

Early Detection of Elevated Serum Procalcitonin Is Required as Warning Sign of Sepsis in Burn Patients

Fory Fortuna, Aditya Wardhana
 Jakarta, Indonesia

Backgrounds: Procalcitonin (PCT) is a marker of the inflammatory response. This biomarker also plays a key role in burn injury, as it is accompanied by systemic inflammatory response syndrome (SIRS). Elevated level of serum PCT possibly interprets the state of inflammation and multiple organ dysfunctions (MOD) with the risk of lethal outcome.

Patients and Methods: We detected high serum PCT level associated with its warning state of inflammation in 3 adult patients. We found that each high PCT level was continued by its state of inflammation. These four patients encounter serum PCT level into more than 10 ng/ml. Sepsis was diagnosed according to American Burn Association Sepsis Criteria.

Results: High elevated PCT serum level (161.70 ng/mL) was detected on the first patient 8 days post burn injury and died on the next 5 days. on the second patient, high PCT serum level (40.81 ng/mL) detected 9 days after burn injury and died on the next 2 days. The third patient was detected with high PCT serum level (12.28ng/mL) 2 days after burn injury was died on the next 2 days. The pediatric patient was detected with high PCT level (23.41 ng/ml) 11 days after burn injury and died on the next 4 days.

Summary: We found that it is important to initiate PCT measurements in burn patients at the time of admission. Daily measurement of PCT levels is needed for an early diagnosis and treatment of burn sepsis, monitoring therapy and MOD prevention.

Keywords: PCT measurements, burns, tangential excision, MEBO, STSG

Latar Belakang: Procalcitonin (PCT) merupakan salah satu penanda inflamasi yang juga berperan dalam luka bakar, terutama yang diikuti dengan SIRS. Peningkatan kadar PCT dalam darah menunjukkan keadaan inflamasi dan kemungkinan gagal organ.

Pasien dan Metode: Kami mendeteksi kenaikan kadar PCT yang berhubungan dengan kejadian inflamasi pada 4 pasien. Kadar PCT yang tinggi (diatas 10 ng/ml) berhubungan dengan inflamasi. Sepsis didiagnosa sesuai dengan kriteria sepsis dari American Burn Association.

Hasil: Kenaikan kadar PCT (161.70 ng.ml) dideteksi pada pasien pertama 8 hari setelah kejadian dan pasien meninggal 5 hari sesudahnya. Kenaikan kadar PCT serum (40.81 ng/ml) dideteksi pada hari ke-9 setelah kejadian dan pasien meninggal hari ke-2 setelah terdeteksi. Pasien ke-3 dideteksi dengan kenaikan PCT serum (12.28 ng/ml) 2 hari setelah terbakar dan meninggal 2 hari sesudahnya. Pasien ke-4 adalah anak-anak yang dideteksi dengan peningkatan kadar PCT (23,41 ng/ml) 11 hari setelah terbakar dan pasien meninggal 4 hari sesudahnya.

Ringkasan: Pemeriksaan kadar PCT perlu dilakukan pada saat awal pasien masuk ke rumah sakit. Pemeriksaan berkala kadar PCT perlu dilakukan untuk diagnosis dini dan tatalaksana sepsis pada luka bakar, pemantauan terapi dan pencegahan gagal organ.

Kata Kunci: PCT measurements, burns, tangential excision, MEBO, STSG

Procalcitonin (PCT) is a protein which consist of 116 amino acids. It was discovered 25 years ago as a prohormone of calcitonin produced by C-cells of the thyroid gland cleaved by proteolytic enzymes into the active hormone intracellular. There are two source of serum PCT, the thyroid PCT and "inflammatory" PCT. Detectable PCT in the plasma during inflammation is not produced

in c-cells of the thyroid (Russwurm et al. 1999), and the dynamic changes during initial stages of inflammation are the same in thyroidectomized individuals. The probable sites of PCT production in inflammation are the neuroendocrine cells in the lungs or intestine. The PCT production during inflammation is linked to the bacterial endotoxin and inflammatory cytokine (TNF

