

## Oxidative Stress and Antioxidative Status in the Acute Pancreatitis

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### 1. Introduction

Acute pancreatitis is the inflammatory condition of a gland, including an invasion into, to a lesser or greater extent, the surrounding tissues, and also the contiguous or distant organs (Braganza, 2001; Frossard et al., 2008).

The analysis of the processes, occurring in the course of acute pancreatitis, has made it possible to define this disease as the one which comprises of two phases.

Initially, the hyperstimulation of the immunological system with the excessive local activation of the cells of inflammatory focus in the pancreas occurs, and later on, as a result, the systemic response, expressed as Systemic Inflammatory Response Syndrome (SIRS), develops.

Compensatory Anti-inflammatory Response Syndrome (CARS) causes early organic complications (Gamaste, 1994; Toouli et al., 2002; Yousaf & McCallion, 2003).

The intensification of an inflammatory response, hypoxia and the occurrence of oligovolemic shock may result in the clinical development of Multi-Organ Dysfunction Syndrome (MODS), which is defined as the more advanced stage of SIRS. In this period, greater susceptibility to bacterial infections and fungal infections and, consequently, an increased mortality rate, caused by blood poisoning, is observed. Multi-Organ Dysfunction Syndrome requires the application of the powerful methods of supporting the organism of a patient (Song et al., 2003).

Acute pancreatitis is a disease of an unpredictable course. It is, usually, a reversible process, in which the pain ailments of the abdomen undergo regression and the activity of pancreatic enzymes returns to its normal level.

In 70 - 75% of cases, this process becomes subjected to the self-limitation and has the properties of interstitial inflammation. However, in 5 - 15%, a form characterized by severe, necrotic course may develop.

In this case, local complications and multi-organic complications are alike present

The morbidity rate in case of acute pancreatitis in Poland is estimated to be at the level of 240 cases per 1 million in a year.

The mortality rate amounts to 5 - 10% in total. However, in the cases of severe course, it amounts to approximately 35% (Baillie, 1997; Balthazar et al., 2002; Beger et al., 1997; Lund

et al., 2006; Munoz, & Katerndahl 2000; Mutinga et al., 2000; Song, 2003). In pathomorphology, the oedemic and the necrotic form of acute pancreatitis, which constitutes an unfavourable development of the oedemic form, or is developing as a separate form of the disease from the beginning is observed (Banks & Freeman, 2006; Yousaf et al., 2003).

In Atlanta, in 1992 (Bradley, 1993), an obligatory classification of acute pancreatitis was drawn up; this classification it assumes the division into:

- acute pancreatitis of mild course.
- acute pancreatitis of severe course, which means the occurrence of one of the following states:
  - local complications: necrosis, false cyst and abscess,
  - organic dysfunction,
  - meeting 3 or more criteria on the Ranson scale (Ranson, 1997),
  - obtaining 8 or more points on the APACHE II scale II (Lankisch et al., 2002; Song, 2003).

Acute pancreatitis results in the destruction of the acinar cells, which results in the handicap of the extra-secretory functions of the pancreas. What may also contribute to the damage to the acinar cells and releasing active proteases and other enzymes into the parenchyma of the pancreas, is the obstruction of the pancreatic ducts and increase in pressure in them connected with that or the intra-cellular activity of chemical substances (Braganza, 2000; Sharma & Howden, 1999).

Nowadays, there is more and more information about the chain of events, occurring after the release of active enzymes into the pancreatic parenchyma. However, the mechanism of the activation of the zymogens at molecular level still remains unknown (Braganza, 2001; Song et al., 2003).

## 2. Causes of acute pancreatitis

The causes of acute pancreatitis may be divided into: mechanical, toxic, metabolic, infection-related, vascular, genetic and idiopathic (Yadav & Lowenfels, 2006).

### 2.1 Mechanical causes

The most frequent cause of acute pancreatitis is choledocholithiasis and alcohol.

It is estimated that both of these etiological factors are the cause of as many as 80% of cases of the disease.

In medical literature, the connection between choledocholithiasis and acute pancreatitis was a subject of publication for the first time in 1909 (Song et al., 2003).

Large stones, of the diameter of 20 mm and more, cause increase in the risk of the acute inflammation of the gall bladder.

The risk of acute pancreatitis increases if the diameter of the stones does not exceed 5 mm.

Their being jammed in the duodenal papillae and the occurrence of acute pancreatitis is also made more likely by the shape of concretions if it is similar to that of mulberry fruit.

