Original Article

Serum procalcitonin as a predicting value in severity and prognosis of CAP in sickle cell patients

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ABSTRACT

Background: The Pneumonia Severity Index (PSI) and CURB-65 predict outcomes in community acquired pneumonia but have limitations. **Materials and Methods:** The study evaluated if procalcitonin in community-acquired pneumonia provides prognostic information with the PSI and CURB-65 in sickle cell adult patients. Twenty sickle cell positive adult patients with a clinical and radiographic diagnosis of community acquired pneumonia were scored using PSI and CRUB-65, and measured procalcitonin levels. **Results:** They were 12 female 60% and 8 males 40%with mean of age 46.0 ± 10.26 and were stratified with PSI, CRUB65 and sampled for procalcitonin level for PSI class I (3) patients 15%, class II (10) patients 50%,class III (3) patients 15%, class IV(one) patient 5% & class V (3) patients 15% with mean of 2.55 ± 1.276 were CRUB65 0 (2) patients 10% 1 (11) patients 55% two (3) patients 15%, three (4) patients 20%with mean of 1.45 ± 0.94 proclacitonin >0.25 (8) patients 40% and >0.50 are (12) patients 60% with mean of 1.098 ± 1.346. **Conclusion:** Procalcitonin levels on admission predict severity of community-acquired pneumonia in sickle cell patients with a similar prognostic accuracy as PSI and CRUB65 and use of procalcitonin as an adjunct to existing rules may offer additional prognostic information in high risk patients as sickle cell positive patients, further studies must address whether adding PCT to risk scores can increase their safe implementation in clinical practice. This was the scope for patients with sickle cell.

Key words: Procalcitonin level, predicting value, sickle cell positive adult patient

INTRODUCTION

To optimize and to reduce unnecessa ry hospital admission rates, professional organizations have developed prediction rules and propagated guidelines to stratify patients with community-acquired pneumonia (CAP), based on predicted risk for mortality.[1,2] Pneumonia severity index (PSI) is a well-validated scoring system that assesses the risk of death in a two-step algorithm and was developed to identify patient at low risk for mortality.[3] However, it is complex and strongly dependent on age, limiting its general implementation in routine care. The less complex CURB65 (confusion, urea >7 mmol·L^{-1}, respiratory frequency ≥30 breaths·min^{-1}, low blood pressure (systolic value <90 mmHg or diastolic value ≤60 mmHg) and age ≥65 yrs) score, focuses on five predictors.[4] This score is easier to calculate, but has a slightly inferior prognostic accuracy. Both risk scores were validated for the prediction of mortality only, and their ability to predict other CAP-associated adverse outcomes is not validated. Both scores have limitations for clinical use, including practicability, risk of miscalibration, and only moderate sensitivity and specificity, which leads to hospitalization of patients where outpatient treatment would have been preferable.[5] Thus, additional risk factors and prognostic biomarkers potentially

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enhance the prognostic performance of these established risk scores in CAP patients. Several inflammatory markers, such as leukocyte (WBC) counts and C-reactive protein (CRP) levels, are traditionally used in the evaluation of pulmonary infections. However, the value of these markers remains very limited. Recently, procalcitonin (PCT) has emerged as a promising alternative. Its level increases rapidly in bacterial infections but remains low in viral diseases. High plasma concentrations of PCT are typically seen in sepsis, meningitis and pneumonia.[6-10] PCT also seems to be a prognostic factor in sepsis and pneumonia.[11,12] The prognostic value of procalcitonin measurement beyond existing prediction rules is unclear. Masia *et al*. (2005)[13] observed that patients with high PSI scores had higher procalcitonin levels associated with mortality and complications, but Beovic *et al*. (2005)[14] found no association between procalcitonin and PSI score. These single center studies were limited by small sample sizes and used older procalcitonin assays with low sensitivity.[15] It was hypothesized that an early procalcitonin measurement would aid risk assessment beyond that available from the PSI and CURB-65 in critical cases as sickle cell patients. Patients with sickle cell anemia are at greatly increased risk to pneumococcal infections, especially meningitis, but also to bacteremia. Some of these patients also have roentgenographic evidence of acute pulmonary infiltrates, and in such cases, there is little reason to doubt the diagnosis of pneumococcal pneumonia. However, a more common event, seen in 38% to 45% of patients with sickle cell anemia, is an acute abacteremic febrile episode with a pulmonary infiltrate.[16-18] Such episodes constitute the most common single reason for hospitalization of patients with SS hemoglobin. Although presumed to represent pneumonia, more than half of these cases lack bacterial confirmation, and the patients have prolonged fever despite administration of antibiotics [Table l]. For this condition, it was unable to identify randomized control trial on efficiency and safety of antibiotic approach for people with sickle cell disease suffering for CAP, randomized control trials need to establish the options of antibiotic.

