Hypothesis: Compartmentalization of cytokines in intraabdominal infection

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Background. *Although the proximal role of systemic cytokines in the infectious-inflammatory cascades is well recognized, the magnitude and meaning of its intraperitoneal levels in peritonitis have received little attention. We hypothesized that in peritonitis a significant and clinically relevant cytokine-mediated inflammatory response is compartmentalized in the peritoneal cavity.*
Methods. *MEDLINE was used to search the literature for all articles dealing with experimental, primary, and secondary bacterial peritonitis and cytokines.*
Results. *Bacterial peritonitis is associated with an immense intraperitoneally compartmentalized cytokine response, with plasma levels of cytokines representing only the tip of the iceberg. Although certain amount of cytokines may be beneficial to the peritoneal defense mechanisms, higher levels correlate with adverse outcome. Thus it is plausible to look at acute peritonitis as initially a combined infective (microorganism) and inflammatory (cytokines) process. The clinical significance of the distinction between peritoneal inflammation and infection and the relevance of our findings to the stratification and treatment of peritonitis are discussed.*
Conclusions. *Current surgical and antibiotic therapy for peritonitis is able to clear the peritoneal cavity of infective concentration of bacteria, but many patients continue to die of an uncontrolled activation of the inflammatory cascade. We suggest that one potential venue for therapeutic progress is the modulation of the compartmentalized peritoneal inflammatory response. (Surgery 1996;119:694-700.)*

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THE INGRESS OF BACTERIA into the peritoneal cavity initiates a complex and well-characterized intraperitoneal inflammatory response involving anatomic, physiologic, microbiologic, cellular, immunologic, and molecular considerations.[1,2] Recent advances in molecular biology have permitted the identification of various cytokines as the key proximal links, mediating systemic and local sepsis and tissue injury, in the infectious-inflammatory cascades. The characteristics of the different cytokines and their physiologic and pathologic role in culture-positive or -negative sepsis are the subject of excellent reviews,[3-6] and the potential of anticytokine therapeutic strategies have been summarized recently.[7-9] In this review we examine the role of cytokines in intraabdominal infection.

CYTOKINES IN EXPERIMENTAL PERITONITIS

The induction of experimental peritonitis leads to both local and systemic inflammatory responses. Endotoxin, produced by gram-negative bacteria, is considered to be the initiator of the ensuing cytokine chain reaction. From the peritoneal cavity it reaches the systemic circulation via the lymphatic system.[10] Absorption is increased in the presence of increased intraabdominal pressure[11] and decreased when lymph is drained externally through a thoracic duct fistula.[12] Furthermore, plugging the diaphragmatic lymphatics with platelet-rich plasma or scarring the diaphragm with sandpaper or talc powder in the early stages of experimental peritonitis reduces mortality.[2] Endotoxin, however, is not essential for the release of cytokines, because peritoneal macrophages obtained after cecal ligation-puncture (CPL) in endotoxin-tolerant mice exhibit spontaneous release of tumor necrosis factor (TNF)–α, interleukin (IL)-1, and IL-6. This finding suggests that macrophages can be primed to release cytokines by other nonendotoxin mechanisms such as operative trauma.[13]

The induction of experimental peritonitis is followed by a complex pattern of cytokine kinetics. After CPL is performed, peak plasma levels of TNF-α are detected at 2 hours, followed by up-regulation of IL-1 and IL-6.[14] Mayoral et al.[15] measured plasma and peritoneal levels of cytokines and correlated survival with a reduction of TNF-α plasma levels. Lack of response to therapy was

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associated with persistently elevated concentrations of TNF-α and IL-1 in the peritoneal fluid.[16]

Peritoneal TNF-α significantly increased 2 hours after the induction of experimental peritonitis. Plasma levels were also elevated but much less so than after intravenous Escherichia coli injection. Systemic pretreatment with anti-TNF-α antibodies decreased mortality after the intravenous challenge but was ineffective in peritonitis.[17] Peritoneal macrophages obtained after CPL produced increasing amounts of TNF-α and IL-1, but levels of the 1a subunit decreased, indicating an early shift in peritoneal macrophage function from antigen recognition to production of cytokines.[18] After CPL was performed, peritoneal levels of TNF-α and IL-1 were significantly elevated, the magnitude of response adversely correlating with outcome. Levels were lower in animals pretreated with intraperitoneal induction of endotoxin tolerance.[19] Intravenous anti-TNF-α antibodies reduced plasma IL-1 and IL-6 levels and mortality after intravenous *E. coli* administration but not after the induction of *E. coli* peritonitis. In contrast, systemic anti-lipopolysaccharide antibodies were protective in the peritonitis model. A striking reduction of plasma bacterial count and levels of TNF-α, IL-1, and IL-6 occurred, but peritoneal levels of cytokines remained elevated.[20] In an *E. coli* model of peritonitis the addition of interferon-γ to the inoculum has increased the mortality and the level of plasma TNF-α and IL-6. Blockade of serum interferon-γ with neutralizing antibodies improved survival but was not associated with a decrease in TNF-α and IL-6 in survivors, suggesting an independent detrimental role of interferon-γ.[21]

