



The Significance of Procalcitonin and C-Reactive Protein in Diagnostic Tests for Respiratory Adenovirus Infections in Children

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Abstract

Background: This study aims to answer the question if procalcitonin tests allow distinguishing bacterial from AdV infections in cases in which acute phase values are significantly elevated. **Methods:** 40 patients of infant and toddler age were divided into two patient groups (n = 23) and (n = 17) for comparison based on PCT 0.5 µg/L. AdV was determined by polymerase-chain-reaction. **Results:** The PCT value in Group 1 is 0.21 ± 0.12 µg/L, median 0.2, and 1.56 ± 1.07 µg/L, median 1.3 ($p = 0.0001$) in Group 2. At a cut-off value of <0.5 µg/L, C-reactive protein, leucocytes, age, fever temperature, and the duration of fever did not differ significantly. This conclusion also applies to a PCT value to <0.9 µg/L. **Conclusions:** In AdV infections, CRP values of >40 mg/L are observed in more than 80% of patients. A clinically relevant conclusion of our findings is that independent of CRP levels antibiotic therapy is not indicated up to PCT levels of 0.5 µg/l.

Keywords

Adenovirus, Respiratory Infection, Procalcitonin, C-Reactive Protein, Antibiotics, Children

Subject Areas: Virology

1. Introduction

Adenovirus (AdV) infections differ in type and severity. The most prevalent are infections of the airways. The percentage of febrile infections is approximately 10%, according to the literature [1]-[4].

In a fraction of patients with respiratory AdV infections, an increase in acute phase values is observed. The

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physician is confronted with the question as to whether this is a distinctive feature of the AdV infection or due to bacterial superinfection. Antibiotic therapy would be indicated in bacterial infection, but not in the former case.

This study aims to answer the question as to whether Procalcitonin (PCT) tests allow to distinguish bacterial from AdV infections in cases in which acute phase values are significantly elevated [3] [4].

2. Patients and Methods

The investigations were carried out in the pediatric department of a local hospital as part of routine medical care.

This involves the retrospective analysis of data from 40 children with Polymerase-chain-reaction (PCR) verified, clinically significant respiratory AdV infections who have the following diagnosed medical conditions: Tonsillopharyngitis (n = 18), upper airway infection (n = 16), pneumonia (n = 4), obstructive bronchitis (n = 2). To answer the research question of this study, we divided the patients into 2 groups: Group 1: PCT < 0.5 µg/L (n = 23), group 2 ≥ 0.5 µg/L (n = 17).

The collected patient information included the patient's age and gender, temperature, length of hospital stay, length and type of therapy as well as the month of disease onset.

Diagnostic testing comprised the following: C-reactive protein (CRP), leukocytes and percentage of neutrophils, chest X-rays if pneumonia is suspected, PCT (KRYPTOR, ThermoFisher, Henningsdorf, Germany), Interleucin (IL)-6 (Elescys IL-6 test, Roche Diagnostics GmbH Mannheim, Germany), blood cultures (BACTEC FX, Heidelberg, Germany), throat swabs for group A streptococci (StrepA test) (möLab GmbH, Langenfeld, Germany); influenza virus RNA detection by PCR.

AdV testing was performed by collecting a nasopharyngeal swab specimen for human AdV DNA testing by real-time polymerase chain reaction (PCR) [5] on the first and second day of fever (median 1.5).

Statistics

Statistical analysis was performed using the SPSS program (SPSS Inc., an IBM Company Headquarters, 233 S. Wacker Drive, 11th floor Chicago, Illinois 60606).

The analysis involved the calculation of the median, minimum and maximum values due to the non-normal distribution of the data. Comparison of the rates was performed using the Wilcoxon rank test for paired samples and the Mann-Whitney U test for independent samples.

Rates were calculated by chi² test or Fisher's exact test. The correlation was determined by calculation of correlation coefficient "r" and Spearman's rank correlation coefficient "r_s". The results are statistically significant with a p-value of ≤0.05.

3. Results

The data from patient group 1 (n = 23) was compared to the data from patient group 2 (n = 17) based on PCT < 0.5 µg/L and ≥0.5 µg/L. All additional results follow this method (**Table 1** and **Table 2**).

The PCT value in Group 1 is 0.21 ± 0.12 µg/L (mean ± SD), median 0.21, and 1.56 ± 1.07 µg/L, median 1.3 (p = 0.0001) in Group 2.

