Treatment and Prophylaxis of Infections

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Intraabdominal Infections: Classification, Mortality, Scoring and Pathophysiology

Summary: Studies on intraabdominal infections have been difficult to compare in the past due to a missing system of classification for peritonitis. According to a recently developed classification system, secondary peritonitis, including spontaneous acute peritonitis, postoperative peritonitis and posttraumatic peritonitis, is the most common complication of severe intraabdominal infections. In several studies the mortality rate of postoperative peritonitis was still between 60% and 79%. Scoring systems were developed, some of them with the idea to predict mortality in peritonitis. Although the APACHE II score cannot predict the outcome of peritonitis in an individual patient, it is a reliable, valid and objective system for risk stratification in intraabdominal infections. Local trauma or bacterial contamination is responsible for an acute phase reaction, which involves the release of certain cytokines such as TNF-alpha, interleukin-1 (IL-1) and interleukin-6 (IL-6). The IL-6 seems to play an important role in the mechanism of the acute phase reaction, acting on hepatocytes to release acute phase proteins (e. g. CRP). Preliminary results of investigations of IL-6 levels in peritonitis indicate a possible role for IL-6 as a predictor of the outcome of peritonitis.

Zusammenfassung: *Intraabdominelle Infektionen. Mortalität, Klassifizierung und Pathophysiologie.* Studien zu intraabdominellen Infektionen waren in der Vergangenheit auf Grund einer fehlenden Klassifikation der Peritonitis schwer zu vergleichen. In einem erst vor kurzem entwickelten System zur Klassifikation der Peritonitis ist die sekundäre Peritonitis, die die spontane akute Peritonitis, die postoperative und die posttraumatische Peritonitis beinhaltet, die häufigste Form einer komplizierten intraabdominellen Infektion. In mehreren Studien lag die Letalität der postoperativen Peritonitis immer noch zwischen 60 und 79%. Es wurden „Scores" entwickelt, einige davon mit der Absicht, die Letalität der Peritonitis vorauszusagen. Obwohl der APACHE II Score den individuellen Verlauf einer Peritonitis nicht voraussagen kann, stellt er doch ein zuverlässiges, gültiges und objektives System zur Risikostratifizierung bei intraabdominellen Infektionen dar. Lokale Schädigung des Gewebes und bakterielle Kontamination setzen die Akut-Phase-Reaktion in Gang, bei der es zur Freisetzung einiger Zytokine wie TNFalpha, Interleukin-1 (IL-1) und Interleukin-6 (IL-6) kommt. IL-6 scheint eine wichtige Rolle in der Akut-Phase-Reaktion zu spielen, indem es u. a. zu einer Freisetzung von Akut-Phase Proteinen wie C-reaktives Protein aus den Hepatozyten führen kann. Vorläufige Messungen von IL-6 während der Peritonitis deuten auf eine mögliche Rolle des IL-6 als Verlaufsparameter einer Peritonitis hin.

Classification

Scientific studies on patients with intraabdominal infections show problems of interpretation and comparability due to variable diagnostic criteria, unmeasured severity of disease and unclear outcome measures.

A practical classification system that includes all aspects of intraabdominal infections such as chemical peritonitis, intraabdominal abscess, spontaneous peritonitis and traumatic peritonitis was proposed by *Wittmann* [1] (Table 1). Although peritonitis and intraabdominal infections are used synonymously, they are not necessarily the same. According to *Nystroem* et al. [2], the definition of intraabdominal infection is based on preoperative information with clinical signs of peritonitis, intraoperative information (diffuse or localized infection), and postoperative information (positive bacteriological culture). In most cases surgeons have to deal with secondary peritonitis, which is usually defined as an acute, suppurative inflammation of the peritoneal cavity, arising as a consequence of primary disease of the abdominal viscera, of blunt or penetrating trauma, or of operations within peritoneal spaces [3].

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Table 1: Classification of peritonitis.

