

Is serum procalcitonin a reliable diagnostic marker in children with acute respiratory tract infections? A retrospective analysis

Heike Schützle · Johannes Forster ·
Andrea Superti-Furga · Reinhard Berner

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Abstract

Introduction Acute respiratory tract infections (ARI) in children are often treated with antibiotics even without evidence of bacterial infection. Serum procalcitonin (PCT) is elevated in bacterial but not in viral infections.

Patients and methods We performed a retrospective analysis of children in the PID-ARI.net study on respiratory infections to address the question of whether plasma PCT could potentially distinguish between bacterial infections requiring antibiotic therapy and viral ARI. We analysed data on 327 children who had been included in the German PID-ARI.net study and in whom nasopharyngeal aspirates had been analysed with a 19-valent multiplex reverse transcription-polymerase chain reaction–enzyme-linked immunosorbent assay for viral and atypical bacterial pathogens. Serum PCT was determined using a quantitative immunoassay (BRAHMS Kryptor PCTsensitive, Henningsdorf, Germany). We then focussed specifically on those children who were treated with antibiotics and therefore had been suspected of having bacterial infection but who had a serum PCT level lower than 0.1 ng/ml.

Results Out of 327 children, 132 had serum PCT levels below 0.1 ng/ml. Of these 132, 38 children had been treated with antibiotics. After exclusion of 26 patients (with critical illnesses, antibiotics on admission or for reasons other than ARI), 12 children remained for further evaluation. Of these

12 children, four had atypical pneumonia; four others had positive virus testing, and, in the last four, the aetiology of ARI remained unknown; evidence of bacterial infection could not be detected in any.

Conclusions Taken the results of this retrospective analysis, serum PCT values below 0.1 ng/ml might be a marker to identify children with acute respiratory tract infection in whom antibiotic treatment could be withheld. However, only a prospective intervention trial will prove the general safety of this limit.

Keywords Respiratory tract infection · Children · Procalcitonin · Antibiotic treatment

Introduction

Acute respiratory tract infections (ARI) account for the majority of antibiotic prescriptions in children. In most cases, however, antibiotics are given without clear evidence of clinically significant bacterial infection. The bacterial organism is isolated and identified as the causative agent in a minority of cases only. Several studies have shown that procalcitonin (PCT), a prohormone of calcitonin (normally produced by thyroid C cells), is elevated in bacterial infections but remains low in viral infections [9, 19, 21, 24]. As known so far, bacterial endotoxins are the main stimulus for PCT induction [6, 13]. Christ-Crain et al. [4] have shown recently that a PCT-guided therapeutic strategy in adult patients with lower respiratory tract infections can substantially and safely reduce antibiotic use. These promising results have been confirmed in further intervention trials by the same authors in patients with community-acquired pneumonia and chronic obstructive pulmonary disease [5, 25]. The aim of this retrospective analysis was

H. Schützle · A. Superti-Furga · R. Berner (✉)
Department of Paediatrics and Adolescent Medicine,
University Medical Center Freiburg,
Mathildenstrasse 1,
79106 Freiburg, Germany
e-mail: reinhard.berner@uniklinik-freiburg.de

J. Forster
Department of Paediatrics St. Hedwig, St. Josef's Hospital,
Freiburg, Germany

to evaluate the potential of PCT in distinguishing bacterial infections—or, more specifically, those needing antibiotic treatment—from viral respiratory tract infections in paediatric patients. The analysis was performed on data of the *PID-ARI.net* study, a comprehensive epidemiological study on acute respiratory tract infections in Germany [27].

