Dysregulation of T cell-macrophage network in severe acute pancreatitis.

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Cytokines play an integral role in the 'cross-talk' between phagocytes and T-lymphocytes that regulates the evolution from innate to adaptive responses after an inflammatory stimulus. In-vitro studies of lymphocytes show dysregulation of this network in polytrauma, burns and sepsis [1-3], and suggest that glutathione depletion [4], as in states of oxidative stress, is involved.

Oxidative stress in the vascular compartment [5,6], frustrated phagocytosis with 'overt secretion' of elastase by neutrophils [7], and dysregulation of T-lymphocyte responses leading to inappropriate immunosuppression [8,9], are early features of human acute pancreatitis and are more pronounced in those whose disease evolves towards complications or death. The cytokine IL-2 is crucial for ensuring adequate numbers of cytotoxic T-helper (CD8+) lymphocytes. It is secreted by activated T, cells, in parallel with Interferon-γ of which Neopterin is a specific marker [10]. Reverse-phase HPLC was used to measure Neopterin and creatinine simultaneously, by fluorescence and ultra-violet detectors, respectively [10]. Of 38 patients with acute pancreatitis, 27 recovered spontaneously, while 11 had a severe outcome. Urine specimens were obtained upon admission, 12 hourly to day 3, and daily to day 5. Data were corrected for the variable time-lag between onset of symptoms and presentation/diagnosis (Figure 1).

Urinary Neopterin/creatinine ratios in acute pancreatitis patients exceed control values from the time of admission onwards. However, there was no difference between the ratios in subgroups with mild and severe disease at any time-point (Figure 1) even when 'area under the curve' was used to compute integrated Neopterin responses (Figure 2). Given that Interferon-γ and IL-2 are co-secreted by activated T, cells, these data are in keeping with inappropriate IL-2 mediated recruitment of cytotoxic T-helper cells and neutrophil elastase and cytokines [12].

Since oxidative stress has been invoked in dysregulation of T-lymphocyte responses, these results rationalise the benefits reported from parenteral antioxidants in experimental and human acute pancreatitis [reviewed in 13]. They also suggest that the measurement of Neopterin in urine may offer a non-invasive and convenient way to detect restoration of IL-2 responses upon antioxidant therapy of pancreatitis - at least when sepsis does not complicate the issue.

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