Aggressive management of surgical emergencies

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ABSTRACT

Increasing evidence suggests that two factors significantly influence outcome in a surgical emergency – premorbid health and the degree of inflammation during the first 24 h following trauma. Repeat observations suggest that the depth of post-trauma immunoparalysis reflects the height of early inflammatory response. Administration to surgical emergencies, as was routine in the past, of larger amounts of fluid and electrolytes, fat, sugar and nutrients seems counterproductive as it increases immune dysfunction, impairs resistance to disease and, in fact, increases morbidity. Instead, strong efforts should be made to limit the obvious superinflammation, which occurs during the first 24 h after trauma and, thereby, reduce the subsequent immunoparalysis. Several approaches show efficacy in limiting early superinflammation such as strict control of blood glucose, avoidance of stored blood when possible, supply of antioxidants, live lactic acid bacteria and plant fibres. This review focuses mainly on use of live lactic acid bacteria and plant fibres, often called synbiotics. Encouraging experience is reported from clinical trials in liver transplantation, severe pancreatitis and extensive trauma. Immediate control of inflammation by enteral nutrition and supply of antioxidants, lactic acid bacteria and fibres is facilitated by feeding tubes, introduced as early as possible on arrival at the hospital.

KEYWORDS

Surgical emergency – Superinflammation – Synbiotics – Lactic acid bacteria – Plant fibres

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There are two main factors which determine outcome in severe medical and surgical emergencies and after extensive surgery – the premorbid health condition and the determination and efficacy with which early treatment is instituted. Increasing evidence suggests a clear association between the extent of the acute phase response during the period of early physical and mental stress, the nervous phase, and the extent of immunoparesis which develops during the subsequent so called immune phase – the more pronounced the inflammatory response, the deeper will be the subsequent immunoparesis. The nervous phase is characterised by a fast and large increase in pro-inflammatory cytokines and acute phase proteins especially, but also in inflammatory cells, especially neutrophils. Repeat measurements of cytokines were done in an Austrian study during different stages of liver transplantation; if IL-6 and TNF- α increased more than 6-fold by the end of the operation, the patients always developed postoperative infections.¹

Limited need of calorie supply

The early, exaggerated, acute-phase response and cytokine storm is most pronounced in the elderly, persons with

chronic diseases, in those with a poor life-style and poor nutritional habits, and in neutropenic individuals. It is often aggravated by the supply of certain pharmaceuticals, including antibiotics, which paralyse immune responses such as macrophage function. It is also made worse by aggressive supply of nutrients, especially when the parenteral route is used. Hyperalimentation should not be routine practice as administration of larger amounts of fluid and electrolytes, fat, sugar and nutrients increases immune dysfunction, impairs resistance to disease and increases morbidity (as discussed in Bengmark²). In fact, large amounts of calories are not needed for the first 10–14 days, as demonstrated in two well-designed randomised studies in 300 and 195 patients who underwent major general surgery.^{3,4} In the first study, which lasted for up to 15 days, total parenteral nutrition (TPN) was compared to infusion of only 1000–1500 kcal/day of glucose. The nitrogen loss during the first week was reduced to about half in the glucose-supplied group compared to the TPN group, but no differences in morbidity or mortality were observed, and the authors concluded ‘overfeeding seems to be a larger problem than underfeeding’.³ In the second study, performed at Memorial-Sloan-Kettering Cancer Center in New York, the patients were randomised to either early

enteral supplementation with a so called immuno-enhancing diet (Impact, Novartis) or only i.v. crystalloid infusions. The daily intake of calories was low in both groups – 1000 kcal and 400 kcal, that is 61% and 22% of defined goals (25 kcal/kg/day). No differences in the number of minor, major or infectious complications, number of wound infections, mortality or length of were observed between the groups.⁴

It is increasingly understood that early nutrition has greater effects on bacterial flora and the immune system and less on the body, which seems to be the main reason why, in numerous studies, early enteral nutrition has shown superiority over parenteral. A controlled study, which compared enteral nutrition and TPN after liver resection found no differences in nutritional parameters: retinol binding protein (RBP), transferrin, pre-albumin, and 3-methylhistidine, but huge differences in immune parameters – lymphocyte count (114 versus 66; $P < 0.05$), PHA response (103 versus 78; $P < 0.05$) and natural killer (NK) cells (106 versus 49; $P < 0.05$) and outcome, especially septic complications (8% versus 31%; $P < 0.05$).⁵