High PCT values of 1.79; 2.3 and 2.5 µg/L correlated with CRP values of 287.3; 115.5 and 106.4 µg/L. In contrast, CRP values of 18.5; 11.0 and 40.0 mg/L does not correlated with increased PCT values of 1.3; 3.0 and 4.52 µg/L.

No antibiotic therapy was given or therapy was discontinued prematurely in patients with PCT values of 1.3; 2.3; 3.0 and 4.52 µg/L (upper airway infection) who experienced spontaneous defervescence.

The CRP and leucocyte values (total, relative and absolute) also do not reveal significant differences. The IL-6 values are 41.6 ± 41.3 ng/L (mean ± SD), median 24.7 and 92.4 ± 68.8 ng/L, median 76.3 (p = 0.022), respectively.

Information regarding the age, temperature (°C), duration of fever (days), length of hospital stay and therapy is shown in **Table 2**. None of the parameters revealed significant differences between the groups.

In group 2, 7 out of 17 patients had a documented otitis media while group 1 had no similar case.

The PCT groups do not differ significantly with respect to therapy versus no therapy (9:14) and (8:9).

Table 1. Clinical parameters in both patient groups for age, temperature, fever, duration of hospitalization and therapy.

	PCT < 0.5 µg/L N = 23					PCT ≥ 0.5 µg/L N = 17					p-value
	MW	SD	Median	Range	95%CI	MW	SD	Median	Range	95%CI	
Age (month)	22.8	14.0	23	3 - 129	11.1 - 18.3	21.3	7.8	20	13 - 43	18.3 - 26.7	n.s.
Temperature (°C)	39.9	0.5	40.5	39 - 40.9	39.7 - 40.1	39.9	0.6	40.0	39.0 - 40.7	39.6 - 40.2	n.s.
Duration of fever (days)	5.3	2.3	5.4	3 - 12	4.4 - 6.4	4.7	1.2	4.6	1 - 7	3.7 - 5.4	n.s.
Days of fever	1.6	0.8	1.5	1 - 4	1.3 - 2.1	1.6	1.1	1.3	1 - 4	1.3 - 2.3	n.s.
Duration of hospitalization (days)	4.5	1.4	4.5	3 - 8	4.1 - 5.3	4.6	1.7	4.5	2 - 8	3.8 - 5.6	n.s.
Duration of therapy (days)	4.4	1.1	5.0	2 - 5	3.6 - 5.2	6.0	5.0	4.7	1 - 6	1.0 - 1.8	n.s.

Table 2. Laboratory parameters in both patient groups for PCT, CRP, white blood cell count, IL-6.

	PCT < 0.5 µg/L n = 23					PCT ≥ 0.5 µg/L n = 17					p-value
	MW	SD	Median	Range	95%CI	MW	SD	Median	Range	95%CI	
PCT (µg/L)	0.21	0.12	0.2	0.06 - 0.44	0.17 - 0.27	1.56	1.07	1.3	0.5 - 4.5	0.88 - 2.08	0.0001
CRP (mg/L)	40.2	28.0	35.9	4.4 - 100.8	27.5 - 51.3	60.2	67.4	35.6	5.0 - 287.3	21.8 - 95.9	n.s.
White blood cell count (Gpt/L)	17.9	7.0	16.4	6.9 - 30.4	15.3 - 21.3	19.0	7.6	18.4	6.5 - 30.1	13.4 - 21.8	n.s.
Neutrophils (%)	55.6	12.8	59.8	25.9 - 75.2	47.0 - 59.5	60.0	8.2	60.9	45.9 - 74.9	52.3 - 63.7	n.s.
Neutrophile count (Gpt/L)	10.3	4.6	9.8	4.4 - 17.9	8.1 - 12.3	11.6	5.1	10.7	4.4 - 21.4	7.5 - 13.3	n.s.
IL-6 (ng/L)	41.6	41.3	24.7	3.1 - 140.3	19.6 - 63.7	92.4	68.8	76.3	3.1 - 140.3	48.7 - 136.1	0.02

The gender ration of male (n = 23) to female (n = 17) does not achieve statistical significance.

Blood cultures were obtained 11 times (27.9%, Group 1 n = 5, Group 2 n = 6) and all tested pathogen-negative. In particular, all cultures in Group 2 with CRP values above 40 (–287.3) mg/L were sterile.

StrepA throat swabs tested 14 times (35%) negative, particularly in tonsillopharyngitis cases, without evidence of a significant difference in the PCT groups.

