

Predictive value of procalcitonin in respiratory adenovirus infections in children with elevated C-reactive protein levels

Peer review status:

No

Corresponding Author:

Submitting Author:

Dr. Wolfgang H Kunze,
Mr., Children and Adolescent Medicine, Kutasowstr.70, D-04808 - Germany

Article ID: WMC005238

Article Type: Original Articles

Submitted on: 14-Dec-2016, 10:36:28 AM GMT **Published on:** 15-Dec-2016, 10:36:49 AM GMT

Article URL: http://www.webmedcentral.com/article_view/5238

Subject Categories: PAEDIATRICS

Keywords: adenovirus infections, procalcitonin, acute phase parameters, antibiotic therapy

How to cite the article: Kunze W. Predictive value of procalcitonin in respiratory adenovirus infections in children with elevated C-reactive protein levels. WebmedCentral PAEDIATRICS 2016;7(12):WMC005238

Copyright: This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC-BY\)](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Competing Interests:

The authors reports no conflict of interest relevant to this article.

Predictive value of procalcitonin in respiratory adenovirus infections in children with elevated C-reactive protein levels

Author(s): Kunze W

Abstract

Abstract: Adenoviruses (ADV) often cause respiratory infections. They have, in contrast to other respiratory viruses via a potential acute phase parameter (C-reactive protein, leukocytes and interleukin 6) to trigger. ADV infections are associated with increased secretion of IL-6 and TNF- α , which activates the synthesis of acute phase proteins. The exact pathogenic mechanism is still unclear.

Procalcitonin (PCT) offers the possibility, particularly at elevated CRP levels between ADP and bacterial infections to distinguish and thus avoid antibiotic prescriptions.

Introduction

Background: Adenoviruses (ADV) account for a large portion of respiratory infections. Acute-phase parameters are elevated in the majority of cases, which can result in false diagnosis as a bacterial infection and subsequent prescription of antibiotics. The aim of this study was, through the determination of procalcitonin (PCT) and C-reactive protein (CRP) levels, to distinguish between a respiratory ADV infection and a bacterial (super) infection, and to avoid or confirm the need for antibiotic therapy accordingly.

Methods

Patients and Methods: Clinical data and laboratory results were obtained retrospective from 54 patients of a pediatric clinic in the context of a routine diagnostic with PCR-confirmed ADV infection following an initial diagnosis on the basis of a PCT level of 0.5 mg/L or higher. Data collected included age, gender, fever temperature ($^{\circ}$ C), duration of fever, length of hospitalization, antibiotic therapy, and ration of therapy. The following laboratory values were determined: PCT levels, CRP levels, leukocyte count, absolute neutrophil count (ANC), and interleukin-6 (IL-6) levels.

Results

Results: The age (mean \pm SD) of the patients was 23.2 ± 20.3 months, with a median age of 17.5 months; the length of stay in the hospital was 4.5 ± 1.6 days, with a median stay of four days; the fever temperature was $39.8 \pm 0.6^{\circ}$ C, with median temperature of 40° C; the fever duration was 4.9 ± 1.8 days, with a median duration of 5 days. Laboratory values were as follows: CRP: 61.3 ± 60.3 mg/L (median 44.2); leucocyte count: 18.2 ± 6.6 Gpt/L (median 16.6); absolute neutrophil count (ANC): 10.6 ± 4.8 Gpt/L (median 10.1); IL-6: 59.2 ± 55.5 ng/L (median 45.6; 95% CI, 23.1 - 58.1). PCT levels were 0.75 ± 0.6 mg/L (median 0.35; 95% CI, 0.17 - 0.93). CRP levels that were >100 mg/L were measured 11 times, with the following results: 100.8; 106.4; 115.5; 116.8; 131.6; 172.4; 173.6; 183.1; 287.3; 291.0; and 294.3. Of these, eight had PCT levels ≥ 0.5 μ g/L. All laboratory data were well above lab-specific normal values. Of the 54 patients, 31 (57.4%) had PCT levels of < 0.5 mg/L (0.18 ± 0.1 ; median 0.17) and 23 (42.6%) had levels ≥ 0.5 μ g/L (1.49 ± 1.0 ; median 0.12). Age, hospital stay, and fever temperature did not differ significantly between PCT values of < 0.5 mg/L and PCT values of ≥ 0.5 μ g/L. The same was true for CRP, leukocytes, and IL-6 (Table 1). These negative results prompted blood cultures for 17 (31.8%) patients. Tests for group A streptococcal tonsillopharyngitis were also negative ($n = 17$), and tests for influenza virus in 44 patients (81.5%), as well as respiratory syncytial virus (RSV) in infants were also negative. Coinfections with other viruses or bacteria were not investigated. There was no clinical evidence of mixed infections. Using a cut-off value of 0.5 mg/L, the following antibiotic regimens were prescribed: For PCT ≥ 0.5 μ g/L, antibiotic therapy was prescribed for 12 patients (22.2%) and no therapy was prescribed for 11 patients (20.4%); for PCT < 0.5 μ g/L, antibiotic therapy was prescribed for 15 patients (27.8%) and no therapy was prescribed for 16 patients (29.6%). Thus, no therapy was prescribed in 27 patients and therapy was prescribed in the other 27. In 12 of the 27 patients who were administered therapy, the therapy was discontinued prematurely (< 5 days). Thus, 39 patients (72.2%) had either received