The aim of this study was to understand and prove the relationship between the severities of serum PCT levels with CAP in sickle cell patients.

MATERIALS AND METHODS

Cases of study Inclusion criteria: All sickle cell patients admitted to hospital with diagnosis in-line with CAP in hospitalized patients in adult respiratory department of our hospital from July 2011 to July 2012, diagnostic and therapeutic procedures in-line with British Thoracic Society (BTS) and American Thoracic Society (ATS) CAP treatment guidelines. Case exclusion criteria:

1. Age <14 years;
2. Merge different periods of pregnancy;
3. With underlying lung disease can fully explain and lack of imaging pulmonary infiltrates, such as bronchiectasis, pulmonary cyst with infection;
4. According to the ATS/Infection Society 2005 Guide to belong to the medical care associated pneumonia;
5. Refuse blood PCT detection on admission.

Table 1: Age, Sex, Pneumonia Score Index, Procalcitonin and CRUB-65 values

Age (year)	Sex	Sickle Cell	Psi	Pct	CRUB-65
55	Female	+	I	0.27	0
62	Male	+	I	0.28	1
57	Female	+	I	0.25	0
49	Male	+	II	0.45	1
43	Female	+	II	0.50	1
48	Male	+	II	0.51	1
38	Female	+	II	0.28	1
36	Female	+	II	0.43	1
40	Female	+	II	0.55	1
42	Female	+	II	0.43	1
37	Female	+	II	0.34	1
63	Female	+	II	0.50	1
59	Male	+	II	0.65	1
61	Male	+	III	0.78	2
48	Male	+	III	0.76	2
37	Female	+	III	0.69	2
29	Male	+	IV	3.1	3
40	Male	+	V	2.70	3
39	Female	+	V	3.40	3
37	Female	+	V	5.1	3

Prognostic scoring

The PSI was based on 20 factors that are evaluated at the time of clinical presentation and include three demographic characteristics (i.e. age, sex, and nursing home residence), five co-existing illnesses (i.e. active neoplastic disease, congestive heart failure, cerebro-vascular disease, renal disease, and liver disease), five physical examination findings (i.e. pulse rate, respiratory rate, systolic blood pressure, temperature, and mental status), six laboratory measurements (i.e. blood urea nitrogen (BUN), glucose, hematocrit, and sodium levels; partial pressure of arterial oxygen; and arterial pH), and one radiographic finding (i.e. pleural effusion), patients were grouped into five risk classes CURB-65 is an acronym based on a six-point score (range 0-5) that gives one point each for: Confusion; urea >7 mmol/l; respiratory rate ≥30/min; low blood pressure (systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg); and age 65 years or more. While CURB-65 is easy to calculate, it lacks formal assessment of vital signs and oxygen level, a major drawback in light of the importance of assessing oxygenation immediately on arrival in the emergency department.[19] Another drawback of any pneumonia severity score was only measures severity at the time of hospital admission, and usually serial measurements of severity of illness are necessary to make decisions.

Blood procalcitonin measurement

3 ml venous blood was taken into an additive-free test tube from patients before use of antibiotics within 6 h after admission. The serum was centrifuged at 1500 rpm, BRAHMS Diagnostica, Germany production testing equipment and reagents, using a double-antibody sandwich immunoassay chemiluminescence detection of serum PCT levels. Tube samples simultaneous determination of creatinine, urea nitrogen. All report results obtained within an hour.

