The Utility of Procalcitonin-Guided Antibiotic Therapy in the Treatment of Lower Respiratory Tract Infections for Reducing Antibiotic Prescription Rate and Therapy Duration in Pediatrics

Amy L. Clark

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Abstract

Background: Procalcitonin (PCT) is a marker for bacterial infection that can be used as a diagnostic tool to help distinguish viral from bacterial lower respiratory tract infections (LRTI). LRTI is a leading cause of illness in pediatrics worldwide. Most LRTIs in pediatrics are due to viral causes, yet conservative clinical guidelines advise empiric antibiotic therapy because there is no reliable method to determine the etiology of the illness. With the increasing threat of antibiotic resistance, efforts are underway to decrease the use of antibiotics. PCT-guided antibiotic therapy has shown a reduction in the use of antibiotics for adult LRTI. Can PCT-guided antibiotic treatment of LRTIs in a pediatric population reduce the antibiotic therapy duration rate or prescription rate with comparable outcomes to current therapy guidelines?

Method: An exhaustive search was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: procalcitonin, antibiotic, pediatrics, and lower respiratory tract infection. A search on the NIH clinical trials site revealed that there are no trials currently registered relating to the use of PCT-guided antibiotic therapy in pediatrics with lower respiratory tract infections. GRADE was used to assess the quality of relevant articles. Results: Included in this systematic review were two studies that met inclusion criteria. A randomized, multi-center clinical trial with 337 participants demonstrated a statistically significant reduction in the duration of antibiotic therapy, but an increase in the antibiotic prescription rate overall when applying PCT-guided antibiotic therapy. A randomized, single-center clinical trial with 310 participants demonstrated a statistically significant reduction in the duration of antibiotic therapy and antibiotic prescription rate when PCT-guided antibiotic therapy was applied.

Conclusion: PCT-guided antibiotic therapy has been shown to reduce the duration of antibiotic therapy. Furthermore, it is suggested that in less severe LRTI PCT-guided antibiotic therapy can reduce antibiotic prescription rates in a pediatric population. More randomized control trials are needed to increase the statistical power behind these findings. There was no evidence of increased risk of disease-specific adverse events. At this time PCT-guided therapy is recommended to reduce the duration of antibiotic therapy.

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First Advisor
David Keene, MPAS, PA-C

Keywords
Procalcitonin, Antibiotics, Pediatrics, Lower Respiratory Tract Infection, Pneumonia, human

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The Utility of Procalcitonin-Guided Antibiotic Therapy in the Treatment of Lower Respiratory Tract Infections for Reducing Antibiotic Prescription Rate and Therapy Duration in Pediatrics

Amy L. Clark

A Clinical Graduate Project Submitted to the Faculty of the
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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

**Background:** Procalcitonin (PCT) is a marker for bacterial infection that can be used as a diagnostic tool to help distinguish viral from bacterial lower respiratory tract infections (LRTI). LRTI is a leading cause of illness in pediatrics worldwide. Most LRTIs in pediatrics are due to viral causes, yet conservative clinical guidelines advise empiric antibiotic therapy because there is no reliable method to determine the etiology of the illness. With the increasing threat of antibiotic resistance, efforts are underway to decrease the use of antibiotics. PCT-guided antibiotic therapy has shown a reduction in the use of antibiotics for adult LRTI. Can PCT-guided antibiotic treatment of LRTIs in a pediatric population reduce the antibiotic therapy duration rate or prescription rate with comparable outcomes to current therapy guidelines?

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**Results:** Included in this systematic review were two studies that met inclusion criteria. A randomized, multi-center clinical trial with 337 participants demonstrated a statistically significant reduction in the duration of antibiotic therapy, but an increase in the antibiotic prescription rate overall when applying PCT-guided antibiotic therapy. A randomized, single-center clinical trial with 310 participants demonstrated a statistically significant reduction in the duration of antibiotic therapy and antibiotic prescription rate when PCT-guided antibiotic therapy was applied.

**Conclusion:** PCT-guided antibiotic therapy has been shown to reduce the duration of antibiotic therapy. Furthermore, it is suggested that in less severe LRTI PCT-guided antibiotic therapy can reduce antibiotic prescription rates in a pediatric population. More randomized control trials are needed to increase the statistical power behind these findings. There was no evidence of increased risk of disease-specific adverse events. At this time PCT-guided therapy is recommended to reduce the duration of antibiotic therapy.

