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The authors declare that the data presented are original material and have not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all the authors, who have met the requirements for authorship.

ORIGINAL ARTICLE

PROCALCITONIN – GUIDED ANTIBIOTIC THERAPY IN PEDIATRIC PATIENTS: A SYSTEMATIC REVIEW

ABSTRACT

Background: Serum procalcitonin is a useful biomarker in establishing the presence of bacterial infections and has been used in algorithms to guide antibiotic treatment among adults. Its role in pediatric infections, however, remains unclear.

Objectives: This research aims to evaluate the impact of serum procalcitonin in guiding antibiotic therapy among pediatric patients with suspected local or systemic infections.

Methodology: Randomized controlled trials comparing procalcitonin-guided antibiotic therapy to clinically guided therapy in pediatric patients with local or systemic infections were searched through MEDLINE, Cochrane, EMBASE, HERDIN and ClinicalTrials,gov. Hand search in various search engines was also done. Outcomes included antibiotic usage, morbidity and mortality. Two reviewers independently assessed potentially relevant studies. Statistical analysis was conducted using RevMan 5.3 using inverse variance weighting and random effects model.

Results: Five randomized controlled trials were included. Overall, there was a reduction in antibiotic prescription rate in the procalcitonin group compared to controls for all groups (RD -0.13, 95% CI [-0.21,-0.06]; p <0.00001), however, pooled studies were heterogenous. Subgroup analysis showed that for children with pneumonia, procalcitonin guidance significantly reduced antibiotic prescription rate (RD -0.12, 95% CI [-0.21, 0.04], p 0.005), and may have potential in reducing the duration of therapy (95% CI [-6.78, -2,54], p <0.0001) and antibiotic-related adverse effects (RD -0.17, 95% CI [-0.24, -0.10], p<0.00001) compared to controls. In one study on neonates with early onset sepsis, procalcitonin guidance reduced antibiotic prescription rate by 27% (p=0.0009) and duration of therapy by 22.4 hours (p=0.0009). Procalcitonin guidance has no significant impact on antibiotic prescription rate in children with fever without a source (RD -0.11, 95% CI [0.28, 0.05], p=0.19).

Conclusion: Procalcitonin guidance significantly reduces antibiotic prescription rate among children with pneumonia and neonates with early onset sepsis. It has the potential in reducing the duration of antibiotic therapy and antibiotic-related side effects in these populations. On the other hand, it had no impact among children with fever without a source. These results highlight the need for algorithm-based approaches using procalcitonin cut-off values to guide antibiotic therapy in children.

KEYWORDS:
Procalcitonin, early onset sepsis, neonatal sepsis, childhood pneumonia, pneumonia in children

INTRODUCTION

The rational use of antibiotics is crucial in managing pediatric patients with a wide variety of local and systemic infections. The timely initiation and duration of antibiotic use is also clinically relevant in managing patients in different clinical settings. Among children, the most commonly encountered infections include pneumonia both in the ambulatory and hospital setting, fever that may be attributed to a variety of infections, and sepsis mostly being managed in the intensive care units. Most of the clinical signs and symptoms for these infections are non-specific, either caused by a self-limited viral infection, while some may present with occult bacteremia. Because of the difficulty in identifying specific etiologies clinically and using other laboratory parameters, most children receive antibiotics without the causative agent being known. This leads to further misuse and overuse of antibiotics, increases the risk of antibiotic resistance, drug-related side effects and therapeutic costs.

Various attempts have been made in identifying serum biomarkers that could differentiate among bacterial, fungal and viral or noninfectious conditions, aid in risk stratification, and ultimately guide clinicians regarding antibiotic therapy. One of the most extensively studied biomarkers is procalcitonin, and has also been used in algorithms among adult infections in a variety of clinical settings with regards to antibiotic guidance. Procalcitonin is the prohormone precursor of calcitonin expressed primarily in C cells of the thyroid gland. As a prototype of a "hormokine" mediator, procalcitonin can follow either a classical hormonal expression pathway in neuroendocrine cells, or alternatively, in the presence of an infection, a cytokine-like expression pathway in various cell types. The ubiquitous inflammatory release can be induced either directly, via microbial toxins (e.g. endotoxin), or indirectly, via a humoral or cell-mediated host response (e.g. interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6) [1,2].

Procalcitonin has been shown to be a useful biomarker in establishing the presence of bacterial infections, because serum procalcitonin levels are elevated in bacterial infections and falling rapidly once the infection resolves[1-5]. The diagnostic accuracy of procalcitonin was shown to be higher than other biomarkers such as C-reactive protein (Sensitivity 88% vs 75%; Specificity 81% vs 67%) among patients hospitalized for suspected bacterial infections such as pneumonia, UTI, sepsis and meningitis[6].

In a recent meta-analysis by Soni *et al* in 2013 which included 18 trials of adults, neonates and children with various infections, procalcitonin guidance reduces antibiotic use when used to discontinue antibiotics in adult ICU patients and to initiate or discontinue antibiotics in patients with respiratory tract infections[7]. This was the first review that included pediatric patients, however with inconclusive results. Our present systematic review focuses on the use of procalcitonin-guided antibiotic treatment among pediatric patients and includes randomized controlled trials not included in earlier reviews.

This study aimed to conduct a meta-analysis of the use of procalcitonin to guide initiation and duration of antibiotic therapy in pediatric patients with suspected local or systemic infection being treated in an ambulatory, hospital or intensive care unit setting.

METHODS

Search Methods for Identification of Studies

A number of electronic databases [MEDLINE®/PubMed® (1966–September 2015); Cochrane Central Register for controlled trials (CENTRAL) published in The Cochrane Library; Excerpta Medica Database (EMBASE); Health

Research and Development Information Network (HERDIN), and search engines such as Google Scholar were searched for appropriate published studies using the search terms "procalcitonin", "antibiotic therapy", "pediatric", "infection", "sepsis", "randomized controlled trial," and synonyms or related terms. Clinical-Trials.gov (National Institutes of Health) was also accessed for unpublished or ongoing trials. Abstracts from relevant scientific forums, conference proceedings and local journals were also searched. Hand searching of citation lists of relevant publications, reviews, meta-analyses and included studies were also done. Experts in the subject were consulted as well.

