Respiratory Medicine (2011) **105**, 1939–1945

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia

Susanna Esposito, Claudia Tagliabue, Irene Picciolli, Margherita Semino, Caterina Sabatini, Silvia Consolo, Samantha Bosis, Raffaella Pinzani, Nicola Principi*

Department of Maternal and Pediatric Sciences, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, Via Commenda 9, 20122 Milano, Italy

Received 12 July 2011; accepted 12 September 2011
Available online 29 September 2011

KEYWORDS
Antibiotic therapy;
Antibiotics;
Children;
Community-acquired pneumonia;
Pediatrics;
Procalcitonin

Summary
In order to evaluate the use of an algorithm based on a procalcitonin (PCT) cut-off value as a means of guiding antibiotic therapy, 319 hospitalised children with uncomplicated community-acquired pneumonia (CAP) were randomised 1:1 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 $\geq$0.25 ng/mL. The final analysis was based on 155 patients in the PCT group and 155 in the control group. In comparison with the controls, the PCT group received significantly fewer antibiotic prescriptions (85.8% *vs* 100%; $p < 0.05$), were exposed to antibiotics for a shorter time (5.37 *vs* 10.96 days; $p < 0.05$), and experienced fewer antibiotic-related adverse events (3.9% *vs* 25.2%; $p < 0.05$), regardless of CAP severity. There was no significant between-group difference in recurrence of respiratory symptoms and new antibiotic prescription in the month following enrollment. The results of this first prospective study using a PCT cut-off value to guide antibiotic therapy for pediatric CAP showed that this approach can significantly reduce antibiotic use and antibiotic-related adverse events in children with uncomplicated disease. However, because the study included mainly children with mild to moderate CAP and the risk of the use of the algorithm-based approach was not validated in a relevant number of severe cases, further studies are needed before it can be used in routine clinical practice.

* Corresponding author. Tel.: +39 02 55032203; fax: +39 02 50320206.
E-mail address: nicola.principi@unimi.it (N. Principi).

0954-6111/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2011.09.003

Introduction

Pediatric community-acquired pneumonia (CAP) is common, particularly in the first years of life.[1] In many cases, it is due to viruses, uncomplicated by bacterial superinfection, has a mild course and, consequently, should not receive antibiotic therapy.[2,3] However, because of the difficulties in identifying its specific etiology clinically and radiologically,[4–6] most children with CAP are treated with antibiotics without the causative agent being known. This leads to a considerable over-use of antibiotics[7,8] that increases the risk of bacterial resistance, the incidence of drug-related adverse events, and therapeutic costs.

A number of attempts have been made to differentiate viral and bacterial infections, and rationalise antibiotic use by means of easily determined biomarkers.[9–14] Those based on serum procalcitonin (PCT) levels have recently aroused considerable interest because preliminary data demonstrate that, also in children, PCT concentrations markedly increase in the presence of bacteremic infection (including CAP), and are more useful than C-reactive protein (CRP) and interleukin-6 levels or white blood cell (WBC) counts in distinguishing bacterial from viral CAP.[11–16] On the basis of these data, it was thought that determining PCT levels may predict bacteremic CAP as a mean of severity, make it easier to identify the patients for whom antibiotic prescription is really mandatory and guide the duration of antibiotic administration.[17] Some studies found a severity-dependent increase in serum PCT, with the highest levels (significantly different from those found in viral cases) being observed in cases of severe invasive bacterial CAP.[17,18] It has been shown that the use of PCT-guided therapy markedly reduces antibiotic prescriptions in adults with lower respiratory tract infections without affecting clinical outcomes[19–26]; however, differently from experience performed in adults, no precise cut-off PCT concentration capable of guiding antibiotic administration in children with CAP has ever been established. Furthermore, as sometimes only a very small number of patients had PCT levels considered useful for differentiating viral and bacterial CAP, it has even been concluded that PCT levels are not very useful when making therapeutic choices.[15,16]

The aim of this study was to evaluate the use of an algorithm based on a PCT cut-off value as a means of guiding the management of antibiotic therapy in hospitalised children with uncomplicated CAP.

