Patterns of Proinflammatory Cytokines and Inhibitors during Typhoid Fever

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Cytokines and inhibitors in plasma were measured in 44 patients with typhoid fever. Ex vivo production of the cytokines was analyzed in a whole blood culture system with and without lipopolysaccharide (LPS). Acute phase circulating concentrations of cytokines (±SD) were as follows: interleukin (IL)-1β, <140 pg/mL; tumor necrosis factor-α (TNFα), 130 ± 50 pg/mL; IL-6, 96 ± 131 pg/mL; and IL-8, 278 ± 293 pg/mL. Circulating inhibitors were elevated in the acute phase: IL-1 receptor antagonist (IL-1RA) was 2304 ± 1427 pg/mL and soluble TNF receptors 55 and 75 were 4973 ± 2644 pg/mL and 22,865 ± 15,143 pg/mL, respectively. LPS-stimulated production of cytokines was lower during the acute phase than during convalescence (mean values: IL-1β, 2547 vs. 6576 pg/mL; TNFα, 2609 vs. 6338 pg/mL; IL-6, 2416 vs. 7713 pg/mL). LPS-stimulated production of IL-1RA was higher in the acute than during the convalescent phase (5608 vs. 3977 pg/mL). Inhibited production of cytokines during the acute phase may be due to a switch from a proinflammatory to an antiinflammatory mode.

Typhoid fever is caused by the facultative intracellular gram-negative bacillus *Salmonella typhi* and occasionally by *Salmonella paratyphi*. Although salmonellae contain lipopolysaccharide (LPS; bacterial endotoxin), the clinical picture of typhoid fever differs from gram-negative sepsis, and the role of endotoxin in the pathophysiology of typhoid fever is controversial [1].

The proinflammatory cytokines interleukin (IL)-1β, tumor necrosis factor-α (TNFα; cachectin), IL-6, and IL-8 have been implicated in the pathogenesis of sepsis caused by gram-negative microorganisms [2–4]. When LPS is injected intravenously into animals or human volunteers, elevated concentrations of these cytokines can be detected, and the symptoms and signs of sepsis are mimicked [5–7]. Elevated circulating levels of TNFα have been correlated with poor prognosis in sepsis, meningococcemia, and cerebral malaria [7–10]. In contrast, in infections with intracellular pathogens, such as *Leishmania* species, *Listeria monocytogenes*, or mycobacteria, administration of TNFα inhibits the outgrowth of the microorganisms, whereas administration of antibodies to this cytokine are detrimental [11–16]. In experimental *Salmonella typhimurium* infection in mice, the role of TNFα is similar to that in other intracellular infections [17–19]. However, in calves with *S. typhimurium* sepsis, the cytokine pattern appears to differ from that seen after intravenously administered LPS. Where TNFα rose 1 h after LPS administration, salmonella sepsis caused a barely detectable increase in TNFα [20].

In contrast to these animal studies, circulating cytokines (TNFα, IL-6, and IL-1β) were elevated in children with typhoid fever in Chile [21]. Butler et al. [22] studied the outcome of typhoid fever in adults in Nepal and found that higher values of IL-6 and soluble TNF receptor p55 were related to poorer outcome.

In 1989, joint research on several aspects of typhoid fever was started between Nijmegen University and Diponegoro University. To obtain more insight into the pathophysiology of typhoid fever, we measured levels of circulating pyrogenic cytokines (IL-1β, TNFα, TNFβ [lymphotoxin], and IL-6) and concentrations of IL-8, the cytokine inhibitor IL-1 receptor antagonist (IL-1RA), and the soluble TNF receptors p55 and p75 (sTNF-R). In addition, we investigated the capacity of blood cells to produce IL-1β, TNFα, IL-6, and IL-1RA ex vivo in the acute and convalescent phases of hospitalized patients with typhoid fever.

We used the whole blood cytokine test as described by van Deuren et al. [23] and Nerad et al. [24]. This assay is simple, reproducible, and especially suitable for use in laboratories that are not particularly well equipped for work with cytokines. In addition, the method may be less artificial than is isolating mononuclear cells over a gradient and probably is a more natural mirror of what happens in vivo, because plasma factors and other cells are left in situ.

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Patients gave informed consent, and guidelines for human experimentation of the Dr. Kariadi Hospital, Diponegoro University, were followed.

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