From the Burn Unit, Division of Plastic Reconstructive and Aesthetic Surgery, Universitas Indonesia, Ciptomangunkusumo Hospital, Jakarta Indonesia. Presented in The 16th IAPS Scientific Meetings In Sibolangit, North Sumatra, Indonesia

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and IL-6) that make it become a marker of the inflammatory response.^{1,2,10}

PCT reacts after 3-6 hours after the administration of endotoxin and peaking at 6-8 hours while CRP peaking at 36-50 hours. PCT half-life is 12-24 hours and it rises before the rise of CRP in acute bacterial infection.^{2, 15} Riedel S et al described that PCT is a useful marker to rule out sepsis and systemic inflammation in the ED.¹⁰ In healthy subjects, PCT levels in circulations are below detection limit. Since elevated PCT level was found in patients with bacterial infection, PCT became an important protein in the detection and differential diagnosis of inflammatory states.² It is known that a long-term elevated values are highly suggestive of an infection, often bacterial, with a systemic response. When plasma PCT values are below 0.5 ng/mL, bacterial sepsis is unlikely. PCT levels above 2 ng/mL are associated with bacterial infection and an increased likelihood of sepsis and progression to severe sepsis, however, other causes should not be excluded. PCT levels between 0.5 and 2 ng/mL, represent a gray zone where sepsis cannot be excluded. Table 1 provides information of the interpretation of PCT values.^{2,3}

A systemic inflammatory response syndrome can lead into sepsis, multiple organ dysfunctions and death accompanying burn injury. Based on the American College of Chest Physicians/Society for Critical Care Medicine

(ACCP/SCCM) consensus conference in 1992, patient with SIRS must have two or more of these clinical manifestations; temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$, heart rate ≥ 90 beats/ minutes, respiratory rate ≥ 20 breaths/ min or PaCO₂ ≤ 32 mmHg or mechanical ventilation, white blood cell count $\geq 12,000/\mu\text{L}$ or $\leq 4000/\mu\text{L}$ or $\geq 10\%$ band forms.^{5,8,9}

Sepsis is a condition of clinical systemic inflammation that is frequently caused by infection. The criteria of burn sepsis had been published by American Burn Association (ABA) in 2007. Sepsis should be considered when three or more of the following criteria are met: temperature ($>39^{\circ}\text{C}$ or $<36^{\circ}\text{C}$), progressive tachycardia (>110 beats per minute), progressive tachypnea (>25 breaths per minute not ventilated or minute ventilation >12 L/minute ventilated), thrombocytopenia ($<100,000/\text{dl}$ and does not apply until 3 days after initial resuscitation), hyperglycemia (untreated plasma glucose >200 mg/dl, >7 units of insulin/hr intravenous drip, or $>25\%$ increase in insulin requirements over 24 hours), and feed intolerance >24 hours (abdominal distension, residuals two times the feeding rate, or diarrhea >2500 ml/day).^{5,8,9}

Delays in diagnosis and treatment of infections have repeatedly been shown lead to worse outcomes in various clinical conditions.^{2,5} PCT also plays important role in monitoring therapy of infections.^{2,14} Guven et al describes that if therapy is delayed, the patient will

Table 1. PCT levels and possible interpretation²

PCT (ng/mL)	Possible Interpretations
<0.05	∞ Normal values
	∞ Local inflammation or infection is possible: systemic inflammatory response unlikely
<0.5	∞ On first day of ICU admission this indicates a low risk for progression to severe sepsis and/or septic shock
	∞ Local inflammation or infection is possible: systemic inflammatory response unlikely
≥ 0.5 and <2.0	∞ Systemic inflammatory response present due to infection, severe trauma, major surgery or cardiogenic shock
	∞ If the patient has a proven infection it could be sepsis
	∞ Likely to be sepsis (systemic inflammatory response associated with infection)
≥ 2.0 and <10	∞ On first day of ICU admission this indicates a high risk for progression to severe sepsis and/or septic shock
	∞ Severe sepsis or septic shock
≥ 10	∞ Organ dysfunction
	∞ High risk of death