Materials and methods

Study design

This prospective, single-centre randomised study consecutively enrolled children with CAP who were hospitalised in the Department of Maternal and Pediatric Sciences of the University of Milan, Milan, Italy. The enrolled children were randomised to receive antibiotics on the basis of a PCT algorithm (PCT group) or in accordance with evidence-based guidelines (control group), according to previous experience performed in adults with CAP.[19–26] The protocol was approved by the Ethical Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, and written informed consent was obtained from both parents or the legal guardian of each child.

Study patients

Fig. 1 shows the trial flow chart. Between October 2008 and September 2010, 419 children with CAP were hospitalised in the Department and assessed for eligibility. The criteria for participating in the study included all of the following: an age of >1 month and <14 years; a diagnosis of CAP made on the basis of clinical signs and symptoms (i.e. a history of fever or cough, tachypnea, dyspnea or respiratory distress, and breathing with grunting or wheezing sounds with rales) and confirmed by chest radiography (i.e. the presence of pulmonary infiltration or segmental or lobar consolidation); no demonstrable complications (i.e. pleural effusion, empyema, lung necrosis, pneumatocele). Children were also excluded if they had received antibiotics in the 10 days preceding admission or if they were suffering from an underlying chronic disease (i.e. anatomic abnormalities of the respiratory tract, immunological deficits, progressing neurological conditions, psychomotor retardation, congenital heart disease, hemoglobinopathy), severe malnutrition or other concurrent infections. The radiological readings were always made by the same pediatric radiologist who was blinded to the clinical information. Moreover, no microbiological evaluation was performed in agreement with what usually happens in routinary pediatric practice (i.e., antimicrobial therapy for pediatric CAP is chosen on the basis of epidemiologic data and guidelines considering the limitations in obtaining an adequate sample for appropriate and comprehensive microbiological evaluation).

The demographic, clinical history and physical examination data were recorded in a previously prepared electronic chart together with the results of the laboratory tests and chest radiography. Fever was defined as an axillary temperature of >37.5 °C, and tachypnea on the basis of the World Health Organisation criteria.[27] CAP severity was assessed using the pediatric criteria of the British Thoracic Society.[28]

Study protocol

The patients were randomised to the PCT or control group using a previously prepared computer-generated randomisation list and sealed envelope. Antibiotics were not administered to the children with admission PCT levels of <0.25 ng/mL, but were immediately given in the case of higher values. The untreated children were given antibiotics only if their PCT levels increased to ≥ 0.25 ng/mL, and continued the therapy until the levels had returned to this value. The children who received antibiotics from the time of admission were treated until their PCT levels were >0.25 ng/mL, and resumed antibiotics only if their PCT levels subsequently increased to more than this value.

The Italian Society of Pediatrics (SIP) guidelines for the management of pediatric CAP were used when choosing the antibiotic regimen.[29] In the case of mild CAP, these guidelines recommend the use of oral amoxicillin for children