Based on existing literature on serum PCT and infections, we hypothesised for this study that a PCT serum concentration of <0.1 ng/ml indicated absence of bacterial disease. A PCT concentration of ≥ 0.25 ng/ml, however, was considered suspect for bacterial infection [4]. We focussed on patients with PCT values of <0.1 ng/ml who were treated with antibiotics and thus, obviously, had been considered as suffering from bacterial infection. All patients not treated with antibiotics and recovering uneventfully were deemed to have had viral infections or self-limiting bacterial ARI. Severely immunocompromised individuals, e.g. children undergoing chemotherapy, stem cell or organ transplant recipients as well as children with an immunodeficiency syndrome, were primarily excluded. We also excluded neonates as several studies have shown higher reference values in this collective, especially within the first 48 h [3, 17]. Patients with other critical underlying conditions (such as with congenital cardiac defects) were excluded as, in these patients, antibiotic treatment is initiated more generously even without clear evidence for bacterial infection. Additionally, we did not take into account patients who had received antimicrobial therapy prior to admission since PCT concentration may decrease rapidly in successfully treated bacterial infection [1, 12]. Finally, we excluded children who were treated with antibiotics for reasons other than lower respiratory tract infections (e.g. urinary tract infection).

By evaluating retrospectively the clinical status, course of disease, laboratory markers (e.g. C-reactive protein (CRP)) and microbiological and if available radiographic findings, we analysed whether the above-mentioned PCT cutoff levels are reliable for paediatric patients with ARI and therefore could be used without risk in an intended prospective intervention trial.

Patients and methods

From August 2004 to October 2006, a total of 1,154 nasopharyngeal aspirates and tracheal secretions were collected from paediatric patients presenting in the emergency room at the University Children's Hospital Freiburg, Germany, with clinical signs of ARI. Only few samples were included from patients already hospitalised for more than 72 h with secondary onset of respiratory illness. Specimens were tested by a 19-valent multiplex reverse transcription (RT)-polymerase chain reaction (PCR)-enzyme-linked assay for 13

viral and four atypical bacterial pathogens [27]. Bacteriologic findings of nasopharyngeal aspirates were not evaluated as in most cases it is impossible to decide whether a positive culture represents either colonisation or significant infection, especially in young children.

In 327 of the study patients (aged 1 month to 17 years, mean age 22 months; 189 boys and 138 girls), serum samples (obtained on admission or at the time of respiratory sample collection) for retrospective PCT measurement were available. These serum samples were left after routine diagnostics. Serum had been stored for up to a maximum of 3 months at -20°C until analysed. PCT testing was performed with a time-resolved amplified cryptate emission technology assay (BRAHMS Kryptor PCTsensitive, Henningsdorf, Germany). This assay has a functional assay sensitivity of 0.06 ng/ml. Further diagnostic workup including chest radiograph had been performed at the discretion of the attending physician.

Results

Serum PCT concentration was tested in a total of 327 patients. For overall and detailed results, see Table 1. PCT values <0.1 ng/ml were found in 132 patients (132/327; 40.4%). In 86 of these 132 patients, multiplex RT-PCR revealed at least one virus (65.2%). Rhinovirus was the most common pathogen, found in 52 cases (60.5%), followed by respiratory syncytial virus (RSV) and adenovirus in 18 and 16 (20.9% and 18.6%) cases, respectively; 22 samples were tested positive for two or more viruses (data not shown). Pneumonia was diagnosed by chest radiography in 40 patients (40/132; 30.3%); 20 had bronchopneumonia; 15 had lobar pneumonia and five had atypical pneumonia. CRP values of ≤ 40 mg/l were found in 90.2% of these samples (119/132). A CRP of ≤ 40 mg/l has been considered previously as indicative for non-bacterial ARI [13]. Nasopharyngeal aspirates were positive for *Bordetella pertussis* in three children. All six children with atypical pathogens in nasopharyngeal specimen (in five cases *Mycoplasma pneumoniae*, in one case *Chlamydia pneumoniae*) had PCT values <0.1 ng/ml.

