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Procalcitonin in severe acute respiratory syndrome (SARS)

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KEYWORDS
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Summary Objective and methods. The role of procalcitonin (PCT) in severe acute respiratory syndrome (SARS) has not been highlighted so far. We described retrospectively eight cases of sepsis from pneumonia of various microbiological aetiologies including two due to SARS, compared their PCT concentrations and provided further descriptors of SARS as a viral pneumonia.

Results. Like any viral pneumonia, patients with SARS had low PCT levels in contrast to bacterial or fungal pneumonia.

Conclusions. In the setting of pneumonia with a finding of low PCT, testing for SARS should be considered, especially if there is a positive travel or contact history. During a SARS epidemic, we also strongly advocate isolating all suspected community acquired pneumonia with a low PCT level.

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Introduction

Procalcitonin (PCT) is a recently described innovative marker of severe sepsis.1 Concentration increases in bacterial infections but remains low in viral infections making it a useful marker for distinguishing between bacterial and viral infections.2,3 Severe acute respiratory syndrome (SARS) had been documented to be due to a novel coronavirus which has caused a rapidly progressive pneumonia in all age sectors in an epidemic manner with high fatality rate.4,5 Rapid and accurate diagnostic tools are critical in the management of this potentially fatal disease. There are limitations to the current existing diagnostic tools. A low PCT level may provide an additional useful case definition to this deadly viral pneumonia.

Method and materials

PCT concentrations were measured for patients on admission to our medical intensive care unit (MICU) for severe sepsis from community-acquired pneumonia according to the American College of Chest Physicians/Society of Critical Care Medicine criteria. These patients presented during the peak SARS outbreak period in our country from March to July this year. In vitro PCT levels were measured in serum samples by use of KRYPTOR immunoanalyser (DYAMED Biotech) available in a service laboratory.
at National University Hospital, Singapore. The upper limit of normal was 0.5 ng/ml.

### Results

All patients with viral pneumonia including two patients with SARS had low PCT level of less than 1 ng/ml (Table 1). In contrast, PCT concentrations were raised in bacterial and fungal pneumonia with the exception of mycoplasma pneumonia.

### Discussion

Procalcitonin, a 14-kDa protein encoded by the

| Case no. | Age (yr) / gender | Comorbidities | Diagnosis             | Radiological finding                                      | Microbiology results                                                                 | PCT level (ng/ml) | Mechanical ventilationa |
|----------|-------------------|---------------|-----------------------|-----------------------------------------------------------|--------------------------------------------------------------------------------------|------------------|------------------------|
| 1        | 71 / Female       | Diabetes, autoimmune hypothyroidism | SARS                  | Bilateral lower lobe ground glass opacification            | Nasopharyngeal aspirate SARS-CoV RT-PCR and anti-SARS-CoV Ig G titer positive Seeb    | 0.11             | Yes                    |
| 2        | 43 / Female       | Hypertension  | SARS                  | Bilateral lower lobe consolidations                        | Sputum and blood cultures positive for Klebsiella pneumoniae                          | 0.74             | Yes                    |
| 3        | 65 / Male         | Gastric non-Hodgkin lymphoma 2001 with gastrectomy and chemotherapy | Klebsiella pneumonia | Airspace shadowing in right mid and upper zones            | All \(>10\), highest 27                                                              |                  |                         |
| 4        | 76 / Male         | None          | Pulmonary tuberculosis | Bilateral patchy fluffy infiltrate with cavitation Multilobar consolidations | AFB smear positive                                                                  | 5.42             | Yes                    |
| 5        | 33 / Male         | Type 1 diabetes on insulin, melioidosis with meningitis and osteomyelitis 2002 | Melioidosis | Blood and respiratory cultures positive for Burkholderia pseudomallei | Bronchoalveolar lavage cytology positive for PCP                                       | 79.24            | Yes                    |
| 6        | 55 / Male         | Renal transplant 1988 | PCP pneumoniac       | Bilateral diffuse groundglass consolidation predominantly in the perihilar regions |                                               | 2.58             | Yes                    |
| 7        | 47 / Male         | Bronchial asthma, newly diagnosed HIV positive Malaria | ? CMVd pneumonia | Fine alveolar infiltrate in the perihilar regions bilaterally | Low grade CMV viraemia. Bronchoscopic lavage negative                                  | 0.07             | No                     |
| 8        | 45 / Female       | Migraine      | Mycoplasma pneumonia | Infiltrate in left mid lung field obscuring left cardiac border | Significant rise in serum mycoplasma titre                                            | <0.06            | No                     |

a Mechanical ventilation was indicated for severe type 1 respiratory failure from acute respiratory distress syndrome or severe pneumonia.

