CHAPTER 13

Secondary Peritonitis and Cytokines

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Introduction

Peritonitis is still a life threatening complication for every surgical patient, which can occur after trauma, intra-abdominal operations or spontaneously.[1] Depending on localization or cause the mortality rate of peritonitis is between 40-70% according to literature. The principles of peritonitis treatment established by Kirschner, e.g., source control, debridement and lavage, are still valid.[2-4] Even the development of new, potent antibiotics within the last twenty years did not dramatically reduce the mortality rate of peritonitis. Intensive care therapy has influenced the survival of peritonitis patients. However, the treatment was focused on symptomatic treatment of organ dysfunction.[5] With the identification and recombinant development of cytokines the possibility to influence the course of peritonitis before organ dysfunction seem to available soon. Our knowledge of the pathophysiological immune response during peritonitis has been enlarged during the last 10 years. However, a uniform, efficient immunological concept of peritonitis treatment is not yet available. The purpose of this chapter is to summarize the main developments in cytokines in secondary peritonitis with regard to experimental and clinical studies.

Peritonitis and Cytokines in Experimental Models

Endotoxin which is released from cell walls of disintegrating gram-negative pathogens is a major trigger for cytokine release in peritonitis, although it may not be the only cause for macrophage cytokine production.[6] Peritonitis results in protease activation and protease inhibitor consumption, especially in the peritoneal fluid.[7] This may lead to a breakdown of C3 complement and IgG in peritonitis exudate.[8] Bacterial components other than endotoxin may induce dysfunction in the peritoneal macrophages capacity to produce proinflammatory cytokines during sepsis and peritonitis.[9,10]

However, endotoxin can be frequently detected in the peritoneal exudate and plasma of patients with peritonitis.[11,12] The activation of macrophages in peritonitis leads to a complex release of cytokines.[13] This activation occurs via specific LPS receptors, e.g., CD14, CD11/18 family, LPS receptor, scavenger receptor. The identification of specific cell membrane targets for LPS has important implications for immunotherapy.[14,15]

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It has been demonstrated that the infusion of either LPS or TNF can mimic the effects of sepsis.[16] Proinflammatory cytokine levels correlated with the prognosis of peritonitis and treatment failure. Reduced TNF plasma levels correlated with increased survival;[17] constantly increased peritoneal levels correlated with poor outcome.[18] The demonstration of detrimental TNF effects lead to the concept to block endotoxin or TNF. However, there was early evidence that I.V. anti-TNF antibodies decreased mortality only in I.V. sepsis and not in peritonitis.[19] Anti-TNF-antibodies reduced IL-1 and IL-6 plasma levels in I.V. sepsis and not in peritonitis. Anti-LPS-antibodies, however, were able to induce protection in peritonitis and to reduce pathogens, plasma TNF, IL-1 and IL-6 levels. The peritoneal cytokine levels remained unchanged.[20] Conversely, peritoneal cytokine production correlates with outcome in peritonitis and pretreatment with monophoryl lipid A as well as induction of endotoxin tolerance may reduce cytokine production.[21]

Dosage of Cytokines

The effect of cytokines on the immune response—beneficial or detrimental—may depend on the dose and the concentration of cytokines.[22] Anti-TNF-antibodies administration after CLP induction increased the mortality, while the addition of TNF increased the survival rate.[23] Interferon-γ increased TNF and IL-6 plasma levels and subsequent mortality. Blocking interferon-γ resulted in increased survival without any effect on the cytokine levels.[24] It seems to be likely that Interferon-γ increases sensitivity of cells to endotoxin.[25]

Function of Peritoneal Cells

Peritoneal macrophages may change their function during the course of peritonitis and therefore may influence the immune modulation. While antigen recognition is the main function during the early phase, cytokine production prevails during later stages of peritonitis. TNF plasma levels may be lower during peritonitis compared to I.V. induced sepsis.[26] Anti-TNF-antibodies reduced migration of granulocytes and monocytes into the peritoneum with increased number of pathogens.[27] Inflammatory cytokines may induce adhesion and fibrinogen production by stimulation of plasminogen activation inhibitor in mesothelial cells.[28,29] The mortality decreasing effect of Pentoxifyllin which is known to decrease TNF production in peritonitis may be due to reduced adhesion and fibrinogen production.[30] Peritoneal macrophages and mesothelial cells are responsible for initiation, amplification and termination of the inflammatory response. The surface of mesothelial cells, where bacteria colonize, may be an important place of interaction between macrophages and mesothelial cells.[31] Microbial colonization of the peritoneal mesothelial surface is a rapid and stable phenomena following penetration injury to the distal bowel. Mesothelial populations are resistant to intraperitoneal lavage.[32] *S. aureus* adherence to mesothelial cells is increased following preincubation of mesothelial cells with IL-1. Treating mesothelial cells with IFN-γ reduces adherence of *S. aureus*.[33] Other cell population in the peritoneum have not been studied until recently. Mast cells in the vicinity of blood vessels may be important for the synthesis of leukotrienes which are responsible for PMN recruitment.[34,35]