We then examined the 38 patients with a PCT <0.1 ng/ml who received antibiotic treatment. After exclusion of five patients who were treated with antibiotics for other reasons (e.g. urinary tract infection), 17 patients who had already started with antibiotics prior to admission and of four children with chronic illnesses (see Table 4), 12 patients remained. As Table 2 shows, all 12 patients had a positive chest radiography for pneumonia. Four patients were diagnosed with atypical pneumonia, either radiologically or microbiologically or both. Seven patients had positive virus testing. Two patients with positive virus and atypical

Table 1 Results and diagnostic parameters for all patients and divided on the basis of PCT value (column 3 includes results of column 2 and column 4 those of column 5)

	1 All patients	2 PCT <0.1 ng/ml	3 PCT <0.25 ng/ml	4 PCT ≥0.25 ng/ml	5 PCT ≥0.5 ng/ml
<i>n</i>	327	132 (40.4%)	225 (68.8%)	102 (31.2%)	63 (19.3%)
Male/female	189/138	74/58	132/93	57/45	31/32
Positive virus testing ^a	213 (65.1%)	86 (65.2%)	149 (66.2%)	64 (62.7%)	34 (54%)
RSV	50 (23.5%)	18 (20.9%)	33 (22.1%)	16 (25%)	9 (26.5%)
Adenovirus	42 (19.7%)	16 (18.6%)	27 (18.1%)	14 (21.9%)	9 (26.5%)
Rhinovirus	112 (52.6%)	52 (60.5%)	84 (56.4%)	27 (42.2%)	14 (41.2%)
hMPV	15 (7.0%)	5 (5.8%)	10 (6.7%)	3 (4.7%)	3 (8.8%)
Enterovirus	27 (12.7%)	11 (12.8%)	20 (13.4%)	7 (10.9%)	5 (14.7%)
Parainfluenza virus 1–4	12 (5.6%)	5 (5.8%)	9 (6.0%)	3 (4.7%)	0
Influenza virus A + B	18 (8.5%)	7 (8.1%)	12 (8.1%)	6 (9.4%)	3 (8.8%)
Coronavirus	7 (3.3%)	3 (3.5%)	8 (5.4%)	2 (3.1%)	1 (2.9%)
Chest radiography completed	254 (77.7%)	94 (71.2%)	173 (76.5%)	81 (79.4%)	51 (81%)
Infiltrate	124 (37.9%)	40 (30.3%)	74 (32.9%)	50 (49%)	38 (60.3%)
Lobar pneumonia	54 (43.5%)	15 (37.5%)	30 (40.5%)	24 (48%)	19 (50%)
Bronchopneumonia	62 (50%)	20 (50.0%)	38 (51.4%)	24 (48%)	17 (44.7%)
Atypical pneumonia (PCR-positive in one case)	8 (6.5%)	5 (12.5%)	6 (8.1%)	2 (4%)	2 (5.1%)
CRP ≤40 mg/l	253 (77.4%)	119 (90.2%)	201 (89.3%)	52 (51%)	26 (41.3%)
Median (mg/l)		7	8	36	80
Mean (mg/l)		13,5	15,6	63,6	83,3
Min/max (mg/l)		3/84	3/133	3/260	3/260
Positive blood culture	10	4	6	4	3
<i>Corynebacterium</i> spp.	1	1	1		
<i>Staphylococcus aureus</i>	1	1	1		
<i>Haemophilus influenzae</i>	1		1		
<i>Streptococcus pneumoniae</i>	2			2	2
<i>Salmonella enteritidis</i>	1			1	1
Coagulase-negative <i>Staphylococci</i>	4	2	3	1	
Antibiotic treatment ^b	128 (39.1%)	38 (28.8%)	74 (32.9%)	54 (52.9%)	38 (60.3%)
Atypical pathogen (PCR) ^c	6	6	6	–	–
<i>B. pertussis/parapertussis</i>	5	3	4	1	1

^aRespiratory syncytial virus (RSV), adenovirus, enterovirus, rhinovirus, parainfluenza virus types 1–4, influenza virus A/B, human metapneumovirus (hMPV), coronavirus

^bContinuation or beginning of antibiotic treatment

^c*Mycoplasma (M.) pneumoniae* (five cases), *Chlamydomphila (C.) pneumoniae* (one case), *Legionella pneumophila* (no case)

pathogen testing were classified as suffering from atypical infections. In another four patients, aetiology stayed unknown. CRP was ≤40 mg/l in 11 cases and 43 mg/l in one case. In one patient, blood culture was positive for coagulase-negative staphylococci. As far as one can tell from retrospective analysis of patients' charts, neither the clinical course nor the diagnostic parameters mentioned above revealed signs of a bacterial infection requiring antimicrobial therapy in any of these 12 children.