Selection of Studies

Two reviewers independently assessed the abstract of the articles that were identified as a result of the systematic literature search. Full text articles of relevant studies were retrieved and independently reviewed by the reviewers. Studies were included if they fulfilled the following inclusion criteria: (1) randomized controlled trial; (2) neonates, children and adolescents with known or suspected local or systemic infections being treated in an ambulatory, hospital or intensive care unit setting; (3) interventions included initiation and duration of antibiotic therapy guided by procalcitonin plus clinical criteria; (4) primary outcomes included antibiotic usage (antibiotic prescription rate, total antibiotic exposure, duration of antibiotic therapy); and (5) secondary outcomes included morbidity (length of hospitalization, recurrence of infection, antibiotic side effects), mortality, and quality of life. Studies with the following criteria were excluded: published in non-English language, not a randomized controlled study, not reporting relevant outcomes.

Data Extraction and Quality Assessment

Data on the methodological quality and clinical characteristics of the included trials were extracted independently and in duplicate by both review authors. Disagreements were resolved by discussion or if required, a third author was consulted. The risk of bias for each included study was assessed using the Cochrane risk of bias tool. Domains that were assessed included sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting[8].

Data Synthesis and Analysis

Statistical analysis was conducted using Review Manager Software (RevMan ver. 5.3; The Cochrane Collaboration, Oxford, UK). The decision to pool studies was based on the specific number of studies with similar questions and outcomes. If a meta-analysis could be performed, subgroup and sensitivity analysis were based on clinical similarity of the available studies and reporting of mean and standard deviation. The pooling method involved inverse variance weighting and a random effects model.

RESULTS

Results of the Search

A flow diagram of selection of studies included in this meta-analysis is shown in Figure 1. MEDLINE was searched until September 2015 for randomized controlled trials using the following search terms: procalcitonin; antibiotic therapy; pediatric, infections. A total of 5 studies were retrieved but only 4 met the eligibility criteria. Abstracts were screened and full text articles were retrieved for appraisal and eventually included in the study. One study was excluded because it studied procalcitonin as a diagnostic marker for bacteremia rather than therapeutic

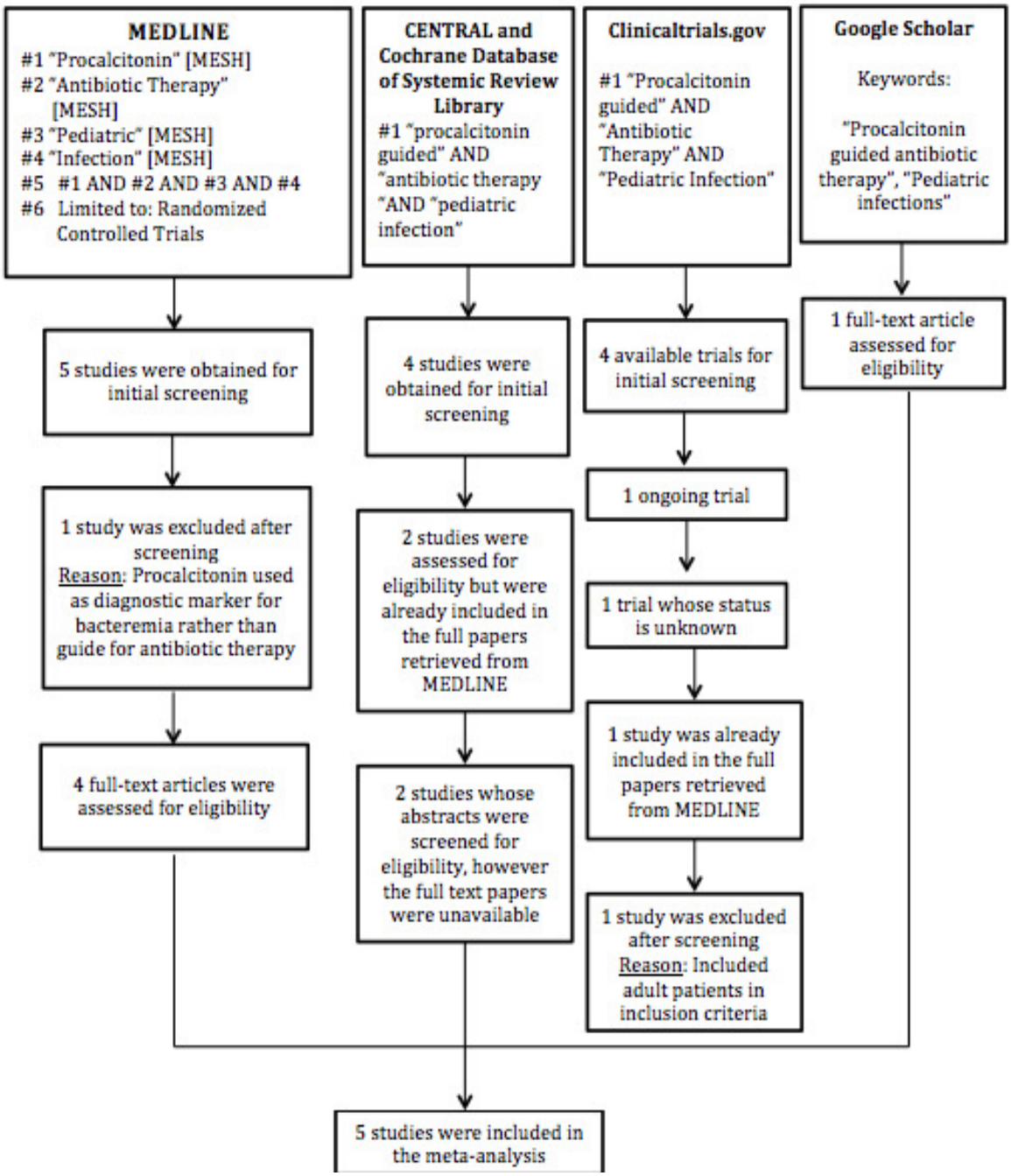

Figure 1. Flow Diagram of Search Strategy

guide for antibiotic therapy. A thorough search was done in HERDIN (Health Research and Development Information Network) and EMBASE (Excerpta Medica Database) but did not yield any results. A search for systematic reviews was conducted in CENTRAL (Cochrane Central Register of Controlled Trials) and Cochrane Database of Systematic Reviews and 4 studies were obtained for screening. Two studies were already included in the trials searched from MEDLINE. Abstracts of the remaining two studies were obtained and screened for eligibility,