Statistical analysis

Data were described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student's *t* test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency less than 5. The *P* values less than 0.05 were considered significant. All calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15.0 for Microsoft Windows.

RESULTS

Twenty patients were sickle cell positive (12 females and 8 males) with mean age 46.00 ± 10.26, and stratified with PSI, CRUB-65 and sampled for procalcitonin level for PSI class I (3) patients 15%, class II (10) patients 50%, class III (3) patients 15%, class IV (1) patient 5% and class V (3) patients 15% with mean of 2.55 ± 1.276 for CRUB-65 (0) 2 patients 10% (1) eleven patients 55% two (3) patients 15%, three (4) patients 20% with mean of 1.45 ± 0.94 proclacitonin >0.25 (8) patients 40% and >0.50 were (12) patients 60% with mean of 1.098 ± 1.346 [Figures 1-3] [Tables 2-7].

Table 2: Procalcitonin mean and standard deviation in different levels of PCT

PSI	Mean	N	SD
1	0.267	3	0.02
2	0.464	10	0.10
3	0.743	3	0.05
4	3.100	1	1.23
5	3.733	3	1.35
Total	1.099	20	

Table 3: Percentage of male to female

Sex	Frequency	Percent
Female	12	60.0
Male	8	40.0
Total	20	100.0

Table 4: Frequency c, value and percentage of PSI

PSI	Frequency	Percent
1	3	15.0
2	10	50.0
3	3	15.0
4	1	5.0
5	3	15.0
Total	20	100.0

Table 5: Frequency, Value and Percentage of CRUB-65

CRUB65	Frequency	Percent
0	2	10.0
1	11	55.0
2	3	15.0
3	4	20.0
Total	20	100.0

Table 6: Correlation of Procalcitonin to PSI and CRUB-65

Item	No.	Minimum	Maximum	Mean	Std. Deviation
Age	20	29	63	46.0	10.260
PSI	20	1	5	2.55	1.276
PCT	20	0.25	5.10	1.0985	1.34679
CRUB 65	20	0	3	1.45	0.945
Valid N (listwise)	20				

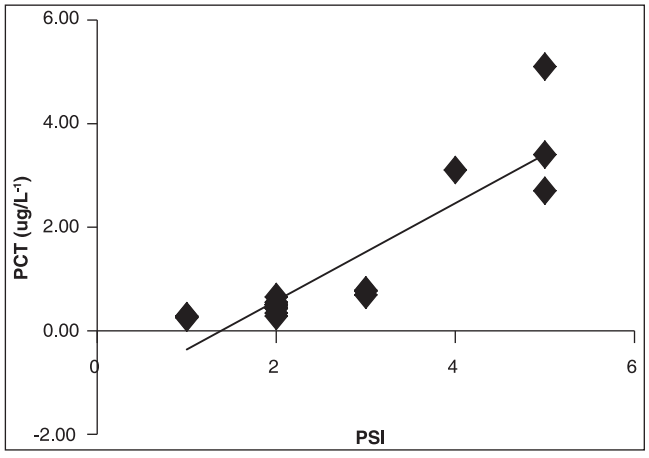

Figure 1: Correlation between PSI and serum procalcitonin (PCT, µg/L) among cases

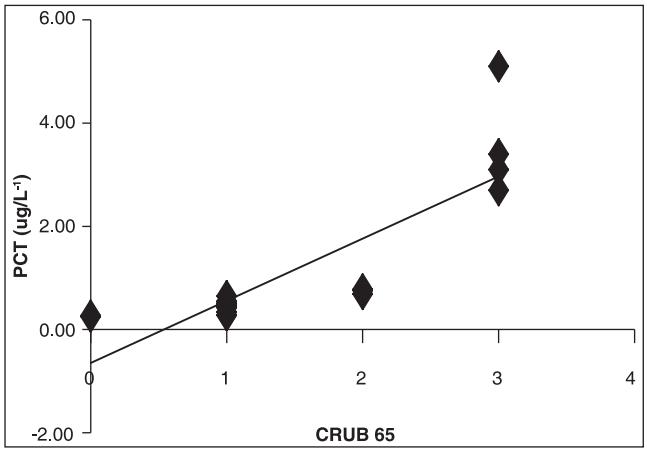

Figure 2: Correlation between CRUB-65 and serum procalcitonin (PCT, µg/L) among cases