PCT serum concentrations of <0.25 ng/ml were detected in 225 samples (225/327; 68.8%). Concerning positive virus testing, CRP values, chest radiograph findings or the number of patients treated with antibiotics, results were comparable to the subgroup of 132 samples with a PCT of <0.1 ng/ml (see Table 1 for detailed results). A total of 74 patients received

antibiotic treatment (74/225; 32.9%). After exclusion of 42 patients according to the criteria mentioned above, 32 children remained for further evaluation. Retrospectively, clinical course and diagnostic workup could not rule out bacterial infection in seven children (7/32; 21.8%). As shown in Table 3, five out of seven patients had an infiltrate on chest X-ray and CRP values were in all but one case >40 mg/l.

Ten out of 157 blood cultures were positive; for detailed results, see Table 6. All ten cultures were collected by peripheral venipuncture in patients without implanted plastic materials (no consecutive blood cultures were collected). Two patients with positive blood and nasopharyngeal aspirate cultures for *Streptococcus pneumoniae* had clinical and radiographic pneumonia along with elevated laboratory markers including leukocyte count and CRP. PCT values in

Table 2 Patients with PCT <0.1 ng/ml and antibiotic treatment, n=12 (patients treated with antibiotics prior to admission, patients with critical illnesses or children treated with antibiotics for reasons other than ARI were excluded)

Patient	Pathogen (viral/atypical)	Chest radiograph	CRP ^a [mg/l]	PCT [ng/ml]	Blood culture	Antibiotic
Female, 1 1/12 years	∅	Pneumonia	6	0.0	–	Ampicillin
Female, 13 9/12 years	∅	Atypical pneumonia	43	0.02	–	Clarithromycin
Female, 2 1/12 years	Rhinovirus, enterovirus, coronavirus	Bronchopneumonia	3	0.02	–	Ampicillin
Male, 7 10/12 years	∅	Pneumonia	20	0.05	Positive ^b	Ampicillin
Male, 4 6/12 years	Rhinovirus, <i>M. pneumoniae</i>	Atypical pneumonia	7	0.06	Negative	Erythromycin
Male, 7 9/12 years	Rhinovirus	Bronchopneumonia	25	0.07	–	Ampicillin
Female, 2 years	Rhinovirus	Pneumonia	20	0.07	–	Ampicillin
Female, 5 years	Rhinovirus, enterovirus	Atypical pneumonia	34	0.07	–	Erythromycin
Male, 6 4/12 years	Rhinovirus, <i>C. pneumoniae</i>	Bronchopneumonia	8	0.08	–	Erythromycin/ampicillin
Male, 7 months	RSV, coronavirus	Bronchopneumonia	24	0.08	–	Erythromycin
Female, 6 years	∅	Pneumonia	5	0.08	–	Erythromycin
Male, 4 10/12 years	∅	Bronchopneumonia	6	0.09	Negative	Ampicillin

^a CRP measurement at the same time as PCT measurement^b Positive for coagulase-negative staphylococci

these patients were as high as 38.9 and 10.66 ng/ml, respectively. One patient with a positive blood and stool culture for *Salmonella enteritidis* presented in clinically septic condition, showed an infiltration in chest radiography

and elevated CRP and leukocyte counts; PCT was 13.22 ng/ml. *Haemophilus influenzae* was confirmed in one blood culture after the girl had been hospitalised and treated with antibiotics for 8 days (initial cultures negative). The PCT

