

# Peran sitokin IL-1, IL-6, TNF- $\alpha$ dan MIF terhadap terjadinya insufisiensi adrenal relatif pada renjatan sepsis : kajian pada model anak babi = The Role of the cytokines IL-1, IL-6, TNF and MIF in the development of relative adrenal insufficiency in septic shock a study in piglet model

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## Abstrak

Insidens insufisiensi adrenal pada pasien renjatan sepsis dilaporkan sekitar 40-65. Sitokin IL-1 dan IL-6 dapat menstimulasi sekresi kortisol sedangkan TNF- $\alpha$  serta MIF berperan dalam menghambat pembentukan kortisol. Penelitian ini bertujuan untuk mengetahui peran IL-1, IL-6, TNF- $\alpha$  dan MIF dalam terjadinya insufisiensi adrenal relatif pada renjatan sepsis. Penelitian eksperimental dilakukan di laboratorium FKH IPB berlangsung selama 6 bulan April-September 2015. Model anak babi yang dipakai berumur 6-8 minggu dengan berat badan 5-10 kg. Pemilihan sampel dengan consecutive sampling dengan total n = 20. Anak babi diberikan infus endotoksin dengan dosis 50 ug/kg BB. Sampel darah untuk analisis IL-1, IL-6, TNF- $\alpha$ , MIF, ACTH, kortisol, 17 OHP, DHEA, androstenedion diambil sebelum pemberian endotoksin dan tiap 15 menit hingga terjadi renjatan sepsis, kemudian dilakukan uji synacthen. Pemeriksaan imunohistokimia dilakukan pada kelenjar adrenal, hipofisis, dan hipotalamus. Dari 19 anak babi yang dianalisis mengalami renjatan sepsis dalam waktu 60 menit. Karakteristik sampel tidak berbeda bermakna antara kedua kelompok. Kadar IL-6 pada kelompok IAR dibandingkan dengan kelompok tanpa IAR berbeda bermakna pada menit ke-45 0,65 0,5-4,32 pg/dL vs. 0,54 0,51-0,61 pg/dL, p = 0,008. Kadar IL-1 antara kelompok IAR dibandingkan kelompok tanpa IAR tidak berbeda bermakna. Kadar TNF- $\alpha$  pada kelompok IAR dibandingkan dengan kelompok tanpa IAR berbeda bermakna pada menit ke-15 1862,5 327,9-4511,14 pg/dL vs. 155,38 24,67-394,10 pg/dL, p = 0,002 dan menit ke-30 4295,76 246,9-5913,37 pg/dL vs. 422,90 101,05-4129,42 pg/dL, p = 0,007. Kadar MIF kelompok IAR dibandingkan dengan kelompok tanpa IAR berbeda bermakna pada saat renjatan sepsis 25,28 18,45-30,64 ng/dL vs. 11,30 7,1-15,14 ng/dL p = 0,003. Pemeriksaan imunohistokimia hanya pada hipotalamus yang menunjukkan pewarnaan terhadap IL-1, IL-6, TNF- $\alpha$  dan MIF pada kelompok dengan IAR. Pada renjatan sepsis dan insufisiensi adrenal relatif kadar TNF- $\alpha$  meningkat pada menit-menit awal, kemudian kadar IL-6 meningkat kemudian serta terakhir kadar MIF meningkat pada saat renjatan sepsis. Kadar IL-1 tidak terdapat perbedaan antara kedua kelompok. Kata kunci: IL-1, IL-6, insufisiensi adrenal relatif, MIF, renjatan sepsis, TNF- $\alpha$

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Incidence of adrenal insufficiency in septic shock ranged between 40 ndash 65. The mechanism of relative adrenal insufficiency in septic shock is caused by inflammatory mediators. This study aimed to identify the role of IL 6, IL 1 in stimulating ACTH and cortisol release, and the role of TNF and MIF in inhibiting the level of ACTH and cortisol in septic shock with relative adrenal insufficiency RAI in order to develop guidelines for relative adrenal insufficiency marker. Experimental study was conducted in Veterinary Faculty, Bogor Agricultural Institute for 6 months Apri ndash September 2015. Piglet models Sus scrofa aged 6 ndash 8 weeks weighing 5 ndash 10 kg. Consecutive sampling was used with total 20 piglets. Piglet models were given 50 ug kg endotoxin infusion Escherichia coli O111 B4 Sigma chemical, St. Louis, MO, USA. Blood sample for analysis of IL 1, IL 6, TNF, MIF, ACTH, cortisol, 17 OHP, DHEA,

androstenedione was collected before endotoxin administration and every 15 minutes until septic shock occurred. Piglet models were monitored using PiCCO monitor. Stimulation test was then performed using synthetic corticotropin Synacthen and blood sample was collected again along with immunohistochemistry examination of the adrenal, pituitary and hypothalamus glands. From 19 study subjects analyzed, all subjects had septic shock in 60 minutes. Study subject characteristics in each group were similar. The level of IL 6 at 45 minutes had a significant difference compared to the group without RAI  $0.65 \pm 0.5$  vs.  $4.32 \pm 0.54$  pg dL,  $p = 0.008$ . The level of IL 1 during septic shock were not significantly different between both groups. The level of TNF in RAI group had significant difference compared to the group without RAI at 15 minutes  $1862.5 \pm 327.9$  vs.  $4511.14 \pm 155.38$  pg dL,  $p = 0.002$  and at 30 minutes  $4295.76 \pm 246.9$  vs.  $5913.37 \pm 422.90$  pg dL,  $p = 0.007$ . The level of MIF in group with RAI during septic shock had a significant difference compared to the group without RAI  $25.28 \pm 18.45$  vs.  $30.64 \pm 11.30$  ng dL,  $p = 0.003$ . Immunohistochemistry staining of IL 1, IL 6, TNF, and MIF was observed only in the hypothalamus glands of the RAI group. In septic shock and relative adrenal insufficiency, TNF increased in earlier minutes, then IL 6 increased and later MIF increased in septic shock condition. IL 1 level had no difference increment for both groups. **Keywords** IL 1, IL 6, MIF, relative adrenal insufficiency, septic shock, TNF