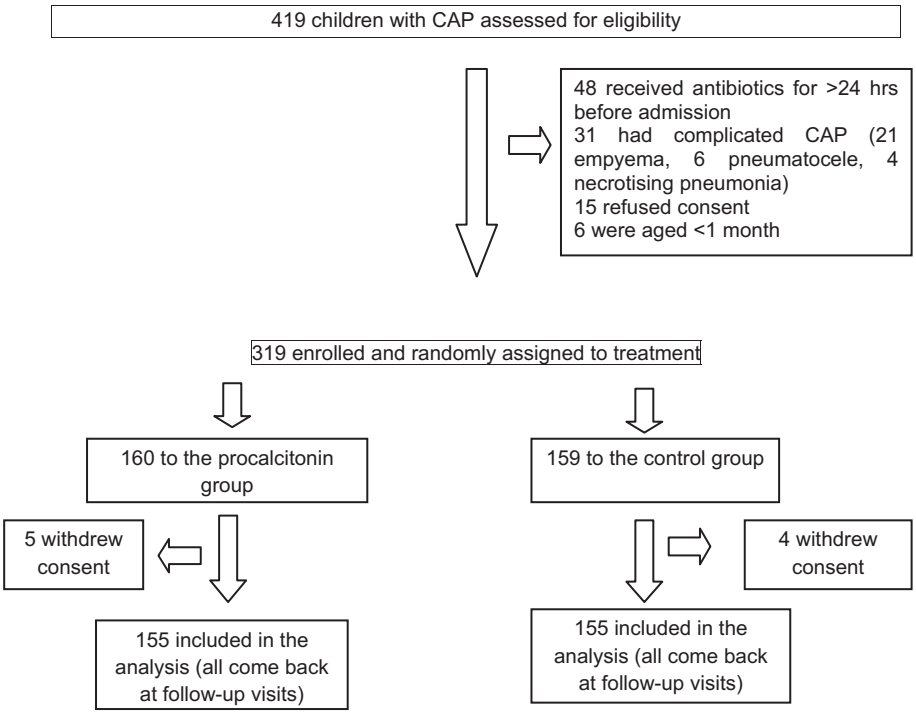


Figure 1 Study flow chart.

aged <4 years and oral clarithromycin for those aged ≥ 4 years; in severe cases regardless of age, the recommended treatment is oral amoxicillin-clavulanate or intravenous (i.v.) cefotaxime plus oral or i.v. clarithomycin.

The children in the control group were always treated in accordance with the SIP guidelines: antibiotic monotherapy chosen on the basis of age if mild; combined beta-lactam and macrolide therapy if severe. The duration of administration in the control group was that recommended by the SIP (i.e. 7—14 days depending on disease severity).

All of the patients were clinically reassessed every day during hospitalisation. Untreated children showing no reduction in the clinical signs and symptoms of disease after three days could be treated with antibiotics regardless of their PCT levels. Moreover, in the case of severe clinical deterioration and regardless of their PCT levels, the children in both groups could be treated with antibiotics (if previously untreated) or their treatment could be modified on the basis of their pediatrician's judgment.

The children were discharged when they had been fever-free for 48 h, their vital signs had been stable for 24 h, and they had returned to their pre-admission status. Upon discharge, the parents were given a leaflet providing general trial information for their primary care pediatricians, and all were instructed to return to the hospital for check-ups 14 ± 2 and 28 ± 3 days after admission or in the case of any new episode of fever with respiratory symptoms. At these follow-up visits, they were evaluated by a blinded researcher (CT) who defined the outcome. Children were considered definitively cured when no respiratory sign and symptom were found at the control visit. Recurrence was defined as the reappearance of respiratory signs and symptoms at the control visit. Adverse events potentially derived from antibiotic use (i.e., abdominal pain, vomiting, diarrhea, skin eruptions) were daily monitored in all the children receiving these drugs during the period of their administration and in the five days after. For each of them, the total duration in days of persistence and the need for specific drug administration was registered.

All of the clinical and laboratory data collected during the hospital stay and follow-up were recorded in the same electronic chart in which the admission data were recorded.

Serum PCT measurements

PCT was measured using a rapid and sensitive immunoassay with a functional sensitivity of 0.06 ng/mL (KryptornPCT, Brahms, Henningsdorf, Germany). The coefficients of variation at concentrations of 0.1 ng/mL, 0.25 ng/mL, 0.5 ng/mL and 10 ng/mL were respectively 16%, 7%, 5% and 3%.

The blood samples for measuring serum PCT were taken as early as possible, typically upon admission or at most within 6 h of admission, and the results were available 60 min later. PCT levels were measured every two days until discharge, and during the two follow-up visits. The analyses were made by the validated laboratory of the Department of Maternal and Pediatric Sciences of the University of Milan.

Statistical analysis

Pre-study power calculations (with 90% power) showed that 76 patients in each group were necessary to detect a 15% lower antibiotic use, considering that 100% of children hospitalized for CAP were treated with antibiotics and assuming a two-tailed test and a 5% level of significance.