no antibiotics or had discontinued antibiotic therapy at the time of the positive ADV result. Overall, for all included parameters, no significant difference was seen in patients on the basis of a PCT cut-off value of 0.5 mg/L.

Discussion

Discussion: PCT determination opens the possibility for the use of elevated CRP levels to differentiate between ADV and bacterial (super)-infections, and therefore to avoid unnecessary prescription of antibiotics. All examining physicians documented a high proportion of CRP values greater than 40 mg/L [1-3]. Lin et al. report that CRP levels are greater than 40 mg/L in 80.4% of cases and above 100 mg/L in 37% of cases, but in only 5.4% of cases are CRP levels less than 10 mg/L [1]. Leukocyte counts have also be observed to be clearly elevated. Leukocyte counts > 15 Gpt/L have been confirmed in 77% of cases [2]. The same applies to absolute neutrophil count, with median values of 9.6 Gpt/L (5.4 - 13.9) confirming this. IL-6 as an acute phase protein is also found at elevated values, with a reported value of 131 ± 90.6 ng/L [4]. The consequence of these laboratory data would be antibiotic therapy for a large number of respiratory ADV infections, since a bacterial origin is indicated both in the clinic, and by laboratory data and radiological findings that mimic a case of pneumonia [1-2].

PCT has been used primarily as a diagnostic marker for bacterial infections, especially sepsis and its severity [5]. This method is also used to verify antibiotic therapy for lower respiratory tract infections. In children with acute respiratory infections, a PCT value of 0.1 mg/L has been recognized as a marker indicating that antibiotic therapy is not required [6].

The fact that the majority of studies have documented that a high proportion of ADV infections were treated with antibiotic therapy without adverse consequences raises the question of whether this is possible also with clearly elevated acute phase parameters. Hardly any findings on this exist in the international literature.

Our data were collected at a time when the problem of elevated CRP levels with subsequent antibiotic therapy were not yet given adequate attention. With regard to antibiotic therapy, of 303 patients, 123 (40.6%) were treated with antibiotic therapy and 180 (59.4%) were treated without antibiotics. Only 63 out of 123 patients (51.2%) were given an antibiotic for a duration of ≥ 5 days; 60 out of the 123 patients (48.8%) ended the regimen prematurely (< 5 days)

upon the finding of a positive ADV result. So, only 63/303 (20.8%) patients were treated with antibiotics for a period of ≥ 5 days. In a total of 240/303 (79.2%) cases, no antibiotic therapy was given or it was prematurely ended (< 5 days) [7].

This raises the question of the relevance of a PCT value of 0.5 mg/L as a criterion for or against antibiotic therapy, especially for respiratory ADV infections.

In contrast to ADV, influenza [8], as well as RSV and EBV, infections do not exhibit elevated PCT values.

ADV infections with elevated CRP and blood cultures without pathogen detection are delineated from "mixed infections", i.e. ADV infections with evidence of bacterial pathogens. This concept is not one of a bacterial (super)-infection rooted in an impairment of the immune system, but instead represents a bacterial disease that is independent from the virus infection. A literature search was confined to one publication that tried unsuccessfully to describe a relationship between a PCR-confirmed ADV infection and a bacterial superinfection. Elenius et al.[9], in a study of 16 patients, showed that in contrast to 12 patients with CRP levels elevated to over 40 mg/L, PCT levels were elevated over 0.5 mg/L in only 2 patients.

This finding was interpreted as indicating the possibility of a bacterial infection.

In agreement with our results, this study presents evidence that, in contrast with elevated CRP levels, PCT levels are only slightly elevated.

PCT is a first-line marker of sepsis. High levels indicate an increased risk of sepsis. Induction of PCT requires activation of an immune response and an inflammatory reaction of a particular strength [5]. These types of immune mechanisms proceed with less intensity in ADV infections, and produce smaller amounts of PCT.

