Comparison of Procalcitonin Guidance-Administered Antibiotics with Standard Guidelines on Antibiotic Therapy in Children with Lower Respiratory Tract Infections: A Retrospective Study in China

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Abstract

Objective: To establish the efficacy of an algorithm based on the biomarker procalcitonin (PCT) to reduce antibiotic exposure in pediatric patients with lower respiratory tract infection (LRTI).

Materials and Methods: The clinical data of 357 patients (<14 years of age) who were discharged home with LRTI from January 1, 2010 to July 31, 2016 were analyzed. Antibiotic exposure, antibiotic prescription rate, length of hospital stay, and antibiotic-associated adverse effects were compared between the PCT group (n = 183) and the standard group (n = 174) using SAS 9.1.3 software. Results: The overall adverse effect rates were similar in both the PCT and standard groups: 42 (22.95%) and 51 (29.31%), respectively. The length of hospital stay was not significantly different between the PCT (9.96 ± 5.81 days) and standard groups (10.58 ± 4.24 days) (difference: –0.62%; 95% CI: –1.68 to 0.43). Antibiotic prescribing rates were significantly different in the PCT group compared to the standard group: 54.64% versus 83.91% (difference: –29.26%; 95% CI: –38.31, –20.22; p = 0.23). Mean duration of antibiotic exposure in the PCT group (3.98 ± 2.17 days) was lower than the standard groups (6.66 ± 5.59 days) (difference: –2.68%; 95% CI: –3.21 to –2.16). Conclusion: This study showed that PCT guidance of antibiotic treatment in children and adolescents with LRTI reduced the duration of antibiotic exposure and antibiotic prescribing rates, but did not affect the adverse effect rate and length of hospital stay. © 2017 S. Karger AG, Basel

Keywords
Antibiotic therapy · Pediatric therapeutics · Respiratory tract infections

Significance of the Study

• This study showed that procalcitonin (PCT) guidance of antibiotic treatment in children and adolescents with lower respiratory tract infection (LRTI) reduced duration of antibiotic exposure and antibiotic prescribing rates, but did not affect the adverse effect rate and length of hospital stay. Hence, these data provide further evidence that PCT guidance of antibiotic treatment in children with LRTI was feasible.
Lower respiratory tract infections (LRTI), such as bronchiolitis and pneumonia, are among the most important causes of morbidity and mortality in the childhood [1–3]. Approximately 2 million children aged ≤5 years of age die each year because of LRTI [1]. Thus, pediatric LRTI is a widespread problem of profound economic and social importance to children and communities worldwide. The LRTI clinical diagnosis is mainly based on causes of LRTI, clinical symptoms, signs, laboratory tests, and clinical imaging [4, 5]. However, the clinical symptoms and signs of LRTI caused by different pathogens are very similar and are often difficult to identify [2]. Laboratory tests and clinical imaging (chest radiographic) cannot clearly determine whether the LRTI is caused by bacteria or viruses or other pathogens [2]. Unfortunately, antibiotic abuse is common in the treatment of LRTI [6, 7]. Between 80 and 90% of all antibiotics are prescribed in the primary care setting, mostly for respiratory tract infections [7]. The non-evidence-based prescription of antibiotics is very high [8]; despite the predominantly viral origin of the infection, as many as 75% of patients with LRTI are treated with antibiotics [9]. Diagnostic uncertainty and an over-reliance on abnormal lung sounds on auscultation can be reasons for over-prescribing antibiotics in children with LRTI, as well as the children’s parents expectations and demands [10], thereby leading to considerable overuse of antibiotics that increases the risk of bacterial resistance, the incidence of drug-related adverse events, and therapeutic costs [11]. Appropriate diagnosis can reduce the use of excess antibiotics [12].

Procalcitonin (PCT) can provide an experimental rationale and a diagnostic lead to distinguish bacterial from viral infections [3–5, 11, 13, 14]. PCT is an established biomarker of bacterial infections and is widely used in high-income countries, particularly in hospital settings [15, 16]. PCT measurements flag the presence and track the status of systemic bacterial infection, thereby helping the clinician determine the necessity and optimal duration of antibiotic therapy in patients with respiratory symptoms. Findings from several studies have shown that use of clinical algorithms based on the ranges of PCT cut-offs can lead to important reductions in antibiotic use [17–21]. Hence, the objective of this study was to compare the adverse medical outcomes and reduction of the duration of antibiotic treatment in children with LRTI between the use of PCT guidance-administered antibiotics and treatment based on standard guidelines.