Table 3 Patients with PCT ≥0.1 and <0.25 ng/ml and antibiotic treatment, n=20 (patients treated with antibiotics prior to admission, patients with critical illnesses, or children treated with antibiotics for reasons other than ARI were excluded)

Patient	Pathogen (viral/atypical)	Chest radiograph	CRP ^a [mg/l]	PCT [ng/ml]	Blood culture	Antibiotic
Male, 6 11/12 years	Rhinovirus	Bronchitis	18	0.1	–	Ampicillin
Male 2 9/12 years	Rhinovirus	Pneumonia	3	0.1	Negative	Ampicillin
Male, 2 months	hMPV	Pneumonia	8	0.11	–	Cefotiam
Female, 4 3/12 years	Rhinovirus	Pneumonia	25	0.11	–	Ampicillin
Male, 1 2/12 years	<i>Adenovirus, rhinovirus</i>	<i>Pneumonia</i>	<i>56</i>	<i>0.11</i>	<i>Negative</i>	<i>Ampicillin</i>
Female, 7 months	Rhinovirus, coronavirus	Bronchitis	49	0.12	–	Cefaclor
Male, 2 2/12 years	RSV	Bronchopneumonia	<3	0.13	–	Ampicillin
Female, 1 month	RSV	Bronchopneumonia	<3	0.13	Negative	Ceftazidime
Female, 1 1/12 years	hMPV	Bronchitis	80	0.14	Negative	Ampicillin
Male, 5 6/12 years	Rhinovirus	Bronchopneumonia	48	0.15	–	Ampicillin
Female, 6 3/12 yr	∅	Atypical pneumonia	54	0.15	Negative	Erythromycin
Male, 10 months	Rhinovirus	Bronchitis	8	0.15	Negative	Cefaclor
Male, 4 11/12 years	Rhinovirus	Bronchopneumonia	16	0.16	Negative	Ampicillin
Female, 3 3/12 years	Enterovirus	Bronchitis	28	0.17	Negative	Ampicillin
Male, 3 2/12 years	<i>Parainfluenza virus</i>	<i>Pneumonia</i>	<i>122</i>	<i>0.19</i>	–	<i>Ampicillin/sulbactam</i>
Female, 1 7/12 years	∅	Normal	3	0.19	Negative	Ampicillin
Male, 1 year	RSV	Bronchitis	12	0.22	Negative	Ampicillin
Female, 8 months	RSV, rhinovirus	Bronchopneumonia	32	0.22	–	Amoxicillin
Male, 10 years	∅	<i>Pneumonia</i>	<i>60</i>	<i>0.24</i>	<i>Negative</i>	<i>Ampicillin/doxycycline</i>
Male, 2 months	∅	<i>Pneumonia</i>	<i>6^b</i>	<i>0.24</i>	–	<i>Piperacillin/netilmicin</i>

In these patients (*italicized rows*), clinical cause and diagnostic workup gave suspicion of bacterial (super) infection

^a CRP measurement at the same time as PCT measurement^b CRP 134 mg/l after approximately 44 h (no PCT measurement at the same time)

value was 0.13 ng/ml at that time whereas the initial value had been 4.6 ng/ml. In addition, four blood cultures were positive for coagulase-negative staphylococci, one for *Corynebacterium* spp. and one for *Staphylococci aureus*. PCT values were below 0.1 ng/ml in four cases, 0.11 and 0.3 ng/ml in one case each. Only one patient with detection of coagulase-negative staphylococci was treated with antibiotics for pneumonia. In none of these six patients were reliable clinical or laboratory signs for bacteraemia or sepsis present (Tables 1, 2, 3, 4, 5 and 6).

