Opinion from Italy

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Introduction

The incidence of acute pancreatitis has been increasing progressively in recent decades, and at present it is estimated annually at 100 cases per million [1, 2]. Its clinical presentation ranges from mild edematous pictures with a benign evolution in a few days (about 80% of cases) to necrotic forms characterized by a severe clinical course (20% of cases). At present the overall estimated mortality is about 10%: 1%–2% in edematous forms and 20%–30% in necrotic ones [2, 3].

Necrotic acute pancreatitis usually presents one of two different clinical stages. The early one is the “toxic stage” and is due to the reabsorption in the blood circulation of activated pancreatic enzymes and of vasoactive and cytolytic products released from pancreatic parenchima and from retroperitoneal fat. These substances, after their secretion into the circulation, generate a toxic action which can lead to multiple organ failure.

Until a few years ago the toxic stage was responsible for most of the deaths due to severe acute pancreatitis; now, thanks to intensive care improvements, an increasing number of patients come out of the toxic phase and develop the next stage, characterized by septic phenomena due to the overinfection of the pancreatic necrosis, thus called the “septic stage.”

Sterile Necrotic Pancreatitis: Clinical Picture

The toxic stage of necrotic pancreatitis shows different clinical pictures. Hypotension is the most frequent sign and is mainly caused by both absolute and relative hypovolemia. The absolute hypovolemia is determined by fluid sequestration and by the hydroelectrolitic depletion due to the alteration of the capillary permeability. This condition can worsen because of the relative hypovolemia caused by a vasodilatation due to the chinines and other vasoactive peptides released in the circulation system. It is possible to recognize a first hemodynamic stage characterized by a low cardiac output, hypovolemia, high peripheral resistance, and high peripheral oxygen extraction rate [4]. Circu-
lating hyperdynamism and a reduction of the peripheral resistences and of the oxygen extraction, all of which typically occur in the diseases with a systemic metabolic defect, are seen with the reestablishment of a normal volemia. In patients with a depressed myocardial function, where the hyperdynamism cannot occur, serious cardiovascular symptoms can already be present in the early stages because of the inability of the cardiac pump to satisfy peripherical demands.

Renal failure is another frequent systemic manifestation of necrotic pancreatitis. Two main pathogenetic mechanisms lead to this event: hypovolemia, which represents the initial condition of the renal damage, and hypoperfusion, in the case of shock. However, other factors probably concur, such as the direct action of circulating toxic substances and enzymes, the glomerular capillaries blockage caused by disseminated intravascular coagulation, and mechanical factors due to retroperitoneal haemorrhagic infiltration and to edema. Lungs are also frequently involved in necrotic pancreatitis. The severe form of hypoxemia which can sometimes be observed is mainly related to an impairment of the air-blood barrier resulting in arterovenous shunts of the alveolar capillary bed. Other alterations, such as hydrotorax, base atelectasis, and bronchopneumonic infections, can contribute to the development of a respiratory failure. The pathophysiology of these complications has not yet been clarified, and different pathogenetic mechanisms are suspected. First of all, a specific alveolar damage due to the action of the phospholipase A₂ on the alveolar lipidic surfactant, and the effects of other proteolitic enzymes and active amines are suspected. Furthermore, the microvascular alteration caused by disseminated intravascular coagulation can contribute to the production of perialveolar edema. Lastly, retroperitoneal edema, abdominal distension, and diaphragmatic overelevation can worsen the respiratory failure.

**Overinfection of Necrosis**

In patients with necrotic pancreatitis who overcome the toxic stage of the disease, the most frequent and feared long-term complication is the bacterial over-infection of the pancreatic necrotic areas. Necrotic areas are in fact an ideal culture medium for bacterial growth. The vascular isolation of the necrotic tissue, as the microthrombosis phenomena black out the action of antimicrobial drugs, explains the high frequency of septic overinfection at this site.

The intestinal gram-negative bacteria, in particular *Escherichia coli*, *Pseudomonas*, *Proteus*, and anaerobic bacteria, are the most frequent bacteria involved in these processes. It is interesting to show the increasing pathogenetic role that has been given to the bacterial translocation phenomenon [5]. In fact, the intestinal mucosal ischemia, related to the shock and the consequent peripheral vasocostriction, often present during a severe acute pancreatitis, leads to the distortion of the ”tight junctions” between the mucosal cells. After that,