

## C-Reactive Protein as an Indicator of Bacterial Infection of Adult Patients in the Emergency Department

Yi-Ling Chan, MD; Hao-Chin Liao, MD; Pei-Kuei Tsay<sup>1</sup>, PhD; Shy-Shin Chang, MD; Jih-Chang Chen, MD; Shiumn-Jen Liaw, MD

**Background:** This investigation evaluates the feasibility of using C-reactive protein (CRP) levels as an indicator of bacterial infection of adult patients in the Emergency Department (ED), by comparing them with clinical signs and routine laboratory tests.

**Methods:** One hundred and fifty adult atraumatic patients admitted through the ED of Linkou Chang Gung Memorial Hospital were consecutively enrolled. Seventy-nine patients had documented infection, and 58 had no infection. Body temperature (BT), white blood cell (WBC) count, CRP levels, and the presence of systemic inflammatory response syndrome (SIRS) were compared between the infected and uninfected groups.

**Results:** SIRS was the most sensitive indicator of bacterial infection (sensitivity 84.8%), but it had a 37.9% false-positive rate. BT and WBC count were more specific (at 89.7% and 84.5%) but less sensitive (at 48.1% and 43.0%, respectively). Using Youden's Index, the best cut-off value for CRP was 60 mg/l (sensitivity 67.1%, specificity 94.8%, positive predictive value 94.6%, and negative predictive value 67.9%). The area under the receiver operating characteristics (ROC) curve was highest for CRP (at 0.88), followed by BT (at 0.77) and WBC (at 0.67) (all  $p < 0.05$ ).

**Conclusion:** CRP is a better indicator of bacterial infection than either BT or WBC count for adult atraumatic ED patients. A low serum CRP level cannot safely be used to exclude the presence of infection.  
(*Chang Gung Med J* 2002;25:437-45)

**Key words:** C-reactive protein, bacterial infection, emergency department, sepsis, systemic inflammatory response syndrome.

Patients presenting with fever, tachycardia, hyperventilation, and leukocytosis with no known stimulus such as trauma, burns, or pancreatitis are usually presumed to have sepsis, a typical body response to infection.<sup>(1)</sup> Sepsis is a major cause of morbidity and mortality, and early institution of an

appropriate antimicrobial regimen is associated with improved survival.<sup>(2)</sup> Clinical signs of infection and routine laboratory tests are, however, not specific and can be misleading. Infection can be present in some patients without sepsis, particularly in the debilitated and elderly. Acutely ill patients,

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From the Department of Emergency Medicine, Chang Gung Memorial Hospital, Taipei; <sup>1</sup>Center of Biostatistics, Chang Gung University, Taoyuan.

Received: Aug. 22, 2001; Accepted: Feb. 26, 2002

Address for reprints: Dr. Shy-Shin Chang, Department of Emergency Medicine, Chang Gung Memorial Hospital, 5, Fu-Shing Street, Kweishan, Taoyuan 333, Taiwan, R.O.C. Tel.: 886-3-3281200 ext. 2505; Fax: 886-3-3287715; E-mail: sschang@cgmh.org.tw

however, frequently present signs of sepsis, even when no bacterial infection can be demonstrated. The widespread use of antibiotics for all these patients presents problems of antibiotic resistance, drug toxicity, and increased medical costs. Identifying patients who are likely to benefit from an antimicrobial agent is a priority. Since sepsis response involves the release of a wide array of inflammatory mediators,<sup>(3)</sup> it has been suggested that some of these mediators could be used as markers of infection or sepsis severity.<sup>(4,5)</sup> As these mediators may be increased in other inflammatory conditions, none is specific for infection.