Materials and Methods

This study was a single-center retrospective cohort study conducted at Changzhou Second People’s Hospital Affiliated to Nanjing Medical University (CZSPH), an academic tertiary facility located in Changzhou, Jiangsu Province, China. The selected patient population consisted of all CZSPH pediatric ward patients (<14 years of age) who had been discharged home with LRTI in 2 different medical business management periods. Based on the hospital medical business management, the patients received antibiotics according to standard guidelines between January 1, 2010 and December 31, 2011, and these were the standard group. Others received antibiotics based on a PCT algorithm between January 1, 2015 and July 31, 2016, and were the PCT group. The PCT group was determined using standard laboratory techniques on a Cobas® 6000 e601 (Roche, Germany). Except for the PCT measurements, all monitoring was similar between the PCT group and the standard group.

Exclusion criteria were recent hospitalization, severe immunosuppression, life-threatening medical comorbidities (e.g., respiratory failure and heart failure) leading to possible imminent death, hospital-acquired pneumonia (development of pneumonia ≥48 h after hospital admission or hospitalized within 14 days before presentation), chronic infection necessitating antibiotic treatment and a clear alternative diagnosis (e.g., heart, liver and kidney, and other chronic diseases).

The diagnosis of LRTI was based on the textbook Pediatrics and Children with Community-Acquired Pneumonia Management Guidelines [22, 23]. The treatment for both patient groups was based on existing experience, expertise, and local protocols. Antibiotic use was in accordance with recommendations from up-to-date evidence-based guidelines. The decision to start antibiotic treatment was not affected by any trial. In all patients, antibiotics were started based on a clinical suspicion of infection or microbiological evidence of infection. This decision was fully at the discretion of the treating pediatrician. All patients were clinically reassessed to follow the resolution of the infection on days 3, 5, and 7, and at discharge.

Based on the PCT algorithm, initiation or continuation of antibiotics was strongly discouraged if PCT was <0.1 μg/L and discouraged if levels were ≤0.25 μg/L. Conversely, the algorithm encouraged antibiotic intervention if PCT levels were ≥0.25 μg/L and strongly encouraged antibiotic intervention if PCT was >0.5 μg/L. During follow-up, all patients in the PCT group had repeated PCT testing, and the algorithm recommended an early stop of antibiotics when PCT dropped to <0.25 μg/L. For patients with initial PCT >10 μg/L, the algorithm recommended stopping antibiotics if PCT levels had decreased to ≥80%, and strongly recommended stopping antibiotics when the decrease was ≥90%. The attending pediatrician was free to decide whether or not to continue antibiotic treatment in patients who had reached these thresholds. Reasons for non-adherence were recorded.

Patient data were obtained from the electronic records as well as the paper charts. To assure patient anonymity, the extracted variables were limited to demographics (age, sex), past medical history (previous history of admissions/antibiotic-resistant organisms, comorbidities), admission category, reason for admission, admission date, discharge date, infectious disease diagnosis and treatment characteristics (antimicrobial name, class, and duration), results of microbiological cultures and laboratory, imaging...
findings, antibiotic-related side effects (including diarrhea, nausea, vomiting, and allergic reactions) as judged by the treating physician, documented follow-up plan at discharge, and outcome (readmission/return to pediatric department, antimicrobial complications). The Changzhou Second People’s Hospital Ethics Committee approved the study protocol. Privacy and personal information was protected.

**Statistical Analysis**

SAS 9.1.3 software (SAS Institute, Cary, NC, USA) was used for data analyses. A Student t test or Wilcoxon rank sum test for continuous variables and χ² test for categorical variables were applied for the comparison between the PCT group and the control group. Odds ratios (OR) and 95% CI were calculated logistic regression. All hypothesis tests were 2-sided, and a 2-tailed p value of <0.05 was considered as indicating statistical significance.