Local Response

Local TNF production is an important factor for tissue damage and organ dysfunction. Peritoneal macrophage TNF mRNA increased after CLP and i.p. LPS injection; however, TNF mRNA decreased faster after i.p. LPS injection. Both forms of

infection are able to induce TNF production in lungs and liver.[36] Bacterial infection of the peritoneal cavity may induce a slow release of cytokines which are important for the local immune response. IL-1 may induce the lethal effects of sepsis and TNF may be more important to launch the local immune response.[37] Increased local, intestinal IL-6 production has been demonstrated after CLP[38] and TNF levels were higher in portal vein than in hepatic veins.[39]

Within encapsulated abscess LPS binding protein (LBP) and bactercidal/permeability increasing protein (BPI) have been measured. LBP binds to the lipid A component of the bacterial endotoxin and facilitates its delivery to the CD14 antigen on the macrophage where inflammatory cytokines are released. The neutrophil granular protein bactericidal/permeability increasing protein (BPI) competes with LBP for endotoxin binding and functions as a molecular antagonist of LBP-endotoxin interactions. Within abscess cavities BPI is available in sufficient quantities for effective competition with LBP for endotoxin. BPI may attenuate the local inflammatory response and the systemic toxicity of endotoxin release during gram-negative infections.[40] Endotoxin derived from enteric bacteria might play an important role in the pathogenesis of lung injury and anti-endotoxin agents, such VVN1 222-5 appear to protect against endogenous bacterial endotoxin related disorders in severe hemorrhagic shock.[41,42]

Effect of Cytokines and Growth Factors in Peritonitis

Different results were reported when cytokines or growth factors were added in peritonitis. G-CSF increased survival rate in peritonitis, probably by reducing TNF levels.[43-45] High dose G-CSF decreased endotoxin and TNF, increased peripheral neutrophils and improved cardiopulmonary function.[46] Conversely, macrophages, which produce G-CSF, were not pivotal after bacterial translocation or septic shock in the knock-out mouse model.[47] GM-CSF, which was administered after the onset of peritonitis, was not beneficial and inhibited the neutrophil migration into the peritoneal cavity.[48] IL-1, an inflammatory cytokine, downregulated TNF and IL-6 plasma levels, decreased organ dysfunction and mortality when added before the induction of peritonitis.[49] This is supported by the finding that blockade of Kupffer cells decreased IL-1 and survival.[50] IL-2, which is known to be essential for immune response after thermal injury and CLP[51] induced influx of neutrophils in peritonitis and increased survival.[52] IL-2 administration and induction of peritonitis should be performed simultaneously to achieve a protection by IL-2.[53]

Anti-Endotoxin-Antibodies

The notion that anti-endotoxin-antibodies may be beneficial in peritonitis by reduction of cytokines[54] is further supported by other studies. Pretreatment with anti-endotoxin-antibodies were protective in peritonitis and reduced plasma TNF levels and splenocyte TNF production.[55] E5 monoclonal antibodies reduced mortality, endotoxin and TNF in peritonitis, but not endothelin.[56] Endotoxin neutralizing protein (ENP) decreased endotoxin and TNF; however, mortality was only reduced when ENP was added together with gentamicin.[57]

Further studies with anti-endotoxin antibodies were published with controversial results. Some of them, however, revealed important pathophysiological mechanisms of the function of anti-endotoxin-antibodies. Type specific anti-endotoxin-antibodies were protective in peritonitis by Fc-mediated clearance of both bacteria and endotoxin.[58]

IgG and IgM anti-LPS mAbs exert protective capacity by extracellular neutralization of LPS, while Fc-receptor mediated cellular uptake also may serve to bypass macrophage activation and TNF secretion by promoting internalization and intracellular neutralization.[59] While some recent reports demonstrated significant activity of antibodies, not all anti-endotoxin antibodies have been demonstrated to bind to endotoxin or to be beneficial in peritonitis. Selected models may have a clear influence on the results.[60-63]

Pathogens

Treatment failures of intra-abdominal infection may be due in part to the presence of resistant pathogens at the site of infection.[64] Enterococcus plays an important role in the mechanisms of bacterial synergism in experimental peritonitis.[65,66] The LPS induced cytokine immune response and the bacterial surface characteristics may be more important for the killing of invading pathogens than previously thought.[67] In vitro studies have revealed that antibiotics may release different amounts of endotoxin depending on the type of Penicillin binding protein.[68] There may be important functional relationships between the immune response and resistant pathogens not yet clarified.[69,70]