however the full text papers were not available for review. A total of four studies were identified from Clinicaltrials.gov, one of which was already included in the trials searched from MEDLINE. Three study protocols were identified, one of which is an ongoing multicenter trial on procalcitonin-guided antibiotic therapy on suspected neonatal early-onset sepsis. Another study protocol whose current trial status is unknown, deals with procalcitonin-guided antibiotic therapy in pediatric ICU patients. Another ongoing trial included adult patients. Hand search was also done in various search engines such as Google Scholar and one more article was found to fit the study criteria. A total of 5 studies were eventually included in the meta-analysis.

Characteristics of Included Studies

A total of 5 studies were included in the study with a total enrolment of 1,352 pediatric patients. These studies were pooled into clinically similar groups that were reviewed separately: (1) children aged 1 month to 18 years old with pneumonia; (2) children between 1 to 36 months with fever without a source; (3) term or near term (>/= 34 weeks) infants with early onset sepsis. Characteristics of these studies are described in the Appendix.

Two studies[9,10] evaluated the use of an algorithm based on procalcitonin (PCT) cut-off value vs. standard care guidelines as a means of guiding antibiotic therapy among children with community acquired pneumonia (CAP). In the study by Baer[9], 337 children aged 1 month to 18 years old presenting with lower respiratory tract infection to the emergency departments were randomized to receive antibiotics either according to a PCT guided algorithm established for adult lower respiratory tract infections or standard care guidelines. The algorithm provides PCT based decision categories for the likelihood of requiring antibiotic treatment for bacterial LRTI: "definitely'' (>0.5 μg/L), ''probably'' (0.26–0.5 μg/L), ''probably not'' (0.1–0.25 μg/L), and ''definitely not'' (<0.1 μg/L). For all patients, discontinuation of antibiotics was encouraged upon clinical stabilization and when PCT values fell below 0.25; for patients with initial PCT values >10 μg/L when levels decreased below 90% of the initial value. Continuation of treatment on day 5 was determined according to the following algorithm: >1 μg/L: 7 days, 0.51–1 μg/L: 5 days, 0.26–0.5 μg/L: 3 days, and ≤0.25 μg/L: no antibiotic. In the control group, antibiotic treatment was initiated based on physician assessment and clinical guidelines for a duration of 7–10 days for uncomplicated CAP and 14 or more days for complicated CAP. In the study by Esposito[10], 319 hospitalized children aged <1 month to < 14 years with uncomplicated community-acquired pneumonia (CAP) were randomized to be treated on the basis of the algorithm or in accordance with standard guidelines. The children in the PCT group did not receive antibiotics if their PCT level upon admission was <0.25 ng/mL, and those receiving antibiotics from the time of admission were treated until their PCT level was ≤0.25 ng/mL. Children in the control group were treated according to standard care guidelines: antibiotic monotherapy chosen on the basis of age if mild; combined beta lactam and macrolide if severe. The duration of administration in the control group was that recommended by clinical guidelines (7-14 days depending on disease severity).

Two studies[11,12] evaluated PCT guided antibiotic therapy among children with fever without a source. In the study by Manzano[11], 384 children aged 1 to 36 months presenting to a pediatric emergency department (ED) with fever and no identified source of infection were eligible to be included in a randomized controlled trial. Patients were randomly assigned to PCT+ (result revealed to the attending physician) and PCT− (result not revealed) group. In the PCT+

group, prophylactic antibiotic was given in children with a PCT of 0.5 ng/ml or higher (moderate or severe risk of bacterial infection). In the study by Nazemi[12], 200 children 3 to 36 months of age with fever without a source were studied. The PCT group received antibiotics according to PCT concentration, careful past medical history and some laboratory tests. Patients with PCT less than 0.1 ng/ml did not receive antibiotic, those with PCT levels between 0.1 ng/ml to 0.5 ng/ml received antibiotics according to decision made by physician, and all patients with PCT higher than 0.5 ng/ml received antibiotic treatment. The control group received antibiotics according to usual practice of careful history and physical examination and additional laboratory tests if needed.

One study by Stocker[13] evaluated procalcitonin-guided antibiotic therapy for suspected neonatal early-onset sepsis. A total of 121 term and near-term infants (gestational age ≥34 weeks) with suspected early-onset sepsis were randomly assigned either to standard treatment based on conventional laboratory parameters or to PCT-guided treatment. Minimum duration of antibiotic therapy was 48–72 h in the standard group, whereas in the PCT group antibiotic therapy was discontinued when two consecutive PCT values were below predefined age-adjusted cut-off values based on a procalcitonin normogram.

Risk of Bias in Included Studies

A detailed summary of the methodological quality of each included study is shown in the Appendix. The risk of bias of the studies included in this systematic review is generally judged to be low (see Figure 2).

All 5 studies are randomized controlled trials, however the study by Nazemi[12] did not provide sufficient information on the sequence generation and method of allocation concealment.

Due to the nature of the study design, physicians in the PCT group cannot be blinded with regard to procalcitonin levels since this will be their main guide for antibiotic therapy. Lack of blinding of study patients, on the other hand, is not likely to influence outcome measures of the studies (antibiotic exposure). The primary investigators or outcome assessors were blinded in three of the trials[9,10,11] however there was no mention whether outcome assessment was blinded in two studies[12,13].