MIXED EFFECTS OF CYTOKINES AND ANTICYTOKINE THERAPY IN EXPERIMENTAL PERITONITIS

Beneficial cytokines administration and adverse or nonbeneficial anticytokine therapy. As in systemic sepsis[3, 22] peritoneal cytokines are beneficial at a certain dose in supporting local host defenses, but excessive concentrations are detrimental. The helpful local activity of cytokines in early peritonitis was hinted at by studies showing that anti-TNF-α antibodies provided protection in intravenous infection models but were not effective in experimental peritonitis.[17, 20] Treatment with anti-TNF-α serum inhibited the migration of granulocytes and monocytes from bone marrow to the circulation and hence to the peritoneal cavity and enhanced the growth of L. monocytogenes in various tissues.[23] In addition, anti-TNF-α antibodies given intraperitoneally in experimental peritonitis increased mortality, a trend that was reversed by the administration of TNF-α.[24]

In another study prophylactic and therapeutic use of anti-TNF-α antibody in a rabbit model of *E. coli* peritonitis significantly lowered systemic TNF-α concentration but did not ameliorate the physiologic effects of sepsis and survival.[25]

Pretreatment with IL-1 decreased the plasma TNF-α and IL-6 response, histologic end-organ damage, and mortality rate after the induction of *E. coli* peritonitis.[26] Similarly, Kupffer cell blockade was associated with decreased IL-1 production and increased mortality after CPL.[27] Intraperitoneal IL-2 administered before *E. coli* peritonitis occurred was protective by inducting a neutrophil influx into the peritoneal cavity.[28] Protection was achieved only when bacteria and IL-2 were given by the same intraperitoneal route; intravenous IL-2 was not effective.[29] IL-10 appears to be a "good" cytokine, suppressing the induced production of proinflammatory cytokines (e.g, TNF-α). Inhibition of endogenous IL-10 with anti-IL-10 antibodies before CPL increased the mortality rate[30]; systemic administration of exogenous IL-10 prolonged the survival rate in septic mice.[31]

Anticytokine therapy beneficial. Chalkiadakis et al.[32] demonstrated the advantages of blocking TNF-α. Systemic administration of pentoxifylline, which inhibits the release of TNF-α,[8] reduced the fatality rate after the induction of peritonitis in the closed ileal loop rat model.[32] Another effect of pentoxifylline was to reduce peritoneal fibrinogen deposits and adhesion formation, because both are enhanced by TNF-α, IL-1, and IL-6, which have been shown both individually and synergistically to stimulate plasminogen activator inhibitors by mesothelial cells.[33, 34] Other investigators demonstrated that intraperitoneal administration of pentoxifylline improved survival after CPL in burned mice through the down-regulation of proinflammatory cytokines.[35]

Recombinant IL-1 receptor antagonist administered to rats 3 hours after CPL was performed significantly ameliorated clinical sepsis, survival rate, and histologic evidence of organ damage.[36] Pretreatment with anti-IL-6 antibodies protected mice given intraperitoneal lethal doses of E. coli.[37]

Treatment with granulocyte colony-stimulating factor improved survival after CPL was performed.[38-40] The mechanism involved is probably the ability of granulocyte colony-stimulating factor to suppress TNF-α release from macrophages.[40]

CYTOKINES IN PRIMARY PERITONITIS

The dynamics of cytokines in the plasma and peritoneum were determined simultaneously in primary or spontaneous bacterial peritonitis in patients with cirrhosis and primary peritonitis complicating chronic ambulatory peritoneal dialysis (CAPD). Peritoneal mesothelial cells from patients with CAPD peritonitis were found to be stimulated to produce TNF-α, IL-1, IL-6, and IL-8.[41, 42] Also, peritoneal macrophages collected from patients undergoing CAPD during an episode of peritonitis secreted increased amounts of IL-1 com-

pared with those collected during an infection-free period.[43] In another study infected peritoneal dialysate from which macrophages had been isolated inhibited the production of TNF-α by those macrophages, illustrating a possible regulatory mechanism.[44]