**Results**

In the 2 study periods, a total of 357 patients who were diagnosed with LRTI and virtually treated at the CZSPH were found in the medical records, with 174 patients comprising the standard group (between January 1, 2010 and December 31, 2011) and 183 patients comprising the PCT group (between January 1, 2015 and July 31, 2016). The baseline characteristics of both groups are shown in Table 1. The baseline characteristics were similar in both groups (p ≥ 0.11). Blood culture, sputum culture, and urine antigen testing showed evidence of typical respiratory pathogens, mainly *Streptococcus pneumoniae*, with the other 5 major bacteria being (in order of detection rate) *Haemophilus parainfluenzae*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Haemophillus influenzae* (data not shown) in both groups.

Prescription rates and antibiotic exposure in the PCT group were significantly decreased compared to standard group: from 83.91 to 54.64% and 6.66 ± 5.59 to 3.98 ± 2.17 days, respectively (Table 2). The reduction in antibiotic prescription rates were 94.87–74.19% (95% CI: –37.57, –3.79; p = 0.16) for pneumonia, 84.93–47.83% (95% CI: –51.47, –22.74; p = 0.16) for bronchitis, 95.65–82.76% (95% CI: –28.97, 3.18; p = 0.22) for bronchiolitis, and 64.10–37.04% (95% CI: –46.88, –7.25; p = 0.33) for other categories. The reduction in mean duration of antibiotic exposure were 7.41–4.43 (95% CI: –4.13, –1.81) for pneumonia, 5.82–3.24 (95% CI: –3.13, –2.03) for bronchitis, 9.27–5.08 (95% CI: –5.82, –2.56) for bronchiolitis, and 5.36–3.35 (95% CI: –2.69, –1.33) for other categories.

Recommendations about the duration of antimicrobial treatment for the PCT group were not followed in 26 patients. At the beginning of treatment, pediatricians immediately gave antibiotics to 7 patients because they judged that infection could not be ruled out, in accordance with the algorithm (PCT concentration <0.25 μg/L). Conversely, pediatricians did not give antibiotics to 5 patients because they believed that PCT concentrations of more than 0.5 μg/L were clearly explained by noninfectious events. During antimicrobial treatment, pediatricians stopped antibiotics for 6 patients because

| Table 1. Baseline characteristics of patients |
|---------------------------------------------|
|                                            |
| **Procalcitonin group**  | **Standard group**  | **χ²(Z)** | **p** |
| (n = 183)                     |                     |           |       |
| Males                         | 86 (46.99)          | 80 (45.98) | 0.037 | 0.847 |
| Females                       | 97 (53.01)          | 94 (54.02) |       |       |
| Age, years                    | 5.46 ± 3.04         | 5.62 ± 2.68 | t = 0.521 | 0.603 |
| BT ≥38.5°C                    | 100 (54.64)         | 83 (45.36) | Z = –1.145 | 0.252 |
| CRP, mg/L                     | 10.70 (9.50, 17.60) | 11.55 (8.90, 25.30) | Z = –2.864 | 0.004 |
| WBC×10⁹ cells/L              | 8.30 (6.70, 12.40)  | 9.95 (7.50, 22.40) | Z = –2.864 | 0.004 |
| PCT, μg/L                     | 0.23 (0.09, 0.36)   | –          |       |       |
| **Diagnosis**                 |                     |           |       |
| Pneumonia                     | 31 (16.94)          | 39 (22.41) | 1.695 | 0.193 |
| Bronchitis                    | 69 (37.70)          | 73 (41.95) | 0.672 | 0.412 |
| Bronchiolitis                 | 29 (15.85)          | 23 (13.22) | 0.495 | 0.482 |
| Other categories              | 54 (29.51)          | 39 (22.41) | 2.330 | 0.127 |

Values are presented as n (%), means ± SD, and medians (95% CI). PCT, procalcitonin; BT, body temperature; CRP, C-reactive protein; WBC, white blood cells.
they regarded the infection as clinically cured, despite persistently raised PCT above 0.5 μg/L. Conversely, antibiotics were unduly continued for 8 patients as pediatricians judged that infection was not cured and still needed antibiotics, in accordance with the algorithm (PCT concentration <0.25 μg/L).