Attrition bias was generally assessed to be low risk for all studies. In one study where there were a few patients not accounted at the end of the trial, an intention-to-treat analysis was done[9]. In another trial[11], 12% of the initial randomized

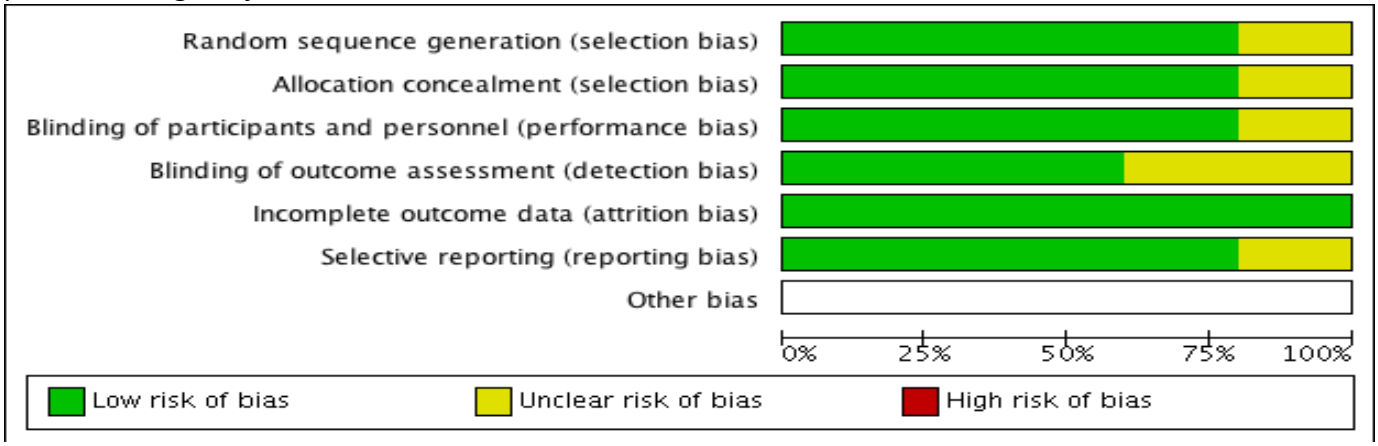

Figure 2. Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

subjects were not accounted in the final results mainly because of lack of blood sample, which is still within acceptable limits (<15% of enrolled patients). Follow up was complete in all three studies[10,12,13]. Overall, all significant outcome measures were reported, whether statistically significant or not.

Outcomes

Procalcitonin-guided vs. standard care guidelines (control) on Antibiotic prescription rate

Figure 3 shows the forest plot on the effect of procalcitonin-guided versus standard care guidelines on antibiotic prescription rate of children with pneumonia, fever of unknown source, and neonates with sepsis. The pooled sample size from all five studies included 615 pediatric patients for each group. Overall, there was significant reduction in antibiotic prescription rate in the PCT group compared to controls (risk difference -0.13; 95% CI [-0.21, -0.06], p value 0.0005). However, results are inconclusive since pooled results of the five studies were heterogeneous (Chi^2 = 11.20, df = 4, I^2 = 64%).

Due to statistical heterogeneity of the combined studies, a subgroup analysis was performed based on clinical similarity of the included patients and outcomes. Two studies[9,10] addressed procalcitonin-guided antibiotic therapy among children with pneumonia and lower respiratory infections, however only the subgroup of patients with CAP in the Baer study[9] were included. Those with non-CAP lower respiratory tract infection were excluded. The pooled sample size from these studies included 263 children in the PCT group and 262 children in the control group. Overall, there was significant reduction in antibiotic prescription rate in the PCT group compared to controls (risk difference -0.12; 95% CI [-0.21, -0.04], p value 0.005). The pooled data were homogenous (Chi^2 = 1.93, df = 1, I^2 48%) [Figure 4].

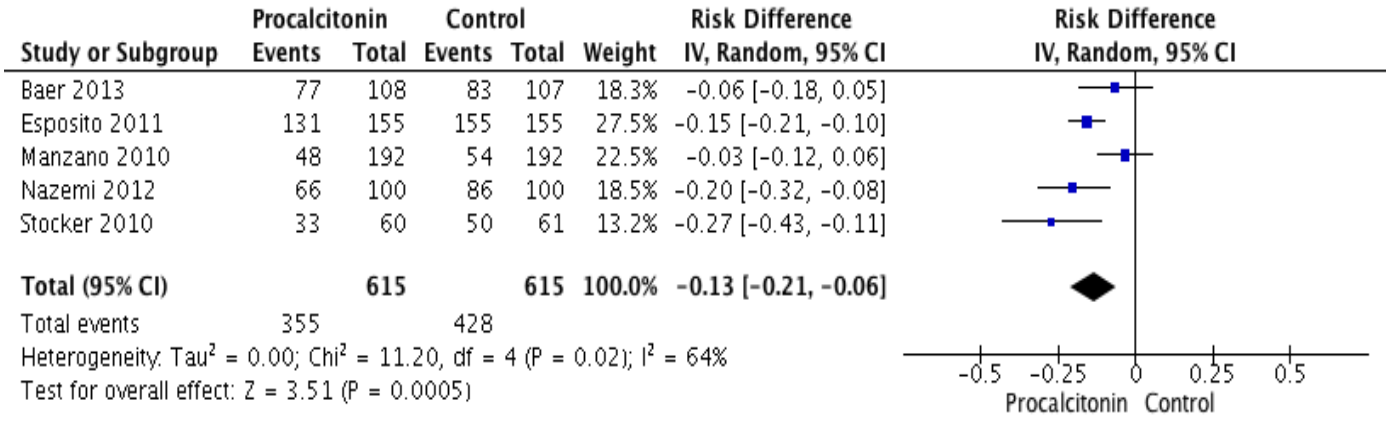

Figure 3. Forest plot comparison: Procalcitonin-guided vs. standard care guidelines on Antibiotic prescription rate

