

C-Reactive Protein in the Diagnosis of Community-Acquired Pneumonia

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Qualitative determination of C-reactive protein (CRP) was evaluated as a diagnostic method for community-acquired pneumonia. Paired serum and pleural fluid samples from child patients were examined with a CRP test, compared to bacterial cultures, counterimmunoelectrophoresis and immunoassay. The CRP test gave excellent parameters of sensitivity, specificity and predictive values for the diagnosis of bacterial pneumonia.

Key Words: C-reactive protein, community-acquired pneumonia, children.

C-Reactive protein (CRP) is an acute phase protein, synthesized by the liver in response to various stimuli [1]. The induction of CRP synthesis is triggered by a number of cytokines that are released into the inflammatory region, chiefly the pyrogenic cytokine interleukin-6 (IL-6). Fibroblasts, lymphocytes, promyelocytes and active macrophages are sources of IL-6 [2,15]. CRP levels are higher in inflammatory pleural effusions than in other types of effusion [5,9,16,22].

Most severe pneumonia episodes in childhood are caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Nowadays, as a consequence of effective vaccination against Hib, *S. pneumoniae* has become the only significant bacterial cause of community-acquired pneumonia in preschool age, normal healthy children [6-10]. Differentiation between viral and bacterial pneumonia, if possible, would be of utmost importance for clinicians. In young children, the most important problem is how to differentiate between pneumonias caused by respiratory virus versus *S. pneumoniae*. Moreover, mixed infections caused by virus and bacteria, especially by

respiratory syncytial virus and pneumococci, are common [7,8]. Since the assessment of the specific microbial aetiology of pneumonia is difficult, nonspecific inflammatory parameters and the type of infiltration in a chest radiograph are widely used for this purpose [6]. Serum samples for the determination of CRP concentration have been more useful than other materials, such as pleural effusion, for differentiation between bacterial and viral pneumonia in children [8]. The basic principle of the test is that when the fluid sample is mixed with the antiserum solution, the CRP reacts specifically with anti-human CRP antibodies to yield insoluble aggregates. The light absorbance of these aggregates in the sample is proportional to the concentration of CRP [12,16].

We studied the diagnostic value of CRP in bacterial pneumonia, especially regarding *S. pneumoniae* and Hib aetiology.

Materials and Methods

Paired serum and pleural effusion samples from 265 child patients were analyzed for CRP. The samples were centrifuged at 2000 g for 10 min. to remove blood and other matter. Bacterial cultures (BC) were made from the pleural effusion samples. Counterimmunoelectrophoresis (CIE) and dot-enzyme-linked immunosorbent assays (Dot-ELISA) were performed on the paired pleural fluid and serum

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Table 1. Results of comparative bacterial culture (BC), counterimmunoelectrophoresis (CIE), Dot-ELISA and C-reactive protein (CRP) assays for 265 paired pleural fluid and serum samples

Antigens	Pleural fluid samples				Serum samples		
	BC	CIE	Dot-ELISA	CRP	CIE	Dot-ELISA	CRP
<i>Streptococcus pneumoniae</i>	40	51	68	68	21	24	24
<i>Haemophilus influenzae b</i>	12	22	36	36	7	13	13
<i>Staphylococcus aureus</i>	6	6	6	6	6	6	6
<i>Neisseria meningitidis</i>	1	1	1	1	1	1	1
Unknown (*)	-	-	-	25	-	-	28
Total	59	80	111	136	35	44	72

(*) samples with negative BC and immunological tests, but with a positive CRP.

Table 2. Evaluation of the use of C-reactive protein (CRP) in the diagnosis of 265 paired pleural fluid and serum samples compared to the (BC + CIE + Dot-ELISA) tests for pleural fluid and (CIE + Dot-ELISA) for serum samples (given as percent concordance)

Parameters	Pleural fluid	Serum
Sensitivity	100.0	100.0
Specificity	87.8	87.3
positive predictive value	81.6	61.0
Negative predictive value	100.0	100.0
Prevalence	42.0	16.6
Accuracy	91.0	89.5

samples, according to routine procedures [17,18]. CRP was detected using a latex-agglutination test in which a suspension of latex particles sensitized with specific anti-CRP antibodies agglutinates in the presence of an acute phase protein. This semiquantitative test detects 6 to 250 mg/L of CRP (Ebram Lab. Products Ltd, S. Paulo).