Chest X-rays were performed in 5 patients, of which 4 (80%) had infiltrations consistent with pneumonia. The distribution of the infiltrations between the two groups was 75 and 25%, respectively.

34 patients (85%) were tested for influenza virus A and B infection by PCR with negative results.

In group 1 and 2, the distribution of upper airway infections, tonsillopharyngitis, pneumonia and obstructive bronchitis was 56.3 vs. 43.7, 55.6 vs. 44.4, 75 vs. 25 and 50 vs. 50%, 57.5 vs. 42.5% related to all diagnoses, respectively (**Table 3**).

Antibiotic therapy was prescribed 17 times (42.5%), 9 of them (52.9%) were discontinued prematurely. Twenty three patients (57.5%) did not receive medication. The prescription rate was evenly distributed. No significant difference in the two groups with respect to the duration of therapy and treatment was observed. No correlations between the individual findings were found overall ($r_s = 0.141$) (**Figure 1**).

4. Discussion

There is wide agreement in the medical literature that acute phase values, CRP in particular, may be elevated in respiratory AdV infections. The data vary depending on study design.

Data on the relationship between CRP in AdV infections to PCT are not available.

The following data on average CRP values in AdV infections has been documented: 50.4 mg/L [6], 68.3 mg/L (8 - 196.7) [7]. An in-house investigation of 265 PCR-verified respiratory AdV infections revealed the following CRP distribution: <40 mg/L 58.9%, ≥40 - <80 mg/L 26.8%, ≥80 - <120 mg/L 9.8%, >120 mg/L 4.5% (unpublished results). Other investigators established CRP values of >60 mg/L in 35.8% [8], >70 mg/L in 22.5% [9], >40 mg/L in 56%, >100 mg/L in 20% [10]. Lin *et al.* found CRP values of >40 mg/L in 80.4% and >100

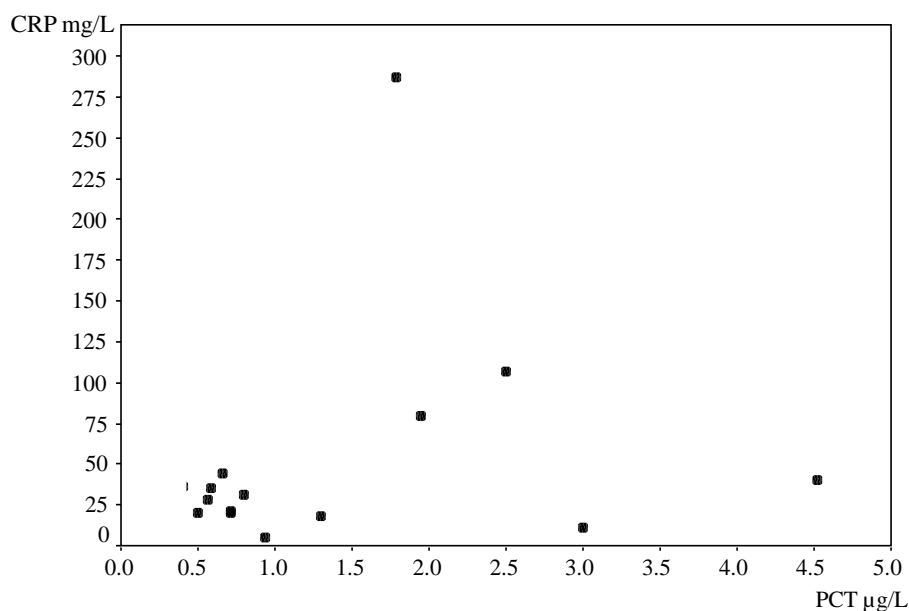


Figure 1. Correlation PCT-CRP ($r_s = 0.141$).

Table 3. Data on the percentage in both patient groups for gender, diagnostic and therapeutic parameters.

		PCT < 0.5 µg/L %	PCT ≥ 0.5 µg/L %	p-value
Patients		57.5	42.1	0.0001
Gender	Male	59.2	64.7	
	Female	47.8	35.3	n.s.
Blood culture	Blood culture	21.7	35.3	
	No blood culture	78.3	64.7	n.s.
Streptococcus A-test	Positive	0	0	
	Negative	46.2	53.8	n.s.
Influenza-virus-PCR	Negative	54.8	45.2	n.s.
Chest X-ray	Infiltration	66.7	33.3	
	No infiltration	0	0	n.s.
Diagnoses	Infection of the upper airways	54.6	56.2	
	Tonsillopharyngitis	22.7	18.8	
	Pneumonia	18.2	18.8	
	Obstruktive bronchitis	4.5	6.2	
	Total	54.6	37.5	n.s.
Therapy	Antibiotics	47.8	64.3	
	No antibiotics	52.2	35.7	n.s.
Therapy	<5 days	22.7	37.5	
	≥ 5 days	22.7	25.0	
	No antibiotics	54.6	37.5	n.s.
Therapy (days)	No/prematurely terminated therapy ≤5 days	77.3	62.5	
	Therapy ≥5 Tage	22.7	37.5	n.s.