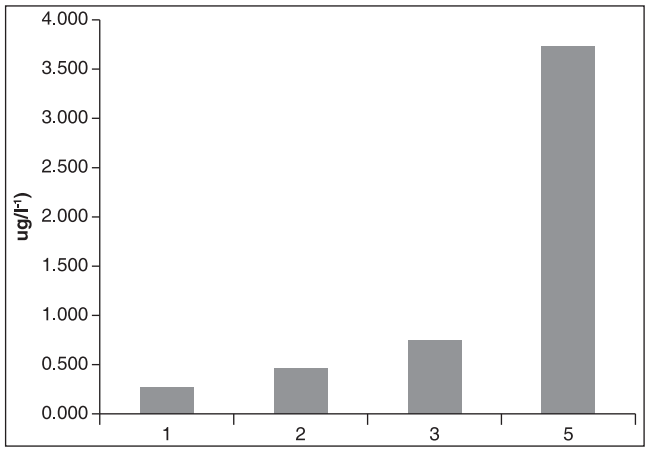

Figure 3: Mean serum procalcitonin (PCT, μg/L) according to PSI categories among cases

Table 7: Correlations

Spearman's rho	PCT
PSI	
Correlation Coefficient	0.924
P value	0.000
N	20
CRUB 65	
Correlation Coefficient	0.908
P value	0.000
N	20

Increasing severity of CAP related to PSI and CRUB-65 was associated with a pronounced gradual increase of PCT. Mean PCT levels were 0.256 ± 0.02 (0.25-0.27) in PSI class I and CRUB-65 class 0, 0.464 ± 0.10 (0.28-0.65) in PSI class II and CRUB-65 class 1, 0.743 ± 0.05 (0.69-0.78) in PSI class III and CRUB-65 2, 3.1 (3.1–3.1) in PSI class IV and CRUB-65 3, 3.73 ± 1.23 (2.70–5.1) in PSI class V and CRUB-65 3. Mean for 20 patients 1.098 ± 1.34 for PSI class mean 2.55 ± 1.27 and CRUB-65 score 1.45 ± 0.945. Correlation coefficient PSI to PCT was 0.924 and $P = 0.000$ and CRUB-65 to PCT 0.908 and $P = 0.000$ it is highly significant.

DISCUSSION

The present study confirmed that the blood PCT can be used to judge the condition of the auxiliary pneumonia, 0.25 μg·L^{-1} <PCT <0.5 μg.L^{-1} prompted the limitations of an infection is present, PCT >0.5 μg·L^{-1} prompted severe infection.[20] PCT <0.228 μg L can be used as the cutoff point of the of outpatient CAP patients with low mortality. Hospitalized CAP patients compared with outpatient illness and high mortality, it is necessary to look for severe CAP, PCT cutoff value.

In a large single-center Spanish cohort, an equivalence of the predictions were made by the PSI, CURB-65, and CRB-65 score.[19] This study showed that the CURB-65 score had a slightly lower performance in predicting intensive care unit (ICU) admission and death, probably because it may have given too much weight to age impact. But, compared PSI, CURB-65, and CURB for predicting 30-day mortality in 3181 CAP patients showed that PSI gave higher sensitivity and negative predictive value for mortality than CURB and CURB-65.[21]