C-reactive protein (CRP), in addition to the white blood cell (WBC) count, is currently the most widely used parameter to support a diagnosis of infection. CRP is an acute-phase reactant produced by the liver. Plasma concentrations are normally below 10 mg/l but increase several fold after trauma, infection, inflammation, and other stimuli involving tissue damage.<sup>(6)</sup> Interleukin (IL)-6 is thought to be the main mediator stimulating CRP production, but other cytokines, like IL-1 and tumor necrosis factor, are also involved.<sup>(7,8)</sup> CRP may be useful in diagnosing the onset of sepsis in acutely ill patients<sup>(9,10)</sup> and for indicating successful treatment during follow-up of the clinical course.<sup>(11)</sup> Although large increases can occur in response to infection, no definite correlation between infection and changes in CRP has been documented,<sup>(9)</sup> and using a low CRP level to exclude the presence of infection remains controversial.

This investigation evaluated the feasibility of using CRP levels, as compared to clinical signs of infection and routine laboratory tests, for detecting bacterial infection in the Emergency Department (ED).

## METHODS

One hundred and fifty adult atraumatic patients admitted through the ED of Linkou Chang Gung Memorial Hospital, Taiwan from May 14 to 16, 2001 were consecutively enrolled. Those who were death-on-arrival and those who were referred from wards or intensive care units (ICUs) of other hospitals were not included. All patients were examined for signs and symptoms of infection on ED admission. Clinical and laboratory data collected included age,

gender, admission diagnosis, patient disposition, body temperature (BT), WBC count, CRP levels, and other available information required for the calculation of the Acute Physiology and Chronic Health Evaluation (APACHE II).<sup>(12)</sup> Samples were collected for cultures of blood and other bodily fluids, depending on the clinical symptoms.

Three groups were defined based on the clinical, laboratory, and bacteriologic findings.

### Infected patients

Seventy-nine patients had a definable source of infection and/or positive blood cultures and received antibiotic treatment. A patient was considered to have bacteremia if he or she had a clinical infection and a positive blood culture. A diagnosis of urinary tract infection required the presence of symptoms such as frequency, dysuria, costovertebral angle tenderness, and significant growth of bacteria of  $10^{4-5}$  CFU/ml in urine culture. A diagnosis of pneumonia was based on both respiratory symptoms, such as productive cough, dyspnea, chest pain, and a pneumonic infiltrate that disappeared during antibiotic treatment while the patient recovered. For other foci, distinct radiological or microbiological documentation of the foci and recovery during antimicrobial treatment were required.

### Uninfected patients

The uninfected patient group consisted of 58 patients who, throughout their course of admission to the hospital, had no evidence of infection clinically or in the examinations performed, and received no antibiotic therapy.

### Possibly infected patients

Thirteen patients had an uncertain diagnosis of infection. Two patients suffered from cholecystitis, 2 from hollow organ perforation, and 1 from appendicitis; their blood cultures were either negative or unchecked, and none had an ascites culture. Three female patients had asymptomatic urinary tract infections, along with other diagnoses that became their principal reason for admission. All 3 had negative blood cultures, and none received antibiotic therapy. Eleven patients in this group had a systemic inflammatory response syndrome (SIRS). Since a diagnosis of infection in this group was uncertain, all 13 patients were excluded from the analysis.

The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions of sepsis<sup>(1)</sup> were used to identify patients with sepsis, severe sepsis, septic shock, and SIRS in the uninfected group. The development of septic shock and patient outcomes were documented by chart review. Serum CRP level was measured by laser immunonephelometry (Wako Pure Chemical Industries, Osaka, Japan).

**Statistical analysis**

The Mann-Whitney U test was used to compare independent samples, and the chi-square test (or Fishers exact test when appropriate) was used to compare proportions. The best cut-off value was chosen using Youden's Index.<sup>(13)</sup> The receiver operating characteristic (ROC) curve and the respective areas under the curve (AUC)<sup>(14)</sup> were calculated. Statistical calculations were done using the Statistical Program for the Social Sciences (SPSS, Chicago, IL, USA). All variables were expressed as the median. A value of  $p < 0.05$  was considered significant.