**Keywords:** Procalcitonin, Antibiotics, Pediatrics, Lower Respiratory Tract Infection, Pneumonia, human
Table of Contents

The Utility of Procalcitonin-Guided Antibiotic Therapy in the Treatment of Lower Respiratory Tract Infections for Reducing Antibiotic Prescription Rate and Therapy Duration in Pediatrics ......................................................................................................... 1
Amy L. Clark ...................................................................................................................... 1
Biography ............................................................................................................................. 2
Abstract ............................................................................................................................... 3
Table of Contents ................................................................................................................ 4
List of Tables ...................................................................................................................... 5
List of Abbreviations .......................................................................................................... 5
References ......................................................................................................................... 19
Table I. Characteristics of Reviewed Studies ................................................................... 21
Table II. GRADE Profile .................................................................................................. 22
Table III. Summary of Biases ........................................................................................... 23
List of Tables

Table 1: GRADE Quality of Assessment and Summary of Findings
Table 2: Summary of Biases
Table 3: Characteristics of the Studies

List of Abbreviations

LRTI   Lower Respiratory Tract Infection
CAP    Community-Acquired Pneumonia
RCT    Randomized Clinical Trial
ED     Emergency Department
ICU    Intensive Care Unit
WBC    White Blood Cell
CRP    C-Reactive Protein
AB     Antibiotic
RSV    Respiratory Syncytial Virus
d      day
GRADE  Grading of Recommendations, Assessment, Development and Evaluations
SAE    Serious Adverse Events
NNH    Number Needed to Harm
NNT    Number Needed to Treat
RR     Relative Risk
NIH    National Institute of Health
The Utility of Procalcitonin-Guided Antibiotic Therapy in the Treatment of Lower Respiratory Tract Infections for Reducing Antibiotic Prescription Rate and Therapy Duration in Pediatrics

BACKGROUND

Lower respiratory tract infections (LRTI), including pneumonia, are one of the leading causes of hospitalization and death in children worldwide. In 2010 almost 15 million children ages 5 and under were hospitalized with severe pneumonia, resulting in over 250,000 deaths. The etiology of an LRTI is often difficult to ascertain due to time-consuming cultures with poor sensitivity and specificity, along with a high frequency of contamination. As a result, diagnosis is often based on clinical signs and symptoms such as fever >38.5°C, chest recession, and a raised respiratory rate. The etiology of an LRTI in children has primarily been found to be viral, especially in children under the age of 2 where respiratory syncytial virus is largely the culprit of LRTIs. It is estimated that 1/3 of all LRTIs are caused by mixed viral and bacterial agents. As a child ages, bacterial etiology of an LRTI becomes more common, with Streptococcus pneumoniae being the leading bacterial agent causing LRTI through all ages. As a result of possible mixed etiology and a lack of reliable diagnostic testing to differentiate a viral and bacterial LRTI, most guidelines indicate treating empirically with antibiotics. This has lead to rampant inappropriate treatment of viral infections with antibiotics. In accordance, the ubiquitous use of antibiotics has lead to antibiotic resistant bacteria one of which is Streptococcus pneumonia, the same strain that causes most community-acquired pneumonia (CAP).
To put this problem into perspective, the CDC conservatively estimates that within the United States, “at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections.” The severity of this problem has not gone unrecognized by the federal government. The 2016 Presidential Budget Proposal has allocated $1.2 billion for combating antibiotic-resistant bacteria. Per the National Strategy for Combating Antibiotic-Resistant Bacteria, this money will go towards antibiotic stewardship particularly for the “development and dissemination of licensed point-of-need diagnostic tests that distinguish between bacterial and viral infections in 20 minutes or less.” The idealized ‘point-of-need diagnostic test’ may already be in existence in the form of a qualitative point-of-need procalcitonin (PCT) test.

Among the commonly used biomarkers of bacterial infection, including white blood cell (WBC) count and C-reactive protein (CRP), PCT has risen above and beyond the rest due to its high sensitivity for bacterial infection. PCT is an amino acid peptide that is undetectable in a healthy individual but is noted to rapidly elevate in patients exposed to bacterial endotoxins and, due to a long half-life, remains elevated 12-48 hours after initial exposure. It has been found that a PCT level less than 0.25μg/L has a high negative predictive value in excluding bacterial disease in the setting of CAP. There are currently several commercially available PCT assay tests on the market including one qualitative point-of-need test made by Brahms commonly used to detect PCT level. As a result many studies have been conducted utilizing PCT level to dictate when antibiotics should be delivered. Of particular interest is a Cochrane systematic review titled

*Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections.* It
is based on an adult population that has shown “The use of [PCT] to guide initiation and duration of antibiotic treatment in patients with [acute respiratory tract infection] was not associated with higher mortality rates or treatment failure, but significantly reduced antibiotic consumption.” Given the robust findings of this systematic review,\textsuperscript{18} it seems likely that the point-of-need PCT test will surely permeate throughout many clinical settings as a tool for reducing the use of antibiotics. Children are a likely future target for PCT testing as they, more than adults, suffer from viral LRTI, rather than bacterial.\textsuperscript{6} Thus, great headway could be made in the name of antibiotic stewardship on this front.