Anti-Inflammatory Cytokines

There is a growing body of information available on the onset of inflammatory response in secondary peritonitis. However, there is less information available on the termination of inflammation and the role of anti-inflammatory cytokines. It was generally believed that the anti-inflammatory response is launched after the inflammatory response. However, we and others have demonstrated that both inflammatory and anti-inflammatory cytokines are released simultaneously during the inflammatory response.[71] Anti-inflammatory cytokines seem to suppress inflammatory cytokines. IL-10 administration prolonged survival in septic mice[72] and reduced mortality in severe peritonitis;[73] anti-IL-10-antibodies given before CLP increased mortality rate.[74] Pretreatment with anti-IL-10 increased plasma TNF levels, whereas IL-1 and IFN-γ could not be detected. IL-10 mRNA was observed in liver, spleen and lungs after CLP. The increased mortality rate with anti-IL-10 pretreatment could not be influenced by anti-TNF-antibodies.[75]

TNF exerts its effects by two cell surface receptors, TNF R I and II, also referred to as p55 and p75 receptors, respectively. TNF-R are transmembrane proteins which on cleavage of their extracellular domains result in the release of soluble fragments sTNF-R. sTNF-R increases markedly during infection and may serve to modulate TNF bioactivity. In endotoxin sensitive and resistant mice it was demonstrated that upon infection with LPS or live gram-negative bacteria there may be 2 separately regulated pathways that control sTNF-R shedding. Peritoneal macrophages of endotoxin sensitive mice responded to LPS stimulation; in contrast macrophages of resistant mice showed only a modest response.[76] Endotoxin induces downmodulation of monocyte and granulocyte TNF surface receptors in humans in vivo which may represent a mechanism to reduce excessive activity of TNF during systemic infection.[77]

Second Hit

Trauma may prime macrophages in such a way that a second hit to the immune system by infection or sepsis may lead to inadequate immune response. Trauma induces changes in endotoxin kinetics and PMN function in a model of trauma and posttraumatic peritonitis.[78] Synergism between trauma and infection was observed

for IL-1, but not for TNF.[79] After thermal injury and CLP macrophage production of inflammatory cytokines and arachidonic acid production has been downregulated and was associated with increased mortality.[80]

Therapy

Therapeutic intervention may influence the immune response. Resuscitation with fluids influenced TNF mRNA and IL-1 mRNA production in liver and intestines in intraabdominal sepsis.[81] Topical applied antiseptics or antibiotics may influence cytokine release in the peritoneal cavity or compounds used for other indications than sepsis may affect cytokine production, coagulation disturbances and mortality.[82]

Secondary Peritonitis and Cytokines in Clinical Studies

Increased TNF and IL-6 plasma levels correlated with outcome and APACHE II scores in several studies.[84-86] However, the determination of plasma cytokines is hampered by the interference with plasma proteins and receptors. Cell-associated cytokines may give a more realistic picture of the inflammatory response.[87] The information on the kinetics of cytokines during peritonitis is incomplete. TNF and IL-6 plasma levels were decreased before death in peritonitis and may indicate an anergic response induced by T-cell suppression.[88] However increased elastase production (a marker for PMN activation[89]) and increased neopterin production (a marker for macrophage activation[90]) in peritonitis do not support this notion.

Plasma IL-1 and IL-6 were increased even after large abdominal operations reflecting more the operative trauma than the infection.[91-93] The significance of local cytokine production has been supported by several studies. After colectomy IL-6 levels were higher in portal vein than in systemic circulation[94] supporting the hypothesis of bacterial translocation in portal and lymphatic circulation.[95] Bacterial peritonitis induces local release of proinflammatory cytokines and secondary mediators with subsequent interaction of endothelial cells and neutrophils, microcirculatory dysfunction and tissue damage.[96] The peritoneal cavity may be already cleared from pathogens by lavage, while the local release of inflammatory cytokines may continue.[97] Peritoneal levels of endotoxin, TNF, IL-1, IL-6 and elastase may be several fold higher than systemic levels. Peritoneal TNF and elastase levels decreased in survivors and remain elevated in nonsurvivors.[60] This lead to the conclusion that the mechanisms in sepsis and peritonitis may be similar. However, the immune response occurs in two functional different compartments and the intensity in both compartments may influence outcome.[98] This is also supported by studies in other compartments of the body.[99]

Treatment interventions may influence and modulate cytokine production. IL-6 levels correlated with mean arterial pressure in severe peritonitis. Reoperation caused hypotension which may have induced an early increase in IL-6 plasma levels.[100] Antibiotics can release, according to the type of penicillin binding protein (PBP), different amounts of endotoxin.[101,102] In surgical intensive care patients, PBP 3 specific antibiotics induced more often endotoxin release than PBP 2-specific antibiotics.[103] Several clinical studies with anti-endotoxin-antibodies and anti-TNF-antibodies have been performed in septic patients including patients with peritonitis. The clinical significance of endotoxin is still disputed. Endotoxin may not be the trigger for proinflammatory cytokine release,[104] however, it may help in the early detection of anastomotic leaks by endotoxin determination.[105] HA-1A reduces mortality in septic patients with endotoxemia and lowers serum TNF levels.[106] Other studies were

not successful in reducing the mortality of septic patients. This may be due to conceptual and organizational weakness of some studies. The fact that results from animal experiments and clinical studies are not well reflected in the design of these studies is further supported by many investigators. High circulating levels of IL-1ra and sTNF-R and the relatively small proportion of patients developing Endotoxin Core Antibody depletion may contribute to the limitations of therapies to augment natural defenses against endotoxin or proinflammatory cytokines.[107]