**RESULTS**

Admission diagnoses of the 137 patients included in the analysis are presented in Table 1. Their ages ranged from 18 to 90 (median, 65) years, and 59% (N=81) of the patients were male. The median APACHE II score was 10. Seven patients died, giving a crude mortality rate of 5.1%. Seventy-nine (58%) of the 137 patients were infected, and 58 (42%) were uninfected (Table 2). Fifty (63.3%) of the 79 infected patients had an identified etiological microorganism, and 14 (17.7%) had bacteremia. The most common site of infection was the urinary tract, followed by the lung, soft tissue, and biliary tract (Tables 1, 2). Ten patients had more than 1 site of infection, and 21 patients had more than 1 kind of infecting microorganism (Table 2). Sixteen patients (21.5%) had severe sepsis, and 7 (8.9%) developed septic shock.

SIRS was present in 84.8% of the infected patients and in 37.9% of the uninfected patients ( $p < 0.001$ ). The median BT in infected patients was 37.8°C and in uninfected patients was 36.9°C ( $p < 0.001$ ), while the median WBC counts were 10,800 and 8000/ $\mu$ l ( $p < 0.001$ ), respectively (Table

**Table 1.** Clinical Diagnoses of Study Patients

	No. of patients*	(%)
<b>Infected group</b>		
Urinary tract infection	31	34.8
Pneumonia/empyema/lung abscess	25	28.1
Cellulitis/necrotizing fasciitis	11	12.4
Biliary tract infection/cholecystitis	5	5.6
Wound infection	4	4.5
Ear/nose/throat/deep neck infection	3	3.4
Appendicitis, with positive ascites culture	2	2.2
Liver abscess	2	2.2
Bacteremia	2	2.2
Pancreatitis, with infected pseudocyst	1	1.1
Central line infection	1	1.1
Perianal abscess	1	1.1
Pulmonary tuberculosis	1	1.1
<b>Uninfected group</b>		
Cerebrovascular accident	13	22.4
Malignancy	10	17.2
Gastrointestinal bleeding	9	15.5
Congestive heart failure	7	12.1
Ischemic heart disease	4	6.9
Liver cirrhosis	4	6.9
Chronic renal insufficiency /end-stage renal disease	3	5.2
Chronic lung disease	3	5.2
Diabetic ketoacidosis/nonketotic hyperosmolar syndrome	2	3.4
Miscellaneous	3	5.2

\*Ten patients had more than 1 site of infection.

3). A BT of  $> 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ , fulfilling the SIRS criteria for body temperature, was present in 48.1% of infected patients and in 10.3% of uninfected patients ( $p < 0.001$ ). A WBC count of  $> 12,000/\mu$ l or  $< 4000/\mu$ l, again fulfilling the SIRS criteria, was present in 43.0% of infected patients and 15.5% of uninfected patients ( $p < 0.001$ ); the WBC count had a similar but lower sensitivity and specificity than BT (Table 4).

Using Youden's Index, the best cut-off value for CRP was 60 mg/l. CRP levels were  $\geq 60$  mg/l in 67.1% of infected patients, and in only 5.2% of uninfected patients ( $p < 0.001$ ). Median CRP concentrations in infected and noninfected patients were 100.3 and 5.5 mg/l ( $p < 0.001$ ), respectively (Fig. 1). There was no relationship between CRP levels and the

