

Procalcitonin for detecting community-acquired bacterial pneumonia

Devi Gusmaiyo¹, Finny Fitry Yani¹, Efrida², Rizanda Machmud³

Abstract

Background Pneumonia is a major cause of morbidity and mortality in children under five years of age. Pneumonia can be of bacterial or viral origin. It is difficult to distinguish between these two agents based on clinical manifestations, as well as radiological and laboratory examinations. Furthermore, bacterial cultures take time to incubate and positive results may only be found in 10-30% of bacterial pneumonia cases. Procalcitonin has been used as a marker to distinguish etiologies, as bacterial infections tend to increase serum procalcitonin levels.

Objective To determine the sensitivity, specificity, positive predictive value and negative predictive value of procalcitonin in community-acquired bacterial pneumonia.

Method This cross-sectional study was conducted in the Pediatric Health Department of Dr. M. Djamil Hospital, Padang. Subjects were selected by consecutive sampling. Procalcitonin measurements and PCR screening were performed on blood specimens from 32 pneumonia patients and compared.

Results Of the 32 subjects, most were boys (56.25%), under 5 years of age (99%), and had poor nutritional status (68.75%). Using a cut-off point of 0.25 ng/mL, procalcitonin level had a sensitivity of 92%, specificity 50%, positive predictive value 88%, and negative predictive value 60% for diagnosing bacterial pneumonia. Using a cut-off point of 0.5 ng/mL, procalcitonin level had a specificity of 46%, specificity 83%, positive predictive value 91%, and negative predictive value 25%.

Conclusion A cut-off point of 0.25 ng/mL of procalcitonin level may be more useful to screen for bacterial pneumonia than a cut-off point of 0.5 ng / mL. However, if the 0.25 ng/mL cut-off point is used, careful monitoring will be required for negative results, as up to 40% may actually have bacterial pneumonia. [Paediatr Indones. 2015;55:65-9].

Keyword: community bacterial pneumonia, procalcitonin, PCR

Pneumonia is a leading cause of morbidity and mortality in children under five years of age.¹ The 2007 Indonesian Basic Health Research Report (Riset Kesehatan Dasar, Riskesdas) found pneumonia to be the second leading cause of death in Indonesian children under five, after diarrhea. The prevalence of pneumonia in West Sumatera was 0.7% for infants and 0.8% for children under the age of five.²

It is difficult to distinguish between viral and bacterial pneumonia using clinical manifestations, radiological examinations, and routine laboratory tests. Bacterial cultures require a long incubation time and yield positive results in only 10-30% of patients cultured. A polymerase chain reaction (PCR) method has been used as the gold standard to diagnose bacteremia patients with good sensitivity and specificity.³⁻⁶ However, the PCR method has not been widely used due to its high cost, need for sophisticated equipment, difficult equipment maintenance, and

From the Department of Pediatrics¹, Department of Clinical Pathology², and Department of Community Health³, Andalas University Medical School/Dr. M. Djamil Hospital, Padang, West Sumatera, Indonesia.

Reprint requests to: Devi Gusmaiyo, MD, Pediatrics Department, R.S., Andalas University Medical School/Dr. M. Djamil Hospital, Jl. Perintis Kemerdekaan, Padang, West Sumatera, Indonesia. E-mail: devi_gusmaiyo76@yahoo.com.

requirement of skilled technicians. Procalcitonin has been reported to be the most accurate laboratory test to diagnose bacterial infections, with sensitivity 89%, specificity 94%, positive prediction value 94%, and negative prediction value 90%.⁷

In 2000, the *World Health Organization* (WHO) reported that only 20 of every 100 children with respiratory infections need antibiotic therapy.⁸ It is important to find a marker that can be used to immediately diagnose bacterial pneumonia, so that appropriate antibiotics can be administered. As such, treatment costs and possible side effects can be reduced, and patients' prognoses and disease severity can also be used to determine the need for ICU admission.^{9,10,12} We aimed to assess the diagnostic validity of procalcitonin level in community-acquired bacterial pneumonia compared to PCR result as a gold standard.

Methods

This cross-sectional included children with severe pneumonia who were hospitalized in the Pediatrics Ward of Dr. M Djamil Hospital, Padang, from January to December 2013. Subjects were chosen in a non-probability sampling with consecutive technique. The inclusion criteria were children diagnosed with severe pneumonia according to WHO criteria, who had been ill for <48 hours, had no comorbidities based on history-taking, physical examination, and previous disease history, aged 2 months to 14 years, and whose parents provided written informed consent. We excluded children with nosocomial pneumonia. This study was approved by the Ethics Committee of Dr. M. Djamil Hospital, Padang.