Primary peritonitis
Secondary peritonitis
A. Spontaneous peritonitis (spontaneous acute)
1. GI/Tract perforation
2. Bowel wall necrosis
3. Pelviperitonitis
4. Peritonitis after translocation of bacteria
B. Post-operative peritonitis
1. Leak of an anastomosis
2. Leak of a suture line
3. Stump insufficiency
4. Other iatrogenic leaks
C. Post-traumatic peritonitis
1. Peritonitis after blunt abdominal trauma
2. Peritonitis after penetrating abdominal trauma
Tertiary peritonitis
Intraabdominal abscess

Mortality

Before operative therapy was generally used for the treatment of intraabdominal infections, about 90% of all patients died from sepsis. When the principles of surgical management were established and become commonly used, the mortality dropped to below 50% in large series [4]. After the discovery of penicillin [5] and the dramatic improvements with its use in surgical infections [6], further developments in antibiotic therapy did not affect the mortality risk in intraabdominal infections, and the mortality remained unchanged until the 1970s [7].

Despite advances in the treatment of peritonitis with new operative techniques, more potent antimicrobials, new concepts of hemodynamic, respiratory and renal support, mortality from many forms of intraabdominal infections remains unacceptably high even today [1]. In nine studies of postoperative peritonitis, all done after 1970, the mortality ranged from 60% to 79% [8] (Table 2).

Scoring

Since 1983, a number of systems designed to measure the severity of surgical infection have been developed and published [9–14]. Most of them rely on disease-specific pathology; only one uses physiologic parameters [2].

The APACHE system (acute physiology and chronic health evaluation) is not specific for surgical infections [15–17], but in all other studies validation in new patient populations is limited [11, 12] and there are only a few

Table 2: Mortality in post-operative peritonitis.

Grosdideier	1974	270	195	70%
Dinstl	1974	67	48	72%
Lagache	1975	49	29	60%
Prandi	1975	47	37	79%
Guivarch	1977	100	78	78%
Hollender	1978	30	19	63%
Neidhardt	1978	80	58	73%
Guirlet	1981	32	23	72%
Boissel	1980	33	24	73%

Table 3: Advantages of the APACHE II system for risk stratification in intraabdominal infections.

Advantages
1. Reliable and valid
2. Objective
3. Independent of diagnostic criteria
4. Information collected at the same time
5. Information can be obtained prior to treatment
6. Large range of score with small increments, each of which contribute to the risk
7. Score value and mortality risk comparable with observed mortality

comparative studies in the same patient population [18,19]. Although none of these systems fits all the requirements for grading of intraabdominal infections [20,21], the APACHE II system is recommended by the Surgical Infection Society for risk stratification in intraabdominal infections. Certainly there are several advantages (Table 3), and this system has already been used in several studies of intraabdominal infections [2]. Nevertheless, intraoperative situation, general health status and previous history is neglected in this system [22, 23].

For objective description of the patient population and enhanced understanding of the disease process, clear definitions of outcome measures of intraabdominal infections are necessary. Mortality is defined as death of any cause in the hospital during admission and treatment for the episode of intraabdominal infection, based on the assumption that all deaths are related to the intraabdominal infection. The definition of recovery is dependent on the Acute Physiology Score, temperature, gastrointestinal motor activity, gastrointestinal function and the general health status of the patient. Last but not least, there are definitions of times for onset of disease, beginning of therapy, beginning of trial and scoring warranted [2].

The probability of death can be calculated from a weighted APACHE II score value [14], but *Erra* et al. [24] could demonstrate that the APACHE II score cannot predict the individual development of multiple organ failure or mortality. Instead, they found a good correlation of multiple organ failure and mortality with changes in the PaO_2 fraction of inspired oxygen ratio and serum lactate, creatinine and bilirubin levels. To obtain the average predicted mortality for a group of patients, the total of the individual risks is divided by the number of patients. From the average risk, the predicted number of deaths among

Table 4: Indicators of treatment progress.