**Table 2.** Site of Infection and Causative Organism

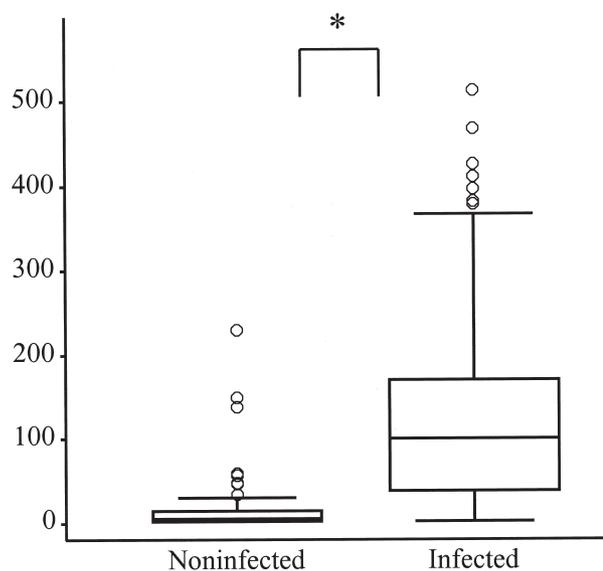
	No. of patients	
<b>Urinary tract</b>		<b>n = 31</b>
<i>Escherichia coli</i>	12	
<i>Pseudomonas aeruginosa</i>	5	
<i>Enterococcus faecalis</i>	4	
<i>Serratia marcescens</i>	2	
<i>Staphylococcus aureus</i>	2	
<i>Klebsiella pneumoniae</i>	2	
<i>Proteus mirabilis</i>	2	
<i>Pseudomonas</i> spp.	1	
<i>Citrobacter diversus</i>	1	
<i>Candida albicans</i>	1	
Unknown	1	
<b>Lung</b>		<b>n = 25</b>
<i>Pseudomonas aeruginosa</i>	5	
<i>Staphylococcus aureus</i>	4	
<i>Streptococcus pneumoniae</i>	2	
<i>Klebsiella pneumoniae</i>	2	
<i>Proteus mirabilis</i>	2	
<i>Serratia marcescens</i>	2	
Viridans streptococcus	1	
<i>Hemophilus influenzae</i>	1	
<i>Escherichia coli</i>	1	
<i>Acinetobacter baumannii</i>	1	
<i>Pneumocystis carinii</i>	1	
<i>Mycobacteria tuberculosis</i>	1	
Unknown	7	
<b>Wound</b>		<b>n = 16</b>
<i>Staphylococcus aureus</i>	4	
Viridans streptococcus	3	
<i>Escherichia coli</i>	1	
<i>Klebsiella pneumoniae</i>	1	
<i>Proteus vulgaris</i>	1	
Prevotella species	1	
Bacteroides sp.	1	
Peptostreptococcus	1	
Unknown	6	
<b>Abdominal (gastrointestinal tract, liver, bile duct, and pancreas)</b>		<b>n = 10</b>
<i>Escherichia coli</i>	4	
<i>Enterococcus faecalis</i>	3	
<i>Klebsiella oxytoca</i>	2	
<i>Citrobacter freundii</i>	2	
<i>Pseudomonas aeruginosa</i>	1	
<i>Klebsiella pneumoniae</i>	1	
<i>Proteus vulgaris</i>	1	
Viridans streptococcus	1	
<i>Enterococcus durans</i>	1	
<i>Enterococcus avium</i>	1	
<i>Clostridium perfringens</i>	1	
Unknown	3	
<b>Central venous catheter</b>		<b>n = 1</b>
<i>Staphylococcus aureus</i>	1	
<b>Unknown</b>		<b>n = 7</b>

**Table 3.** Median Age, Gender, Median APACHE II Score, Mortality, Median BT, WBC, and CRP for Each Group

Parameter	Infected (N = 79)	Uninfected (N = 58)	p
Age (yr)	65 (43-75) <sup>†</sup>	65.5 (47.5-71) <sup>†</sup>	0.955
Gender (M/F)	43/36	38/20	0.192
APACHE II	12 (7-16) <sup>†</sup>	10 (6-12) <sup>†</sup>	0.058
Mortality	6 (7.6%)	1 (1.7%)	0.238
BT (°C)	37.8 (37.1-38.8) <sup>†</sup>	36.9 (36.4-37.3) <sup>†</sup>	< 0.001
WBC (/μl)	10,800 (7410-14,800) <sup>†</sup>	8,000 (6100-10,100) <sup>†</sup>	< 0.001
CRP (mg/l)	100.3 (35.7-170.0) <sup>†</sup>	5.5 (2.0-14.6) <sup>†</sup>	< 0.001

**Abbreviations:** APACHE II: Acute Physiology and Chronic Health Evaluation II; BT: body temperature; WBC: white blood cell count; CRP: C-reactive protein.