Since we planned to analyse the data in subgroups of mild and severe CAP, we doubled the number of patients per group ($n = 152$). Thus, we decided to enrol 160 patients in each group to allow for a 5% drop-out subject. The discrete variables were expressed as absolute numbers (percentages), and the continuous variables as mean values ± standard deviation (SD), unless stated otherwise. The comparability of the treatment groups group was analysed using the Fisher's exact test, the chi-square test, a two-sample *t*-test or the non-parametric Mann–Whitney *U*-test, as appropriate. A double-sided *p* value of <0.05 was considered significant. The statistical analyses were made using SAS software for Windows v. 9.1 (SAS Institute, Cary, NC, USA). The authors kept and analysed all of the data.

Results

Of the children assessed for eligibility, 48 had received antibiotics in the 10 days preceding admission, 31 had complicated CAP (21 pleural effusion or empyema, six pneumatocele, and four necrotising CAP), six were aged <1 month, and the parents of 15 refused to sign the informed consent form. Consequently, 319 children were enrolled and randomly assigned 1:1 to the treatment groups but, as consent was withdrawn during the study in nine cases (five in the PCT group and four in the control group), the final analysis was based on 310 children (155 per group). All the 310 children came to the follow-up visits 14 ± 2 and 28 ± 3 days after admission. Table 1 shows the demographic characteristics of the analysed children. The two groups were comparable in terms of gender, mean age, race, the mean number of respiratory infections (including CAP) in their history, the number of antibiotic courses in the previous six months, urban residence, the number of siblings, the duration of breast-feeding, exposure to cigarette smoke, child-care attendance, history of allergy, previous hospitalisations, and previous vaccinations against pneumococcal infections and influenza. Table 2 shows the clinical, laboratory and radiographic findings upon admission. More than half of the children in both groups had a temperature of >38.5 °C, and a peripheral oxygen saturation (SpO_2) in room air of 92% or slightly higher. Consequently, the CAP was classified as severe in 79 patients in PCT group (50.9%) and 76 in the control group (49.0%). The mean CRP, WBC, neutrophil percentage and PCT values were similar in the two groups. PCT levels were <0.25 ng/mL in 24 of the children in the PCT group (15.5%) and 29 of those of the control group (18.7%). The radiographic findings were also similar in the two groups.

Fig. 2 shows the data regarding antibiotic administration by randomisation group and CAP severity. Twenty-four children in the PCT group (15.5%: 21 [87.5%] with mild CAP and three [12.5%] with severe CAP) were never treated with antibiotics because their PCT concentrations were <0.25 ng/mL until discharge. They did not experience any respiratory problems during follow-up and were considered completely cured at the control visits. Among the 131 children in the PCT group who received antibiotic therapy, PCT monitoring led to its discontinuation after two days in two cases (1.5%), after four days in six (4.6%), after six days in 49 (37.4%) and after eight days in 61 (46.6%); only 10 children (11.5%) received antibiotics for more than eight days, one of whom (with severe CAP) continued for 14 days. In three cases (2.3%), the discontinuation of antibiotic treatment after four days was followed by an increase in PCT values to ≥0.25 ng/mL (respectively 0.50, 0.75 and 0.90). These children, who had persistent respiratory symptoms, therefore resumed antibiotic therapy, which was stopped on day 10 in all cases when their PCT levels had returned to <0.25 ng/mL and they had clinically improved. On the contrary, all of the 155 controls received

Table 1 Demographic characteristics of the study children upon admission.

	Procalcitonin group ($n = 155$)	Controls ($n = 155$)
No. of males (%)	85 (54.8)	88 (56.8)
Mean age ± SD, yrs	4.31 ± 3.76	4.67 ± 3.96
<4 yrs, No. (%)	76 (49.0)	74 (47.7)
≥4 yrs, No. (%)	79 (51.0)	81 (52.3)
Caucasians, No. (%)	139 (89.7)	143 (92.3)
Mean number of respiratory infections in previous 12 months ± SD	2.97 ± 1.85	2.63 ± 1.79
Patients with a history of CAP, No. (%)	9 (5.8)	6 (3.9)
Mean number of antibiotic courses in previous 6 months ± SD	1.88 ± 0.67	1.52 ± 0.64
Urban residence, No. (%)	152 (98.1)	155 (100.0)
At least one older sibling, No. (%)	61 (39.4)	57 (36.8)
Breast-feeding ≥3 months, No. (%)	91 (58.7)	96 (61.9)
Exposure to cigarette smoke, No. (%)	39 (25.2)	33 (21.3)
Full-time child-care attendance,[a] No. (%)	133 (85.8)	128 (82.6)
History of allergy, No. (%)	22 (14.2)	18 (11.6)
Hospitalisations in previous 3 months, No. (%)	1 (0.6)	1 (0.6)
Vaccinated with heptavalent pneumococcal conjugated vaccine, No. (%)	52 (33.5)	58 (37.4)
Vaccinated with influenza vaccine, No. (%)	9 (5.8)	11 (7.1)