Discussion

The retrospective analysis of the present data shows that approximately 40% ($n=132$) of all 327 patients included had a PCT of <0.1 ng/ml and more than two thirds ($n=225$) had <0.25 ng/ml. We hypothesised that a PCT <0.1 ng/ml indicated absence of bacterial infection or—even more important—absence of bacterial infection requiring antibiotic treatment. In patients with PCT values of <0.25 ng/ml,

bacterial infection was assumed to be unlikely. To find out whether these hypotheses were robust, we considered ARI in patients not treated with antibiotics to definitely have been of viral aetiology or self-limiting bacterial infection. We estimated it appropriate to exclude five patients from our analysis who were treated with antibiotics for other reasons (e.g. urinary tract infection), 17 patients who had already started with antibiotics prior to admission and of four children with chronic illnesses since these patients would also be excluded from a prospective trial. We then had a closer look into the remaining 12 patients with serum PCT concentrations of <0.1 ng/ml who started with antibiotic treatment on admission (postulating that in these patients bacterial respiratory tract infection had been suspected on admission by the paediatrician in charge). Specifically, were there children with low PCT who nevertheless proved to have bacterial infection? As far as could be judged from retrospective analysis of clinical, laboratory, microbiological or radiological findings in these 12 children, there was no substantial criterion for underlying bacterial infection. Antibiotic treatment could probably

Table 4 Patients with PCT <0.1 ng/ml and antibiotic treatment who were excluded, $n=20$

Patient	Reason for exclusion	Pathogen (viral/atypical)	Chest radiograph	CRP [mg/l]	PCT [ng/ml]
Male, 9 months	Antibiotic pretreatment	Rhinovirus	Normal	83	0.08
Female, 6 10/12 years	Antibiotic pretreatment	∅	Pneumonia	37	0.07
Female, 2 6/12 years	Antibiotic pretreatment	∅	Pneumonia	14	0.07
Male, 3 11/12 years	Antibiotic pretreatment	RSV, adenovirus, <i>B. pertussis</i>	Normal	5	0.05
Male, 4 1/12 years	Antibiotic pretreatment	∅	Normal	42	0.08
Male, 5 months	Cystitis	RSV	Bronchopneumonia	19	0.04
Female, 8 9/12 years	Sickle cell disease	∅	Pneumonia	64	0.08
Male, 3 8/12 years	Antibiotic pretreatment	Influenza A	Bronchopneumonia	3	0.02
Female, 10 months	Pyelonephritis	Rhinovirus	–	27	0.03
Male, 11 months	Former premature infant with severe chronic lung disease	Adenovirus, rhinovirus	Bronchopneumonia	3	0.05
Male, 2 2/12 years	Staphyloidermia	∅	–	7	0.09
Male, 10 9/12 years	Antibiotic pretreatment	∅	Bronchopneumonia	49	0.06
Male, 2 months	Antibiotic pretreatment	<i>B. pertussis</i>	–	–	0.03
Female, 8 months	Staphyloidermia	Enterovirus	Normal	3	0.04
Female, 5 7/12 years	CHARGE syndrome	Rhinovirus	Bronchopneumonia	29	0.09
Female, 2 1/12 years	Congenital heart defect	Adenovirus, rhinovirus	Pneumonia	5	0.04
Male, 12 years	Antibiotic pretreatment	<i>M. pneumoniae</i>	Atypical pneumonia	26	0.08
Male, 14 1/12 years	Antibiotic pretreatment	<i>B. pertussis</i>	Normal	3	0.08
Male, 11 months	Antibiotic pretreatment	∅	Normal	6	0.05
Male, 15 4/12 years	Antibiotic pretreatment	<i>M. pneumoniae</i>	Pneumonia	84	0.07
Male, 11 months	Antibiotic pretreatment	∅	–	12	0.07
Male, 3 months	Antibiotic pretreatment	Rhinovirus, <i>B. pertussis</i>	Normal	3	0.06
Male, 8 months	Antibiotic pretreatment	HMPV, adenovirus	Pneumonia	3	0.06
Female, 3 months	Aspiration pneumonia	∅	Normal	–	0.09
Female, 3 10/12 years	Antibiotic pretreatment	∅	Pneumonia	29	0.08
Female, 17 5/12 years	Antibiotic pretreatment	Adenovirus	Atypical pneumonia	24	0.04