Rates of side effects from antibiotic treatment and hospitalization were similar in both study groups and in the subgroup of patients (Table 2).

Discussion

In this study, a PCT-guided strategy significantly reduced the antibiotic prescription rate and antibiotic exposure. Specifically, PCT guidance was associated with a reduction in antibiotic prescription rate from 83.91 to 54.64%, antibiotic exposure from 6.66 to 3.98 days in PCT-guided patients relative to standard guidelines. Similar results were also shown for each subgroup. The analysis showed that most effects of PCT testing in children had low probability of bacterial infection. These observations could indicate that using PCT as a biomarker might help to rule out nonbacterial infection in children with LRTI and thus improve the therapeutic management.

The reduction in antibiotic duration was most pronounced in the subgroup of patients with bronchitis, which is not consistent with a report [3] that showed the most pronounced reduction in antibiotic duration in the subgroup was in patients with community-acquired pneumonia. The reduction in antibiotic prescription rate of this study did not correspond to the main randomized ProPAED trial, in which antibiotic prescribing rates were not significantly different in PCT-guided patients compared to controls. The difference could be due to several factors: (1) pediatricians in China have a high rate of prescribing antibiotics in general, as a previous study [24] showed that there was a high proportion of prophylactic use of antibiotics in children with LRTI, and (2) national strategies for the rational use of antibiotics have been carried out in recent years in China.

The PCT values between 0.2 and 5 ng/mL were more useful in differentiating viral and bacterial LRTI, while values below 0.5 ng/mL were not sufficiently sensitive and specific in children with LRTI. Therefore, pediatricians should reconsider their diagnosis when PCT concentrations are low. Therefore, knowledge of PCT concentrations might lead to earlier and more adequate diagnoses and treatments [25].

The finding of this study showed that PCT guidance in children with LRTI did not reduce the length of hospital stay and antibiotic prescription rate, despite reduced duration of antibiotic treatment in the PCT group. A probable explanation could be that the length of hospital stay might depend on many factors that are not directly linked to the duration of antibiotic treatment. Another possibility could be the perceived need by pediatricians to continue to monitor children who received very short-term antibiotics, which might also explain the similar lengths of stay between the PCT and standard groups. Another explanation could be that the prophylactic use of antibiotics in children with LRTI-caused virus infection reduced subsequent complications and decreased hospital stay. These factors are generally independent of PCT levels.

Conclusion

This study showed that PCT guidance of antibiotic treatment in children and adolescents with LRTI reduced the duration of antibiotic exposure and antibiotic pre-

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**Table 2.** Antibiotic exposure, prescription rate, adverse effects, and length of hospital stay

|                                | Procalcitonin group (n = 183) | Standard group (n = 174) | Rate difference, % (95% CI) | Odds ratio (95% CI) | Mean difference, % (95% CI) |
|--------------------------------|-----------------------------|------------------------|-----------------------------|-------------------|-----------------------------|
| Antibiotic exposure, days      | 3.98 (3 [3 – 5])            | 6.66 (6 [5 – 7])       | −2.68 (−3.21, −2.16)        |                   |                             |
| Antibiotic prescription rate   | 100 (54.64)                 | 146 (83.91)            | −29.26 (−38.31, −20.22)     | 0.23 (0.14, 0.38)  |                             |
| Adverse effect rate from       | 42 (22.95)                  | 51 (29.31)             | −6.36 (−15.46, 2.74)        | 0.72 (0.45, 1.16)  |                             |
| antibiotics                    |                             |                        |                             |                   |                             |
| Length of hospital stay, days  | 9.96 (9 [5 – 12])           | 10.58 (9 [8 – 11])     | −0.62 (−1.68, 0.43)         |                   |                             |

Values are presented as means (medians [IQR]) and n (%).
scribing rates, but did not affect the adverse effect rate or length of hospital stay. A careful use of PCT-guided strategy in children with LRTI could reduce antibiotic selective pressure with potential benefits in the era of multiple drug-resistant bacterial strains.

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Disclosure Statement
The authors report no conflicts of interest.

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