CAP: community-acquired pneumonia; SD: standard deviation.
[a] 5–6 days/week, 6–8 h/day. No significant between-group difference.

Table 2 Clinical, laboratory and radiographic findings upon admission.

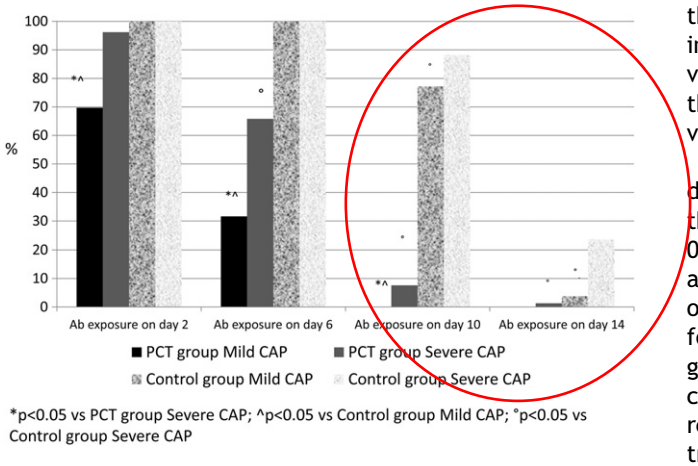
	Procalcitonin group (n = 155)	Controls (n = 155)
Clinical findings, mean value ± SD		
Axillary temperature, peak day value (°C)	38.8 ± 0.85	38.6 ± 0.96
SpO_2 in room air, %	91 ± 4	92 ± 5
Laboratory findings, mean value ± SD		
CRP, mg/dL	8.8 ± 4.7	7.1 ± 3.9
WBC, cells/μL	16,300 ± 4250	15,155 ± 6140
Neutrophils, %	76 ± 14	67 ± 19
PCT, ng/mL	1.82 ± 1.76	1.79 ± 1.88
Positive blood cultures, No. (%)	2 (1.3)	1 (0.6)
Radiographic findings, No. (%)		
Reticulonodular infiltrate	55 (35.5)	60 (38.7)
Segmental or lobar consolidation	61 (39.3)	58 (37.4)
Bilateral consolidation	39 (25.2)	37 (23.9)

CRP: C-reactive protein; PCT: procalcitonin; SD: standard deviation; SpO_2: peripheral oxygen saturation; WBC: white blood cell count. No significant between-group difference.

antibiotics for at least seven days, 128 (82.6%) for 10 days, 39 (25.2%) for 12 days, and 21 (13.5%) for 14 days. The between-group differences in both the rate and duration of antibiotic exposure was statistically significant ($p < 0.05$).

Table 3 shows the data regarding outcomes by randomisation group and CAP severity. The evolution of CAP was similar in the two groups, as shown by the duration of fever, oxygen therapy and hospitalisation; the number of respiratory problems during the follow-up and the incidence of recurrences were also quite similar. One child in the PCT group (0.6%) and six (3.9%) in the control group were brought to the Department 2–3 weeks after discharge because of persistent cough, and all were diagnosed as having acute bronchitis; their PCT levels were always <0.25 ng/mL. The child in the PCT group and four of the controls were treated with antibiotics. All were considered cured at the time of the final visit 28 days after admission.

Possibly or probably antibiotic-related adverse events were significantly more frequent among the control group than in the PCT group (25.2% *vs* 3.9%; $p < 0.05$) regardless of CAP severity. The most frequent adverse event in both groups was diarrhea registered in about 70% of the children who experienced signs and symptoms potentially due to antibiotic administration in both groups. None of the study children discontinued antibiotic administration because of an adverse event and none received any therapy to face these problems.