We recorded subjects' age, gender, and clinical findings such as cough, body temperature, respiratory rate per minute, nasal flaring/chest wall retraction, and rhonchi upon auscultation. Subjects underwent antero-posterior chest radiographs and 2 mL blood specimens were obtained from the cubital vein using aseptic and antiseptic techniques. Using the blood specimens, we examined procalcitonin levels and performed PCR analysis to assess for bacterial vs. viral etiologies in Biomedical Laboratory of Andalas University Medical School. The analysis was performed by using the 2x2 table.

Results

During the study period there were 55 children hospitalized with diagnoses of bronchopneumonia/pneumonia, 32 of whom were included in the study. We excluded 7 children with congenital heart disease, 2 children with sepsis since hospital admission, 4 children who received previous antibiotic treatment, 4 children whose blood specimens were accidentally lysed so as to be unusable, and 6 children whose parents refused participation.

The characteristics of subjects are shown in **Table 1**. The ratio of males to females was 9:7. The largest age group was 1 to 4 years (16/32) and the ratio of good nutritional status to poor nutritional status was 5:11.

Sensitivity, specificity, positive predictive value, and negative predictive value are shown in **Table 2**. There were 24 patients with bacterial infections, based on both procalcitonin examination and PCR methods. However, 26 patients were considered positive for bacterial infection based on PCR methods alone, so the sensitivity of procalcitonin (using a cut-off point of 0.25 ng/L) was 92%. There were 3 pneumonia patients with non-bacterial agents of infection based on procalcitonin examination and PCR methods, while 6 patients were negative for bacterial infection

Table 1. Characteristics of study subjects (n=32)

| Characteristics | N |
|--------------------|----|
| Gender | |
| Male | 18 |
| Female | 14 |
| Age group | |
| 2-11 months | 15 |
| 1-4 years | 16 |
| 5-12 years | 1 |
| Nutritional status | |
| Good | 10 |
| Poor | 22 |

Table 2. Sensitivity, specificity, positive predictive value, and negative predictive value of procalcitonin (cut-off point 0.25 ng/mL) compared to the PCR method

| Procalcitonin level | PCR | | Total |
|----------------------------|----------|----------|-------|
| | Positive | Negative | |
| Procalcitonin ≥ 0.25 ng/mL | 24 | 3 | 27 |
| Procalcitonin < 0.25 ng/mL | 2 | 3 | 5 |

Sensitivity: 92%, specificity: 50%, positive predictive value: 88%, negative predictive value: 60%

Table 3. Sensitivity, specificity, positive predictive value, negative predictive value of procalcitonin examinations (cut-off point of 0.5 ng/mL) compared to the PCR method

| Procalcitonin level | PCR | | Total |
|--------------------------------|----------|----------|-------|
| | Positive | Negative | |
| Procalcitonin ≥ 0.5 ng/mL | 11 | 1 | 12 |
| Procalcitonin < 0.5 ng/mL | 15 | 5 | 20 |

Sensitivity: 46%, specificity: 83%, positive predictive value: 91%, negative predictive value: 25%

incidence of pneumonia was in 1 to 5-year-old and decreased with age.

Various risk factors can increase the incidence and severity of disease, as well as death due to pneumonia, including nutritional status, vitamin A and zinc supplementation, vaccinations, cigarette smoke, and air pollution.¹⁵ We also had more pneumonia patients with poor nutritional status (22/32) than

Table 4. Comparison of diagnostic accuracy between procalcitonin threshold values of 0.25 ng/mL and 0.5 ng/mL

| Cut-off point | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---------------|-------------|-------------|---------------------------|---------------------------|
| 0.25 ng/mL | 92% | 50% | 88% | 60% |
| 0.5 ng/mL | 46% | 83% | 91% | 25% |

based on PCR methods alone, so the specificity of procalcitonin was 50%.

Table 3 shows the results of using a procalcitonin cut-off point of 0.5 ng/mL. The procalcitonin diagnostic accuracy obtained was sensitivity 46%, specificity 83%, positive predictive value 91%, and negative predictive value 25%.