Can PCT-guided antibiotic treatment of LRTIs in a pediatric population reduce the antibiotic prescription rate or therapy duration with comparable outcomes to current therapy guidelines?

METHODS

A comprehensive search of accessible medical databases was conducted using Medline-Ovid, Web of Science, and CINAHL using the keywords procalcitonin, pediatric, lower respiratory tract infections, and antibiotic. The search was then narrowed to include only English language articles. Studies chosen included prospective randomized clinical trials (RCT) that evaluated for antibiotic rate and duration in the application of PCT-guided antibiotic therapy in the treatment of LRTI in pediatrics as compared to standard guidelines. The included studies were evaluated for bias and assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).\textsuperscript{19} No relevant trials in accord with the particular parameters of this review are registered with the National Institute of Health (NIH) at this time.
RESULTS

The initial database search unveiled 22 articles, two of which met inclusion criteria. Both studies\textsuperscript{20,21} are randomized clinical control trials containing primary data on human subjects. The characteristics of both studies are summarized in Table 1.

**Baer et al**

This randomized, multi-center, clinical trial\textsuperscript{20} investigated the application of a PCT algorithm for the determination of antibiotic therapy in pediatric patients presenting with an LRTI as compared to standard clinical care guidelines. The primary outcome assessed was the rate of antibiotic prescriptions. While the secondary outcomes assessed were the duration of antibiotic treatment, antibiotic side effects, hospitalization rates, and serious adverse events (SAE) including disease specific failure. Additionally subjective information was collected in the form of a diary on the patient’s perceived impairment of daily activities.\textsuperscript{20}

Children presenting with an LRTI to one of two emergency departments (ED) in Switzerland were randomly assigned to either the PCT-guided group or the standard clinical care group (control group). Physicians treating with PCT guidance were instructed to prescribe antibiotics in accordance with the likelihood of a bacterial infection as indicated by the following PCT levels: definitely (> 0.5 \(\mu\)g/L), probably (0.26 - 0.5 \(\mu\)g/L), probably not (0.1 - 0.25 \(\mu\)g/L), definitely not (< 0.1 \(\mu\)g/L). PCT levels were taken on days 1, 3, and 5. On Day 5, PCT levels were measured and if >1 \(\mu\)g/L then antibiotic therapy was continued for 7 days; if between 0.51-1 \(\mu\)g/L, then therapy continued for 5 days; if between 0.26-0.5 \(\mu\)g/L then therapy continued for 3 days; and if \(\leq\) 0.25 \(\mu\)g/L then antibiotic therapy was stopped. Moreover, if the patient’s PCT levels fell...
to less than 90% of the initial PCT (in the case that the initial PCT > 10 μg/L) antibiotics were also discontinued. If a physician at anytime felt as though the child had severe co-morbidities, hemodynamic or respiratory instability, or an emerging need for the ICU they could be given antibiotics regardless of their PCT level. The control group was treated with antibiotics per the physician assessment and clinical guidelines for a duration of 7 to 10 days for uncomplicated CAP and 14 or more days for complicated CAP.  

Inclusion criteria consisted of only patients between the ages of 1 month and 18 years presenting with acute LRTI. Acute LRTI included non-CAP (bronchitis and bronchiolitis) and CAP. All patients had a fever of at least 38°C and at least one sign and one symptom of LRTI. Possible signs included tachypnea, dyspnea, wheezing, late inspiratory crackles, bronchial breathing, and pleural rub. Possible symptoms included cough, sputum production, pleuritic pain, and poor feeding. CAP was confirmed by new or increasing alveolar infiltrate found on chest radiograph. All patients unable to give written consent and/or had language barriers were excluded from the trial. Furthermore, all patients with severe immune depression, cystic fibrosis, acute croup, and a hospital stay within the previous 14 days or with another serious infection were excluded from the trial. Follow up consisted of a phone call from a pediatrician blinded to patient allocation 14 days after randomization. Full clinical recovery was determined at that point. Follow up was incomplete for 2% of patients, all of who were within the control group.  