Figure 1. 37 year-old-male patient with combustio grade II a-b 34% flame burn

almost assuredly die before the diagnosis is established. The emergency medicine physician must start empiric or presumptive therapy rapidly before confirmation of the diagnosis. WBC, CRP, and PCT levels may provide a clue of sepsis. But, PCT has excellent sensitivity and specificity.⁴

PCT serum levels is a useful diagnostic marker in management of sepsis before the detection of bacteria.^{2,4} The use of PCT measurement to guide antibiotic therapy should be a practical approach in critically ill patients with suspected sepsis.^{2,4,6,14} It is known that a long-term sustained elevation of PCT in sepsis indicates poor prognosis.¹

PATIENTS AND METHODS

Case 1

Our first patient is a 37 year-old-male patient with grade II a-b 34% flame burn (Figure 1). SIRS was detected on the day of admission around six hours after burn injury, by the presence of tachycardia (110x/minutes), tachypnea (26x/minutes) and leucocytosis (21.300/ μ L). PCT level on admission was unknown. Sepsis was detected on the 9th day after admission by the presence of

Case 1

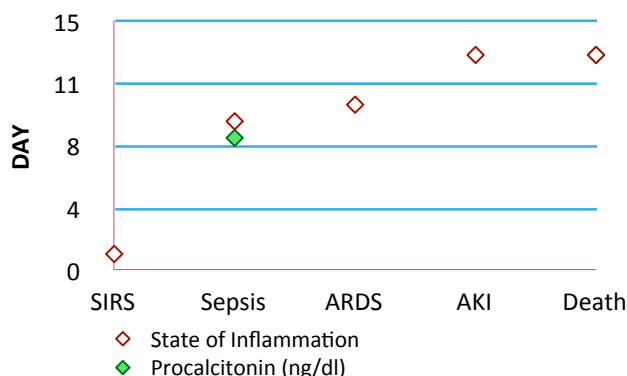


Figure 2. Very high PCT serum level (161,70 ng/dl) that possibly signify severe sepsis and organ dysfunction was detected a day before sepsis was clinically present, 2 days before ARDS, 4 days before AKI and death 15 hours after serum PCT level was detected reached into 527,1 ng/dl.

hyperthermia (39,3 °C), progressive tachycardia (158x/minutes), progressive tachypnea (46x/minutes), and 20 cc of residual fluid out through nasogastric tube (NGT). PCT level was detected high (161.70ng/ml) on the 8th day inward which means a day before sepsis was clinically present, and the presence of acute respiratory distress syndrome (ARDS) was detected on the 10th day (PaO₂/FiO₂=155,06). Acute kidney injury (AKI) was detected on the 13th day 15 hours before death (ureum/creatinine(mg/dl); 102/3,1) with the level of

Case 2

serum PCT reach 527,1 ng/mL (Figure 2)

The second patient is a 43 year-old-male patient with grade IIa-b 64,5% flame burn (Figure 3). SIRS was detected at the time of admission around 4 hours after burn, by the presence of tachycardia (98x/minutes), tachypnea (22x/minutes) and leucocytosis (27.600/dl). PCT level on admission was not measured (Figure 4). Sepsis occurred on the 3rd day by the presence of hyperthermia (39,2°C), progressive tachycardia (116x/minutes), thrombocytopenia (82,000/ μ L), and three times residual fluid out through NGT, while PCT



Figure 3. 43 year-old-male patient with combustio grade IIa-b 64,5% TBSA caused by flame.