<sup>†</sup>: Interquartile range.

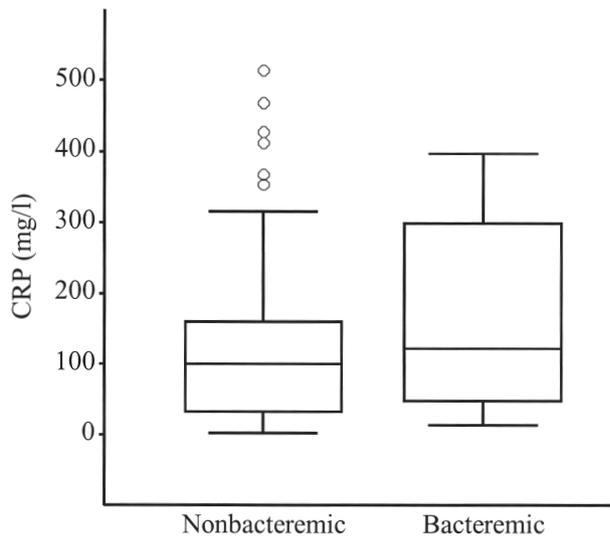


**Fig. 1** Box plot (with interquartile range) of C-reactive protein (CRP) concentrations in infected and uninfected patients. \* $p < 0.001$ .

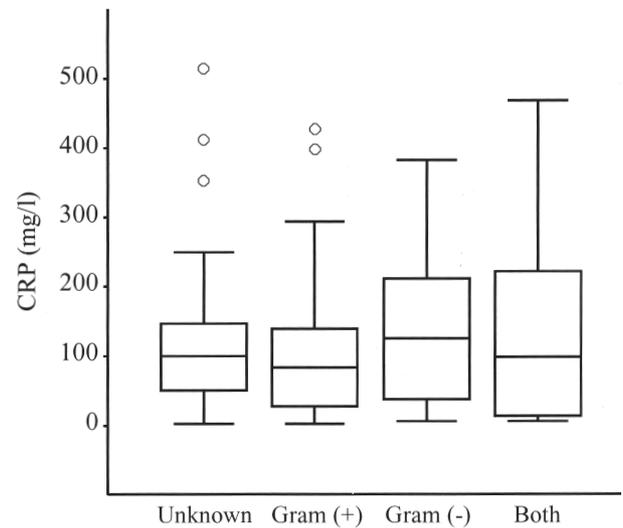
**Table 4.** Clinical Parameters and CRP for the Diagnosis of Adult Infection in the Emergency Department (%)

Parameter	Sensitivity	Specificity	Positive predictive value	Negative predictive value
SIRS	84.8 (67/79)	62.1 (36/58)	75.3 (67/89)	75.0 (36/48)
BT > 38 °C or < 36 °C	48.1 (38/79)	89.7 (52/58)	86.4 (38/44)	55.9 (52/93)
WBC > 12,000/ $\mu$ l or < 4000/ $\mu$ l	43.0 (34/79)	84.5 (49/58)	79.1 (34/45)	52.1 (49/94)
CRP (cut-off 60 mg/l)				
All	67.1 (53/79)	94.8 (55/58)	94.6 (53/56)	67.9 (55/81)
SIRS	70.1 (47/67)	90.9 (20/22)	95.9 (47/49)	50.0 (20/40)
No SIRS	50.0 ( 6/12)	97.2 (35/36)	85.7 ( 6/ 7)	85.4 (35/41)

**Abbreviations:** SIRS: systemic inflammatory response syndrome; BT: body temperature; WBC: white blood cell count; CRP: C-reactive protein.