Fine *et al*. (1971) reported that all class I patients and many class II and III patients were candidates for outpatient therapy, which led to significant cost savings whereas class IV and V patients, associated with high mortality, were hospital managed. PSI score was limited, due to the impact of age on the score, and the possibility of underestimating the severity of illness in younger populations while overestimating the severity in an elderly population and patients with co-morbidities.[22] Also, the PSI is a measure of mortality risk, not of pneumonia severity. Another score, which is a modified form of the BTS rule, the CURB-65 has the benefit of being easy to calculate and simple to use. The CURB-65 score was developed in a study of 1068 prospectively studied patients with CAP from three countries, UK, New Zealand, and Nether-lands. A study from the German Community-acquired pneumonia competence network (CAPNETZ) recently found that PCT levels on admission improve the prognostic performance of CRB-65 (confusion, respiratory rate ≥30 breaths·min^{-1}, low blood pressure (systolic value <90 mmHg or diastolic value ≤60 mmHg) and age ≥ 65 yrs) score.[23] However, a large USA-based CAP study, found that only a moderate additive value of PCT when compared with the PSI and CURB-65 scores[24], which was the initiation of the present study agreed that serial PCT measurement may help to assess resolution of CAP.[25] Similarly, another Spanish study found that higher follow-up PCT concentrations were associated with development of complications and death. This study has limitations. Exclusion of patients with dementia, immunosuppression, concomitant infections and active intravenous drug abuse limits its generalizability. So, this study confirmed the predictive value of PCT in combination with PSI or CURB-65 in regard to serious adverse events in adult CAP, and much less for mortality prediction which coincided with the current study. Needless to say, readily measurable biomarkers that reflect the severity of CAP and outcome could be helpful as additional prognostic tools. The present study confirmed that PCT was a good predictor of pneumonia severity.[26-28] Patients with a higher CRB-65 score had significantly higher PCT levels. In contrast, CRP and WBC were not correlated to the severity of the disease. The present study has some limitations. The number of outpatients was limited, and the use of procalcitonin alone and in combination with CRB-65 should clearly be studied in this population. Also, the number of patients at high risk was also small, raising the concern whether the present observations can be expanded to other group. In another A acute bronchitis review study, noted that a procalcitonin level less than 0.1 ng/mL may be able to safely discriminate between acute bronchitis and

CAP but that more data were needed.[29] However, clinical prediction rules have two important limitations: Physicians may misapply or not remember them, and within a given risk category there can be a significant range in outcome. We therefore sought to determine whether procalcitonin could address these concerns, first as a standalone test and then as a layer on top of clinical risk assessment. Our primary goal was to determine how procalcitonin might enhance existing CAP prediction rules and decision making in sickle cell patients. We recognize that physicians often do not explicitly calculate the PSI in daily clinical practice. However, the same factors that comprise PSI and other prediction rules also go into the bedside clinical judgment as many physicians use to guide their decisions. Our results therefore suggest that procalcitonin may aid decision making in high-risk patients as sickle cell defined explicitly or implicitly with the PSI or a similar tool, but, we did not emphasize that procalcitonin level should be used in isolation to make clinical decisions and to replace physician assessment.

The current CAP guidelines recommend that the clinically high-risk patients be hospitalized and that the ICU admission be considered for patients in highest risk categories.[30,31] Of interest, Marrie and Huang (2007)[31] found that many clinically high-risk patients might be safely treated at home. Our data suggest that procalcitonin may aid in identifying PSI/CURB-65 high-risk patients who will rarely experience mortality and other complications. Thus, there could be considerable benefits, both in terms of conserved resources and antibiotic management, if one could better stratify high-risk patients. Prospective studies are needed to determine whether procalcitonin can improve physician management decisions and outcomes in high-risk patients as sickle cell patients.

CONCLUSION

Procalcitonin levels on admission, predict severity of CAP in sickle cell patients with a similar prognostic accuracy as PSI and CRUB-65 and use of procalcitonin as an adjunct to existing rules may offer additional prognostic information in high-risk patients as sickle cell positive patients.

Future studies must address whether adding PCT to risk scores can increase their safe implementation in clinical practice. This was the scope for patients with sickle cell.