The concept of immunonutrition is attractive but attempts to modify nutrition to increase the enhancing ability on the immune defence has met with limited success. An excellent meta-analysis, from 2001, based on 22 randomised trials with a total of 2419 patients compared the use of specific commercial immunonutrition solutions with standard enteral nutrition solutions in surgical and critically ill patients. Immunonutrition was associated with lower infectious complications (RR, 0.66; 95% CI, 0.54–0.80), but seemed not to offer any advantage of decreased mortality; the pooled risk ratio (RR) of mortality was 1.10 (95% CI, 0.93–1.31).⁶

Over-reacting neutrophils

Severe trauma, major surgery and severe sepsis will, in parallel with a significant decrease in lymphocytes, induce a significant, sometimes disproportionate, increase in circulating and tissue neutrophils accompanied by persistent decline in T-4 helper lymphocytes and elevation of T-8 suppressor lymphocytes.⁷ It is suggested that a T-4/T-8 lymphocyte cell ratio of < 1 is a sign of severe immunosuppression and prediction of complications such as multiple organ dysfunction syndrome, as observed in patients with myocardial infarction, acute pancreatitis, multiple severe trauma and in oncology ICU patients.⁸ An early and larger increase in circulating neutrophils is accompanied by tissue infiltration of neutrophils, which are responsible for common post-trauma/postoperative dysfunctions such as paralytic ileus,^{9,10} bone marrow suppression, endothelial cell dysfunction, and often leads to tissue

destruction and organ failure, particularly in lungs,^{11–15} intestines,¹⁴ liver,¹⁵ and kidney.¹⁶ Neutrophil infiltration of distant organs,¹⁷ especially of the lungs¹¹ are also characteristic findings of patients dying in sepsis, which already 20 years ago was suggested to be a consequence of ‘generalised autodestructive inflammation’.¹⁷ The extent of neutrophil infiltration is aggravated by mechanical therapeutic efforts such as handling of the bowels during operation,⁹ and ventilation of the lungs.¹⁸ Poor nutritional status, pre-existing immune deficiency, obesity, diabetes and high levels of blood sugar¹⁹ contribute to immune deterioration and to increased expression of molecules such as NF- κ B, COX-2, LOX and iNOS.^{20,21}

The lungs are the most common target

Post-shock mesenteric lymph has been shown to activate the mechanisms leading to acute lung injury,²² and diversion of thoracic duct lymph can prevent trauma/haemorrhagic shock-induced lung injury.²³ These observations seem to explain why the early, most frequently observed, and most severe clinical manifestations of organ failure are seen in the lungs. In severe acute pancreatitis, the organ systems most often involved in early (within 24 h) single organ failure are pulmonary (91%,²⁴ 81%²⁵), renal (4.5%,²⁴ 5%²⁵) and coagulation (4.5%,²⁴ 14%²⁵). Extensive neutrophil infiltration of the lungs, but also other distant organs, is a characteristic finding in patients dying in sepsis. The degree of oxidative stress and of neutrophil activation and tissue infiltration, especially in the lungs, appears to be the main determining factor of outcome.²⁶

Monitoring immunoparesis

A major problem is the lack of reliable tools for routine monitoring of the extent of immunoparesis. In recent years, the expression of human leukocyte antigen-DR (HLA-DR) was heralded as a reliable marker of immunoparesis, with several studies, especially in severe acute pancreatitis, supporting the efficacy of measuring monocyte HLA-DR density to reflect severity of disease and outcome.^{27,28} However, it seems mainly to reflect the degree of immunoparesis when measured in the immune phase and appears less useful, when most needed, in the early nervous phase.^{29–31} Studies of HLA-DR levels in cardiac surgery patients before surgery and in the immediate (first 24 h) postoperative period found no predictive value for increased risk of SIRS/sepsis or infectious complications.³² The lack of reliable early markers of poor outcome gives considerable interest to the observation of sticky neutrophils before surgery in patients who develop postoperative infections.³³ The use of the neutrophil/lymphocyte ratio, as suggested by Zahorec (normal 5.5–8.4, high level of stress 18–36, extreme stress > 36),⁸ is worth further exploration.

Figure 1. Histological sections of lungs 24 h after caecal ligation and puncture. (A) After placebo treatment; (B) after treatment with bioactive fibres; and (C) after treatment with live lactic acid bacteria and bioactive fibres. Reproduced with the permission of Dr Ozer Ilkgul, Izmir, Turkey.