From a total of 946 eligible LRTI patients initially presented, 50% (473) were chosen for evaluation of which 339 met inclusion criteria with 2 withdrawing consent after randomization. Patients were randomized using variable block randomization with stratification for the two EDs and for the type of LRTI. Ultimately 169 (107 with CAP
and 62 with non-CAP) were enrolled in the control group and 168 (108 with CAP and 60 with non-CAP) were in the PCT-guided group. Baseline patient characteristics were similar in both treatment groups.²⁰

Antibiotic prescription rates were found to unexpectedly, and without much statistical significance, increase with PCT guidance. The duration of antibiotic therapy however, was decreased as expected. There were 62% from the PCT-guided group and 56% of the control group that were given antibiotics within 14 days of randomization, with a calculated difference of 6% (95% CI -5%, 16%; P=0.359). While the mean duration of antibiotic therapy was 4.5 days in the PCT-guided group, it was 6.3 days for the control group amounting to a statistically significant mean difference of -1.8 days (95% CI -3.1, -0.5; P = 0.039). Antibiotic side effects were not significantly different between both groups, at 39% and 38% for PCT-guided and the control group respectively, the difference being 1% (95% CI -10, 12). Likewise, the rate of adverse events including complications of LRTI or disease specific failure was not significantly different at 23% and 20% for the PCT-guided group and the control group respectively, with a rate difference of 2% (95% CI -6, 11). There were 62% of the PCT-guided group and 60% of the control group who were hospitalized with 2% difference (95% CI -8,12). Of the 79% of patients who returned their diaries, the study investigators did not find any significant difference in the impairment of daily activities between the two groups.²⁰

The authors discussed limitations of this study, including an acknowledgement that “pediatricians in Switzerland have a low rate of prescribing antibiotics in general.” Thus, a possible reasoning for the failure of PCT guidance to reduce the antibiotic prescription rate within their study. They also felt that the PCT cut-off levels used to
Esposito et al

This prospective, randomized, single-center control trial\textsuperscript{21} studied the utility of a PCT cut-off value to guide antibiotic therapy in pediatrics hospitalized with CAP as compared to the standardized clinical guidelines recommended by the Italian Society of Pediatrics. The primary outcome studied was the comparative rate of antibiotic prescriptions; whereas the secondary outcomes were the duration of antibiotic therapy, the rate of antibiotic side effects, and the return of LRTI symptoms requiring antibiotic therapy.\textsuperscript{21}

Eligibility criteria in this study\textsuperscript{21} centered on all children between the ages of 1 month and 14 years who were hospitalized at the Department of Maternal and Pediatric Sciences at the University of Milan with certain clinical signs and symptoms. The signs and symptoms indicated included: history of fever, cough, tachypnea, dyspnea and respiratory distress, breathing with grunting or wheezing sounds with rales, and having confirmed radiographic findings on chest x-ray including pulmonary infiltrate or segmental or lobar consolidation. Of the 419 eligible patients, 100 were excluded because of complications such as pleural effusion, empyema, lung necrosis, pneumatocele, antibiotics taken within the past 10 days prior to admission, chronic disease, severe malnutrition, and other concurrent infections. The remaining 319 patients were allocated to treatment groups by computer-generated randomization and sealed envelope. Of the
319 patients randomized, 9 withdrew consent; leaving 155 in both the PCT-guided group and the control group. Baseline characteristics were balanced across both groups.21

The PCT algorithm applied to the PCT-guided group had very strict parameters. Both group participants had their PCT levels taken within 6 hours of admittance. While the control group all went on to receive antibiotics for no less than 7 days, the PCT-guided group were only given antibiotics if their initial PCT level was greater than or equal to 0.25 μg/L. All patients’ PCT levels were monitored every other day until discharge and at the follow up visits, Day 14 and 28 after admission. If at any point an individual’s PCT levels in the PCT-guided group dropped below the 0.25 μg/L cut-off level, the antibiotics were discontinued. Likewise, if PCT levels rose above 0.25 μg/L patients were given antibiotics. If the physician felt that an untreated child showed no reduction or worsening clinical signs or symptoms at any time, antibiotics were given regardless of PCT level.21

Overall, there was a statistically significant decrease in antibiotic rate and exposure in the PCT-guided group as compared to the control group (p < 0.05). Of the PCT-guided group, 14% were able to avoid antibiotics altogether, leaving 86% who took antibiotics. This was compared to the baseline of the control group, in which 100% took antibiotics (p < 0.05). Among the children in the PCT group, 1.5% discontinued antibiotics after 2 days, 4.6% after 4 days, 37.4% after 6 days, 46.6% after 8 days and only 11.5% received antibiotics beyond 10 days. Three of the patients who had discontinued antibiotics in the PCT-guided group went on to see a secondary spike in PCT level ≥ 0.25μg/L, resulting in a resumption of antibiotics until day 10, at which point symptoms resolved and PCT levels had dropped below 0.25μg/L. The control group saw
that 100% of patients received antibiotics for no less than 7 days, 82.6% for 10 days, 25.2% for 12 days and 13.5% for 14 days. Within the PCT-guided and control group, 0.6% and 3.9% respectively returned 2 to 3 weeks after discharge for worsening respiratory symptoms; all of who were considered cured 28 days after admission. This study found significantly more antibiotic-related adverse events in the control group versus the PCT-guided group at a rate of 25.2% and 3.9% (p < 0.05) respectively. 21