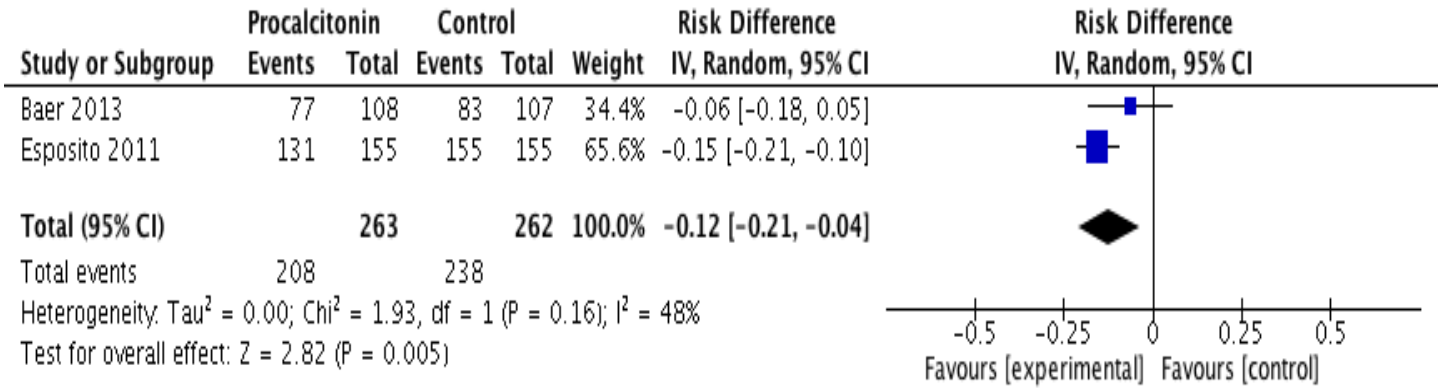

Figure 4. Forest plot comparison: Procalcitonin-guided vs. standard care guidelines on Antibiotic prescription rate among children with pneumonia

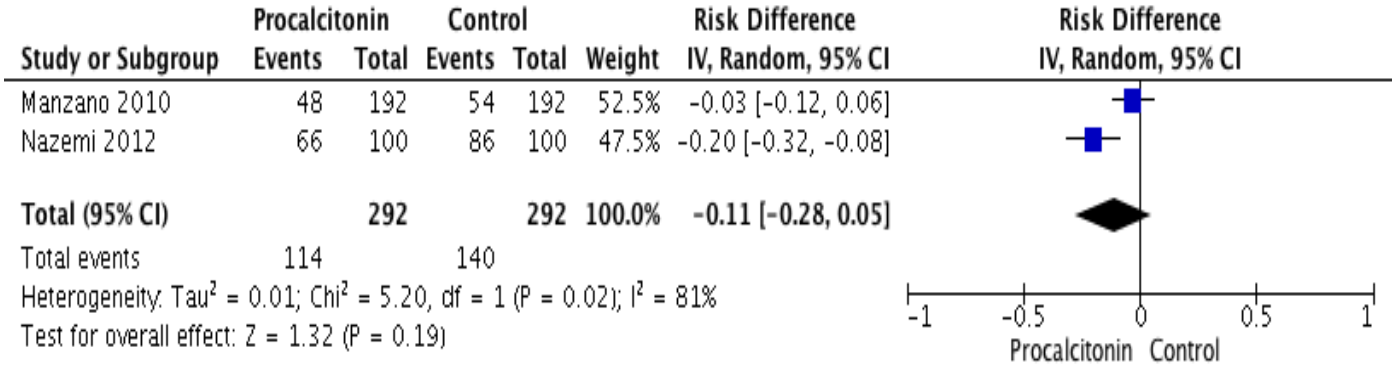

Figure 5. Forest plot comparison: Procalcitonin-guided vs. standard care guidelines on Antibiotic prescription rate among children with fever of unknown source

Two studies[11,12] addressed procalcitonin-guided antibiotic therapy among children aged 1 to 36 months with fever of unknown source. The pooled sample size from these studies included 292 children in each of the groups. Overall, procalcitonin-guided therapy did not reduce antibiotic prescription rate among these patients (risk difference -0.11; 95% CI [-0.28, -0.05], p value 0.19). The pooled data were also shown to be heterogenous (Chi^2 = 5.20, df = 1, I^2 81%) [Figure 5].

Table 1. Summary of Antibiotic Usage Outcomes

Outcome	Author, Year	N	PCT-Guided Therapy*	Control	Difference PCT-CTRL (95% CI)	*P* Value
Children ages 1 month to 18 years old with pneumonia						
ABT prescription rate, %	Baer, 2013	215	77/108 (71.3%)	83/107 (77.6%)	-0.06 [-0.18, 0.05]	0.29
	Esposito, 2011	310	131/155 (84.5%)	155/155 (100%)	-0.15 [-0.21, -0.10]	<0.05
Duration of ABT, days	Baer, 2013	212	5.7 (5 [0-9])+	9.1 (10 [4.5-12.3])+	-3.4 [-5.11, -1.7]	<0.001
	Esposito, 2011	287	5.37 ± 2.3	10.96 ± 1.3	-5.59 (-6.03, -5,15)	<0.001
Children ages 1 – 36 months with fever of unknown source						
ABT prescription rate, %	Manzano,2010	384	48/192 (25%)	54/192 (28%)	-0.03 [-0.12, 0.06]	0.49
	Nazemi, 2012	200	66/100 (66%)	86/100 (86%)	-0.20 [-0.32, -0.08]	0.0007
Neonates with early-onset sepsis						
ABT ≥72 hrs, %	Stocker, 2010	121	33/60 (55%)	50/61 (82%)	-0.27 [-0.43, -0.11]	0.0009
Duration of ABT, hours	Stocker, 2010	121	79.1	101.5	-22.4	0.012

NOTE: Abbreviations: PCT, procalcitonin; ABT, antibiotics; CTRL, control; CI, confidence interval; N, total number of patients
* Values are mean unless specified
+ Mean (Median [Interquartile range])