Figure 2 The Benchmark flocare autopositioning regurgitation-resistant tube. (A) Photograph of the tube; (B) X-ray showing the tube *in situ*; (C) photograph of expanding tube coil in the small intestine; and (D) photograph at laparotomy showing the end of the tube and its coil anchored in the upper jejunum. (A) Reproduced with the permission of Nutricia BV, Amsterdam, The Netherlands; (B,C) reproduced with the permission of Dr Gerardo Mangiante, Verona, Italy.

Preventing immunoparesis

Pharmaceutical drugs have largely failed in attempts to control inflammation and infection. In addition to avoidance of a large supply of nutrients, salt and electrolytes and transfusion of stored blood, and minimal use of drugs, the most effective tools tried to date to prevent hyperinflammation, immunoparesis and subsequent infections and adhesion formation seem to be to supplemental antioxidants, prebiotic fibres and probiotic lactic acid bacteria.^{34–37} A synbiotic formulation, Synbiotic 2000 Forte™ (see below), administered orally before the trauma (Ilkgul *et al.*, personal communication) or by subcutaneous injection³⁸ of the lactic acid bacteria in the synbiotic cocktail effectively prevented both neutrophil accumulation and tissue destruction in the lungs (Fig. 1A–C). The average neutrophil count as well as values of myeloperoxidase, malonaldehyde, and nitric oxide in lung tissues, all reflecting an elevated inflammation, were significantly lower in the animals treated with the synbiotic composition containing live lactic acid bacteria; all differences between treatment groups and placebo were statistically significant ($P < 0.05$).

New tools for immunonutrition

Synbiotic 2000™ (Medipharm, Kågeröd, Sweden and Des Moines, Iowa, USA) constitutes an attempt to formulate a pro- and prebiotic composition based on extensive studies of more than 500 different lactic acid bacteria and their ability to survive the harsh environment of the upper gastrointestinal tract, adhere to human mucosa, influence the expression of NF-κB, produce pro- and anti-inflammatory cytokines, ferment various plant fibres, and produce antioxidants. When tried in various clinical situations (*e.g.* severe acute pancreatitis, extensive trauma and liver transplantation), this formulation has been found to be effective in reducing both postoperative infections and preventing SIRS and MOF.^{34–37}

Highest priority should be given to enteral supply of nutrients aimed as nutrition for flora and to boost the immune system. For this, a feeding tube which is easy to introduce and quick to reach the upper small intestine is required. This is why I developed the auto-positioning and regurgitation-resistant tube (Fig. 2A–D), now marketed by the Nutricia group (Amsterdam, The Netherlands), and aimed to be used without the assistance of endoscopy or X-ray. A recent study reports successful early insertion in 12/16 (75%) of acute pancreatitis patients with the head of tube reaching the ligament of Treitz within a median of 12 h.³⁹ Another recent study reports successful placement within 24 h in 78% of patients with normal gastric emptying compared to 14% with standard straight tubes ($P = 0.041$), and in patients with impaired gastric empty-

ing (as most ICU patients) 57% compared to 0% with standard tubes ($P = 0.07$).⁴⁰

Conclusions

There is a need for a new generation of nutrition formulas. Those currently used are, to a large extent, based on the same concept as parenteral formulas and made mainly to satisfy calorific need and to support a positive nitrogen balance. The new formulas should mimic natural foods and be rich in plant ingredients, plant fibres and antioxidants such as polyphenols and curcumenoids. The finding that the critically ill have often lost their entire lactobacillus flora⁴¹ supports the need to supply new flora.

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The author is a Member Academia Europaeae and Emeritus Professor at Lund University, Lund, Sweden. He has been an Honorary Visiting Professor at University College London (UCL), London University, UK with affiliation to the Departments of Hepatology and Surgery since 1999.