APACHE II score	Exudate clear
Elastase	Anastomosis healing
TNF, IL-1, IFN-γ ?	No abscess
CRP	Gram stain negative
IL-6 ?	

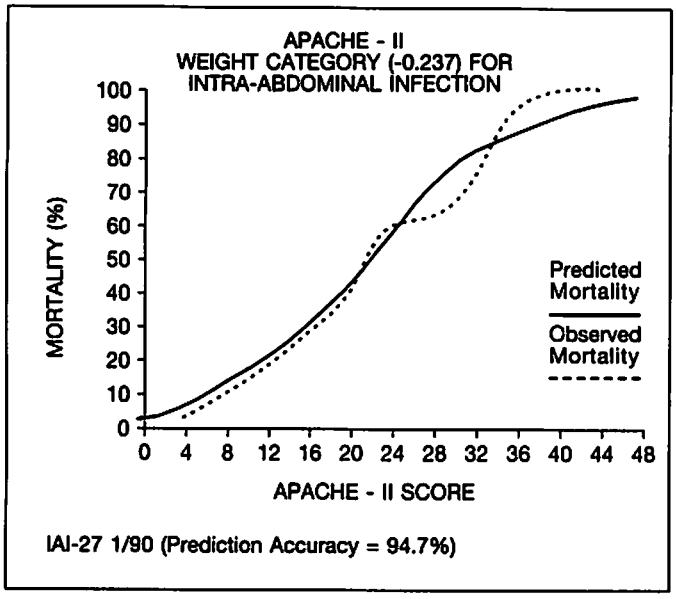


Figure 1: APACHE II – weight category (-0.237) for intraabdominal infection.

the group is calculated [2]. In a study with 271 intraabdominal infections with a weight category of -0.237, the prediction accuracy amounted to up to 94.7% [25] (Figure 1).

At the moment it is not known precisely which intraoperative information is relevant for the prognosis, i.e., which information ultimately can improve the prediction rule. Before new prognostic parameters are added to the severity score, however, these parameters should be able to improve the prediction independently. Several indicators for treatment progress have been used thus far or are under investigation (Table 4), among them are the inflammatory mediators elastase, tumor necrosis factor (TNF)-alpha and interleukin-6 (IL-6). There is also information derived intraoperatively from the peritoneal cavity.

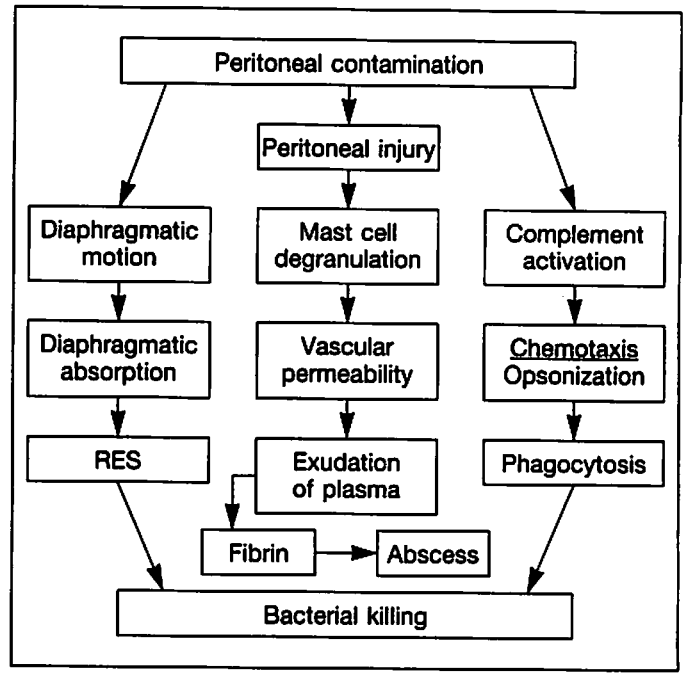
Pathophysiology

The peritoneal cavity, the largest preformed extravascular space in the body, has a functional exchange surface of approximately 1.8 square meters [26]. Although the entire surface participates in fluid and low molecular weight solute exchange, particulate matter is absorbed specifically by the diaphragmatic lymphatics [27, 28].