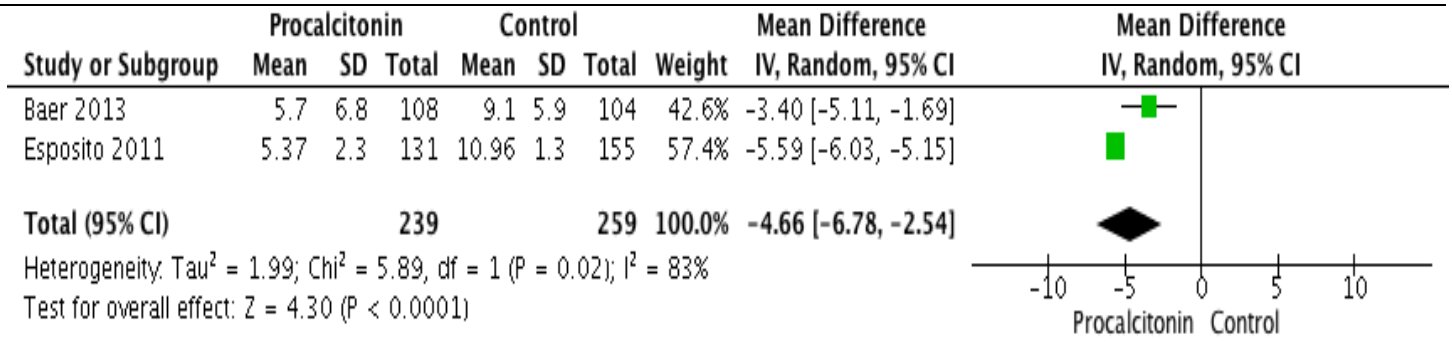

Figure 6. Forest plot comparison: Procalcitonin-guided vs. standard care guidelines on Duration of antibiotic therapy among children with pneumonia

One study[13] is the only trial which evaluated procalcitonin-guided antibiotic therapy for suspected neonatal early onset sepsis. A total of 121 neonates were included in the study, and results showed that the proportion of neonates on antibiotics ≥ 72 hours was reduced by 27% by using a procalcitonin nomogram in guiding therapy (p value 0.0009) [Table 1].

Procalcitonin-guided vs. standard care guidelines (control) on Duration of Antibiotic therapy

Data on two studies involving procalcitonin-guided antibiotic therapy among children with pneumonia[9,10] were pooled. Results of the meta-analysis showed that the duration of antibiotic therapy was shortened in the PCT group compared to the control group by a mean of 4.66 days (CI -6.78, -2.54); p value 0.0001) [Figure 6]. However, no definite conclusion can be made since pooled data from these two studies were

heterogenous (Chi^2 = 5.89, df = 1, I^2 83%). Among neonates with early onset sepsis, the duration of antibiotic therapy was decreased by 22.4 hours (p value 0.012) [Table 1]. The studies by Manzano[11] and Nazemi[12] did not provide such outcome measures.

Procalcitonin-guided vs. standard care guidelines (control) on antibiotic side effects

Data on two studies involving procalcitonin-guided antibiotic therapy among children with pneumonia[9,10] were pooled. Results of the meta-analysis showed that procalcitonin-guided therapy had a lower incidence of adverse effects caused by antibiotics compared with treatment using standard care guidelines (risk difference -0.17, CI -0.24, -0.10); p value <0.00001) [Figure 7]. However, results are inconclusive since the pooled data from the studies were heterogeneous (Chi^2 = 2.36, df = 1, I^2 58%). The other three studies did not provide any data on such outcomes.

Other Morbidity Outcomes

Tables 2 and 3 provide detailed summaries on the morbidity outcomes of the five studies. The study by Baer[9] on children with pneumonia showed no significant difference on rate and duration of hospitalization, and duration of antibiotic side effects among the two groups (Table 2). The study by Esposito[10] further divided patients according to pneumonia severity into mild and moderate CAP. Results showed that there was significant decrease in duration of hospitalization in the PCT group compared to the control group both in patient with mild CAP (risk difference -0.91, 95% CI [-1.69, -0.13], p value 0.02] and severe CAP (risk difference -0.92, 95% CI [-1.58, -0.26], p value 0.007). There was no significant difference in both groups on duration of fever, duration of oxygen therapy, recurrence of respiratory symptoms and new antibiotic prescription rate (Table 2).

In the study by Manzano[11] on procalcitonin guided therapy among children with fever of unknown source, there was no significant difference in rate of hospitalization between the two groups (risk difference -0.03, 95% CI [-0.12, 0.06], p value 0.49). In the Nazemi study[12], duration of fever was likewise not significantly reduced in the procalcitonin group compared to the control group (Table 3). In the study by Stocker on neonatal sepsis[13], there was no significant reduction in recurrence of infection in procalcitonin-guided versus standard therapy (risk difference -0.08, 95% CI [-0.25, 0.09], p value 0.38) [Table 3].

DISCUSSION

One of the major challenges in managing local and systemic infections especially in the pediatric age group is distinguishing bacterial from viral etiologies since clinical criteria for diagnosis often overlap with non-infectious causes. Most often this leads to excessive antibiotic prescription even for viral causes of infections, leading to negative consequences such as development of antibiotic resistance. Hence, various methods to rationalize antibiotic treatment are mandatory especially to susceptible populations. Procalcitonin has been studied as a useful guide in antibiotic therapy and several algorithms have been proposed regarding cutoff values used in initiation, intensification and discontinuation of antibiotics in adults with sepsis and respiratory tract infections. Most researches and reviews have been conducted in adults.

In systemic infections, including sepsis, procalcitonin levels are generally greater than 0.5 to 2 ng/mL, but often reach levels >10 ng/mL, which correlates with severity of illness and a poor prognosis. In patients with respiratory tract infections, procalcitonin levels are less elevated, and a cutoff of >0.25 ng/mL seems to be most predictive of a bacterial respiratory tract infection requiring antibiotic therapy[2,6].