*p<0.05 vs PCT group Severe CAP; ^p<0.05 vs Control group Mild CAP; °p<0.05 vs Control group Severe CAP

Figure 2 Antibiotic (Ab) exposure by treatment group and CAP severity.

Discussion

In most of the pediatric CAPs, particularly in those with mild to moderate signs and symptoms, etiology of the disease is not routinely performed because methods to identify the infecting agent(s) are generally unreliable in children or, when able to give correct information, too invasive to be ethically acceptable. Consequently, because CAP can have a rapid negative evolution, almost all the children receive an antibiotic treatment even when the disease could be due to viruses. However, because an excessive use of antibiotics can lead to negative consequences, methods to rationalize antibiotic treatment of pediatric CAP are considered mandatory. This is the first prospective study using an algorithm based on a PCT cut-off value to guide antibiotic therapy in children with CAP of unknown etiology, and the results show that this approach can significantly reduce antibiotic use and antibiotic-related adverse events.

The cut-off value of 0.25 ng/mL was the same as that used in some adult clinical trials to select subjects with lower respiratory tract infections in whom antibiotic administration was to be strongly discouraged or recommended.[23–25] As in these trials, our findings demonstrated that the algorithm based on a PCT level of 0.25 ng/mL was not inferior to the clinical guidelines for pediatric CAP therapy in terms of clinical outcomes, and was more effective in reducing antibiotic exposure and antibiotic-related adverse events. A number of studies have shown that only PCT values of between 0.5 and 2 ng/mL are useful in differentiating viral and bacterial CAP[10–12,15]; lower values are not sufficiently sensitive and specific because of the significant overlap of data collected from children with viral, bacterial or mixed infection.

However, our data seem to overcome the problem of the differentiation of viral from bacterial infections because that they clearly suggest that a PCT cut-off value of 0.25 ng/mL can be useful in separating the cases of pediatric CAP that, regardless of etiology, do not need antibiotic treatment or, even if due to bacteria, can be treated for a shorter time than that usually recommended by the guidelines. The use of the algorithm allowed 15% of the children to avoid antibiotics altogether, and significantly reduced the duration of administration in most of the cases treated upon admission, without any increased risk of a negative evolution even in severe cases. None of the untreated children experienced any recurrence of CAP or

Table 3 Outcomes by treatment group and CAP severity.

Variables	Procalcitonin group ($n = 155$)		Control group ($n = 155$)	
	Mild CAP ($n = 76$)	Severe CAP ($n = 79$)	Mild CAP ($n = 79$)	Severe CAP ($n = 76$)
Duration of fever, mean days ± SD	2.01 ± 1.76	2.88 ± 2.01	2.16 ± 1.96	2.52 ± 2.22
Duration of oxygen therapy, mean days ± SD	0	3.4 ± 1.99	0	3.88 ± 1.58
Length of hospital stay, mean days ± SD	4.7 ± 2.88	5.01 ± 2.43	5.61 ± 1.99	5.93 ± 1.70
Outcomes on day 28 ± 3				
Recurrence of respiratory symptoms, No. (%)	0 (0.0)	1 (1.3)	2 (2.5)	4 (5.3)
New antibiotic prescription, No. (%)	0 (0.0)	1 (1.3)	1 (1.3)	3 (3.9)
Antibiotic-related adverse effects, No. (%)	1 (1.3)^	5 (6.3)°	18 (22.7)	21 (27.6)

CAP: community-acquired pneumonia; n.a.: not applicable; SD: standard deviation. *$p < 0.05$ *vs* severe CAP in procalcitonin group; ^$p < 0.05$ *vs* mild CAP in control group; °$p < 0.05$ *vs* severe CAP in control group. No other significant between-group difference.

respiratory symptoms in the following weeks, and the three who resumed antibiotics after discontinuation because of slight increases in their PCT levels did not show any clinical deterioration. Furthermore, regardless of disease severity, the outcomes in the children in the PCT group who were treated with antibiotics were substantially positive and no different from those of the children who received antibiotics for longer in accordance with the Italian guidelines.

