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# Intestinal permeability changes, systemic endotoxemia, inflammatory serum markers and sepsis after Whipple's operation for carcinoma of the pancreas head

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ABSTRACT

*Pourpose:* The aim was to evaluate the relationship between failure of gut barrier function, inflammatory markers and septic complications after pancreatoduodenectomy for pancreatic adenocarcinoma.
*Methodology:* 44 patients were enrolled in this prospective observational clinical study and underwent curative open pancreatoduodenectomy for adenocarcinoma of the head of the pancreas. All patients underwent assessment of intestinal permeability using the lactulose/manitol excretions ratios (L/M ratio), endotoxemia, IL-1β, IL-6, CRP, and elastase levels before surgery and on postoperative days 1, 3 and 7. Septic complication was defined as a specific clinical condition related to infection by bacterium, virus, or fungus in a specific organ/compartment with positive culture.
*Results:* Septic complications developed in 25% of patients. There were no significant differences in preoperative L/M ratio, endotoxine, CRP, IL-1β, IL-6, and elastase levels between sepsis-positive and sepsis-negative groups. All patients showed a significant increase in intestinal permeability, endotoxemia, IL-1, IL-6, CRP and elastase on the first postoperative day. At postoperative day 7, the sepsis-positive group continued to demonstrate an increase in intestinal permeability, endotoxemia and elastase; a significant difference was observed between the two groups ($P = 0.02$), whereas there was no significant difference in IL-1, IL-6, and CRP levels.
*Conclusion:* The pattern of change of intestinal permeability, systemic endotoxemia, and elastase concentration in the postoperative period is significantly higher in patients in whom sepsis develops, while the concentration of IL-1β, IL-6 and CRP do not permit to distinguish infection from inflammation.


All cells in the body constantly communicate with each other under normal physiological conditions and after surgical or accidental injury. An array of regulatory proteins produced and secreted by lymphocytes and other cells have a role in the cascade of the immune response to trauma [1,2]. A surgical trauma is an acute injury with changes in biochemistry, metabolism, and visceral function via the neuro-endocrino-immune system. The immune response is largely orchestrated by endogenous mediators called cytokines [3–5]. The systemic immunoinflammation underlying SIRS (Systemic Inflammatory Response Syndrome) and MODS (Multiple Organ Dysfunction Syndrome) in the presence or absence of infection is not fully understood. A breakdown of gut barrier function has been incriminated [6,7].

The "gut origin of sepsis" hypothesis suggests that a major stress insult may cause failure of gut barrier function, the permits the translocation of bacteria and endotoxin. The translocation of bacteria and endotoxin triggers splanchnic cytokines to perpetuate and exacerbate a systemic immunoinflammatory response that may result in organ failure. This concept is supported by data from animal studies in experimental models [8]. The situation in humans is less clear [9], because there is poor concordance with animal studies [10].

Moreover, endotoxemia may be evident in the patients with shock [11], after burns [12], with sepsis [13]. This may indirectly confirm the experimental evidence by demonstrating that gut barrier dysfunction occurs under similar insults in humans. However the significance of increased intestinal permeability, bacterial translocation and systemic endotoxemia, in relevant clinical scenarios (e.g sepsis, shock, burns, etc.) in humans is poorly

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understood.

A number of studies have investigated the relationship between failure of the gut barrier function and septic complications [14–16]. However the data from these studies have been discordant, with some studies suggesting that gut barrier dysfunction is associated with the development of sepsis [16] whereas others did not find an association [14,15]. Despite the trend toward decreased postoperative mortality rate [17,18], the morbidity rates associated with pancreatoduodenectomy are still relatively high at 20–56% [19,20]. Among the various morbidities reported after pancreatoduodenectomy, infectious complications remain a significant issue, despite technical and pharmacological efforts to address them. Optimal infection control is emerging as an indicator of quality in surgery. Some studies [20–23] have focused on risk factors for infections associated with pancreatic resection. Only the study of Kanwar et al. [15] has attempted to determine the influence of abnormal gut barrier function on the risk of septic complications in patients undergoing pancreatectomy for carcinoma of the pancreas. Therefore the aim was to evaluate the relationships between failure of gut barrier function, endotoxemia, inflammatory serum markers (Interleukin-1β, interleukin-6, C-reactive protein, and elastase) and septic complications after pancreatoduodenectomy for adenocarcinoma of the head of the pancreas.