Local trauma or bacterial contamination of the peritoneum triggers inflammatory responses. Degranulation of peritoneal mast cells releases vasoactive substances with an outpouring of fluid rich in complement and serum opsonins to bind bacteria (Table 5). The opsonized bacteria are either removed by lymphatics or engulfed *in situ* by phagocytic cells [29].

Another important defense mechanism is triggered by C3a and C5a released during complement activation. The increased vascular permeability increases the influx of neutrophils and is responsible for the fibrin formation [30].

Table 5: Peritoneal contamination.



Infections and major trauma cause via tissue damage a complex and unspecific reaction of the organism, the acute phase reaction, consisting of a local and a systemic part. By degranulation of mast cells histamine is released, which in combination with kinins, prostacyclines and leukotrienes causes a collapse of the peripheral circulation. Parallel to this collapse, free radicals, leukotrienes and histamine cause a generalized enhancement of permeability in the peripheral circulation and the peritoneal lining. Free radicals are responsible for the membrane damage by lipid peroxydation and release of toxic granulation products. A diminished peripheral oxygen utilization, causing a breakdown of mitochondrial function, leads to hypoxia and acidosis. Early activation of complement and subsequent release of chemotactic

Table 6: Acute phase reaction.

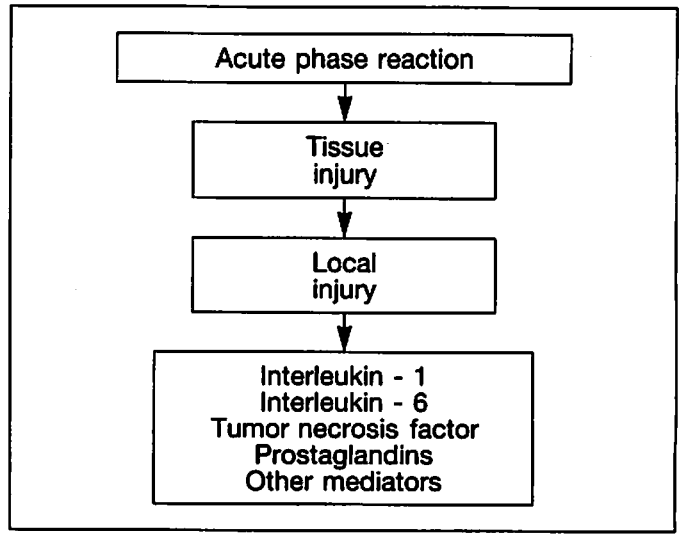
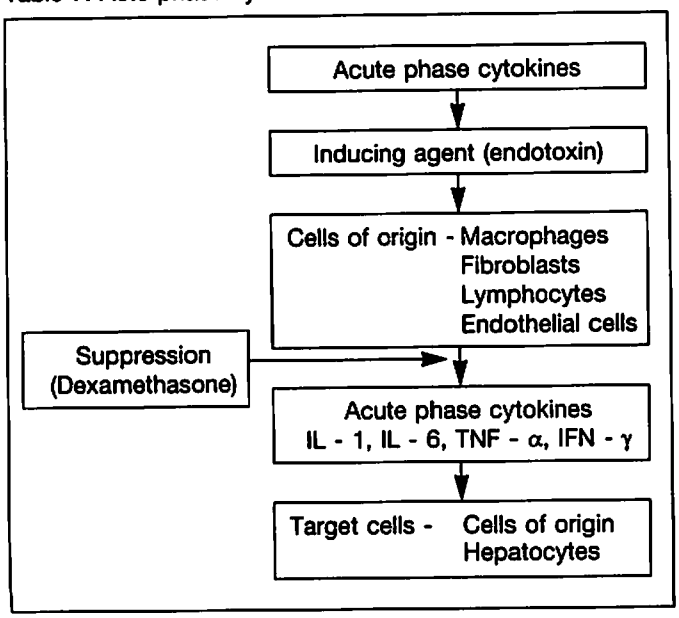


Table 7: Acte phase cytokines.



factors (C3a, C5a) is followed by an invasion of granulocytes and macrophages [30,31] (Table 6).