Table 2. Summary of Morbidity Outcomes

Outcome	Author, Year	N	PCT-Guided Therapy	Control	Difference PCT-CTRL (95% CI)	*P* Value
Children ages 1 month to 18 years old with pneumonia						
Hospitalization, %	Baer, 2013	215	67/108 (62%)	68/107 (63.6%)	-0.01 (-0.1, 0.1)	0.82
Duration of hospitalization, days	Baer, 2013	211*	2.6 (2[0-4])+	2.9 (2[0-5])+	-0.3 (-1.2, 0.6)	0.52
	Esposito, 2011	(310)				
	Mild CAP	155	4.7 ± 2.88	5.61 ± 1.99	-0. 91 (-1.69, -0.13)	0.02
	Severe CAP	155	5.01 ±2.43	5.93 ± 1.70	-0.92 (-1.58, -0.26)	0.007
Duration of fever, mean days ± SD	Esposito, 2011					
	Mild CAP	155	2.01 ± 1.76	2.16 ± 1.96	-0.15 (-0.74, 0.44)	0.62
	Severe CAP	155	2.88 ±2.01	2.52 ± 2.22	0.36 (-0.31, 1.03)	0.29
Duration of oxygen therapy, days ± SD	Esposito, 2011	(310)				
	Mild CAP	155	0	0	0	-
	Severe CAP	155	3.4 ± 1.99	3.88 ± 1.58	-0.48 (-1.05, 0.08)	0.10
Antibiotic side effects, %	Baer, 2013	181*	42/90 (47%)	51/91 (56%)	-0.09 (-0.24, 0.05)	0.20
	Esposito, 2011	(310)	6/155 (3.8%)	39/155 (25.2%)	-0.21 (-0.29, -0.14)	<0.0001
	Mild CAP	155	1/76 (1.3%)	18/79 (22.7%)	-0.21 (-0.31, -0.11)	<0.001
	Severe CAP	155	5/79 (6.3%)	21/76 (27.6%)	-0.21 (-0.33, -0.1)	0.002
Duration of antibiotic side effects, days	Baer, 2013	181*	1.7 (0[0-2])+	1.8 (1[0-3])+	-0.1 (-0.7,0.5)	0.73
Safety, %	Baer, 2013	215	23/108 (21.3%)	20/107 (18.7%)	2 (-9.13)	0.63
Recurrence of respiratory symptoms, %	Esposito, 2011	(310)	1/155 (0.6%)	6/155 (3.9%)	-0.03 (-0.06, 0)	0.05
	Mild CAP	155	0/76 (0%)	2/79 (2.5%)	-0.02 (-0.06, 0.02)	0.24
	Severe CAP	155	1/79 (1.3%)	4/76 (5.3%)	-0.04 (-0.10, -0.02)	0.16
New antibiotic Prescription, %	Esposito, 2011	(310)	1/155 (0.6%)	4/155 (2.6%)	-0.02 (-0.04, 0.01)	0.18
	Mild CAP	155	0/76 (0%)	1/79 (1.3%)	-0.01 (-0.05, 0.02)	0.48
	Severe CAP	155	1/79 (1.3%)	3/76 (3.9%)	-0.03 (-0.08, 0.02)	0.30

NOTE: Abbreviations: PCT, procalcitonin; ABT, antibiotics; CTRL, control; CI, confidence interval; N, total number of patients; CAP, community acquired pneumonia

* Number of individuals with available data for a given endpoint

\+ Mean (Median [Interquartile range])

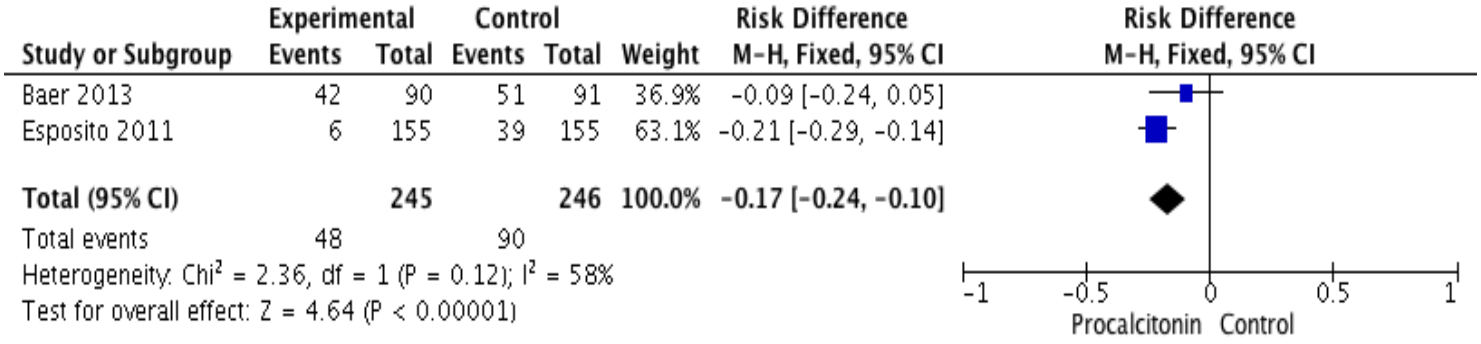

Figure 7. Forest plot comparison: Procalcitonin-guided vs. standard care guidelines on antibiotic side effects among children with pneumonia

Table 3. Summary of Morbidity Outcomes

Outcome	Author,Year	N	PCT-Guided Therapy	Control	Difference PCT-CTRL (95% CI)	*P* Value
Children ages 1 – 36 months with fever of unknown source						
Hospitalization rate, %	Manzano, 2010	384	48/192 (25%)	54/192 (28%)	-0.03 (-0.12, 0.06)	0.49
Duration of fever, days	Nazemi, 2011	200				
	< 3 days		18/100 (18%)	22/100 (22%)	-0.04 (-0.15, 0.07)	0.48
	3-5 days		45/100 (45%)	44/100 (44%)	-0.01(-0.12, 0.14)	0.89
	> 5 days		37/100 (37%)	34/100 (34%)	0.03 (-0.10, 0.16)	0.66
Neonates with early sepsis						
Recurrence of infection, % §	Stocker, 2009	121	19/60 (32%)	24/61 (39%)	-0.08 (-0.25, 0.09)	0.38

NOTE: Abbreviations: PCT, procalcitonin; ABT, antibiotics; CTRL, control; CI, confidence interval; N, total number of patients
§ Recurrence of infection = proportion of newborns treated with antibiotics ≥ 120 h

Procalcitonin levels decrease to <0.25 ng/mL as infection resolves, and a decline in procalcitonin level may further guide in decisions about discontinuing antibiotic therapy[14].

Among children with community acquired pneumonia, procalcitonin with a threshold of 1 ng/ml is more sensitive and specific and has greater positive and negative predictive values (Sn 86%, Sp 87.5%, PPV 90.2%, NPV 80%) than CRP, IL-6, or white blood cell count for differentiating bacterial and viral causes of the disease[15]. Procalcitonin levels of 1 ng/ml or greater had also better specificity, sensitivity and predictive value than CRP, interleukin 6 and interferon-alpha in children for distinguishing between viral and bacterial infections such as sepsis and meningitis[16].