## Materials and methods

From April 2009 to July 2016, 44 patients (pts) consecutively (26 men, 18 women; mean age 66.8 years) were enrolled in this prospective observational clinical study. Patients underwent elective curative open pancreatoduodenectomy for adenocarcinoma of the head of pancreas (Tables 1 and 2).

In Fig. S1 (supporting information) are reported exclusion criteria. A bile culture was systematically performed in patients undergoing preoperative biliary drainage, but not systematically during operation. The patients were classified as grade I, II, or III according to the American Society of Anesthesiologists (ASA) grading system (Table 1). The risk of infection was assessed by the NNISS (National Nosocomial Infections Surveillance System) and the SENIC (Study on the Efficacy of Nosocomial Infection Control) scales [24,25] (Table S1, supporting information). The NNISS and SENIC scores have been extensively validated; higher scores on these scales indicate a greater risk of infection.

The study protocol was approved by the Ethical Committee of Faculty of Medicine of the University of L'Aquila. Informed consent was obtained by every patient.

Nutritional status was assessed by means of Nutrition Risk Screening 2002 (NRS) or Kondrup Score [26] (Table S2, supporting information). One hour before surgery, prophylactic antibiotics were administered (Cefotaxime: 2g i.v.) followed postoperatively by further two doses. Prophylactic subcutaneous heparin was given daily until discharge from hospital.

Anesthesia was performed in both groups using the same procedure (Table S3, supporting information). The abdomen was opened through a bilateral subcostal incision. Spread of disease was evaluated by careful exploration (Appendix S1, supporting information). The incidence of septic complications and organ failure was monitored up to the 30$^{th}$ postoperative day and tabulated prospectively. The American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference definition of sepsis was used for this study [27] (Table S4, supporting information).

The onset of sepsis was defined, as recommended by the Consensus Conference [27], as the day on which the site of infection was identified. Therefore septic complication was defined as a

**Table 1**
Pancreatic cancer: clinical patients' characteristics.

| Parameters | Overall population n° = 44 | Sepsis-positive n° = 11 (25%) | Sepsis-negative n° = 33 (75%) | P value |
|---|---|---|---|---|
| Age (yrs) [mean (range)] | 66.8 (44–84) | 66.2 (44–80) | 67.3 (48–84) | 0.34 |
| Sex ratio (M:F) | 26:18 | 7:4 | 19:14 | 0.28 |
| Body mass index (BMI) [mean (range)] | 20.9 (16.1–30.8) | 20.2 (16.1–29.6) | 21.3 (16.4–30.8) | 0.58 |
| ASA grade: | | | | |
| I | 3 (6.8%) | 1 | 2 | |
| II | 16 (36.3%) | 3 | 13 | |
| III | 25 (56.8%) | 7 | 18 | 0.04 |
| Blood transfusion: | | | | |
| No. of pts | 8 | 3 | 5 | 0.03 |
| Risk score: | | | | |
| -SENIC | | | | |
| 1 | 9 (20.4%) | 1 | 8 | 0.68 |
| 2 | 18 (40.9%) | 3 | 15 | 0.76 |
| 3 | 17 (38.6%) | 7 | 10 | 0.03 |
| 4 | / | | | |
| -NNISS | | | | |
| 0 | 8 (18.1%) | 1 | 7 | 0.72 |
| 1 | 17 (38.6%) | 2 | 15 | 0.78 |
| 2 | 19 (43.1%) | 8 | 11 | 0.03 |
| 3 | / | | | |
| Creatininemia[a](mg/dL) | 1.1 (0.8–1.3) | 1.0 (0.8–1.1) | 1.2 (0.7–1.3) | 0.34 |
| Total bilirubin[a](mg/dL) | 2.8 (1.2–12.6) | 3.0 (1.1–12.6) | 2.6 (1.2–10.4) | 0.44 |
| Preoperative biliary drainage | | | | |
| No. of pts with jaundice | 21 (47.7%) | 5 (45.4%) | 16 (48.4%) | 0.58 |
| Postoperative hospitalization (days[a]) | 17.2 (11–66) | 19.2 (15–66) | 16.8 (11–32) | 0.02 |

ASA = American Society of Anesthesiologists.
SENIC = Study on the Efficacy of Nosocomial Infection Control.
NNISS = National Nosocomial Infections Surveillance System.
[a] Values are median with interquartile range in parenthesis.