Diagnostic parameters, such as sensitivity, specificity and predictive values [4] and the *kappa* (k) concordance index [3] for CRP were evaluated in comparison with the gold standard tests, BC, CIE and Dot-ELISA for bacterial antigen detection [17,18].

Results

Among the 265 pleural fluid samples from children with suspected community-acquired pneumonia, 59 (or

22 percent) gave a positive BC, 40 being *S. pneumoniae*, 12 Hib, 6 *S. aureus* and a single case of *Neisseria meningitidis* C. All these positive pleural fluid cultures were positive in the CRP test. The 77 negative pleural fluid cultures were also positive for CRP (Total: 59 + 77 = 136 positive CRP pleural fluid samples) (Table 1). When all (BC + CIE + Dot-ELISA) tests were considered, 111 positive results were obtained and the following parameters were reached: sensitivity equal to 100%, specificity equal to 87.8%, and positive and negative predictive values equal to 81.6% and 100%, respectively (Table 2). A *kappa* (k) concordance index of 0.82 (almost perfect concordance) with $Z_0 = 10.25$ ($Z_c = 1.96$; $p < 0.001$ for the 95% confidence interval) was obtained for the CRP-pleural fluid test in comparison with the (BC + CIE + Dot-ELISA) tests.

Among the 265 serum samples from the same patients, CIE and Dot-ELISA gave 44 positive tests and CRP gave 72 positives. The following parameters were obtained for these serum samples: sensitivity equal to 100%, specificity equal to 87.3% and positive and negative predictive values of 61% and 100%, respectively (Table 2). A substantial *kappa* concordance index of 0.70 with $Z_o = 4.63$ for $Z_c = 1.96$, $p < 0.001$; for the 95% confidence interval) was obtained for the CRP test of the total serum samples.

Discussion

Several studies have suggested C-reactive protein concentrations of 20 mg/L or 40 mg/L as a screening limit for bacterial infections [5,13,14]. Considering the concentration limit >40 mg/L to differentiate between viral and bacterial respiratory infections, Korppi and Kroger [8] found the best positive and negative predictive values of 0.76 and 0.55, respectively, to support the presence of bacterial pneumonia. Turay et al. [21] found for pleural fluid CRP levels >30 mg/L, a sensitivity of 93.7%, a specificity of 76.5% and a positive predictive value of 98.4%, when these authors screened inflammatory pleural effusions. However, the definitive value of CRP for the differentiation between viral and bacterial respiratory infections has thus far remained unresolved [8,19]. Although pleural fluid CRP levels may be used to discriminate parapneumonic effusions from other types of exudative effusion, a CRP level above 30 mg/L, highly suggestive of pneumonia, is not specific, since there are a number of other conditions that stimulate CRP synthesis, such as pulmonary infarction, inflammation and neoplasia.

In pneumonia, the close proximity of infection and tissue damage in the lung parenchyma to the pulmonary circulation produces an immunological stimulus for systemic CRP synthesis. The CRP response that is mediated by cytokines would be expected to be greater in pneumonia cases where there is more tissue damage [20]. When there is infective exacerbation of chronic obstructive airways disease (purulent bronchitis), it is sometimes difficult to exclude pneumonia on the basis of the radiological findings. This is because there are

often chronic lung markings, or shadowing, due to a coexistent disease, such as pulmonary fibrosis or pneumoconiosis. Furthermore, it is important to distinguish between endobronchial and parenchymal infection, because the bacterial pathogens are often not the same and they may require different antibiotics. The most common bacterial pathogen in community-acquired pneumonia is *S. pneumoniae*, which is sensitive to amoxicillin, and on the other hand, atypical bacterial infection with *Mycoplasma pneumoniae*, *Legionella pneumophila* or *Chlamydia pneumoniae* may also occur, and these require the use of erythromycin. A more useful role for CRP is monitoring the response of pneumonia to antibiotic therapy [23].

In this study, CRP tests were used only as a qualitative determination (+ or -), and thus we were not able to deduce how many cases in the series were caused by virus, since the titers were not measured. These parameters gave high sensitivity and specificity when pleural fluid and/or serum samples were employed. However, pleural fluid samples were superior, with a predictive value (probability of disease in a patient with a positive CRP test) of 81.6%, higher than the 61% determined for serum samples. Thus, the detection of CRP in pleural fluid may prove to be a rapid, practical, and accurate method to define bacterial pneumonia. Although the CRP assay is not cheap, it is quick to perform and could be used as a routine procedure.

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