Several published reviews have studied the use of procalcitonin in initiating or discontinuing antibiotics in various patient populations suspected with local or systemic infections. A Cochrane review of 14 trials with 4221 adults with acute respiratory infections who received an antibiotic treatment either based on a procalcitonin algorithm or usual care/guidelines showed that the use of procalcitonin to guide initiation and duration of antibiotic treatment in patients with acute respiratory infections was not associated with higher mortality rates or treatment failure. Antibiotic consumption was significantly reduced across different clinical settings and acute respiratory infection diagnoses[17].

Another systematic review included 14 trials that investigated the use of procalcitonin algorithms for antibiotic treatment decisions in adult patients with respiratory tract infections and sepsis from primary care, emergency department and intensive care unit. Results showed that the use of procalcitonin algorithms in antibiotic guidance showed consistent reduction in antibiotic prescription and/or duration of therapy in low-acuity primary care and emergency department patients, and shorter duration of therapy in moderate- and high-acuity emergency department and intensive care unit patients. This study also proposed specific procalcitonin algorithms for low-, moderate-, and high-acuity patients as a basis for future trials aiming at reducing antibiotic overconsumption[18].

There has been a significant gap in literature on procalcitonin-guided antibiotic therapy in the pediatric setting and this systematic review aims to fill in this gap.

A meta-analysis by Soni[7] included two studies on pediatric patients, one which included

children with fever of unknown source and one on neonatal sepsis, however pooling of data cannot be done due to lack of clinical similarity between the two studies. Our present systematic review included three more studies and results showed that overall, procalcitonin guidance may reduce antibiotic prescription rate among patients with pneumonia, fever of unknown source and in neonates with early onset sepsis. However, results are inconclusive since there is significant heterogeneity among the studies (Chi^2 = 11.20, df = 4, I^2 = 64%). This is due to the differing population, type of infection and the different cut-off values used in initiation and discontinuation of antibiotics. The Baer[9] and Esposito[10] studies assessed children with pneumonia and used cutoff values > 0.25 ng/mL in initiating antibiotic therapy, which is similar to algorithms in adults with respiratory tract infections. The Manzano[11] and Nazemi [12] studies examined children with fever without a source, and used cutoff values ≥ 0.5 ng/mL in initiating antibiotic therapy. The Stocker[13] study examined neonates with suspected early-onset sepsis and used an age-adjusted procalcitonin normogram to determine antibiotic therapy. Hence, future research should focus on determining optimal procalcitonin cut-off values in different pediatric age groups and types of infections. This would further aid in identifying those who would benefit from antibiotic therapy and those whom antibiotics can be safely withheld.

Subgroup analysis was done which showed that among children with pneumonia, procalcitonin guidance significantly reduced antibiotic prescription rate and may aid in shortening the duration of antibiotic therapy. These results on lowering antibiotic prescription rate with procalcitonin guidance are consistent in studies of adults with respiratory tract infections[7]. Furthermore, procalcitonin guidance may also reduce adverse side effects associated with antibiotic use, most commonly diarrhea, among these patients.

Among patients with fever of unknown source, pooled data on studies by Manzano[11] and Nazemi[12] showed that procalcitonin guidance did not significantly reduce antibiotic usage among these patients. Morbidity outcomes, such as duration of fever and hospitalization were likewise not significant in this group.

One study on neonates with suspected sepsis showed that procalcitonin guidance significantly reduced proportion of neonates started on empiric antibiotic therapy, as well as decreased the duration of antibiotic therapy. Data on morbidity and mortality outcomes, however, is lacking. There is currently an ongoing multicenter randomized superiority and non-inferiority intervention study among neonates which could provide useful data on the efficacy of procalcitonin guidance among neonates, its safety and additional data on morbidity and mortality outcomes[19].

One limitation of our review is that all randomized controlled trials included in this review were published. There were two studies, one which involved pediatric ICU patients and one which involved children pneumonia, whose abstracts were published but data were insufficient to be included in our analysis. Full texts were likewise not retrieved from their respective authors, hence were excluded from this review. Publication bias therefore cannot be totally excluded. This study also focused on the use of procalcitonin as a therapeutic guide whether or not to prescribe antibiotics in specific pediatric infections rather than a diagnostic tool, hence we did not evaluate the sensitivity and specificity of the test.

Further studies are therefore needed to determine whether procalcitonin-guided antibiotic therapy can be recommended among pediatric patients. Moreover, studies can also

focus on other clinically susceptible children, including immunocompromised groups such as cancer patients with concurrent infections, children with sepsis, osteomyelitis or surgical patients at risk for postoperative infections. Furthermore, the studies were mostly conducted in the hospital where there is closer and more continuous monitoring of disease outcomes. Further studies can look into evaluating the usefulness of procalcitonin-guided approach in the primary care setting.

Another limiting factor regarding the use of procalcitonin-guided therapy is that the test itself is considerably more expensive than other routine laboratory tests and unavailable in most clinical settings. Hence, future studies can also venture into the cost-effectiveness of procalcitonin-guided therapy in pediatric infections before it can be routinely used.

CONCLUSIONS

Based on available studies, procalcitonin-guided antibiotic therapy significantly reduces antibiotic prescription rate and may have potential benefits in shortening the duration of antibiotic therapy and lowering antibiotic-related side effects among children with pneumonia. It may also be useful in reducing antibiotic prescription rate and shortening the duration of therapy among neonates with early-onset sepsis. On the other hand, procalcitonin guidance has no significant impact on antibiotic treatment among children with fever without a source. Evidence on safety, morbidity and mortality outcomes are insufficient and calls for additional trials. Future research should also focus on determining optimal procalcitonin cut-off values in various pediatric age groups and types of infections, and its cost effectiveness before it can be used in routine clinical practice. There is insufficient evidence whether procalcitonin-guided antibiotic therapy can be recommended among pediatric patients with various local or systemic infections.

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