Authors cited the small sample size to be a limitation as well as the fact that all of the patients were hospitalized with uncomplicated CAP. It was acknowledged that this study poorly represented children with a more severe disease particularly those with bacterial CAP resistant to commonly used antibiotics and children being treated in an outpatient setting. Further study on the safety of utilizing a PCT-based algorithm to treat CAP was recommended.21

**DISCUSSION**

In the end, both trials 20,21 adequately answered the clinical question: can PCT-guided antibiotic treatment of LRTIs in pediatric populations reduce the antibiotic prescription rate or therapy duration with comparable outcomes to current therapy guidelines? PCT guidance can reduce antibiotic prescription duration; but only in certain situations does it appear to reduce the antibiotic prescription rate. Both trials 20,21 show statistically significant evidence that antibiotic therapy duration can be reduced with the application of a PCT algorithm (RR of 0.68 and 0.48, for the Baer et al and Esposito et al trial respectively, see Table II). Yet the trials differed in regard to the effect PCT-guided therapy has on the rate of antibiotic initiation. The Esposito et al trial 21 found that PCT-guided therapy greatly reduces the antibiotic initiation rate (RR of 0.85) while the Baer et
al trial\textsuperscript{20} found that PCT guidance actually increases the antibiotic prescription rate as compared to the control group (RR of 1.13). The mixed findings could be due to a multitude of variables, including differences between the two study populations, standard practice guidelines and regional clinician preferences.

Contradictory outcomes of antibiotic prescription rates can be attributable to differences in the average level of patient illness between the two studies. For example, the average study participant in the Esposito et al trial\textsuperscript{21} had a PCT level of 1.8ug/L while the average PCT level in the CAP group in the Baer et al trial\textsuperscript{20} was 4.5ug/L, despite using the same PCT assays.\textsuperscript{20} This indicates that the study population within the Esposito et al trial was perhaps less ill than the CAP patients within the Baer et al trial. Which could have contributed to the relative success of the Esposito et al trial in reducing antibiotic prescription as compared to the Baer et al trial.\textsuperscript{20,21}

This same phenomenon was appreciated in the adult trials as summarized in the Cochrane systematic review,\textsuperscript{18} where they found large differences between the rates of antibiotic prescription in the PCT group for different clinical settings. For example, the rate of antibiotic prescription in the PCT group while in a primary care office was 23\%, in the emergency department it was 73\%, and in the ICU it was 100\%. Assuming that the severity of illness correlates with clinical setting (ie, the ICU treats more severe illness than primary care), there is an obvious trend within the PCT group towards an increased antibiotic prescription rate in the more severely ill.\textsuperscript{18}

A similar pattern was revealed in the breakdown of the Baer et al trial\textsuperscript{21} into non-CAP and CAP groups, with the non-CAP group being less ill than the CAP group. Within the Baer et al PCT-guided group, 45\% of the non-CAP patients received an antibiotic
prescription while 71% of patients in the CAP group received antibiotics. Severity of illness appears to play as important of a roll in children as is it does in adults. The author of the Cochrane systematic review\textsuperscript{18} concluded that for “patients at low risk for severe bacterial infection, a [PCT] algorithm is used to determine whether antibiotics should be initiated at all; in higher risk patients [PCT] was mainly used to determine when treatment could be safely discontinued.”\textsuperscript{18} The results of the Esposito et al\textsuperscript{21} and Baer et al trials\textsuperscript{20} indicate that this conclusion may hold true for both children and adults alike. Thus, in exploring a possible cause for the difference in outcome between the two studies,\textsuperscript{20,21} an answer for the clinical question may have been clarified.

