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Clinical Potential of C-Reactive Protein and Procalcitonin Serum Concentrations To Guide Differential Diagnosis and Clinical Management of Pneumococcal and *Legionella* Pneumonia▽†

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We retrospectively analyzed the records of 61 hospitalized patients with community-acquired pneumonia (CAP) caused by *Streptococcus pneumoniae* or *Legionella pneumophila*. We found that serum procalcitonin and sodium concentrations were significantly lower, and ferritin levels were significantly higher, in patients infected with *L. pneumophila* than in those infected with *S. pneumoniae*. The ratio of C-reactive protein to procalcitonin significantly distinguished between the groups. High procalcitonin levels were associated with an adverse clinical course.

Community-acquired pneumonia (CAP) may be caused by either *Streptococcus pneumoniae* or *Legionella pneumophila* (5, 19). The initiation of adequate empirical antimicrobial therapy can be challenging, since *S. pneumoniae* and *L. pneumophila* have partly contrasting antimicrobial susceptibility patterns (11). We thus questioned whether the determination of C-reactive protein (CRP) and procalcitonin (PCT) levels in serum could be helpful for the differential diagnosis of *S. pneumoniae* or *L. pneumophila* infection. While determination of CRP levels can be helpful for the differentiation between viral and bacterial pulmonary infections (7), elevated PCT levels have been linked to a poor prognosis in CAP and specifically in *Legionella* pneumonia (9, 15). However, while PCT was linked to the severity of the underlying cause, CRP was more closely linked to the presence of infections in a prospective study (8).

We retrospectively analyzed the records of 61 patients admitted to the University Hospital of Innsbruck (Innsbruck, Austria) between 2005 and 2008 with CAP caused either by *S. pneumoniae* ($n = 37$) or by *L. pneumophila* ($n = 24$). Pneumonia was diagnosed on the basis of clinical criteria and laboratory evidence of infection and was confirmed by radiographic evidence. For species diagnosis, urinary antigen tests for *S. pneumoniae* or *L. pneumophila*, the latter detecting serotype 1 (BinaxNOW; Inverness Medical, ME), were used (1, 4, 5, 10, 17).

Baseline laboratory parameters were determined by routine automated tests, and data were available from day 1 (admission) and days 5 to 7. PCT levels were determined by a time-resolved amplified cryptate emission technology assay (Brahms AG, Henningsdorf, Germany) (2).

All statistical analyses were performed with the SPSS statistical package (version 11.5; SPSS, Chicago, IL). For nonnormally distributed data. nonparametric tests were applied (Mann-Whitney test). The Spearman rank correlation technique was used for analysis of associations. All tests were two-sided, and a P value of <0.05 indicated statistical significance. Binary logistic regression analysis was used to identify parameters predictive of the patient outcomes. The ratio of CRP concentrations to PCT concentrations was calculated, and the logarithmic values were used to identify cutoffs for discrimination between *L. pneumophila* and *S. pneumoniae* infections. The diagnostic value of these cutoffs was evaluated by calculating sensitivity, specificity, and positive and negative predictive values (PPV and NPV).

While no statistically significant differences with regard to baseline demographical data became evident between CAP patients suffering from *L. pneumophila* versus *S. pneumoniae* infections (see Table S1 in the supplemental material), patients with *L. pneumophila* pneumonia had significantly lower PCT levels at admission (mean ± standard error of the mean [SEM], 6.76 ± 1.74 μg/liter) than patients with *S. pneumoniae* pneumonia (20.94 ± 3.99 μg/liter) ($P < 0.01$) (Fig. 1A). Although CRP levels were not significantly different between the two groups, a log CRP/PCT ratio resulted in excellent discrimination between *L. pneumophila*- and *S. pneumoniae*-infected patients ($P < 0.001$) (Fig. 1B). A log CRP/PCT ratio below 0.5 was rather indicative of *S. pneumoniae* infection (NPV, 54.1%; PPV, 83.3%; sensitivity, 54.1%; specificity, 83.3%), whereas a log CRP/PCT ratio greater than 1.25 was more likely to reflect *L. pneumophila* infection (NPV, 66.7%; PPV, 61.5%; sensitivity, 33.3%; specificity, 86.5%).