Table 4 shows that the procalcitonin cut-off point of 0.25 ng/mL had higher sensitivity than that of 0.5 ng/mL. Hence, the lower value would be better for screening patients. However, it is important to continue vigilant patient observation for those with negative results (i.e., procalcitonin < 0.25 ng/mL) because the negative predictive value was 60%, indicating the possibility that 40% of these patients actually have bacterial infections, despite their lower procalcitonin level.

Discussion

In our study, there were more male than female subjects (18/32 males). Similarly, Kisworini *et al.* and Beyeng *et al.* had more boys than girls in their studies, with 55% and 59.4%, respectively.^{13,14} Our largest subject age group was under five years (99%), with children aged 2-11 months comprising 46%, and those aged 1-4 years comprising 53%. This result was similar to studies by Kisworini *P et al.* and Beyeng *et al.* which had mean subject ages of 16 and 11 months, respectively.^{13,14} The peak

good nutritional status. Gozali also showed that nutritional status significantly affects pneumonia incidence.¹⁶

Several studies have shown that procalcitonin can be used as diagnostic marker and to examine the severity of bacterial infection. However, procalcitonin is not useful for viral and local bacterial infections, as procalcitonin levels increase during systemic bacterial infection.¹⁷ Lacour *et al.* investigated about the superiority of procalcitonin in the threshold of 0.5 ng/mL compared by the peripheral blood analysis and C-reactive protein (CRP) as the specific marker of bacterial infection with sensitivity of 93%, specificity of 74%, positive predictive value of 60%, and negative predictive value of 96%.¹⁸ Lacour *et al.* compared procalcitonin and C-reactive protein (CRP). They found that using a threshold value of 0.5 ng/mL, procalcitonin level had sensitivity of 93%, specificity of 74%, positive predictive value of 60%, and negative predictive value of 96% and was superior to CRP as a marker of bacterial infection.¹⁸

We found that using a procalcitonin cut-off point of 0.25 ng/mL had the following procalcitonin diagnostic accuracy: sensitivity 92%, specificity 50%, positive predictive value 88%, and negative predictive value 60%. A meta-analysis study conducted by Simon *et al.*²⁰ reported that the sensitivity and specificity of procalcitonin was higher than those of CRP to distinguish between bacterial and viral infections (sensitivity 92% vs. 86% and specificity 73% vs.

70%, respectively). Another study also reported that procalcitonin (cut-off point 0.25 ng/mL) had higher diagnostic accuracy than that of CRP and that total leukocytes can differ between community-acquired pneumonia and infection cause.²¹ O' Connor *et al.* reported that procalcitonin had sensitivity 89%, specificity 94%, positive predictive value 94%, and negative predictive value 90% in diagnosing bacterial infections.⁷

Using the cut-off point of 0.5 ng/mL, procalcitonin level had a sensitivity of 46%, specificity 83%, positive predictive value 91%, and negative predictive value 25%. These values reflect the poor ability of procalcitonin as a diagnostic tool at this cut-off point to detect pneumonia caused by bacteria, but it would be more specific in ruling out pneumonia caused by non-bacterial agents.

Cahayasari *et al.* conducted a study in 49 children with neutropenia and fever. They reported that a procalcitonin threshold >0.84 ng/mL had sensitivity of 77.8%, specificity of 87.1%, and accuracy of 83.7% for detecting bacterial infection.²² Also, Herawaty *et al.* conducted a study in children aged 3-36 months who were suspected of having bacterial infections and reported that increased procalcitonin ≥ 2 ng/mL was related to severity of the disease, bacteremia, and sepsis.²³

Christ-Crain *et al.* conducted a study in patients with lower respiratory tract infections and reported that procalcitonin levels >0.25 ng/mL indicate a bacterial cause and antibiotic therapy can be started.¹¹ The prospective study by Esposito *et al.* used a procalcitonin cut-off point of ≥ 0.25 ng/mL at hospital admission for determining antibiotic use. The antibiotic would not be administered if procalcitonin level was <0.25 ng/mL, in an effort to significantly reduce antibiotic administration and its possible side effects.²⁴

In conclusion, a procalcitonin cut-off point of 0.25 ng/mL can be used to screen for bacterial pneumonia as compared to a procalcitonin cut-off point of 0.5 ng/mL. However, monitoring should be continued if the result is negative, because there is a 40% chance that they do indeed have bacterial pneumonia. It is required to find another diagnostic tool with high sensitivity and specificity in identifying community bacterial pneumonia in children.