IL-6 was detectable in the peritoneal dialysate of 3 of 21 noninfected patients undergoing CAPD, whereas levels were extremely high in two patients who had bacterial peritonitis; these levels returned to normal as the peritonitis subsided.[45] Peritoneal levels of IL-6 and IL-8 rose in parallel in CAPD peritonitis after the initial rise in TNF-α. IL-8 levels corresponded to the number of leukocytes in the dialysate.[46] The peak of TNF-α was early, short-lasting, and followed by a higher elevation of IL-6. Elevations in both correlated with increased peritoneal permeability.[47]

The levels of TNF-α, IL-6, and neopterin were elevated in the peritoneal fluid of patients with spontaneous bacterial peritonitis; increased levels correlated with adverse outcome.[48] In a similar study peritoneal levels of TNF-α and IL-6 were drastically elevated in infected patients, whereas plasma levels of these cytokines were only slightly increased. Peritoneal levels decreased within the first 48 hours of effective antibiotic therapy.[49]

CYTOKINES IN SECONDARY PERITONITIS

Estimation of systemic cytokine levels in patients with secondary bacterial peritonitis implies that increased TNF-α and IL-6 concentrations are associated with an adverse outcome. IL-6 levels also correlate with the APACHE II score.[50-52] Conversely, Hamilton et al.[53] reported decreasing plasma levels of TNF-α and IL-6 before death in secondary peritonitis, suggesting an anergic immune status.

In a prospective clinical study levels of cytokines were measured in the plasma and peritoneal exudate of patients undergoing serial, planned relaparotomies for severe intraabdominal infections.[54] The peritoneal levels of endotoxin, TNF-α, IL-1, IL-6, and elastase were many times higher than the simultaneously measured plasma levels. Plasma levels of TNF-α, IL-6, elastase, and neopterin remained elevated in those patients who eventually died. Peritoneal TNF-α and elastase levels decreased during repeated laparotomies in survivors but remained elevated in the nonsurvivors.

HYPOTHESIS: PERITONEAL COMPARTMENTALIZATION OF THE INFLAMMATORY RESPONSE

We hypothesized that the peritoneal inflammatory response in peritonitis is like the systemic response because it uses identical mechanisms of humoral and cellular response, but the two responses occur in two functionally separate compartments—peritoneal and systemic—and the intensity of both correlates with outcome.

Bacterial peritonitis results in the local release of proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8, which in turn stimulate the production of secondary mediators (e.g., nitric oxide, arachidonic acid metabolites), which in turn activate interactions between endothelial cells and neutrophils to produce microcirculatory damage and tissue injury.[55] In addition, elevations of neopterin, indicating enhanced activation of macrophages,[56] and elastase, a marker of activation and degranulation of polymorphonuclear cells,[57] are observed.

Peritoneal levels of cytokines in peritonitis are much higher than are systemic levels, indicating a compartmentalized inflammatory process and suggesting that cytokines do not equilibrate readily between the peritoneal cavity and plasma. The largest fraction of peritoneal cytokines probably derives from macrophages after they contact bacteria and their byproducts. In addition, damage to the intestinal barrier may allow the translocation of luminal endotoxin or even certain cytokines into the portal and lymphatic circulation.[58] Intestinal IL-6 production, for example, was increased after CPL was performed.[59] Another source of cytokines is the operation performed to induce (in animals) or to treat (in patients) the peritonitis itself. Plasma levels of IL-1 and IL-6 are elevated after major abdominal operations; the extent of the response increases with the magnitude of the operative trauma.[60-62]

The peritoneal compartmentalization of cytokine response in intraabdominal infection is analogous to that shown in experimental pancreatitis in which portal vein TNF-α levels were higher than those measured in the hepatic vein,[63] and after colectomy, in which IL-6 levels were higher in the portal vein than the systemic circulation.[64] Clearly, plasma levels of cytokines in intraabdominal infections (a spillover from the peritoneal cavity or produced systematically) represent only the tip of the iceberg. Although most clinical studies hitherto measured circulatory cytokine levels, it appears that local peritoneal cytokine concentrations, exerting their effects in a paracrine fashion, are more likely to be of primary biologic and clinical importance.