Another likely cause of the differing outcomes between the two trials,\textsuperscript{20,21} could be the largely different approaches taken with the control groups. The Esposito et al study\textsuperscript{21} gave 100% of control patients antibiotics while the Baer et al trial\textsuperscript{20} gave 56% of the control patients antibiotics. Interestingly, the Esposito et al PCT-guided group reduced antibiotic prescription rates to levels comparable to the Baer et al\textsuperscript{20} control group. The Baer et al trial, as discussed earlier, was conducted in Switzerland, where antibiotic prescription rates tend to be lower than that the rest of Europe or the United States.\textsuperscript{18,20} Perhaps explaining why PCT guidance had not had the same comparative reduction in antibiotic prescriptions rates as it had in other parts of the world such as Italy where the Esposito et al trial was held.\textsuperscript{21}

To summarize, the RCTs\textsuperscript{20,21} answered the clinical question, confirming that a PCT algorithm can reduce the antibiotic duration and also reduce the antibiotic initiation rate in cases of less severe illness. This review further went on to discuss the regional differences in LRTI clinical guidelines. In doing so, the review highlighted a possible
tendency for more stringent clinical guidelines to reduce antibiotic initiation rates equally as well as PCT-guided protocol.

Both trials\textsuperscript{20,21} were found to have a few shared limitations. First, due to the nature of the study neither trial was able to blind the physician. The physician was required to know treatment allocation in order to follow correct treatment protocol. Attempts could have been made at blinding the patient with a placebo yet there is little to suggest that a patient’s PCT level would change as a result. Second and most importantly, neither trial reported a rate of adherence to the PCT algorithm. The Baer et al\textsuperscript{20} trial advised physicians to overrule the PCT algorithm in cases where the patient had a “life-threatening infection”. Likewise, the Esposito et al trial\textsuperscript{21} stated that “in the case of severe clinical deterioration and regardless of their PCT levels, children in both groups could be treated with antibiotics or their treatment could be modified on the basis of their pediatrician’s judgment.” Lack of accountability for changes in treatment protocol not only risks the significance of the results but also allows for the influence of physician bias. The third shared limitation of both studies\textsuperscript{20,21} is the relatively small sample size of either trial.

Both trials\textsuperscript{20,21} had their own unique limitations. The Baer et al trial\textsuperscript{20} included patients who had recently taken antibiotics prior to initiation, potentially compromising the initial PCT level and the outcomes relating to antibiotic initiation and duration. The Esposito et al trial,\textsuperscript{21} on the other hand, was limited by allocation bias. Although a computer randomized treatment protocol, the delivery of the selected treatment plan was by sealed, unnumbered envelope. This provided the physician with the potential to change the order of treatment allocation. Furthermore, the Esposito et al trial studied only
hospitalized children with uncomplicated CAP. Therefore, it poorly represented patients with severe disease or treatment in an outpatient setting.

Based on the GRADE criteria, the combined quality of evidence of the two studies reviewed is moderate. Further randomized clinical control trials with larger sample sizes are needed to increase the statistical power behind these findings particularly in the varying clinical settings. Additionally, research into the optimal PCT cut-off levels in children with LRTI is needed in order to fully minimize antibiotic prescription rates within this population.

CONCLUSION

With every antibiotic prescription written, the risk of antibiotic resistance increases. Point-of-need PCT testing is trending toward becoming the tool of the future to differentiate between viral and bacterial LRTI. Studies on adult patients have shown a reduction in antibiotic prescription rates and duration of therapy with the application of PCT-guided antibiotic therapy. Likewise, the evidence presented in this review indicates that the use of a PCT-guided algorithm in children can reduce the duration of antibiotic therapy and it can reduce the antibiotic prescription rate in cases of low acuity LRTI.

There is a substantial and universal benefit to society and individuals in the reduction of antibiotic use. It is morally imperative that efforts be made in this regard. For the purpose of reducing the duration of antibiotic therapy in all clinical settings, the benefit of implementing PCT-guided therapy as a standard of practice outweighs any risks. Thus, as the point-of-need PCT test becomes more available, its use is recommended in guiding antibiotic therapy in pediatrics presenting with LRTI. Until that time however, stricter clinical guidelines dictating antibiotic use should be followed.
References