Fewer antibiotic prescriptions to treat respiratory infections have a number of advantages for patients and society as a whole. As found in this study, the incidence of antibiotic-related adverse events is significantly reduced, but so is the cost of treatment and the potential risk of the emergence of bacterial resistance. All of these positive consequences have been recorded in adult studies[19–26] but, given the frequency of respiratory tract infections in the first years of life[30] and the present recommendations for the treatment of CAP in children,[1,6,28,29,31,32] it is possible that they may be even more significant in pediatrics. With very few exceptions, most experts suggest systematically administering antibiotics in all cases of CAP because of the difficulty in identifying its etiology in young and uncooperative patients.[1,6,28,29,31,32] Moreover, although not precisely defined, the recommended duration of administration is never less than seven 7 days even in mild cases.[1,6,28,29,31,32]

Further studies are needed before this PCT-based algorithm can be used in everyday practice. Our trial involved a relatively small number of children, all of whom had uncomplicated CAP. Consequently, it is underpowered to evaluate the safety of this algorithm approach when used in children with more severe disease or in patients suffering from bacterial CAP due to pathogens with lower sensitivity to commonly used antibiotics. It was also conducted in a hospital, where the monitoring of disease outcomes is continuous and significantly closer than is possible in a community setting. We did not assess whether the PCT-guided approach to pediatric CAP can be used by the primary care pediatricians who diagnose and treat the majority of cases, and where the near-patient test for PCT determination at the moment available can be easily performed. Some adult studies have clearly shown that general practitioners are usually reluctant to use repeat blood sampling,[21] and unwilling to avoid antibiotic therapy or reduce the duration of administration in patients with CAP.[22] However, on the basis of our results, it is reasonable to believe that the introduction of a PCT-based algorithm may be extremely useful in managing pediatric CAP in the community as well as in hospitals.

Conflict of interest

The authors have no potential conflict of interest to declare.

Acknowledgement

This study was supported by the Italian Ministry of Health (Bando Giovani Ricercatori 2007).

References

1. Principi N, Esposito S. Management of severe community-acquired pneumonia of children in developing and developed countries. *Thorax* 2010 [Epub Oct 21].
2. Cilla G, Oñate E, Perez-Yarza EG, Montes M, Vicente D, Perez-Trallero E. Viruses in community-acquired pneumonia in children aged less than 3 years old. High rate of viral coinfection. *J Med Virol* 2008;**890**:1843–9.
3. Cevey-Macherel M, Galetto-Lacour A, Gervaix A, Siegrist CA, Bille J, Bescher-Ninet B, et al. Etiology of community-acquired pneumonia in hospitalized children based on WHO clinical guidelines. *Eur J Pediatr* 2009;**168**:1429–36.
4. Isaacs D. Problems in determining the etiology of community-acquired childhood pneumonia. *Pediatr Infect Dis J* 1989;**8**: 143–8.
5. Esposito S, Blasi F, Bellini F, Allegra L. Principi N and the Mowgli study group. Characteristics of Mycoplasma pneumoniae and Chlamydia pneumoniae infections in children with pneumonia. *Eur Resp J* 2001;**17**:241–5.
6. Principi N, Esposito S. Paediatric community-acquired pneumonia: current concepts in pharmacological control. *Expert Opin Pharmacother* 2003;**4**:761–77.
7. Esposito S, Blasi F, Allegra L. Principi N and the Mowgli Study Group. Use of antimicrobial agents for community-acquired lower respiratory tract infections in hospitalised children. *Eur J Clin Microbiol Infect Dis* 2001;**20**:647–50.