INFLAMMATION VERSUS INFECTION

With the previously mentioned findings in mind it is plausible to look at acute peritonitis as initially a combined *infective* (microorganism) and *inflammatory* (cytokines) process. Surgical and antimicrobial therapy addresses the former component but does not always halt the latter. In patients undergoing daily, staged, planned relaparotomies for severe intraabdominal infection, the peritoneal cavity became sterile after 4 to 6

days of the antibiotic and operative therapy, but 12% of the patients died.[65] The scenario in which bacterial peritonitis is cured, but inflammatory peritonitis accompanied by hypercytokinemia persists, represents tertiary peritonitis, a term coined to describe that subgroup of patients who go on to have multiple organ dysfunction and die despite "successful" operations, effective antibiotics, and maximal supportive therapy.[66]

Situations in which infection is solved but residual compartmentalized inflammation persists are not limited to the peritoneal cavity. After successful treatment of bacterial meningitis concentrations of IL-6 in the cerebrospinal fluid remain elevated.[67] Elevated amniotic fluid IL-6 correlates much better with histologic acute chorioamnionitis than do bacteriologic cultures.[68] The presence of fever or leukocytosis at the conclusion of a course of antibiotic treatment after an operation for intraabdominal infection sometimes represents local residual cytokine-mediated inflammation rather than continuing infection. This is a self-limited condition, and spontaneous resolution is expected with no need for further antibiotic therapy.[69]

It is also likely that operations performed in patients in whom the inflammatory response is already switched on and in whom macrophages are in a primed state may act as a "second hit," escalating the systemic inflammatory response syndrome and precipitating multiorgan dysfunction syndrome.[13, 70] Local intraperitoneal measurements of cytokines taken before and after these operative procedures would better define the contribution of the reoperative treatment of peritonitis to the cytokine response.

CLINICAL RELEVANCE

Stratification. The compartmentalization of the cytokine cascades in peritonitis fits the concept that the circulating systemic concentration of cytokines may be misleading and not reflect their tissue concentration or local biologic activity.[6, 55, 58, 71] The use of cytokine serum concentrations in the form of a cytokine scoring system[72] has been frustrated by the fact that circulatory concentrations of free bioactive cytokines may be negligible, yet significant amounts of cytokine are present at the tissue level such as in the peritoneal cavity.[73] Therefore in outcome prediction local estimation of cytokines may better reflect the severity of an initially local process such as peritonitis. The pharmacokinetics of cytokines is characterized by plasma half-life and clearance measured in minutes and a few hours, respectively.[74, 75] Analogous figures for peritoneal cytokines are not available, but it is conceivable that the compartmentalized cytokines are relatively protected from inactivation by the liver or reticuloendothelial system, leading to prolonged biologic activity. Future studies measuring serial peritoneal cytokine concentrations during laparotomy or recorded from drain fluid could represent an important research tool to further quantitate and characterize the dynamics of the peritoneal cytokine response.

Treatment. Continuous arteriovenous hemofiltration improved survival in a canine model of septicemia[76] but not in a canine model of "ongoing" peritonitis.[77] A possible reason is that a predominantly extravascular process such as peritonitis may not be directly affected by removal of intravascular products such as cytokines. Is direct removal of cytokines from the peritoneal cavity possible and beneficial? Is peritoneal toilet, beyond its role to remove bacteria and adjuvants of infection, effective in decreasing the intraperitoneal levels of cytokines? Does antibiotic treatment started before (as opposed to after) the evacuation of peritoneal pus augment the local endotoxin-induced cytokine release?[78, 79] Do planned reoperations for severe intraabdominal infection cause a "second hit" escalation of the inflammatory response? When is infection cured but inflammation persists? Measurements of peritoneal cytokines should provide the answers.

Of course, cytokines are but one component of the complex systemic and peritoneal inflammatory cascade, albeit an important and proximal one. If peritoneal cytokines at a certain concentration and at a particular time are advantageous to the normal peritoneal inflammatory response, then the notion of "don't block local cytokines: remove the excess cytokines from the systemic circulation"[80] could be correct. At specific levels (high) and a certain phase (late), however, peritoneal compartmentalized cytokines probably cause persistent end-organ damage and "spill over" to produce adversely high levels in the systemic circulation. It is possible that to be effective, novel anticytokine strategies should be directly used at the site of cytokine production such as the peritoneal cavity instead of systemically. Notably, modulation of inflammation resulting from intraabdominal infection was not effective when attempted systemically.[17, 20, 25, 28, 29, 77] Conversely, the efficacy of granulocyte-macrophage colony-stimulating factor was enhanced when administered directly at the site of a subsequent intraperitoneal infective challenge.[39] In the future rapid intraoperative peritoneal assays for cytokines may guide specific intraperitoneal therapy.

CONCLUSIONS

The literature reviewed strongly supports the notion that bacterial peritonitis is associated with a significant and mainly compartmentalized peritoneal cytokine response that reflects the severity of the disease and its prognosis. Current surgical and antibiotic therapy for

peritonitis is able to clear the peritoneal cavity of infective concentrations of bacteria, but patients continue to die of an uncontrolled activation of the inflammatory cascade. More experimental and clinical studies are required to distinguish between the local beneficial and adverse effects of cytokines, including the magnitude and timing of cytokine elaboration and the value of local versus systemic blockade of cytokine action.

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