Conclusions

Endotoxin and cytokines play an important role in secondary peritonitis and contribute to the outcome of this life-threatening complication. The effect cytokines may have on the immune response depends on concentration, location and other co-factors, e.g., BPI and LBP. The addition of growth factors and cytokines to the treatment arsenal in peritonitis may not be advocated at this time with regard to the controversial results in animal and clinical studies. Cells and pathogens in the peritoneal cavity interact with each other and cytokines play an important part in this communication. However, our information on this network is rather limited. Therapeutic interventions, e.g., resuscitation, antibiotics, surgery, modulate the cytokine levels and thereby the immune response. The blockade of cytokines and endotoxin was not successful in most clinical studies. Newly developed anti-endotoxin-antibodies and compounds which block the endotoxin-induced activation of cells seem to be more promising. The concept of anti-inflammatory response in humans is not yet clear and needs further investigations and well planned studies to reveal the pathophysiological consequences of cytokines in secondary peritonitis.

References

1. Malungoni MA. Pathogenesis and treatment of intra-abdominal infection. Surg Gynecol Obstet 1990; 171(Suppl):31-34.
2. Schein M, Gecelter G, Freinkel W, Gerding H, Becker PJ. Peritoneal lavage in abdominal sepsis. A controlled clinical study. Arch Surg 1990; 125(9):1132-1135.
3. Wittmann DH, Aprahamian C, Bergstein JM. Etappenlavage: Advanced diffuse peritonitis managed by planned multiple laparotomies utilizing zippers, slide fastener, and Velcro analogue for temporary abdominal closure. World J Surg 1990; 14(2):218-226.
4. Nathens AB, Rotstein OD. Therapeutic options in peritonitis. Surg Clin North Am 1994; 74(3):677-692.
5. Offenbartl K, Bengmark S. Intraabdominal infections and gut origin sepsis. World J Surg 1990; 14(2):191-195.
6. Ayala A, Kisala JM, Felt JA et al. Does endotoxin tolerance prevent the release of inflammatory monokines (interleukin 1, interleukin 6, or tumor necrosis factor) during sepsis? Arch Surg 1992; 127(2):191-196.
7. Delshammar M, Lasson A, Ohlsson K. Proteases and protease inhibitor balance in peritonitis with different causes. Surgery 1989; 106(3):555-562.
8. Billing A, Kortmann H, Frohlich D, Jochum M. Breakdown of C3 complement and IgG in peritonitis exudate—pathophysiological aspects and therapeutic approach. Prog Clin Biol Res 1989; 308:527-533.
9. Ayala A, Deol ZK, Lehman DL et al. Does endotoxin play a major role in inducing the depression of macrophage function during polymicrobial sepsis? Arch Surg 1995; 130(11):1178-1184.