8. Nascimento-Carvalho CM. Pharmacotherapy of childhood pneumonia. *Expert Opin Pharmacother* 2010;**11**:225—31.
9. Nohynek H, Valkeila E, Leinonen M, Eskola J. Erythrocyte sedimentation rate, white blood cell count and serum C-reactive protein in assessing etiologic diagnosis of acute lower respiratory infections in children. *Pediatr Infect Dis J* 1995;**14**: 484—90.
10. Korppi M, Heikanen-Kosma T, Leinonen M. White blood cells, C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children. *Eur Resp J* 1997;**10**:1125—9.
11. Toikka P, Irjala K, Juvén T, Virkki R, Mertsola J, Leinonen M, et al. Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. *Pediatr Infect Dis J* 2000;**19**:598—602.
12. Gendrel D, Raymond J, Coste J, Moulin F, Lorrot M, Guerin S, et al. Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs viral infections. *Pediatr Infect Dis J* 1999;**18**: 875—81.
13. Moulin F, Raymond J, Lorrot M, Marc E, Coste J, Iniguerz J, et al. Procalcitonin in children admitted to the hospital with community acquired pneumonia. *Arch Dis Child* 2001;**84**: 332—6.
14. Khan DA, Rahman A, Khan FA. Is procalcitonin better than C-reactive protein for early diagnosis of bacterial pneumonia in children? *J Clin Lab Anal* 2010;**24**:1—5.
15. Korppi M, Remes S, Heiskanen-Kosma T. Serum procalcitonin concentrations in bacterial pneumonia in children: a negative result in primary healthcare settings. *Pediatr Pulmonol* 2003; **35**:56—61.
16. Korppi M, Remes S. Serum procalcitonin in pneumococcal pneumonia in children. *Eur Respir J* 2001;**17**:623—7.
17. Krüger S, Ewig S, Papassotiriou J, Kunde J, Marre R, von Baum H, et al. CAPNETZ Study Group. Inflammatory parameters predict etiologic patterns but do not allow for individual prediction of etiology in patients with CAP: results from the German competence network CAPNETZ. *Respir Res* 2009;**10**: 65.
18. Müller F, Christ-Crain M, Bregenzer T, Krause M, Zimmerli W, Mueller B, et al. ProHOSP Study Group. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. *Chest* 2010;**138**:121—9.
19. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004;**363**:600—7.
20. Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, et al. Müller B for the ProHOSP study group. Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. *BMC Health Serv Res* 2007;**7**:102.
21. Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, et al. Procalcitonin-guided antibiotic vs standard approach for acute respiratory tract infections in primary care. *Arch Intern Med* 2008;**168**:2000—7.
22. Kristoffersen KB, Søgaard OS, Wejse C, Black FT, Greve T, Tarp B, et al. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission — a randomized trial. *Clin Microbiol Infect* 2009;**15**:481—7.
23. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections. The ProHOSP randomized controlled trial. *JAMA* 2009;**302**:1059—66.
24. Schuetz P, Batschwaroff M, Dusemond F, Albrich W, Bürgi U, Maurer M, et al. Effectiveness of a procalcitonin algorithm to guide antibiotic therapy in respiratory tract infections outside of study conditions: a post study survey. *Eur J Clin Microbiol Infect Dis* 2010;**29**:269—77.
25. Burkhardt O, Ewig S, Haagen U, Giersdorf S, Hartmann O, Wegscheider K, et al. Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection. *Eur Respir J* 2010;**36**:601—7.
26. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. PRORATA trial group. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010;**375**:463—74.
27. World Health Organization. *Pocket book of hospital care of children. Guidelines for the management of common illnesses with limited resources*. WHO Press; 2005. pp. 72—81.
28. British Thoracic Society. Standards of Care Committee. British Thoracic Society guidelines for the management of community acquired pneumonia in childhood. *Thorax* 2002;**57**(Suppl. 1): i1—24.
29. Ranganathan SC, Sonnappa S. Pneumonia and other respiratory infections. *Pediatr Clin North Am* 2009;**56**:135—56.
30. Esposito S, Principi N. Emerging resistance to antibiotics against respiratory bacteria: impact on therapy of community-acquired pneumonia in children. *Drug Res Up* 2002;**5**:73—87.
31. McIntosh K. Community-acquired pneumonia in children. *N Engl J Med* 2002;**346**:429—37.
32. Atkinson M, Yanney M, Stephenson T, Smyth A. Effective treatment strategies for paediatric community acquired pneumonia. *Expert Opin Pharmacother* 2007;**8**:1091—101.