<table>
<thead>
<tr>
<th>Method</th>
<th>Baer et al</th>
<th>Esposito et al</th>
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</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomized Clinical Trial, multi-center, 2 emergency departments in Switzerland. Computer generated list with web-based patient allocations.</td>
<td>Randomized Clinical Trial, single-center, Department of Maternal and Pediatric Sciences at the University of Milan, Milan, Italy. Computer generated list with sealed envelope allocation.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Inclusion Criteria</strong>: Children Age &gt;1 month to &lt;18 years presenting with Acute LRTI(^a) to the ED regardless of AB treatment history. Temperature ≥ 38°C.</td>
<td><strong>Inclusion Criteria</strong>: Children Age &gt;1 month to &lt;14 years hospitalized with CAP(^b) confirmed with CXR(^d).</td>
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<tr>
<td><strong>Exclusion Criteria</strong>: unable to get written consent or language barriers, severe Immune suppression(^b), cystic fibrosis, acute croup, hospital stay within previous 14 days or other severe infection.</td>
<td><strong>Exclusion Criteria</strong>: Complications such as pleural effusion, empyema, lung necrosis, pneumatocele. AB taken within the past 10 days prior to admission. Chronic disease(^e), severe malnutrition, other concurrent infections.</td>
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<tr>
<td><strong>Included in this analysis</strong>: 337 out of 339 randomized patients: 2 post randomization exclusions (2 withdrew consent)</td>
<td><strong>Included in this analysis</strong>: 310 out of 319 randomized patients: 9 post randomization exclusions (9 withdrew consent)</td>
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<tr>
<td><strong>Interventions</strong></td>
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<tr>
<td>Guiding antibiotic decisions in acute LRTI patients with repeated PCT measurements.</td>
<td>Guiding antibiotic decisions in CAP patients with repeated PCT measurements.</td>
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<tr>
<td><strong>Algorithm used for antibiotic therapy</strong>:</td>
<td>Algorithm used for antibiotic therapy:</td>
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<tr>
<td><strong>Initiation</strong>: AB treatment likelihood at admission per PCT levels:</td>
<td><strong>Initiation</strong>: AB treatment at admission if PCT ≥ 0.25 μg/L AB were given to untreated children if their PCT levels increased to ≥ 0.25 μg/L.</td>
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<tr>
<td>Definitely ( &gt; 0.5 μg/L)</td>
<td>Discontinue: When PCT levels dropped below 0.25 μg/L.</td>
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<tr>
<td>Probably (0.26 - 0.5 μg/L)</td>
<td><strong>Exceptions to algorithm</strong>: Untreated children showing no clinical reduction in signs or symptoms or with clinical deterioration were given AB regardless of PCT level.</td>
<td></td>
</tr>
<tr>
<td>Probably not (0.1 - 0.25 μg/L)</td>
<td><strong>Monitor</strong>: PCT levels taken within 6h of admission and every other day until discharge and at both follow up visits.</td>
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</tr>
<tr>
<td>Definitely not (&lt; 0.1 μg/L)</td>
<td><strong>Control</strong>: All patients received AB per the Italian Society of Pediatrics (SIP) guidelines. Antibiotic therapy was given between 7-14 days depending on severity.</td>
<td></td>
</tr>
<tr>
<td>Continuation of AB on day 5 of treatment if PCT:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1 μg/L : 7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.51 - 1 μg/L : 5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.26 -0.5 μg/L : 3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.25 μg/L: no antibiotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinue: when the patient stabilized and when PCT &lt; 0.25 μg/L or when PCT levels fell to less than 90% of the initial PCT in the case that the initial PCT &gt; 10μg/L.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exceptions to algorithm</strong>: severe co-morbidity, hemodynamic or respiratory instability, or emerging ICU need.</td>
<td></td>
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</tr>
<tr>
<td><strong>Monitor</strong>: clinical assessment and PCT taken at day 1, 3 and 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control</strong>: AB 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prescription rate within 14 days of randomization</td>
<td>Antibiotic prescription rate</td>
<td></td>
</tr>
<tr>
<td>Duration of antibiotic treatment, days</td>
<td>Duration of antibiotic treatment</td>
<td></td>
</tr>
<tr>
<td>Antibiotic Side Effects</td>
<td>Antibiotic Side Effects</td>
<td></td>
</tr>
<tr>
<td>Duration of Antibiotic Side Effect, days</td>
<td>Reoccurrence of symptoms at day 28</td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Duration of hospitalization</td>
<td></td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety (complications of LRTI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Funding: The division of infectious Diseases and Vaccines, University Children’s Hospital, Basel, Switzerland. Follow up: At 14d from randomization, phone call from pediatrician blinded to treatment allocation. Registration: ISRCTN17057980</td>
<td></td>
</tr>
<tr>
<td>Funding: Unknown</td>
<td>Follow up: 14 ±2d and 28±3d post admission. Blinded pediatrician Registration: none</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) LRTI = Non-CAP (bronchitis, bronchiolitis) or CAP. CAP = LRTI w/new or increasing alveolar infiltrate on CXR.

Acute LRTI diagnosis: Fever ≥ 38°C + at least one sign and one symptom for less than 14 days.

Signs: tachypnea, dyspnea, wheezing, late inspiratory crackles, bronchial breathing, pleural rub.

Symptoms: cough, sputum production, pleuritic pain, poor feeding.