Case 2

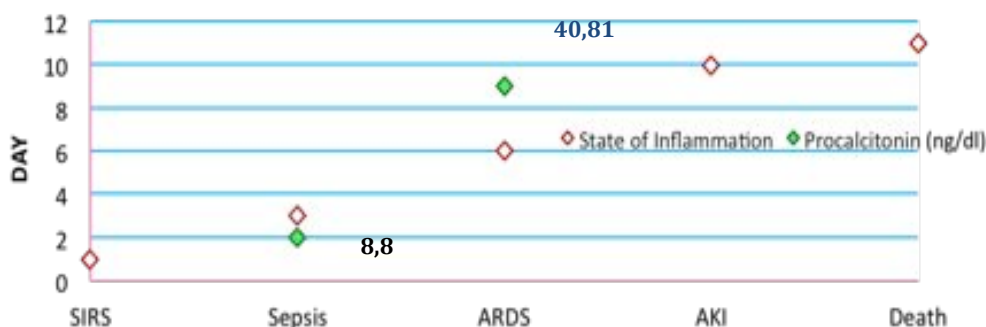


Figure 4. High PCT serum level (8,5 ng/dl) was detected a day before sepsis was clinically present. PCT was not measured until 3 days after ARDS was clinically present. PCT level was reached to 40,81 ng/dl on day 9th. AKI occur on the 10th day and was followed by death.

level reach into 8,8 ng/mL on the 2nd day (a day before sepsis was detected). ARDS occurs on the 6th day (PaO₂/FiO₂=160,67). AKI on the 10th day (ureum/creatinine(mg/dl); 84/1,32) a day before death, while the high elevated level that indicate severe sepsis or organ dysfunction was detected on the 9th day (40,81 ng/mL), a day before AKI.

Case 3

It is a 35 year-old-male patient with grade II-III 66% flame burn. SIRS was detected at the time of admission around 5 hours post burn by the presence of tachycardia (94x/minutes), tachypnea (21x/minutes), leucocytosis (36,400/ μ L) (Figures 5). Sepsis was

detected on the 3rd day by the presence of tachycardia (137x/minutes), tachypnea (30x/minutes), thrombocytopenia (58,000/ μ L), residual fluid out through NGT occurs. PCT level increased to 12,28ng/mL on the 2nd day, which meant a day before sepsis was detected (Figures 6). ARDS occurred on 2nd day after burn (PaO₂/FiO₂=172,5). AKI occurred on the 4th day, 12 hours before death (ureum/creatinine(mg/dl); 77/1,60).

Case 4

The last patient we observed was a 3 year-old-male patient with combustio grade II-III 40% scald burn (Figure 7). Admitted to Burn Unit Cipto Mangunkusumo Hospital four days



Figure 5. 35 year-old-male patient with combustio grade II-III 66% flame burn.