Table 5 Laboratory data, stratified by age and gender

	0–12 months		>12–36 months		>36 months				
	m	f	m	f	m	f			
<i>n</i>	111 (33.9%)	73	38	106 (32.2%)	57	49	110 (33.4%)	59	51
PCT <0.1 ng/ml	51 (45.9%)	33	18	32 (30.1%)	18	14	49 (44.5%)	23	26
PCT <0.25 ng/ml	85 (76.6%)	58	27	62 (58.5%)	33	29	78 (70.9%)	41	37
PCT ≥0.25 ng/ml	26 (23.4%)	15	11	44 (41.5%)	24	20	32 (29.1%)	18	14
PCT ≥0.5 ng/ml	9 (8.1%)	5	4	31 (29.2%)	15	16	23 (20.9%)	11	12
Positive virus testing	83 (74.8%)	53	30	67 (63.2%)	40	27	63 (57.3%)	35	28
Infiltrate	27 (24.3%)	17	10	42 (39.6%)	19	23	55 (50%)	28	27
CRP ≤40 mg/l	95 (85.6%)	62	33	84 (79.2%)	43	41	74 (67.3%)	40	34
Antibiotic treatment	35 (31.5%)	23	12	38 (35.8%)	17	21	55 (50%)	31	24

have been withheld safely. Therefore, we suggest a PCT serum concentration of <0.1 ng/ml as an adequate cutoff value to prospectively guide treatment decision in otherwise healthy children with ARI.

As shown in Table 1 (column 5), 40% of patients with PCT values ≥0.5 ng/ml had not received antibiotics (neither initially nor in the clinical course) without adverse effects as far as could be judged from retrospective analysis. This reflects the very restrictive antibiotic treatment policy in patients with ARI in our institution. Thus, unlike Christ-Crain et al. in adult patients with ARI, we would not strongly encourage initial antibiotic treatment in children presenting with ARI and PCT values ≥0.25 ng/ml (especially ≥0.5 ng/ml) in a prospective intervention trial. The most beneficial cutoff in infants and children still has to be determined.

Remarkably, virus testing was positive in about two thirds of patients with PCT values <0.5 ng/ml and only less in those with a PCT ≥0.5 ng/ml (54%). Comparing the percentages of RSV, adenovirus or rhinovirus detections, there was no relevant difference between high or low PCT values. It is known that viral infections, e.g. RSV, rhinovirus or hMPV,

may facilitate bacterial adherence to respiratory epithelial cells [11, 15, 16] and thus may lead to bacterial superinfection. Therefore, viral–bacterial co-infections might account for a number of cases with PCT values of ≥0.25 ng/ml. On the other hand, previous studies have come to the conclusion that PCT cannot reliably distinguish between viral or bacterial aetiology but reflects more the invasiveness and severity of microbial invasion [2, 9, 13]. Thus, elevated PCT values of ≥0.25 ng/ml might rather indicate the presence of more invasive viral rather than true bacterial infection in some of our patients, too.

These retrospective considerations illustrate again the dilemma in the differentiation between viral and bacterial respiratory tract infections, mainly due to the limitations of viral and especially bacterial detection methods.

A further interesting aspect of our analysis was that all six patients with positive PCR testing for *M. pneumoniae* (*n*=5) or *C. pneumoniae* (*n*=1) had a PCT of <0.1 ng/ml. In another five patients where atypical pneumonia had been diagnosed with radiograph only, PCT concentrations were below 0.25 ng/ml, too. This is in agreement with previous