\(^b\) Immune suppressed = HIV infection with a CD4 count <15% of normal age specific counts, immunosuppressive treatments, neutropenia.

\(^c\) CAP w/clinical S&S: History of fever, cough, tachypnea, dyspnea and respiratory distress, breathing with grunting or wheezing sounds with rales.

\(^d\) Including: pulmonary infiltrate, segmental/lobar consolidation.

\(^e\) Anatomic abnormality of the respiratory tract, immunologic deficits, progressing neurological conditions, psychomotor retardation, congenital heart disease, hemoglobinopathy.
Table II. GRADE Evidence Profile: Quality Assessment and Summary of Findings

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zoning criteria</td>
</tr>
<tr>
<td>No. of Studies</td>
<td>Design</td>
</tr>
<tr>
<td>Ratifies Antibiotic Prescription</td>
<td>No Serious Limitations</td>
</tr>
<tr>
<td></td>
<td>Esposito et al(7)</td>
</tr>
<tr>
<td>Duration of Antibiotic Therapy at or beyond day 7 after randomization(8)</td>
<td>No Serious Limitations</td>
</tr>
<tr>
<td></td>
<td>Esposito et al(7)</td>
</tr>
<tr>
<td>Adverse Event(9)</td>
<td>No Serious Limitations</td>
</tr>
<tr>
<td></td>
<td>Esposito et al(7)</td>
</tr>
<tr>
<td>Antibiotic Side Effects</td>
<td>No Serious Limitations</td>
</tr>
<tr>
<td></td>
<td>Esposito et al(7)</td>
</tr>
</tbody>
</table>


1 In the Esposito et al trial the number of patients on antibiotics at Day 7 was calculated from a summation of the percentages of patients stopping antibiotics on Day 8 or greater. In the Baer et al trial the percentage of patients on antibiotics at Day 7 was used to calculate this figure.

2 Adverse event described as recurrence of symptoms requiring antibiotic (Esposito et al), hospital readmission, co-morbidity in need of antibiotics, or worsening or impact of daily activity (Baer et al).

3 Large difference due to regional differences in clinical guidelines for treatment of LRTI of the control group. In Switzerland, only 56% of the Baer et al control group received an antibiotic prescription as compared to Italy where 100% of the Esposito et al control group received antibiotics.

4 Quality of the evidence was down graded to Moderate due to having only two RCTs.
## Table III. Summary of Biases

<table>
<thead>
<tr>
<th>Bias</th>
<th>Baer et al&lt;sup&gt;Il&lt;/sup&gt;</th>
<th>Support for Judgement</th>
<th>Esposito et al&lt;sup&gt;Il&lt;/sup&gt;</th>
<th>Support for Judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random Sequence Generation (selection bias)</td>
<td>Low Risk</td>
<td>Computer-generated scheme</td>
<td>Low Risk</td>
<td>Computer-generated scheme</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low Risk</td>
<td>Quote: &quot;Patient allocation was concealed by the use of web-based online patient registration.&quot;</td>
<td>Moderate Risk</td>
<td>Quote: &quot;The patients were randomised to the PET or control group using a previously prepared computer-generated randomisation list and sealed envelope.&quot; Envelopes were not numbered.</td>
</tr>
<tr>
<td>Blinding of Participants and Personnel (performance bias)</td>
<td>Unclear Risk</td>
<td>Open-label for the prescribing physician and patients. Follow-up physician was blinded to patient allocation.</td>
<td>Unclear Risk</td>
<td>Open-label for the prescribing physician and patients. Follow-up physician was blinded to patient allocation.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low Risk</td>
<td>Quote: &quot;For endpoint assessment each patient was contacted on day 14 by a study pediatrician blinded to treatment allocation of the child.&quot;</td>
<td>Low Risk</td>
<td>Quote: &quot;At these follow-up visits, (patients) were evaluated by blinded researcher who defined the outcome&quot;.</td>
</tr>
<tr>
<td>Incomplete Outcome (attrition bias) All outcomes</td>
<td>Low Risk</td>
<td>Follow up for clinical recovery: 332/337 (99%)</td>
<td>Low Risk</td>
<td>Follow up for clinical recovery: 310/310 (100%)</td>
</tr>
<tr>
<td>Selective Reporting (reporting bias)</td>
<td>Low Risk</td>
<td>Outcomes correspond to study protocol</td>
<td>Low Risk</td>
<td>Outcomes correspond to study protocol</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear Risk</td>
<td>Adherence to procaloneptin protocol not reported/assessed.</td>
<td>Unclear Risk</td>
<td>Adherence to procaloneptin protocol not reported/assessed.</td>
</tr>
</tbody>
</table>