**Fig. 2** Box plot (with interquartile range) of C-reactive protein (CRP) concentrations in bacteremic and nonbacteremic patients.

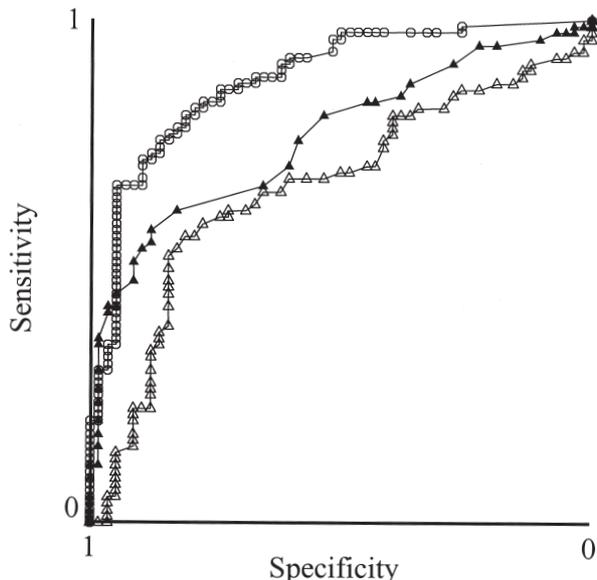


**Fig. 3** Box plot (with interquartile range) of C-reactive protein (CRP) concentrations in patients with infections caused by different pathogens.

presence of bacteremia or the type of infecting bacteria (Figs. 2, 3). The positive predictive value of the CRP level was 94.6%; however, the negative predictive value was 67.9%. In patients with SIRS (N=89), the negative predictive value of CRP was only 50% (Table 3).

Figure 4 shows the ROC curves for CRP, BT,

and WBC count. The area under the ROC curve was greatest for CRP, followed by BT and then WBC (0.88, 0.77, and 0.67, respectively;  $p < 0.05$ ). There were statistically significant differences in the AUC between CRP and BT ( $p = 0.014$ ) and between CRP and WBC ( $p < 0.001$ ), but not between BT and WBC ( $p = 0.102$ ).<sup>(15)</sup>



**Fig. 4** Receiver operating characteristic curves of C-reactive protein (open circles), body temperature (solid triangles), and white blood cell count (open triangles) in the diagnosis of infection.

## DISCUSSION

CRP, an acute-phase protein, has been widely used clinically for many years as a diagnostic tool for infection identification.<sup>(16)</sup> CRP may be particularly helpful when the SIRS diagnostic criteria are less reliable, for example in the presence of other disease processes that affect heart rate, WBC count, or BT. In contrast to most acute-phase proteins for which there are wide plasma level variations (which depend on synthesis, consumption, and catabolic rates), the plasma half-life of CRP is constant under almost all conditions.<sup>(17)</sup> Its plasma level is determined exclusively by its rate of synthesis, which reflects the presence and extent of disease activity.

The present investigation was comprised of a typical, heterogeneous adult atraumatic ED population. When comparing the sensitivity and specificity of CRP with those of clinical signs and routine laboratory tests for the diagnosis of infection, we considered that 3 groups of patients:<sup>(18)</sup> a) those with documented infection; b) those without infection; and c)

those with possible infection, with this final group being eliminated from the analysis. The presence of SIRS was the most sensitive clinical parameter indicating the presence of infection as compared with BT and WBC count, but the false-positive rate was high. A BT or WBC count that fulfilled the SIRS criteria was more specific, but was much less sensitive to infection. Although infected patients had WBC counts that statistically differed from those of uninfected patients in this investigation, many other studies have found no such differences.<sup>(10,19,20)</sup> This is presumably due to different characteristics of the patient populations studied. The present investigation included a broad range of unselected medical patients in the ED, and compared to other studies, had the largest range of variability in the presentation of patients. BT was also found to be a more sensitive (48.1% vs. 43.0%) and specific (89.7% vs. 84.5%) indicator of infection compared with the WBC count. Similar findings were reported by Povia et al.<sup>(9)</sup> These findings imply that in febrile or hypothermic patients, the absence of leukocytosis does not exclude the presence of infection.