References

1. Sautner T, Fugger R, Götzinger P, Mittlböck M, Winkler S, Roth E *et al.* Tumour necrosis factor- α and interleukin-6: early indicators of bacterial infection after human orthotopic liver transplantation. *Eur J Surg* 1995; **161**: 97–101.
2. Bengmark S. Bioecological control of inflammation and infection in critical illness. *Anesthesiol Clin North Am* 2006; **24**: 299–323.
3. Sandström R, Drott C, Hyltander A, Arfvidsson B, Schersten T, Wickström I *et al.* The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann Surg* 1993; **217**: 185–95.
4. Heslin MJ, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PW *et al.* A prospective randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. *Ann Surg* 1997; **226**: 567–80.
5. Shirabe K, Matsumata T, Shimada M, Takenaka K, Kawahara N, Yamamoto K *et al.* A comparison of parenteral hyperalimentation and early enteral feeding regarding systemic immunity after major hepatic resection – the results of a randomized prospective study. *Hepatogastroenterology* 1997; **44**: 205–9.
6. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA* 2001; **286**: 944–53.
7. Menges T, Engel J, Welters I, Wagner RM, Wagner RM, Little S *et al.* Changes in blood lymphocyte populations after multiple trauma. *Crit Care Med* 1999; **27**: 733–40.
8. Zahorec R. Ratio of neutrophil to lymphocyte counts – rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy* 2001; **102**: 5–14.
9. Kalff C, Carlos TM, Schraut WH, Billiar TR, Simmons RL, Bauer AJ. Surgically induced leukocytic infiltrates within the rat intestinal muscularis mediate post-operative ileus. *Gastroenterology* 1999; **117**: 378–87.
10. De Jonge WJ, Van den Wungaard RM, The FO, Ter Bek M-L, Bennink RJ, Tytgat GNJ *et al.* Postoperative ileus is maintained by intestinal immune infiltrates