Pathogenicity in ADV infections follows the stimulation of mononuclear cells as well as the release of IL-6 and TNF-alpha, which in turn activate the synthesis of acute-phase proteins [10]. The exact pathological mechanism, however, remains unclear.

Conclusion

PCT at levels of 0.5 mg/L, notwithstanding the recommendations for antibiotic therapy, can distinguish between ADV infection and bacterial (super) infection in lower respiratory infections, and can be used as a criterion for the decision about antibiotic therapy. With regard to respiratory ADV infections, even with high CRP values, no antibiotic therapy is

recommended in the case of a PCR-confirmed ADV infection, as long as the PCT level is in the vicinity of < 0.5 µg/L, i.e. only slightly elevated. The reports of many investigators teach that decisions are dependent on the clinical picture and the experience of the practitioner, and most are against antibiotic therapy. In the case of borderline elevated CRP and PCT values, close monitoring is recommended.

References

1. Lin CH, Huang YC, Chiu CH, et al. A cluster of adenovirus serotyp 3 infections in children in northern Taiwan: clinical features and laboratory findings. *J Microbiol Immunol Infect* 2007; 40: 302-9.
2. Tabain I, Ljubin-Sternak S, Cepin-Bogovi? J, et al. Adenovirus respiratory infections in hospitalized children. *Pediatr Infect Dis J* 2012; 31: 680-4.
3. Appenzeller C, Amman RA, Duppenhaler A, et al. Serum C-reactive protein in children with adenovirus infection. *Swiss Med Wkly* 2002; 132: 345-50.
4. Kawasaki Y, Hosoya M, Katayose M, et al. Correlation between serum interleukin 6 and C-reactive protein concentrations in patients with adenoviral respiratory infection. *Pediatr Infect Dis J* 2002; 21: 370-4.
5. Meisner M. Procalcitonin – Biochemie und klinische Diagnostik. 1. Auflage – Bremen: UNI-MED, 2010.
6. Schützle H, Foster J, Superti-Furga A, et al. Is serum procalcitonin a reliable marker in children with acute respiratory tract infections? A retrospective analysis. *Eur J Pediatr* 2008; 9: 1117-24.
7. Kunze W, Klemm T, Streidl JP. Clinical features and laboratory findings of respiratory adenovirus infections in children. *pädiat prax* 2016; 86: 257-72.
8. Piacentini E, Sánchez B, Arauzo V, et al. Procalcitonin levels are lower in intensive care unit with H1N1 influenza A virus pneumonia than in those with community-acquired bacterial pneumonia. A pilot study. *J Crit Care* 2011; 26: 201-5.
9. Elenius V, Peltola V, Ruuskanen O, et al. Plasma procalcitonin levels in children with adenovirus infection. *Arch Dis Child* 2011; 97: 582-3.
10. Zsengellér Z, Otake K, Hossain SA, et al. Internalization of adenovirus by alveolar macrophages initiates early proinflammatory signaling during acute respiratory tract infection. *J Virol* 2000; 74: 9655-67.

	mean	SD	95%CI	median	min	max	percentile 25-75
PCT µg/L	0,18	0,1	0,14-0,23	0,17	0,06	0,44	0,09-0,27
CRP mg/L	45,4	31	34,2-56,7	43,7	4,4	116,4	16,1-63,4
WBC Gpt/L	18,9	4,8	14,7-19,0	16,3	9,4	234	13,3-22,0
Neutrophils %	52,4	16,4	45,1-59,7	51,8	22,2	78,1	39,8-68,5
ANC Gpt/L	9,4	4,2	7,5-11,2	9	2	19	6,2-12,9
IL-6 ng/L	40,6	39,4	23,1-58,4	23,5	3	140,3	7,0-83,5

≥0,5 µg/L							
n = 23							
mean	SD	95%CI	median	min	max	percentile 25-75	p-value
1,49	1,0	1,0-1,9,0	0,12	0,5	4,52	0,7-2,0	0,0001
82,8	81,5	47,5-118,1	44,6	5	291	20,5-48,2	n. s.
19,0	7,4	14,8-23,3	18,5	6,5	30,1	14,8-27,1	n. s.
58,7	96	53,1-64,2	61,4	38,1	74,9	52,3-64,6	n. s.
11,3	4,8	8,5-14,0	10,9	3	19	8,8-14,2	n. s.
88,3	65,5	52,5-126,1	76,3	3	240	31-143	n.s.

Table 1

Table 1: PCT, CRP, white blood cells, IL-6 at 0,5 µg/L

< 0,5 µg/L
n = 31