Cytokines are the major signals that orchestrate the immune response to bacterial infection. These signals, generated during infection, include IL-1, IL-2, IL-6, IFN-gamma, TNF-alpha and other mediators. IL-6 and not IL-1 or TNF-alpha appears to be the important mediator of the acute phase protein synthesis [32] (Table 7). In the cellular system IL-6 is involved in the T-cell activation [33–35]. The biological activities of IL-6 partially overlap those of IL-1. Some of the effects of IL-1 are actually caused by IL-6 or synergistic actions of IL- 1 and IL-6 [36–38]. IL-6 stimulates the synthesis of hepatic proteins [39–42], which protect the host against inflammatory actions in acute phase responses and act as an endogenous pyrogen [37] (Table 8).

Many cells, in particular fibroblasts, cells of the monocyte-macrophage lineage and endothelial cells, can secrete IL-6 [43,44].

Increased plasma levels of IL-6 were measured in patients with sepsis or septic shock. The presence of IL-6 on admission appeared to be of prognostic significance, but it is still not known whether IL-6 is directly involved in sepsis in mediating lethal complications or whether it is to be considered as an "alarm hormone" [36]. Whether significant differences exist in the role IL-6 plays in systemic intravascular models of sepsis or in peritonitis as it was demonstrated for TNF-alpha remains unclear [45]. TNF given intravenously evokes the entire spectrum of host responses associated with infection in a dose-dependent fashion [46] (Table 9). As there was no information available on IL-6 levels during the treatment of peritonitis or on a possible correlation between IL-6 levels and outcome of the disease process, we started a prospective study in patients with peritonitis. Some

Table 8: Acute phase reaction – systemic actions of IL-6.

Acute phase reaction Systemic actions of IL-6	
Hypothalamus	– Fever
Hypophysis	– Cortisol
Liver	– Acute phase protein synthesis
Bone marrow	– Leucocytosis
Immune system	– Lymphocyte differentiation and activation

preliminary results will be presented. In ten patients (seven male, three female; mean age 61 years) we measured the changes in serum IL-6 and elastase in plasma before and after treatment by planned intraabdominal lavage ("Etappenlavage") and compared the results with controls. Patients were stratified using the APACHE II score and the Mannheim Peritonitis Index. Nine of ten patients had a diffuse peritonitis and one had a localized intraabdominal infection. Three patients died during the course of their disease.

Upon entrance to the study the patient that died had a plasma elastase level of 218+39 µg/l (mean + SEM), while survivors had a lower but not significantly different elastase level of 133+26 µg/l. Elastase levels in both groups were not significantly decreased after treatment. Non-survivors had an IL-6 level of 1566+1169 pg/ml upon entrance to the study; survivors had a lower but still elevated plasma IL-6 level of 298+116 pg/ml. After abdominal lavage there was a statistically significant decrease in IL-6 levels in survivors compared with levels before treatment and compared with IL-6 levels in those who died ($p<0.05$) [47].

Despite treatment improvements the mortality in peritonitis remains high. For comparison of the results of different studies, stratification of patients and clear definitions of mortality and outcome remain a mainstay. Before adding new prognostic information to the severity score, the prognostic parameter should prove to increase independently the accuracy of the prediction. It appears to us that IL-6 could have such prognostic qualities.

Table 9: TNF versus host response.

TNF versus host response	
TNF dose	**Response**
1	Anorexia
20	Fever – tachycardia ↑ Acute phase proteins
500	Fluid retention Lymphopenia Hypotension
600	↓ Consciousness ↓ Blood pressure Pulmonary edema Oliguria

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