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LETTERS

CLINICAL AND BASIC SCIENCE ASPECTS OF IMMUNE PATHOGENESIS OF SEPSIS AND PERITONITIS

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In the U.S., 500000 patients suffer from sepsis every year, of which 175.000 die. Incidence and mortality rate in Europe are comparable. Despite modern intensive care, mortality from sepsis remains high. This is partially due to aggressive intervention among the increased population of older patients and diagnostic procedures which have become more aggressive. The mortality rate of peritonitis, especially secondary peritonitis, may be up to 70%. Within the peritonitis entity different mortality rates have been observed (28,29), although in large clinical

trials it has been assumed that the pathogenesis of sepsis and peritonitis may be similar. Based on the results in animal models of acute forms of sepsis TNF-α, IL-1 and IL-6 were recognized as major mediators in sepsis (4,22), and it was suggested, that it might be beneficial to block TNF-α (3,24). Unfortunately, large clinical trials with anti-TNF-antibodies (6) or anti-endotoxin-antibodies have not improved survival, although an impact on the development of multi-organ-failure was observed (5). In most of these trials , a heterogenous patient population was studied, neglecting the fact that peritonitis and sepsis differ in several respects.

1. Peritonitis is treated by elimination of the source of sepsis, intraabdominal lavage, and debridement according to the principles set up by Kirschner (1926) (16). In the last two decades several additional surgical methods have been developed for the treatment of peritonitis, e.g., staged abdominal repair (STAR) (29) . Within 24 hours, intraabdominal lavage is repeated until clinical signs, (e.g., bowel wall edema, appearance of exudate, or gram stain) and surgical experience suggest abdominal closure. Intraabdominal compartment syndrom is a menace in case of early abdominal wall closure with consecutive problems in cardiovascular circulation, ventilation and urinary output and may require some form of open abdominal management.

2. The time between onset of symptoms and operation may be up to 72 hours. Endotoxin release and bacterial translocation trigger the mediator cascade with activation of PMN, macrophages and T-cells, leading to systemic reaction (e.g., fever, shock, death). The mediator cascade may be already far advanced when surgery to eliminate the focus can finally take place (25).

3. Trauma or large operations often precede severe peritonitis. While trauma can be associated with immune suppression (e.g., IL-2 downregulation) and macrophage hyperactivation (e.g., TNF-α hypersecretion) (12), trauma followed by intraabdominal sepsis is associated with reduced TNF-α-secretion by macrophages, which may be unresponsive or insensitive to further challenge due

to chronic activation during trauma and sepsis (11). In fact, it was demonstrated for the first time by Munoz et al. (19) that human sepsis is associated with a low capacity of monocytes to produce IL-1α, IL-1β, IL-6 and TNF-α.

4. Peritonitis may also be characterized by peritoneal compartmentalization of the immune response. Endotoxin, cytokines and other mediators (e.g., elastase) are released in higher concentrations in the peritoneal compartment than in plasma. Peritoneal TNF-α, which is difficult to measure in plasma, was predicitive of the outcome of peritonitis (13,26).

Endotoxin, which is released from gram-negative pathogens, is considered to be responsible for the onset of the mediator cascade in intraabdominal infections. However, the quantity of endotoxin necessary for this cascade is often disputed. In aortic aneurysm repair small amounts of endotoxin (5-10 pg/ml) were sufficient to activate the inflammatory (TNF-α, IL-6) and anti-inflammatory (TNF-R I and II, IL-10) response (9). Humans, who, in general, are very sensitive to endotoxin, can metabolize and neutralize endotoxin provided the immune system is intact. In critical care patients small amounts of endotoxin may be sufficient to induce detrimental reactions.

Recently it was demonstrated that in-vitro antibiotics can lead to endotoxin release which was related to the type of penicillin-binding-protein (PBP) of the pathogen (15). PBP-3-specific antibiotics (e.g., cephalosporins) caused more endotoxin release than did PBP-2-specific antibiotics (e.g., imipenem). Clinical data are rare with the exception of two studies in urosepsis (14,23). For the first time it was demonstrated in a pilot study of surgical intensive care patients that in-vivo PBP-3-specific antibiotics (e.g., cefotaxime, ceftriaxone) released more endotoxin than PBP-2-specific antibiotics (e.g., imipenem).

The effect on IL-6 plasma levels also differed with regard to the type of antibiotic (10). It may depend also on the type of pathogen, suggesting pathogens may be more important than had been recently suggested (21). The strategy of

antibiotic therapy can be improved with regard to immune response, timing, dosage, and combination with other compounds.

Immune therapy has been investigated in several ways (e.g., anti-cytokine antibodies, soluble receptors, receptor-blocking agents, biological response modifiers, inhibitors and protective factors). The mortality rate has remained unchanged, with the exception of certain subgroups (7). The shortcomings of anti-TNF-antibodies have been mentioned in several publications (1,2,8). The cytokine network with its implications on feedback mechanisms, the communication between cells, immune compartmentalization, and organ interactions (Multiple Organ Dysfunction Syndrome) in peritonitis are difficult to modulate with just one compound without knowing the effect this compound may have on this system. However, no integrative system is available to include the response of cytokines, mediators, cells and organs in peritonitis or sepsis (20).

Bevor starting further large clinical trials, there may be a rationale for improving our understanding of the pathogenesis of specific forms of sepsis as each has its own clinical features, treatment needs and mediator responses. The determination of cytokines in plasma without relation to other functions of the immune response may not be enough to further clarify the process of sepsis and peritonitis. Some reports have indicated that cell-associated cytokines, cytokines related to cellular function (17,18,19) or the determination of Fc-receptor polymorphism (27) may be more informative of the in-vivo reaction to the challenge of endotoxin. It should also be noted that the strategy for antibiotic therapy in critical care patients should be reevaluated with the new diagnostic tools available.

In conclusion, the mortality of sepsis and peritonitis remains high. Clinical immunomodulatory trials (e.g., TNF-α antibodies) have failed to improve the survival. Specific forms of sepsis have their own clinical feature, treatment needs and mediator patterns and may not respond to a generalized form of inhibitory or

activating immune-therapy. Plasma cytokine levels (e.g., TNF-α) may be inconsistent in sepsis and, with some exceptions, may not be reliable markers of the clinical follow-up. Immune compartmentalization, the state of cellular activation, or genetic polymorphism are important parts of the immune response to sepsis and need further clarification, to improve the outcome of future clinical studies of immunemodulation. At the therapeutic level, the relationship of antibiotics and immune system deserves more attention.

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