10. Ayala A, Deol ZK, Lehman DL et al. Polymicrobial sepsis but not low-dose endotoxin infusion causes decreased splenocyte IL-2/IFN-gamma release while increasing IL-4/IL-10 production. J Surg Res 1994; 56(6):579-585.
11. Schoeffel U, Jacobs E, Ruf G et al. Intraperitoneal micro-organisms and the severity of peritonitis. Eur J Surg 1995; 161(7):501-508.
12. Berger D, Beger HG. The pathophysiological bases of peritonitis therapy. Chirurg 1992; 63(3):147-152.
13. Ertel W, Morrison MH, Wang P et al. The complex pattern of cytokines in sepsis. Ann Surg 1991; 214:141-148.
14. Morrison DC, Lei MG, Kirikae T, Chen TY. Endotoxin receptors on mammalian cells. Immunobiology 1993; 187(3-5):212-226.
15. Ulevitch RJ, Tobias PS. Receptor-dependent mechanisms of cell stimulation by bacterial endotoxin. Annu Rev Immunol 1995:13(Imm.).
16. van der Poll T, van Deventer SJ, Buller HR, Sturk A, ten Cate JW. Comparison of the early dynamics of coagulation activation after injection of endotoxin and tumor necrosis factor in healthy humans. Prog Clin Biol Res 1991; 367:55-60.
17. Mayoral JL, Schweich CJ, Dunn DL. Decreased tumor necrosis factor production during the initial stages of infection correlates with survival during murine gram-negative sepsis. Arch Surg 1990; 125:24-28.
18. Rasmussen LT, Fandrem J, Seljelid R. Dynamics of blood components and peritoneal fluid during treatment of murine *E. coli* sepsis with beta-1,3-D-polyglucose derivatives. II. Interleukin 1, tumour necrosis factor, prostaglandin E2, and leukotriene B4. Scand J Immunol 1990; 32(4):333-340.
19. Bagby GJ, Plessala KJ, Wilson LA et al. Divergent efficacy of antibody to tumor necrosis factor-alpha in intravascular and peritonitis models of sepsis. J Infect Dis 1991; 163(1):83-88.
20. Zanetti G, Heumann D, Gerain J et al. Cytokine production after intravenous or peritoneal gram-negative bacterial challenge in mice. Comparative protective efficacy of antibodies to tumor necrosis factor-alpha and to lipopolysaccharide. J Immunol 1992; 148(6):1890-1897.
21. Astiz ME, Saha DC, Carpati CM, Rackow EC. Induction of endotoxin tolerance with monophosphoryl lipid A in peritonitis: importance of localized therapy. J Lab Clin Med 1994; 123(1):89-93.
22. Natanson C, Hoffman WD, Suffredini AF et al. Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. Ann Intern Med 1994; 120(9):771-783.
23. Echtenacher B, Falk W, Mannel DN, Krammer PH. Requirement of endogenous tumor necrosis factor/cachectin for recovery from experimental peritonitis. J Immunol 1990; 145(11):3762-3766.
24. Kohler J, Heumann D, Garotta G et al. IFN-gamma involvement in the severity of gram-negative infections in mice. J Immunol 1993; 151(2):916-921.
25. Jurkovich GJ, Mileski WJ, Maier RV et al. Interferon gamma increases sensitivity to endotoxin. J Surg Res 1991; 51(3):197-203.
26. McMasters KM, Cheadle WG. Regulation of macrophage TNF alpha, IL-1 beta, and Ia (I-A alpha) mRNA expression during peritonitis is site dependent. J Surg Res 1993; 54(5):426-430.
27. van Furth R, van Zwet TL, Buisman AM, van Dissel JT. Antitumor necrosis factor antibodies inhibit the influx of granulocytes and monocytes into an inflammatory exudate and enhance the growth of Listeria monocytogenes in various organs. J Infect Dis 1994; 170(1):234-237.
28. Whawell SA, Thompson JN. Cytokine-induced release of plasminogen activator inhibitor-1 by human mesothelial cells. Eur J Surg 1995; 161(5):315-318.

29. Thompson JS. The intestinal response to critical illness. Am J Gastroenterol 1995; 90(2):190-200.
30. Chalkiadakis GE, Kostakis A, Karayannacos PE. Pentoxifylline in the treatment of experimental peritonitis in rats. Arch Surg 1985; 120: 1141-1144.
31. Topley N, Mackenzie RK, Williams JD. Macrophages and mesothelial cells in bacterial peritonitis. Immunobiology 1996; 195(4-5):563-573.
32. Edmiston CE Jr, Goheen MP, Kornhall S et al. Fecal peritonitis: Microbial adherence to serosal mesothelium and resistance to peritoneal lavage. World J Surg 1990; 14(2):176-183.
33. Glancey G, Cameron JS, Ogg C, Poston S. Adherence of *Staphylococcus aureus* to cultures of human peritoneal mesothelial cells. Nephrol Dial Transplant 1993; 8(2):157-162.
34. Ramos BF, Qureshi R, Olsen KM, Jakschik BA. The importance of mast cells for the neutrophil influx in immune complex-induced peritonitis in mice. J Immunol 1990; 145(6):1868-1873.
35. Ramos BF, Zhang Y, Qureshi R, Jakschik BA. Mast cells are critical for the production of leukotrienes responsible for neutrophil recruitment in immune complex-induced peritonitis in mice. J Immunol 1991; 147(5):1636-1641.
36. Hadjiminas DJ, McMasters KM, Peyton JC, Cheadle WG. Tissue tumor necrosis factor mRNA expression following cecal ligation and puncture or intraperitoneal injection of endotoxin. J Surg Res 1994; 56(6):549-555.
37. Acton RD, Dahlberg PS, Uknis ME et al. Differential sensitivity to Escherichia coli infection in mice lacking tumor necrosis factor p55 or interleukin-1 p80 receptors. Arch Surg 1996; 131(11):1216-1221.
38. Meyer TA, Noguchi Y, Ogle CK et al. Endotoxin stimulates interleukin-6 production in intestinal epithelial cells. A synergistic effect with prostaglandin E2. Arch Surg 1994; 129(12):1290-1294.
39. Grewal HP, Kotb M, el Din AM et al. Induction of tumor necrosis factor in severe acute pancreatitis and its subsequent reduction after hepatic passage. Surgery 1994; 115(2):213-221.
40. Opal SM, Palardy JE, Marra MN et al. Relative concentrations of endotoxin-binding proteins in body fluids during infection. Lancet 1994; 344(8920):429-431.
41. Bahrami S, Yao YM, Leichtfried G et al. Monoclonal antibody to endotoxin attenuates hemorrhage-induced lung injury and mortality in rats. Crit Care Med 1997; 25(6):1030-1036.
42. Xu D, Qi L, Guillory D et al. Mechanisms of endotoxin-induced intestinal injury in a hyperdynamic model of sepsis. J Trauma 1993; 34(5):676-682.
43. O'Reilly M, Silver GM, Greenhalgh DG et al. Treatment of intra-abdominal infection with granulocyte colony-stimulating factor. J Trauma 1992; 33(5):679-682.
44. Molloy RG, Holzheimer R, Nestor M et al. Granulocyte-macrophage colony-stimulating factor modulates immune function and improves survival after experimental thermal injury. Br J Surg 1995; 82(6):770-776.
45. Lorenz W, Reimund KP, Weitzel F et al. Granulocyte colony-stimulating factor prophylaxis before operation protects against lethal consequences of postoperative peritonitis. Surgery 1994; 116(5):925-934.
46. Eichacker PQ, Waisman Y, Natanson C et al. Cardiopulmonary effects of granulocyte colony-stimulating factor in a canine model of bacterial sepsis. J Appl Physiol 1994; 77(5):2366-2373.
47. Feltis BA, Jechorek RP, Erlandsen SL, Wells CL. Bacterial translocation and lipopolysaccharide-induced mortality in genetically macrophage-deficient op/op mice. Shock 1994; 2(1):29-33.