Conflict of interest

None declared

References

1. Said M. Tepatkah mendiagnosis pneumonia berdasarkan hasil pemeriksaan radiologis semata? In: Manajemen kasus respiratorik anak dalam praktek sehari-hari. Jakarta: Ypnas Suddhaprana; 2007. p. 83-94.
2. Pusat Data dan Surveilans Epidemiologi. Situasi pneumonia balita di Indonesia. Buletin jendela epidemiologi. Jakarta: Pusat Data dan Surveilans Epidemiologi; 2010.
3. Lorente ML, Falguera M, Nogues A, Gonzalez AR, Merino MT, Caballero MR. Diagnosis of pneumococcal pneumonia by polymerase chain reaction (PCR) in whole blood: a prospective clinical study. *Thorax*. 2000;55:133-7.
4. Zhang Y, Isaacman DJ, Wadowsky RM, Rydquist-White J, Post JC, Erlich GD. Detection of *Streptococcus pneumoniae* in whole blood by PCR. *J Clin Microbiol*. 1995;33:596-601.
5. Dominguez J, Gali N, Matas L, Pedroso P, Blanco S, Gimenez M, *et al.* PCR detection of *Streptococcus pneumoniae* DNA in serum samples for pneumococcal pneumonia diagnosis. *Clin Microbiol Infect*. 2001;7:164-6.
6. Murdoch DR. Nucleic acid amplification tests for the diagnosis of pneumonia. *Clin Infect Dis*. 2003;36:1162-70.
7. O'Connor E, Venkatesh B, Lipman J, Mashongonyika C, Hall J. Procalcitonin in critical illness. *Crit Care Resusc*. 2001;3:236-43.
8. World Health Organization. WHO report on infectious diseases 2000. Overcoming antimicrobial resistance. Geneva, 2000. WHO/CDS/2000.2..
9. Limper M, de Kruif MD, Ajubi TL, van Zanten A, Brandjes DP, Duits AJ, *et al.* Procalcitonin as a potent marker of bacterial infection in febrile Afro-Caribbean patients at the emergency department. *Eur J Clin Microbiol Infect Dis*. 2011;30:831-6.
10. Irawati HM, Ponpon S, Idjradinata. Kesesuaian nilai C reaktif protein dan procalcitonin dalam diagnosis pneumonia berat pada anak. *Sari Pediatri*. 2010;12:4.
11. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, *et al.* Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet*. 2004;363:600-7.
12. Setyanto DB. Pemantuan tatalaksana pneumonia. In: Hendarto A, Trihono PP, Oswari H, Gunardi H, editors. State of the art: common problems in hospitalized children.

- Jakarta: IDAI cab DKI Jakarta; 2011. p. 8-19.
13. Kisworini P, Setyati A, Sutaryo. Mortality predictors of pneumonia in children. *Paediatr Indones.* 2010;50:149-53.
 14. Beyeng RTD, Purniti PS, Naning R. Validity of bacterial pneumonia score for predicting bacteremia in children with pneumonia. *Paediatr Indones.* 2011;51:322-6.
 15. Kartasasmita CB. Pneumonia pembunuh balita. *Buletin Jendela Epidemiologi.* 2010;3:22-6.
 16. Gozali A. Hubungan antara status gizi dengan klasifikasi pneumonia pada balita di puskesmas Gilingan Kec Banjarsari Surakarta. [Surakarta]: Universitas Sebelas Maret; 2010.
 17. Arkader R, Troster EJ, Lopes MR, Junior RR, Carcillo JA, Leone C, *et al.* Procalcitonin does discriminate between sepsis and systemic inflammatory response syndrome. *Arch Dis Child.* 2006;91:117-20.
 18. Galetto-Lacour A, Zamora SA, Gervaix A. Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in referral centre. *Pediatrics.* 2003;112:1054-60.
 19. 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.
 20. Simon L, Gauvin F, Amre DK. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis.* 2004;39:206-17.
 21. Muller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, *et al.* Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. *BMC Infect Dis.* 2007;7:10.
 22. Cahayasari F, Reniati L, Chairulfatah A. Kadar procalcitonin pada anak dengan demam netropenia. *Sari Pediatri.* 2012;14:104-9.
 23. Herawaty T, Tumbaleka AR, Widodo DP, Trihono PP, Setyanto DB, Yanuarso PB. Procalcitonin levels in children aged 3-36 months with suspected serious bacterial infection. *Paediatr Indones.* 2010;50:310-5.
 24. Esposito S, Tagliabue C, Picciolli I, Semino M, Sabatini C, Consolo S, *et al.* Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia. *Respir Med.* 2011;105:1939-45.