Moreover, we observed significant differences in concentrations of sodium (132 ± 1.0 mmol/liter for *L. pneumophila* versus 135 ± 1.0 mmol/liter for *S. pneumoniae*; $P < 0.02$), urea (52.2 ± 7.1 mg/dl versus 70.5 ± 5.8 mg/dl; $P < 0.01$), and ferritin (1,372 ± 303 μg/liter versus 929 ± 496 μg/liter; $P < 0.01$) between the two patient groups at baseline (see Table S1 in the supplemental material). Patients who died had persistently high levels of PCT (means ± SEM, 20.1 ± 10.3 μg/liter for patients who died versus 1.4 ± 0.5 μg/liter for survivors; $P < 0.001$) and CRP (13.3 ± 2.3 mg/dl for patients who

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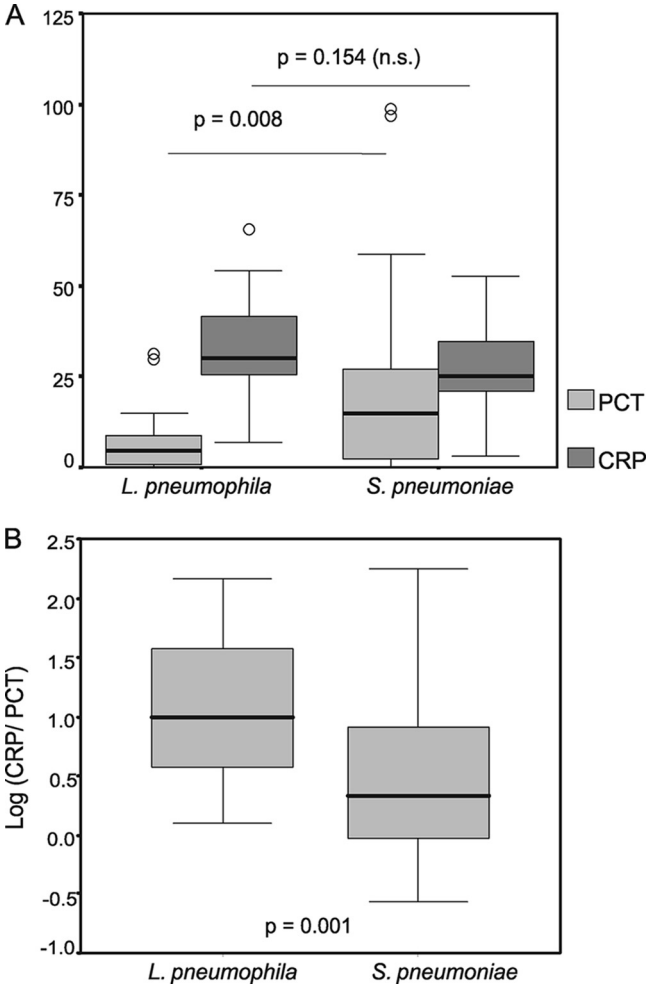

FIG. 1. Differentiation of CAP caused by *Legionella pneumophila* or *Streptococcus pneumoniae* by inflammatory parameters. Box plots of PCT (μg/liter) and CRP (mg/dl) levels, determined for patients with *S. pneumoniae* ($n = 37$) or *L. pneumophila* ($n = 24$) pneumonia at admission (A), and of log CRP/PCT ratios (B) are shown. Groups were compared with a nonparametric Mann-Whitney U test. Differences between the respective groups were considered significant if *P* values were below 0.05.

died versus 8.2 ± 1.3 mg/dl for survivors; $P < 0.02$) (Table 1) at day 5.

During the observation period, 30 of 61 patients were admitted to the intensive-care unit (ICU) for invasive or noninvasive ventilator therapy. Risk factors for ICU admission were high CRP levels on day 5 (mean ± SEM, 12.3 ± 1.7 mg/dl), high PCT concentrations (25.7 ± 4.6 μg/liter on day 1; 10.7 ± 5.2 μg/liter on day 5), impaired renal function, thrombopenia, and anemia (see Table S2 in the supplemental material). Subjects with PCT levels above 10 μg/liter at admission (NPV, 77.8%; PPV, 84%; sensitivity, 72.4%; specificity, 87.5%) or with a log CRP/PCT ratio of <0.5 at admission (NPV, 73%; PPV, 79.2%; sensitivity, 65.5%; specificity, 84.4%) were more likely to be admitted to the ICU than patients with a PCT level of <10 μg/liter and/or a log CRP/PCT ratio of >0.5.