48. Toda H, Murata A, Oka Y et al. Effect of granulocyte-macrophage colony-stimulating factor on sepsis-induced organ injury in rats. Blood 1994; 83(10):2893-2898.
49. Lange JR, Alexander HR, Merino MJ et al. Interleukin-1 alpha prevention of the lethality of Escherichia coli peritonitis. J Surg Res 1992; 52(6):555-559 1992.
50. Callery MP, Mangino MJ, Kamei T, Flye MW. Interleukin-6 production by endotoxin-stimulated Kupffer cells is regulated by prostaglandin E2. J Surg Res 1990; 48(6):523-527.
51. Gough DB, Jordan A, Mannick JA, Rodrick ML. Impaired cell-mediated immunity in experimental abdominal sepsis and the effect of interleukin 2. Arch Surg 1992; 127(7):859-863.
52. Maddaus MA, Simmons RL. Intraperitoneal administration of recoombinant interleukin-2 protects against lethal IP Gram-negative sepsis by induction of a neutrophil influx. Surgical Forum, Chicago, American College of Surgeons 1988:105-106.
53. Chong KT. Prophylactic administration of interleukin-2 protects mice from lethal challenge with Gram-negative bacteria. Infect Immun 1987; 55:668-673.
54. Zanetti G, Glauser MP, Baumgartner JD. Anti-endotoxin antibodies and other inhibitors of endotoxin. New Horiz 1993; 1(1):110-119.
55. Battafarano RJ, Burd RS, Kurrelmeyer KM et al. Inhibition of splenic macrophage tumor necrosis factor alpha secretion in vivo by antilipopolysaccharide monoclonal antibodies. ArchSurg 1994; 129(2):179-180.
56. Lundblad R, Giercksky KE. Synergistic effect of E5 imipenem, and volume support during fulminant intraabdominal sepsis in rats [published erratum appears in J Infect Dis 1995 Aug;172(2):612]. J Infect Dis 1995; 172(1):152-160.
57. Saladino R, Garcia C, Thompson C et al. Efficacy of a recombinant endotoxin neutralizing protein in rabbits with *Escherichia coli* sepsis. Circ Shoc 1994; 42(2):104-110.
58. Burd RS, Cody CS, Raymond CS, Dunn DL. Anti-endotoxin monoclonal antibodies protect by enhancing bacterial and endotoxin clearance. Arch Surg 1993; 128(2):145-150.
59. Burd RS, Battafarano RJ, Cody CS et al. Anti-endotoxin monoclonal antibodies inhibit secretion of tumor necrosis factor-alpha by two distinct mechanisms. Ann Surg 1993; 218(3):250-259.
60. Christ WJ, Asano O, Robidoux AL et al. E5531 a pure endotoxin antagonist of high potency. Science 1995; 268(5207):80-83.
61. Marra MN, Thornton MB, Snable JL et al. Endotoxin-binding and -neutralizing properties of recombinant bactericidal/permeability-increasing protein and monoclonal antibodies HA-1A and E5 [see comments]. Crit Care Med 1994; 22(4): 559-565.
62. Stack AM, Saladino RA, Siber GR et al. A comparison of bactericidal/permeability-versus increasing protein variant recombinant endotoxin-neutralizing protein for the treatment of Escherichia coli sepsis in rats. Crit Care Med 1997; 25(1):101-105.
63. Bailat S, Heumann D, Le Roy D et al. Similarities and disparities between core-specific and O-side-chain-specific antilipopolysaccharide monoclonal antibodies in models of endotoxemia and bacteremia in mice. Infect Immun 1997; 65(2): 811-814.
64. Christou NV, Turgeon P, Wassef R et al. Management of intra-abdominal infections. The case for intraoperative cultures and comprehensive broad-spectrum antibiotic coverage. The Canadian Intra-abdominal Infection Study Group Arch Surg 1996; 131(11):1193-1201.
65. Montravers P, Andremont A, Massias L, Carbon C. Investigation of the potential role of Enterococcus faecalis in the pathophysiology of experimental peritonitis. J Infect Dis 1994; 169(4):821-830.