- that activate inhibitory neural pathways in mice. *Gastroenterology* 2003; **125**: 1137–47.
11. Steinberg KP, Milberg JA, Martin TR, Maunder RJ, Cockrill BA, Hudson LD. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; **150**: 113–22.
 12. Sookhai S, Wang JH, McCourt M, Di Wu Q, Kirwan Hayes D, Redmond HP. A novel mechanism for attenuating neutrophil-mediated lung injury *in vivo*. *Surg Forum* 1999; **50**: 205–8.
 13. Wei L, Wei H, Frenkel K. Sensitivity to tumor promotion of SENCAR and C57BL/6J mice correlates with oxidative events and DNA damage. *Carcinogenesis* 1993; **14**: 841–7.
 14. Kubes P, Hunter J, Granger DN. Ischemia/reperfusion induced feline intestinal dysfunction: importance of granulocyte recruitment. *Gastroenterology* 1992; **103**: 807–12.
 15. Ho JS, Buchweitz JP, Roth RA, Ganey PE. Identification of factors from rat neutrophil responsible for cytotoxicity to isolated hepatocytes. *Leukoc Biol* 1996; **59**: 716–24.
 16. Lowell CA, Bertin G. Resistance to endotoxic shock and reduced neutrophil migration in mice deficient for the Src-family kinases Hck and Fgr. *Proc Natl Acad Sci USA* 1998; **95**: 7580–4.
 17. Goris BJA, te Boekhorst TPA, Nuytink JKS, Gimbrere JS. Multiple-organ failure. Generalized autodestructive inflammation *Arch Surg* 1985; **120**: 1109–15.
 18. Wilson MR, Choudhury S, Takata M. Pulmonary inflammation induced by high-stretch ventilation is mediated by tumor necrosis factor signalling in mice. *Am J Physiol* 2005; **288**: L599–607.
 19. Rassias AJ, Marrin CAS, Arruda J, Whalen PK, Beach M, Yeager MP. Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. *Anesth Analg* 1999; **88**: 1011–6.
 20. O'Brien G, Shields CJ, Winter DC, Dillin JP, Kirwan WO, Redmont HP. Cyclooxygenase-2 plays a central role in the genesis of pancreatitis and associated lung injury. *Hepatobil Pancreat Dis Int* 2005; **4**: 126–9.
 21. Bengmark S. Curcumin: an atoxic antioxidant and natural NF- κ B, COX-2, LOX and iNOS inhibitor – a shield against acute and chronic diseases. *J Parent Ent Nutr* 2006; **30**: 45–51.
 22. Gonzales RJ, Moore EE, Ciesla DJ, Nieto JR, Johnson JL, Silliman CC. Post-hemorrhagic shock mesenteric lymph activates human pulmonary microvascular endothelium for *in vitro* neutrophil-mediated injury: the role of intercellular adhesion molecule-1. *J Trauma* 2003; **54**: 219–23.
 23. Deitch EA, Forsythe R, Anjaria D, Livingston DH, Lu Q, Xu DZ *et al*. The role of lymph factors in lung injury, bone marrow suppression, and endothelial cell dysfunction in a primate model of trauma-hemorrhagic shock. *Shock* 2004; **22**: 221–8.
 24. Johnson CD, Abu-Hilal M, Members of British Acute Pancreatitis Study Group. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut* 2004; **53**: 1340–4.
 25. McKay CJ, Buter A. Natural history of organ failure in acute pancreatitis. *Pancreatology* 2003; **3**: 111–4.
 26. Gomez-Cambronera LG, Sabater L, Pereda J, Cassinello N, Camps B, Vina J *et al*. Role of cytokines and oxidative stress in the pathophysiology of acute pancreatitis: therapeutic implications. *Curr Drug Targets Inflamm Allergy* 2002; **1**: 393–403.
 27. Muehlstedt SC, Lyte M, Rodriguez JL. Increased IL-10 production and HLA-DR suppression in lungs of injured patients precede the development of nosocomial pneumonia. *Shock* 2002; **17**: 443–50.
 28. Pachot A, Monneret G, Brion A, Venet F, Bienvenu J, Mougin B *et al*. Messenger RNA expression of major histocompatibility complex class II genes in whole blood from septic shock patients. *Crit Care Med* 2005; **33**: 31–8.
 29. Mentula P, Kylanpää-Back ML, Kempainen E, Takala A, Jansson SE, Kautiainen H *et al*. Decreased HLA (human leukocyte antigen)-DR expression on peripheral blood monocytes predicts the development of organ failure in patients with acute pancreatitis. *Clin Sci* 2003; **105**: 409–17.
 30. Mentula P, Kylanpää M-L, Kempainen E, Jansson SE, Sarna S, Puolakkainen P *et al*. Plasma anti-inflammatory cytokines and monocyte human leukocyte antigen-DR expression in acute pancreatitis. *Scand J Gastroenterol* 2004; **39**: 178–87.
 31. Yu W-K, Li W-Q, Li N, Li J-S. Mononuclear histocompatibility leukocyte antigen-DR expression in the early phase of acute pancreatitis. *Pancreatology* 2004; **4**: 233–43.
 32. Oczenski W, Krenn H, Jilch R, Watzka H, Waldenberger F, Koller U *et al*. HLA-DR as a marker for increased risk of systematic inflammation and septic complications after cardiac surgery. *Int Care Med* 2003; **29**: 1253–7.
 33. Hidemura A, Saito H, Fukatsu K, Ikeda S, Kitayama J, Matsuda T *et al*. Patients with postoperative infections have sticky neutrophils before operation. *Shock* 2003; **19**: 497–502.
 34. Bengmark S. Bioecological control of perioperative and ITU morbidity. *Langenbecks Arch Surg* 2004; **389**: 12–154.
 35. Bengmark S, Martindale R. Prebiotics and synbiotics in clinical medicine. *Nutr Clin Pract* 2005; **20**: 244–61.
 36. Bengmark S. Bio-ecological control of acute pancreatitis; the role of enteral nutrition, pro- and synbiotics. *Curr Opin Nutr Metab Care* 2005; **8**: 557–61.
 37. Bengmark S. Bio-ecological control of the gastrointestinal tract: the role of flora and supplemented pro- and synbiotics. *Gastroenterol Clin North Am* 2005; **34**: 413–36.
 38. Ilkgul O, Aydede H, Erhan Y, Surucuoglu S, Gazy H, Vatansever S *et al*. Subcutaneous administration of live lactobacillus prevents sepsis-induced lung organ failure in rats. *Br J Int Care* 2005; summer: 52–7.
 39. Karsenti D, Vigulier J, Bourlier P, d'Alteroche L, Barbieux JP, Metman EH *et al*. Enteral nutrition during acute pancreatitis. Feasibility study of a self-propelling spiral distal end jejunal tube. *Gastroenterol Clin Biol* 2003; **27**: 614–7.
 40. Lai CWY, Barlow R, Barnes M, Hawthorne AB. Bedside placement of nasojejunal tubes: a randomized-controlled trial of spiral – vs straight-ended tubes. *Clin Nutr* 2003; **22**: 267–70.
 41. Knight DJW, Ala'Aldeen D, Bengmark S, Girling KJ. The effect of synbiotics on gastrointestinal flora in the critically ill. *Br J Anaesth* 2004; **92**: 307P-308P