Mann-Whitney U-test or Fisher's Exact test were used for statistical analysis. Differences between results are significant at the p-value of <0.05.

mg/L in 37%. Only 5.4% of these patients had a value <10 mg/L [11]. In-house tests (n = 106) revealed CRP values of <20, ≥ 20 - <50, ≥ 50 - <100, ≥ 100 - <120 and ≥ 120 mg/L in 34, 23.6, 30.2, 8.5 and 3.7%, respectively. Values of >200 mg/L were observed in 4 patients [12]. Farng *et al.* determined a CRP of 67.1 ± 49.9 in AdV infections compared to a CRP of 27.8 ± 35.9 mg/L in non-AdV infections ($p < 0.001$) [13]. Values of 32 ± 23 mg/L in AdV infections were significantly elevated compared to influenza (7.1 ± 6.2) and RS-virus infections (9.7 ± 8.1) [14]. Comparable results have been established by Oda *et al.* and Appenzeller *et al.* The CRP of 57 ± 41 mg/L in AdV infections relative to 12 ± 25 mg/L in RSV infections [15] and the CRP of 49 relative to 9 mg/L in Influenza infections [16] was significantly elevated.

The values for leukocytes and absolute neutrophils follow the acute phase reaction principle and are increased in AdV infections [7]-[9] [11]. These values are significantly increased compared to influenza and RS-virus infections as well [12]-[16].

With respect to the diagnostic value of IL-6 in differentiating AdV from bacterial infections it must be noted that this parameter is not suitable to answer the research question, since it follows the acute phase reaction principle identical to CRP and leukocytes [14]. Pathogen detection by blood culture is regarded as proof of bacterial infection. In the literature available to us, we did not find any publication indicative of a PCR-verified AdV infection followed by a blood culture-verified bacterial infection. The detection of pathogen is most likely due to mixed bacterial infection or coinfection, which are reported at an incidence rate of 3% - 5% [6] [8] [12] [17]. Superinfection was ruled out in several studies by blood culture, liquor, urine and throat swab (for A streptococci) tests that tested negative [7] [13] [14] [16]-[18].

CRP was considered the main criterion for differentiating viral from bacterial infections in the 1980s [19]. According to a study by Korppi *et al.*, bacterial coinfection was present in 45% of AdV infections. This interpretation resulted in the prescription of antibiotics [20].

The literature reports that AdV infections may clinically (including laboratory values) and radiologically mimic bacterial infections [7] [9]. As a result, antibiotics were administered in a CRP-value-dependent manner in 60% [16], 75.7% [6], 76% [10] and 91.2% [8] of cases, and administration was discontinued only after the test result was AdV positive. Other studies demonstrate that antibiotics were not administered initially in 64% [11] and 71% [18] of cases. In a study in which 38% of patients received therapy, therapy was discontinued prematurely in 62% of cases without negative consequences [12]. Rocholl *et al.* treated 46% of patients in which a bacterial cause was found in only 2.1% of cases [17].

Diverse antibiotics were prescribed, which turned out to be not indicated in each case [8] [12] [21]. CRP remains without effect [16].

The determination of PCT, which contrary to acute phase values is an immunomodulator with its own diagnostic profile, makes it possible to differentiate bacterial from viral infections.

Based on the combination PCT <0.5 $\mu\text{g/L}$ and CRP <40 mg/L, Galetto-Lacour *et al.* demonstrated a sensitivity of 97% and specificity of 61%, ruling out severe bacterial infection with a probability of <1% and <3% [22]. PCT values of 0.26 (± 0.17) and 0.8 (0 - 4.4) have been established in viral infections [23] [24].

PCT values of < 0.71 $\mu\text{g/L}$ were observed in children who had viral infections [25].

Toikka *et al.* specify a PCT value of ≥ 2.0 $\mu\text{g/L}$ associated with probability of bacterial pneumonia [26].