66. Montravers P, Mohler J, Saint Julien L, Carbon C. Evidence of the proinflammatory role of Enterococcus faecalis in polymicrobial peritonitis in rats. Infect Immun 1997; 65(1):144-149.
67. Cross A, Asher L, Seguin M et al. The importance of a lipopolysaccharide-initiated, cytokine-mediated host defense mechanism in mice against extraintestinally invasive Escherichia coli. J Clin Invest 1995; 96(2):676-686.
68. Jackson JJ, Kropp H beta-Lactam antibiotic-induced release of free endotoxin: in vitro comparison of penicillin-binding protein (PBP) 2-specific imipenem and PBP 3-specific ceftazidime [see comments]. J Infect Dis 1992; 165(6):1033-1041.
69. Muller Alouf, Alouf H, Gerlach JE et al. Human pro- and anti-inflammatory cytokine patterns induced by Streptococcus pyogenes erythrogenic (pyrogenic) exotoxin A and C superantigens. Infect Immun 1996; 64(4):1450-1453.
70. Tanaka Y, Jotwani R, Watanabe K et al. Effect of Escherichia coli lipopolysaccharide on *Bacteroides* fragilis abscess formation and mortality in mice. Microbiol Immunol 1994; 38(2):97-102.
71. Holzheimer RG, Groß J Maseizik T, Steinmetz WG et al. Ischemia and endotoxin mediated inflammatory response (TNF, IL-6, IL-10, TNF-R I + II) in aortic aneurysm repair Shock 1995; 3(Suppl):15-16.
72. Napolitano LM, Campbell C. Interleukin-10 (IL-10) decreases mortality in a lethal murine trauma/sepsis model. Abstract. Proceedings of the Fifteenth Annual Meeting of the Surgical Infection Society. Louisville April 20-22 1992.
73. Kato T, Murata A, Ishida H et al. Interleukin 10 reduces mortality from severe peritonitis in mice. Antimicrob Agents Chemother 1995; 39(6):1336-1340.
74. van der Poll T, Jansen J, Levi M et al. Regulation of interleukin 10 release by tumor necrosis factor in humans and chimpanzees. J Exp Med 1994; 180(5): 1985-1988.
75. van der Poll T, Marchant A, Buurman WA et al. Endogenous IL-10 protects mice from death during septic peritonitis. J Immunol 1995; 155(11):5397-5401.
76. Carpenter A, Evans TJ, Buurman WA et al. Differences in the shedding of soluble TNF receptors between endotoxin-sensitive and endotoxin-resistant mice in response to lipopolysaccharide or live bacterial challenge. J Immunol 1995; 155(4):2005-2012.
77. van der Poll T, Calvano SE, Kumar A et al. Endotoxin induces downregulation of tumor necrosis factor receptors on circulating monocytes and granulocytes in humans. Blood 1995; 86(7):2754-2759.
78. Rokke O, Revhaug A, Giercksky KE. PMN activity and endotoxin kinetics in peritonitis induced after moderate trauma. Acta Chir Scand 1989; 155(10):497-502.
79. Rokke, O, Revhaug A, Seljelid R, Rekvig O. The synergistic effect of trauma and infection on interleukin-1 but not tumor necrosis factor liberation during posttraumatic gram-negative septicemia. Eur Surg Res 1993; 25(1):1-10.
80. Holzheimer RG, Schein M, Wittmann DH. Inflammatory response in peritoneal exudate and plasma of patients undergoing planned relaparotomy for severe secondary peritonitis. Arch Surg 1995; 130(12):1314-1319.
81. Wilson MA, Chou MC, Spain DA et al. Fluid resuscitation attenuates early cytokine mRNA expression after peritonitis. J Trauma 1996; 41(4):622-627.
82. Rosman C, Westerveld GJ, van Oeveren W, Kooi K, Bleichrodt RP. Effect of intraperitoneal antimicrobials on the concentration of bacteria, endotoxin and tumor necrosis factor in abdominal fluid and plasma in rats. Eur Surg Res 1996; 28(5):351-360.
83. Bahrami S, Yao YM, Shiga H et al. Comparison of the efficacy of pentoxifylline and albifyllin (HWA 138) on endotoxin-induced cytokine production, coagulation disturbances, and mortality. Shock 1996; 5(6):424-428.