b All investigations were negative. Postmortem was not performed due to possible high infectious risk. Diagnostic kit for coronavirus was also not available in our hospital at that time. However, we think she likely had SARS as a healthcare worker who had performed a bronchoscopic lavage on her fell ill 3 days after the contact and was subsequently confirmed to have SARS serologically.

c Pneumocystis carinii pneumonia.

d Cytomegalovirus.
Calc-1 gene along with calcitonin and kataclacin, is an innovative diagnostic parameter with kinetics different from other presently available indicators of the inflammatory response. In the animal model, hyperprocalcitoninemia was an early systemic marker of sepsis which correlated closely with severity of acute illness and mortality. Studies of its behavior in patients with bacterial sepsis have found it to be a useful marker of systemic bacterial infection, with greater specificity and sensitivity than acute phase proteins such as C-reactive protein, interleukin-6 and lactate levels even in a medical intensive care unit setting.

The excellent specificity and negative predictive value at a cut-off point of 0.5 ng/ml suggests that this test might be a useful parameter in the management of infective diseases. PCT can help to identify an infectious cause or complication in patients with systemic inflammatory response syndrome (SIRS). It has also been used to distinguish infectious from non-infectious causes of acute respiratory distress syndrome (ARDS). It is moderately increased in local bacterial infection (pneumonia, pyelonephritis), parasitic and fungal infections and is unchanged or only slightly increased in even severe viral infections. A serum PCT level of <$0.4 ng/ml accurately rules out the diagnosis of bacteraemia. Children with bacterial pneumonia had significantly higher PCT than those with sole viral aetiology. PCT has also similarly high diagnostic value in both immunosuppressed and non-immunosuppressed patients with sepsis or severe infections.

SARS is an emerging infectious disease by a novel coronavirus—SARS-CoV which is associated with pneumonia with global impact. It is notable that nearly 40% of the patients developed respiratory failure that required assisted ventilation. In the ICU setting, SARS is essentially ARDS plus intensified respiratory isolation. The clinical presentation and radiologic features of SARS bear some resemblance to the syndrome commonly referred to as ‘atypical pneumonia’. The high incidence of altered liver function, leucopenia, severe lymphopenia, thrombocytopenia, and subsequent evolution into adult respiratory distress syndrome suggest a severe systemic inflammatory damage induced by this human pneumonia-associated coronavirus. The constellation of absence of upper respiratory symptoms, the presence of dry cough, and minimal auscultatory findings with consolidations on chest radiographs may alert the clinician to the possible diagnosis of SARS. However, the clinical and radiographic characteristics of atypical pneumonia are not useful in differentiating these pathogens from usual bacterial pathogens such as S. pneumoniae and H. influenzae. Clinical diagnosis also becomes particularly problematic once the association with travel or case contact is lost. The difficulty of making a firm diagnosis until chest radiographic changes appear has important implications for healthcare personnel and for surveillance.

Early diagnosis by virus isolation or serological testing is essential to halt the spread of SARS. Rapid diagnosis of SARS for infection-control measures and potential treatment will require very sensitive and specific methods. There is still no reference standard (gold standard) test for SARS. Three diagnostic tests are currently available, but all with their limitations.

We have reported two cases of patients with SARS and low PCT levels. This is consistent with the current evidence that SARS is just another viral pneumonia. High initial levels of PCT may be used to exclude SARS to a certain degree of accuracy whereas low PCT in relevant clinical context may prompt further testing for SARS. We recommend that PCT concentrations be determined for every patient presenting with community-acquired pneumonia.

Conclusions

In the setting of pneumonia with a finding of low PCT, with or without a positive contact history for SARS or relevant travel history, testing for SARS should be considered. This may be an additional screen to help narrow the number of patients that require specific SARS testing. However, the true validity of this test requires further prospective testing.