Case 3

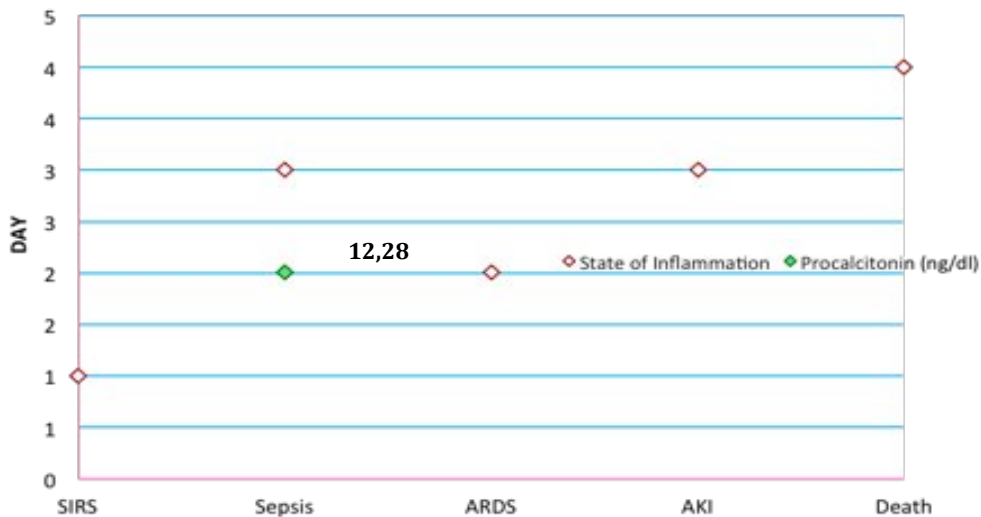


Figure 6. High PCT serum level (12,28 ng/dl) that may indicate severe sepsis and organ dysfunction was detected a day before sepsis was clinically present but on the day that ARDS occur.

after burn. SIRS was still detected on the day of hospitalisation by the presence of tachycardia (135x/minutes), tachypnea (50x/minutes), and leucocytosis (12,700/ μ L). Sepsis occurred on the 10th day post burn by the presence of hyperthermia (40°C), progressive tachycardia (173x/minutes), and progressive tachypnea (25x/minutes. PCT reached to 5,59 ng/mL 5 days after burn that may indicate sepsis, and it was 5 days before clinically sepsis was detected (Figures 8). A day after sepsis was clinically detected PCT was already increasing to 23.41 ng/mL, which meant that severe sepsis might be occurred, and also organ dysfunction. Three

days after high-elevated serum PCT level that indicate severe sepsis was detected, patient got shocked and fall on AKI (ureum/creatinine (mg/dl); 115/0,37) and death 18 hours after AKI was detected.

DISCUSSION

A significant elevation of plasma PCT is found during sepsis. The characteristics that give PCT a theoretical advantage as a marker of systemic bacterial infection over other markers are a virtual absence in health and the different source of inflammatory PCT that can make this



Figure 7. 3 year-old-male patient with combustio grade IIab-III 40 % scald burn.

Case 4



Figure 8. High PCT serum level (5,59 ng/dl) that may signify sepsis was detected 5 days before sepsis was clinically present. A day after sepsis was occurred PCT level reached into 23,41 ng/dl which possibly indicate sepsis and organ dysfunction. Evidently, AKI was happened 3 days after and was followed by death.

biomarker either useful for thyroidectomized subjects or subjects with health thyroid glands. Induction in sepsis and its half-life (12-24 hours) are suitable for daily monitoring of disease progress and therapeutic intervention .^{1,2,11,12,13}

PCT should be measured in patients whom sepsis is suspected, to those who presenting SIRS criteria or perfusion abnormalities or unexplained shock or organ dysfunction.¹ Its ability as prognostic tools makes it should be measured at the time of admission or at any time during hospital stay, when sepsis is suspected.^{2,11,12}

Patients in our case encounter PCT serum level into more than 10 ng/mL, which means lethal level of serum PCT.² We found that these patients had late measurement of serum PCT levels. Because some of them, their PCT serum was detected high (more than 10 ng/mL) before clinically detected as sepsis and PCT serum level were unknown at the time of admission, while the measurement is needed to early diagnosis, and prognosis.¹² Serum PCT level of the patients in this report after treatments such as after fluid therapy, excision of burn eschars, changing the dressing or even

after therapeutic intervention such as after applying allograft or even split thickness skin graft (STSG) weren't yet continuously measured, whereas some study describes that serum PCT levels can be use to monitor therapy of sepsis and other bacterial infections.^{2,14}

SUMMARY

We found that it is important to initiate PCT measurements in burn patients at the time of admission. Daily measurement of PCT levels is needed for an early diagnosis and treatment of burn sepsis, monitoring therapy and MOD prevention. Further study with more objects is needed to prove and discover the role of serum PCT level in burn patients.

Aditya Wardhana,
*Burn Unit, Plastic Surgery Division
 Cipto Mangunkusumo General National Hospital
 Jalan Diponegoro.No.71, Gedung A, Lantai 4.
 aditya_wrdn@yahoo.com*

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