84. Damas P, Ledoux D, Nys M et al. Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. Ann Surg 1992; 215(4):356-362.
85. Fugger R, Zadrobilek E, Gotzinger P et al. Perioperative TNF alpha and IL-6 concentrations correlate with septic state, organ function and APACHE II scores in intra-abdominal infection. Eur J Surg 1993; 159(10):525-529.
86. Patel RT, Deen KI, Youngs D, Warwick J, Keighley MR. Interleukin 6 is a prognostic indicator of outcome in severe intra-abdominal sepsis Br J Surg 1994; 81(9): 1306-1308.
87. Munoz C, Carlet J, Fitting C et al. Dysregulation of in vitro cytokine production by monocytes during sepsis. J Clin Invest 1991; 88(5):1747-1754.
88. Hamilton G, Hofbauer S, Hamilton B. Endotoxin TNF-alpha, interleukin-6 and parameters of the cellular immune system in patients with intraabdominal sepsis. Scand J Infect Dis 1992; 24(3):361-368.
89. Duswald KH, Jochum M, Schramm E, Fritz H. Released granulocyte elastase: An indicator of pathobiochemical alterations in septicemia after abdominal surgery. Surgery 1985; 98:892-898.
90. Strohmaier W, Redl H, Schlag G, Inthorn D. D-erythro-neopterin plasma levels in intennsive care patients with and without septic complications. Crit Care Med 1987; 15:757-760.
91. Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. Br J Surg 1992; 79(8):757-760.
92. Ueo H, Inoue H, Honda M. Production of interleukin-6 at operative wound sites in surgical patients. J Am Coll Surg 1994; 179:326-332.
93. Glaser F, Sannnwald GA, Buhr H. General stress response to conventional and laparoscopic cholecystectomy. Ann Surg 1995; 221:372-380.
94. Riche F, Dosquet C, Panis Y et al. Levels of portal and systemic blood cytokines after colectomy in patients with carcinoma or Crohn's disease. J Am Coll Surg 1995; 180(6):718-724.
95 Deitch EA, Xu D, Franko L, Ayala A, Chaudry IH. Evidence favoring the role of the gut as a cytokine-generating organ in rats subjected to hemorrhagic shock. Shock 1994; 1(2):141-145.
96. Livingston DH, Mosenthal AC, Deitch EA. Sepsis and multiple organ dysfunction syndrome: a clinical-mechanistic overview. New Horizons 1995; 3:257-266.
97. Aprahamian C, Schein M, Wittmann D. Cefotaxime and metronidazole in severe intra-abdominal infection. Diagn Microbiol Infect Dis 1995; 22:183-188.
98. Schein, M, Wittmann, DH, Holzheimer R, Condon RE. Hypothesis: Compartmentalization of cytokines in intraabdominal infection. Surgery 1996; 119(6):694-700.
99. Boujoukos AJ, Martich GD, Supinski E, Suffredini AF. Compartmentalization of the acute cytokine response in humans after intravenous endotoxin administration. J Appl Physiol 1993; 74(6):3027-3033.
100. Sautner T, Gotzinger P, Redl Wenzl EM et al. Does reoperation for abdominal sepsis enhance the inflammatory host response? Arch Surg 1997; 132(3):250-255.
101 Prins JM, van Deventer SJ, Kuijper EJ, Speelman P. Clinical relevance of antibiotic-induced endotoxin release. Antimicrob Agents Chemother 38(6):1211-1218.
102. Sawyer RG, Adams RB, May AK, Rosenlof LK, Pruett TL. Anti-tumor necrosis factor antibody reduces mortality in the presence of antibiotic-induced tumor necrosis factor release. Arch Surg 1996; 128(1):73-77.
103. Holzheimer RG, Hirte JF, Reith B et al. Different endotoxin release and IL-6 plasma levels after antibiotic administration in surgical intensive care patients. J Endotoxin Res 1996; 3:261–267.

104. Kelly JL, O'Sullivan C, O'Riordain M et al. Is circulating endotoxin the trigger for the systemic inflammatory response syndrome seen after injury? Ann Surg 1997; 225(5):530-541.
105. Junger W, Junger WG, Miller K et al. Early detection of anastomotic leaks after colorectal surgery by measuring endotoxin in the drainage fluid. Hepatogastroenterology. 1996; 43(12):1523-1529.
106. Wortel CH, von der Mohlen MA, van Deventer SJ et al. Effectiveness of a human monoclonal anti-endotoxin antibody (HA-1A) in gram-negative sepsis: relationship to endotoxin and cytokine levels [see comments]. J Infect Dis 1992; 166(6): 1367-1374.
107. Goldie AS, Fearon KC, Ross JA et al. Natural cytokine antagonists and endogenous antiendotoxin core antibodies in sepsis syndrome. The Sepsis Intervention Group. JAMA 1995; 274(2):172-177.