Table 6 Results in patients with positive blood culture, *n*=10

Patient	Blood culture result	WBC [G/l]	CRP [mg/l]	PCT [ng/ml]	Antibiotics
Female, 5 months	CoNS	10	6	0.3	–
Male, 7 10/12 years	CoNS	7.4	20	0.05	+
Male, 3 months	CoNS	14.4	3	0.11	–
Male, 3 8/12 years	CoNS	8.9	20	0.08	–
Female, 2 5/12 years	<i>Corynebacterium</i> spp.	6.5	14	0.04	–
Male, 1 6/12 years	<i>Staphylococcus aureus</i>	5.3	3	0.09	–
Female, 1 5/12 years	<i>Haemophilus influenzae</i>	38	3	0.13	+
Female, 3 2/12 years	<i>Streptococcus pneumoniae</i>	18	241	38.9	+
Female, 3 1/12 years	<i>Streptococcus pneumoniae</i>	19	144	10.7	+
Female, 6 months	<i>Salmonella enteritidis</i>	18	230	13.2	+

CoNS coagulase-negative *Staphylococci*

data in adult patients showing that PCT can be helpful in differentiating typical from atypical pneumonia [12]. On the other hand, PCT seems to increase and even correlate with the prognosis of adult patients with community-acquired pneumonia due to *Legionella pneumophila* as shown in a recent study [10]. It is common clinical practice to treat patients with verified or suspected atypical lower respiratory tract infections with macrolides or doxycycline. In the literature, however, the indication for antimicrobial therapy in atypical pneumonia and its effectiveness are discussed rather controversially [8, 22, 23]. Within a possible prospective PCT-guided intervention trial, children with atypical (predominantly *M. pneumoniae* and *C. pneumoniae*, only rare cases of *L. pneumophila* in childhood) respiratory tract infections and PCT levels <0.1 ng/ml would obviously not be treated with antibiotics. Given the controversial discussion on this issue, however, there seems to be no relevant loss of safety withholding antibiotic therapy in these children. If there are strong clinical or radiological hints for atypical pneumonia, respective antibiotic therapy should be discussed.

Concerning the ten cases with positive blood cultures, we retrospectively judged five blood cultures positive for coagulase-negative staphylococci and *Corynebacterium* spp. as bacterial contamination as none of these children presented with clinical symptoms of bacteraemia or sepsis nor did any of the laboratory findings, inclusive of PCT, match with severe bacterial infection. Additionally, we judged the culture positive for *S. aureus* as contamination since the patient did not develop clinical signs of infection (confirmed by personal follow-up call after discharge). Only one of these six patients (with detection of coagulase-negative staphylococci) was treated with antibiotics for pneumonia. We think the PCT values remained low in these patients in absence of veritable bloodstream infection and should not be considered as falsely negative.

Yet, in three clinically very ill patients with blood cultures twice positive for *Streptococcus pneumoniae* and once for *Salmonella enteritidis*, significantly elevated PCT values (38.9, 10.66 and 13.22 ng/ml) were found (in addition to highly elevated CRP and leucocyte counts). This confirms previous studies that report on a significant induction of PCT in septic patients [19, 24].

Korppi and Kroger [14] postulated that a CRP of >40 mg/l made sole viral aetiology of respiratory tract infection in children rather unlikely. In more recent studies, CRP concentrations of even 50 to 60 mg/l have been reported to discriminate more precisely bacterial infection from other types of inflammation [7, 18, 20, 26]. In our study, CRP was ≤40 mg/l in 11 cases and 43 mg/l in one of the 12 patients with a PCT <0.1 ng/ml. None of these patients had clear evidence for significant bacterial infection. Thus, inclusion of the above-mentioned CRP criteria might further support our hypothesis that a PCT serum concentration of <0.1 ng/ml

is an adequate parameter to withhold antibiotic treatment in otherwise healthy children with ARI.

In conclusion, in spite of methodical shortcomings in a retrospective study such as this, we assume that antibiotic therapy could probably have been withheld without adverse effects in these children who suffered from ARI but were otherwise healthy and had PCT concentrations of <0.1 ng/ml. The results of this study give hope that PCT might develop into a reliable marker to identify children with ARI not requiring antimicrobial treatment and consequently help in reducing the tremendous overuse of antibiotics in children with ARI. This hypothesis, however, remains to be proven in a prospective randomised intervention trial.

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