis (no deaths were observed in either cohort). The pooled RR of PCT on mortality did not reach statistical significance (RR = 0.94, 95% CI: 0.69–1.28; p-value = 0.957, Figure 5). No heterogeneity was observed ($I^2 = 0.0\%$) for either outcome.

Stratifications

When stratified by primary diagnosis (i.e. acute bronchitis, community-acquired pneumonia or COPD exacerbation), the results for AB initiation, hospital LOS and mortality were robust and consistent with the pooled results. However, among studies primarily consisting

Figure 3: Weighted mean difference in days of antibiotic use in PCT-guided cohort vs. standard care.

AB, antibiotic; CI, confidence interval; PCT, procalcitonin; SD, standard deviation; WMD, weighted mean difference.

Figure 4: Weighted mean difference in length of hospital stay in days in PCT-guided cohort vs. standard care. CI, confidence interval; HOS, hospital; PCT, procalcitonin; SD, standard deviation; WMD, weighted mean difference.

Figure 5: Relative risk of mortality in PCT-guided cohort vs. standard care. CI, confidence interval; PCT, procalcitonin; RR, relative risk.

of community-acquired pneumonia subjects, AB duration failed to reach statistical significance (WMD = -4.64; 95% CI: -9.40 to 0.11; p-value = 0.055). This is likely because there were only two studies [31, 34] included in this stratification. When AB duration and AB exposure were examined separately, the CIs overlapped with the pooled estimate. However, the three studies that examined AB duration [29, 33, 34] had a pooled WMD that overlapped with zero (WMD = -1.25; 95% CI: -2.92 to 0.43; p-value = 0.144). One study did not specify whether it assessed exposure or duration [30].

Discussion

The findings of this meta-analysis demonstrate that PCT is an effective biomarker in guiding AB therapy in LRTI by reducing AB initiation and use compared to the standard

of care, with no observed adverse effects on hospital LOS and all-cause mortality.

These results are consistent with a number of similar studies on this topic. In a 2009 systematic review, Tang and colleagues assessed the impact of PCT guidance on a number of outcomes in seven RCTs (four of which were included in this review [2, 28, 30, 31], as the three others included septic patients [37–39]) [17]. The review found that, among the four studies that focused on LRTI, PCT-guided patients had reduced odds of initiating ABs (OR: 0.51; 95% CI: 0.29–0.88) but no statistically significant difference was found on the number of days on AB (WMD: 3.07; 95% CI: 0.21–6.35; p-value = 0.07). This could be due to the small number of studies (n = 4), which may have led to an underpowered analysis. In a 2011 systematic review, Li and colleagues used data from eight RCTs (seven of which were included in the current study, as one included patients with ventilator-associated pneumonia [40]) [2, 28–31, 33,

35], and they found reductions in antibiotic prescriptions (RR: 0.69; 95% CI: 0.55–0.88) and duration of antibiotic use (standardized mean difference [SMD]: –1.27; 95% CI: –1.86 to –0.68), whereas the intervention had no effect on mortality (RR: 1.00; 95% CI: 0.98–1.02), ICU admissions (RR: 0.79; 95% CI: 0.57–1.08) or length of hospital stay (SMD: –0.35; 95% CI: –0.77 to 0.06) [15]. Finally, in 2013, a Cochrane review and patient-level meta-analysis that included 14 trials (eight of which were included in this review [2, 28–31, 33–35], the other six were excluded for a variety of reasons [39–43]) found that PCT guidance had no impact on mortality (OR: 0.94; 95% CI: 0.71–1.23) and that PCT-guided patients had lower odds of treatment failure (OR: 0.82; 95% CI: 0.71–0.97), defined based on mortality and various complications [12]. In addition, the 2013 Cochrane review found a lower exposure to ABs among PCT-guided patients (WMD: –3.47; 95% CI: –3.78 to –3.17) and lower odds of initiating ABs (OR: 0.24; 95% CI: 0.20–0.29) [12]. The findings of the present study are consistent with the prior analyses and further strengthen the evidence for the potential benefit of PCT as part of AB stewardship programs. The findings are also qualitatively similar to those of a recently published meta-analysis of PCT use among patients with suspected or confirmed sepsis [44].

Given the growing threat of antimicrobial resistance, the reduction in AB use due to PCT guidance may also have important societal implications. The current study was not designed to assess the impact of PCT guidance on deleterious consequences of AB misuse, such as *Clostridium difficile* infections or allergic reactions, or broader effects on population antimicrobial resistance. Therefore, further research is necessary to assess the impact of PCT on decreasing the incidence of such AB-related events. In addition, many of the studies included in the current analysis combined PCT testing with a training session or an educational program (on AB misuse and how to use PCT). This could have sensitized participating physicians to the problems associated with AB misuse. Further research on medical education programs about PCT could evaluate the impact of PCT testing with and without training.

Of note, while the OR for AB initiation appeared unusually low for one study (OR: 0.01; 95% CI: 0.00–0.02, Briel et al. [28]), this was primarily due to the fact that the study restricted the study population to patients whose physician intended to prescribe AB, thereby creating a large difference in the proportions of patients who initiated AB (control arm = 97%, intervention arm = 25%) and a very low OR. In addition, the study was set in primary care, where many of the patients presented with rhinosinusitis, bronchitis and the common cold – conditions for which use of AB is often not warranted and a biomarker

is particularly helpful for parsing viral infections from bacterial infections. The same trend was observed in the 2013 Cochrane review, in which the OR for AB initiation was lower than the entire population's when the analysis was restricted to patients in primary care settings (OR: 0.10; 95% CI: 0.07–0.14) [12].

Our results are also in line with a recent meta-analysis based on individual patient data [45, 46]. However, that study found a statistically significant reduction in mortality, whereas we only found a trend towards lower mortality in patients assigned to PCT guidance. This difference may be explained by the different approach (i.e. aggregate data analysis vs. individual patient data analysis) and differences in statistical power.

This study was subject to a number of limitations. First, the relatively small number of studies made it challenging to use other meta-analytical techniques, such as meta-regressions, to appraise the effect of independent variables on the pooled estimates. Second, imputation of missing values was necessary for continuous outcomes when means or standard deviations were not available. However, the methods used to transform those variables were validated approaches and were expected to affect both treatment arms equally [21, 22]. Third, the measurement of AB use (exposure and/or duration) varied across studies. A stratification was conducted to address this, but caution is warranted in interpretation of the analysis, as the number of studies in each stratum was low: three studies [29, 33, 34] reported average AB duration conditional on initiation, whereas five studies included subjects who never initiated AB therapy in their calculation [27, 28, 31, 32, 35]. The definition of AB initiation was unclear for one publication [30]. Fourth, it was not possible to assess the extent to which PCT was the primary factor behind AB decision making. Because of randomization, clinical presentations of patients were expected to be similar in both arms. However, other factors could have contributed to AB decision making at the patient level. Fifth, there was considerable heterogeneity for the efficacy outcomes. Although this is not a limitation in itself, this could signal underlying differences between study populations. Because the fixed effects and the random effects models' yielded similar results, it is unlikely that such limitations had a substantial impact on the results.

Conclusions

In light of the positive effect of PCT on reducing AB use with no observed adverse impact on key safety outcomes, the

use of PCT as a biomarker to guide AB treatment has the potential to improve the quality of care for adults with LRTI.

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