PCT values of ≤ 0.5 and <0.1 - 0.42 $\mu\text{g/L}$, respectively, have been established in Epstein-Barr and RS virus infections [27] [28]. In H1N1 influenza virus infections, values of 0.4 (0.1 - 6.1) $\mu\text{g/L}$ have been found [29]. A PCT value of <0.8 $\mu\text{g/L}$ in agreement with the clinical progression makes bacterial infection unlikely. Values of >0.8 $\mu\text{g/L}$ indicate bacterial coinfection with a high degree of sensitivity and specificity [30] [31].

An upper PCT limit of 0.25 and 0.5 $\mu\text{g/L}$ was shown to be useful in clinical practice also with respect to the prescription of antibiotics [32]-[35].

Unlike the mentioned viral infections, a special constellation applies to respiratory AdV infections.

It offers the possibility to trigger an immediate inflammatory response associated with an increase in acute phase values, CRP in particular, which is similar to bacterial infection [16].

No plausible explanation could be found for the cause of this phenomenon, neither by using the currently available diagnostic methods nor in the literature.

To differentiate an AdV infection associated with increased CRP from bacterial superinfection using the established diagnostic methods was therefore not possible in this medical condition.

Only one report by Elenius *et al.* involving 16 children between 0.9 - 8.8 years of age is available on this topic. Fourteen of sixteen patients had a CRP of >40 mg/L and a PCT of <0.5 $\mu\text{g/L}$. Children with moderately elevated

PCT (0.13 - 0.8 µg/L) had pneumonia or otitis media consistent with bacterial coinfection [21].

These observations were confirmed in our patients with median PCT of 1.3 µg/L.

A PCT value of <0.5 µg/L is useful to distinguish medical conditions associated with increased CRP (Inflammation) and is therefore suitable for differentiating AdV infections from bacterial infections that may require antibiotic therapy. Based on our results, the same is true for PCT values between ≥ 0.5 and ≤ 1.3 µg/L.

The clinical constellations in patients with PCT values 2 - 5 µg/L with normal CRP, clinically unremarkable course, no detectable pathogens in blood cultures or Strep A tests, spontaneous decrease of fever, and no antibiotic therapy is pathogenetically not entirely clear but also most likely associated with bacterial coinfection.

This finding confirms the experience shared by many investigators in that no conclusive evidence of systemic bacterial infection can be established despite elevated acute phase values.

Values above 0.5 µg/L may be caused by local or minor bacterial infection or coinfection, provided the infection exceeds a certain threshold of severity.

PCT reactions are induced by both systemic inflammation and bacterial infection. The highest values occur in septic shock. Substantial PCT induction does not occur if the systemic inflammatory reaction is absent during infection. The PCT usually increases to approximately 0.5 µg/L [4].

Severe cell damage that may progress to cell necrosis is being discussed as a possible induction pathway for elevated PCT values. The invasion of adherent monocytes into the damaged tissue triggers chemotactic reactions that break down apoptotic or dead cells and therefore eventually induces PCT production. This inflammatory mechanism can be initiated, for example, by severe tissue trauma, burns, extensive surgery, persistent perfusion defect, cardiogenic shock and also by severe AdV infections via the release of cytokines (interleukin-6, tumor necrosis factor) without bacterial infection being the cause [14]. Monocytes can induce the significant increase of circulating procalcitonin by recruiting parenchymal cells in the infected tissue [36] [37]. This process may result in PCT values between 0.5 and 2.0 µg/L, but these values must be assessed with caution and in consideration of the patient's medical condition, since various non-bacterial (nonspecific) disorders may induce PCT [4]. It is conceivable that this induction pathway may also be involved in respiratory AdV infections associated with severe cell damage (tissue trauma). Th1 activation with subsequent increase in acute phase values occurring in AdV but not in RSV infections is an additional possible mechanism described in the literature [38].

A clinically relevant conclusion of our findings is that independent of CRP levels antibiotic therapy is not indicated up to PCT levels of 0.5 (-2.0) µg/L. In higher PCT values, antibiotic therapy with close monitoring of PCT values is indicated due to the suspicion of a bacterial coinfection. Once PCT levels fall to below 0.5 µg/L antibiotic therapy should be terminated.

The limitations of the study are that it is based on the retrospective investigation of a small number of patients. Additional studies will be essential.

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Conflict of Interest

The authors declare that there is no actual or potential conflict of interest in relation to this article.

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