Other authors have attempted to evaluate the role of CRP in the diagnosis of sepsis in different patient populations, and variable cut-of values for CRP levels have been reported. Matson et al.<sup>(8)</sup> pointed to the fact that "normal" plasma CRP levels in critically ill patients are rarely the same as those found in a healthy population; however, a cut-off for the "normal" concentration was not proposed. Yentis et al.<sup>(21)</sup> investigated changes in CRP accompanying resolution of microbiologically proven sepsis in ICU patients and found all 32 septic episodes had plasma CRP levels above 43 mg/l on diagnosis, with a median of 223 (range, 43-368) mg/l. Kallio et al.<sup>(22)</sup> reported that for 66 cancer patients with suspected infection, the optimal cut-off values for CRP using Youden's Index was 140 mg/l, with a sensitivity of 39% and a specificity of 70%. Ugarte et al.<sup>(19)</sup> investigated 190 critically ill patients and reported the optimal cut-off level for CRP using Youden's Index to be 79 mg/l. The present investigation found the best cut-off value for CRP using Youden's index to be 60 mg/l, with a comparable sensitivity (67.1% vs. 71.8%) but a much higher specificity (94.8% vs. 66.6%) compared with the values of Ugarte et al.<sup>(19)</sup> The difference in specificity between the 2 studies is reasonable, since critically ill patients generally

maintained higher "normal" CRP concentrations than did the ED patients investigated. Both studies for instance, found a comparable median CRP level in infected patients (100.3 vs. 121 mg/l), but a markedly different median CRP level in uninfected patients (5.5 vs. 56 mg/l).

Huang et al.<sup>(18)</sup> investigated 123 acutely ill ED patients with suspected infection and reported that a combination of CRP and WBC count provided a satisfactory predictive value for infection. In this investigation, however, only patients with specific complaints, including fever, chills, or acute distress such as dyspnea, chest pain, consciousness change, abdominal pain, arthralgia, or upper gastrointestinal bleeding, were investigated. Many patients were dropped from the investigation because their CRP levels were unchecked, either because the patients had no fever or seemed uninfected, or because the diagnosis of infection was straightforward. The investigation's results might therefore be hampered by selection bias and sampling error, and should be interpreted with caution.

Since it is a challenge for emergency physicians to accurately assess each patient's disposition, an indicator proving the presence of infection would be as important as one excluding it. The present investigation shows that using a cut-off level of 60 mg/l for CRP provides a good positive predictive value. The negative predictive value however was 67.9%, suggesting that about 1/3 of infected patients will be overlooked if the diagnosis is based solely on the presence of a high CRP level. The negative predictive value for CRP in patients with SIRS was only 50%. Our results show that CRP is a poor marker for excluding infection, particularly in patients with SIRS. SIRS should therefore be managed as sepsis, even if a patient has a low CRP level, unless other insult, such as trauma, burns, or pancreatitis, is documented.

In conclusion, CRP is a good indicator of bacterial infection in adult atraumatic ED patients, being superior to both BT and the WBC count. CRP cannot, however, be used safely as an indicator to exclude the presence of infection.

### Acknowledgments

We are indebted to the staff of the Emergency Department, Linkou Chang Gung Memorial

Hospital, Taoyuan, Taiwan. We thank Yu-Mei Chang, Shu-Chin Tsai, Mei-Chuang Chang, and Li-Ling Lin for their help.

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