REFERENCES

1. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, *et al*. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia: Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730-54.
2. Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, *et al*. European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J 2005;26:1138-80.
3. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, *et al*. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243-50.
4. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, *et al*. Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. Thorax 2003;58:377-82.
5. Schuetz P, Koller M, Christ-Crain M, Steyerberg E, Stolz D, Müller C, *et al*. Predicting mortality with pneumonia severity scores: Importance of model recalibration to local settings. Epidemiol Infect 2008;136:1628-37.
6. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, *et al*. Infectious Diseases Society of America, American Thoracic Society. Infectious diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27-72.
7. Neill AM, Martin IR, Weir R, Anderson R, Chereshsky A, Epton MJ, *et al*. Community acquired pneumonia: Aetiology and usefulness of severity criteria on admission. Thorax 1996;51:1010-6.
8. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157-72.
9. Schuetz P, Albrich W, Christ-Crain M, Chastre J, Mueller B. Procalcitonin for guidance of antibiotic therapy. Expert Rev Anti Infect Ther 2010;8:575-87.
10. Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, *et al*. ProHOSP study group. Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: A prospective, multicenter, randomized controlled trial. BMC Health Serv Res 2007;7:102.
11. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, *et al*. PRORATA trial group. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): A multicentre randomised controlled trial. Lancet 2010;375:463-74.
12. Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, *et al*. Procalcitonin-guided antibiotic use vs. a standard approach for acute respiratory tract infections in primary care. Arch Int Med 2008;168:2000-7.
13. Masiá M, Gutiérrez F, Shum C, Padilla S, Navarro JC, Flores E, *et al*. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patients outcome research team pneumonia severity index. Chest 2005;128:2223-9.
14. Beovic B, Kreft S, Osredkar J, Kese D, Bonac-Tuma B. Serum procalcitonin levels in patients with mild community-acquired pneumonia. Clin Microbiol Infect 2005;11:1050-1.
15. Nylen E, Muller B, Becker KL, Snider R. The future diagnostic role of procalcitonin levels: The need for improved sensitivity. Clin Infect Dis 2003;36:823-4.
16. Barret-Connor E. Acute pulmonary disease and sickle cell anemia. Am Rev Respir Dis 1971;104:159-65.
17. Henderson AB. Sickle cell anemia: Clinical study of 54 cases. Am J Med 1950;9:757-65.
18. Reynolds J. The roentgenological features of sickle cell disease and related hemoglobinopathies. Springfield, Ill, Charles C. Thomas Publisher; 1965.
19. Capelastegui A, Espana PP, Quintana JM, Areitio I, Gorordo I, Egurrola M, *et al*. Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J 2006;27:151-7.
20. Petch MC, Serjeant GR. Clinical features of pulmonary lesions in sickle cell-anemia. Br Med J 1970;3:31.
21. Aujesky D, Auble TE, Yearly DM, Stone RA, Oborosky DS, Meehan TP, *et al*. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. Am J Med 2005;118:384-92.
22. Ewig S, de Roux A, Bauer T, Garcia E, Mensa J, Niederman MS, *et al*. Validation of predictive rules and indices of severity for community acquired pneumonia. Thorax 2004;59:421-7.

23. Krüger S, Ewig S, Marre R, Papassotiriou J, Richter K, von Baum H, *et al*. CAPNETZ Study Group. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across allCRB-65 classes. Eur Respir J 2008;31:349-55.
24. Huang DT, Weissfeld LA, Kellum JA, Yealy DM, Kong L, Martino M, *et al*. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. Ann Emerg Med 2008;52:48-58.
25. Menéndez R, Martinez R, Reyes S, Mensa J, Polverino E, Filella X, *et al*. Stability in community acquired pneumonia: One step forward with markers? Thorax 2009;64:987-92.
26. Hausfater P, Garric S, Ayed SB, Rosenheim M, Bernard M, Riou B. Usefulness of procalcitonin as a marker of systemic infection in emergency department patients: A prospective study. Clin Infect Dis 2002;34:895-901.
27. Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: Correlation with etiology and prognosis. Infection 2000;28:68-73.
28. Polzin A, Pletz M, Erbes R, Raffenberg M, Mauch H, Wagner S, *et al*. Procalcitonin as a diagnostic tool in lower respiratory tract infections and tuberculosis. Eur Respir J 2003;21:939-43.
29. Wenzel RP, Fowler AA 3rd. Clinical practice. Acute bronchitis. N Engl J Med 2006;355:2125-30.
30. Macfarlane JT, Boldy D. Update of BTS pneumonia guidelines: What's new? Thorax 2004;59:364-6.
31. Marrie TJ, Huang JQ. Admission is not always necessary for patients with community-acquired pneumonia in risk classes IV and V diagnosed in emergency room. Can Respir J 2007;14:212-6.

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