We determined that increased PCT levels at days 1 and 5 were also associated with an increased risk of death ($P < 0.05$ in both cases), and multivariate logistic regression analysis indicated that thrombopenia at day 5 and advanced age were risk factors for death.

Patients with *L. pneumophila* infections requiring ICU treatment experienced longer hospital stays ($P < 0.001$), whereas patients with *S. pneumoniae* pneumonia who were admitted to the ICU had a significantly lower survival rate ($P < 0.05$) than patients with an uncomplicated course of disease.

An algorithm for differential diagnosis between *S. pneumoniae* and *L. pneumophila* infection may benefit further from the inclusion of other parameters, such as serum sodium levels, since hyponatremia was often observed in patients with *L. pneumophila* pneumonia (see Table S1 in the supplemental material) (6, 12, 13, 20). Most strikingly, patients with *L. pneumophila* infection presented with significantly increased levels of ferritin, which is the major circulating iron storage protein. This is of interest because *Legionella* species are highly dependent on a sufficient supply of iron (3). However, ferritin is also induced by inflammation, and iron restriction by monocytes, with a subsequent increase in ferritin levels, is a cornerstone

TABLE 1. Comparison of laboratory values, comorbidities, and demographic data between survivors and patients who died from *Legionella* or pneumococcal pneumonia

Parameter[a]	Value (mean ± SEM)		*P*[b]
	Survivors	Dead	
PCT (μg/liter)			
Day 1	12.23 ± 2.66	26.92 ± 6.99	0.08
Day 5	1.42 ± 0.45	20.12 ± 10.3	0.000
CRP (mg/dl)			
Day 1	30.29 ± 1.97	28.11 ± 3.67	NS
Day 5	8.22 ± 1.27	13.32 ± 2.26	0.018
Leukocytes (10^9/liter)			
Day 1	12 ± 1	16 ± 4	NS
Day 5	10 ± 1	19 ± 5	0.049
Hemoglobin (mg/dl)			
Day 1	125 ± 4	112 ± 7	0.017
Day 5	114 ± 4	94 ± 6	0.003
Thrombocytes (10^9/μl)			
Day 1	190 ± 14	200 ± 30	NS
Day 5	359 ± 24	115 ± 24	0.000
Urea (mg/dl)	53.5 ± 3,5	99.4 ± 13.4	0.000
Creatinine (mg/dl)	1.25 ± 0.08	2.12 ± 0.31	0.000
Ferritin (μg/liter)	1,215 ± 348	633 ± 247	NS
Sodium (mmol/liter)	134 ± 1	133 ± 2	NS
Length of hospital stay (days)	15 ± 2	15 ± 4	NS
Age (yrs)	57 ± 2	68 ± 3	0.014
Gender (no. of females/no. of males)	17/31	2/11	NS
No. of patients with:			
L. pneumophila	21	3	NS
S. pneumoniae	27	10	NS
Diabetes mellitus	8	5	NS
COPD	8	5	0.014

[a] PCT, procalcitonin; CRP, C-reactive protein; day 1, admission; day 5, follow-up; COPD, chronic obstructive pulmonary disease.
[b] Statistical significance was calculated by a nonparametric Mann-Whitney test. NS, not significant.

for the development of anemia of chronic disease (18). Thus, intracellular versus extracellular pathogens may cause contrasting regulatory effects on iron homeostasis (14, 16), leading to these observed differences in ferritin expression.

In conclusion, our data link PCT levels to the severity of CAP and further suggest that CRP and PCT in combination are of value for the differential diagnosis between *L. pneumophila* and *S. pneumoniae* infections. Subsequent studies involving higher patient numbers may aid in finding cutoffs for clinically useful predictive values.

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