References

1. Reinhart K, et al. Markers of endothelial damage in organ dysfunction and sepsis. Crit Care Med 2002;30(Suppl. 5): S302–S312.
2. Harbath S, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 2001; 164(6):396–402.
3. Luzzani A, et al. Comparison of procalcitonin and C-reactive protein as markers of sepsis. Crit Care Med 2003;31(6): 1737–1741.
4. Kuiken T, Fouchier RA, Schutten M, Rimmelzwann GF, van Amerongen G, van Riel D, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003; accessed Aug 2, 2003, at http://image.thelancet.com/extras/03art6318web.pdf.
5. Donnelly CA, Ghani AC, Leung GM, Hedley AJ, Fraser C, Riley S, et al. Epidemiological determinants of spread of causal
agent of severe acute respiratory syndrome in Hong Kong. *Lancet* 2003;31:1761–1766.

6. Whicher J, et al. Procalcitonin as an acute phase marker. *Ann Clin Biochem* 2001;38(Pt 5):483–493.

7. Steinwald PM, et al. Elevated calcitonin precursor levels are related to mortality in an animal model of sepsis. *Crit Care (Lond)* 1999;3(1):11–16.

8. Luzzani A, et al. Comparison of procalcitonin and C-reactive protein as markers of sepsis. *Crit Care Med* 2003;31(6):1737–1741.

9. Muller B, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med* 2000;28(4):1226–1228.

10. Procalcitonin in diagnosis of severe infections. *Eur J Med Res* 1996 Apr 18; 1(7):331–333.

11. Du B, et al. Serum procalcitonin and interleukin-6 levels may help to differentiate systemic inflammatory response of infection and non-infectious origin. *Chin Med J* 2003;116(4):538–542.

12. Brunkhorst FM, et al. Discrimination of infectious and non infectuous causes of early acute respiratory distress syndrome by procalcitonin. *Crit Care Med* 1999;27:2172–2176.

13. Harbath S, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med* 2001;164(3):396–402.

14. Schwarz S, et al. Serum procalcitonin levels in bacterial and abacterial meningitis. *Crit Care Med* 2000;28(6):1828–1832.

15. Lotric-Furlan S, et al. Procalcitonin levels in patients with Lyme borreliosis. *Wien Klin Wochenschr* 2002;114(13–14):530–532.

16. Lawn SD, et al. Serum procalcitonin concentrations in patients with pulmonary tuberculosis. *Trans R Soc Trop Med Hyg* 1998;92(5):540–541.

17. Hatherill M, et al. Procalcitonin may help differentiate disseminated herpes simplex viral infection from bacterial sepsis in neonates. *Eur J Pediatr* 2000;159(3):168–169.

18. Hollenstein U, et al. Serum procalcitonin levels in severe *Plasmodium falciparum* malaria. *Am J Trop Med Hyg* 1998;59(6):860–863.

19. Chirouze C, et al. Low serum procalcitonin level accurately predicts the absence of bacteremia in adult patients with acute fever. *Clin Infect Dis* 2002;35(2):15–61.

20. Moulin F, et al. Procalcitonin in children admitted to hospital with community acquired pneumonia. *Arch Dis Child* 2001;84(4):332–336.

21. Procalcitonin as a marker of bacterial sepsis in patients infected with HIV-1. *J Infect* 1997;35(1):41–46.

22. Giamarellos-Bourboulis EJ, et al. Assessment of procalcitonin as a diagnostic marker of underlying infection in patients with febrile neutropenia. *Clin Infect Dis* 2001;32(12):1718–1725.

23. Klinikum der JW. Procalcitonin in patients with and without immunosuppression and sepsis. *Infection* 1996;24(6):434–436.

24. Lee N, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;348(20):1986–1994.

25. Gordon D, et al. Is SARS just ARDS? *JAMA* 2003;290(3):397–399.

26. SARS: experience at Prince of Wales Hospital, Hong Kong. Commentary. *Lancet* 2003;361.

27. Zhou BP, et al. Identification and molecular cloning and sequence analysis of a novel coronavirus from patients with SARS by RT-PCR. *Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi* 2003;17(2):137–139.

28. The SARS Coronavirus: rapid diagnostics in the limelight. (Editorial). *Clin Chem* 2003;49:845–846.