In 3 hours after getting jammed in the duodenal papillae, inflammatory changes in the pancreas occur. It is assumed upon the basis of estimations that if the obstacle is removed within a 24-hour period, acute pancreatitis of severe course occurs in only as few as 6% cases.

The risk increases to 90% if the obstacle is removed later than within a 48-hour period (Baron et al., 1996).

Damage to the alveolar cells resulting from the inflammatory process of the pancreas, may also occur if the bacterial infection of gall coexists with choledocholithiasis. (Liu et al., 1997). Bacterial endotoxins cause the release of cytokines and the occurrence of SIRS.

Pancreas divisum, which means chronic pancreatitis, may be the cause of the acute, recurrent inflammations of this organ, particularly in case of children.

This developmental variety of the pancreas is revealed in case of approximately of 5% population.

The risk of the occurrence of inflammatory changes is connected with the papillary stenosis of the smaller duodenal papilla.

According to estimations, approximately 3% of the cases of acute pancreatitis, described in literature, is caused by a tumour on the pancreas or duodenal papillae (Fan et al., 1993).

Sphincteritis Oddi stenosans, which means the stenotic inflammation of the duodenal papilla, by means of handicapping the outflow of biliary juice and pancreatic secretion, may result in the occurrence of an incident of acute pancreatitis (Song et al., 2003).

Into the group of the mechanical causes able to cause acute pancreatitis, may also be included penetrative and blunt abdomen injuries.

Endoscopic retrograde cholangiopancreatography (ERCP) is also a described cause of the occurrence of acute pancreatitis. The frequency of such cases reaches 2% (Demols & Deviere, 2003; Folsch et al., 1997).

Accidental damage to the Wirsung duct during an operations is a following mechanical cause of acute pancreatitis.

It most frequently occurs during the fixation of the intestine with the stump of the pancreas in the course of operative procedures (Golub et al., 1998, Vaquero-Raya & Molero-Richard, 2005).

A not very frequent cause of acute pancreatitis may be blocking the pancreatic duct or the biliary duct by a lumbricus (*Ascaris lumbricoides hominis*).

Duodenal-pancreatic reflux, occurring in the conducting loop syndrome after a resection procedure on the stomach with the application of the B<sub>2</sub> method, may also be a cause of the occurrence of acute pancreatitis (Frossard & Hadengue, 2001, Gamaste, 1994).

## 2.2 Toxic causes

A frequent factor causing acute pancreatitis is ethyl alcohol (Dufour & Adamson, 2003).

It may cause the oedema of the papillae of Vater, the regurgitation of duodenal contents into the pancreatic ducts and increase in the permeability of the pancreatic ducts.

Ethyl alcohol exerts cytotoxic influence as well because it form the ethyl esters of fat acids, which damage the cells of the pancreas, causing acute alcohol-related pancreatitis (Golub et al., 1998; Schenker & Montalvo, 1998).

It is suspected that some kinds of medications are able to induce acute pancreatitis. This group encompasses: mesalazinum, sulfasalazinum, furosemide, rifampicin, sulphonamides, octreotide, didanozinum, isoniazid, azathioprine, erythromycin, shadowing medications administered in ERCP and others. A rare cause of acute pancreatitis is having been bitten by animals representing venomous species, e.g. by certain species of scorpions.

## 2.3 Infection-related causes

A cause of the occurrence of acute pancreatitis may be bacterial infection.

As a result of translocation, bacteria reach the tissue of the pancreas on their way from the large intestine.

Those bacteria produce endotoxins, which induce releasing pro-inflammatory cytokines, which as a result causes damage to the pancreatic cells.

Viral infection – a virus of epidemic parotid inflammation and HIV is also a described cause of the occurrence of acute pancreatitis.

In case of patients with developed AIDS, the frequency of the occurrence of acute pancreatitis is several hundred times larger than in case of healthy population.

Acute pancreatitis in course of AIDS may be caused by the virus itself, but also the very occurrence of opportunistic infections generates inflammatory processes.

Patients with AIDS frequently come from the backgrounds abusing alcohol and psychoactive substances, which is an additional factor, able to cause acute pancreatitis

This is caused by the co-existence of several factors simultaneously.

Medications administered to patients, for example didanosinum (DDI), may also induce the occurrence of acute pancreatitis.

#### **2.4 Metabolic causes**

Increase in the concentration of triglycerides, particularly above 1000 mg%, may be a factor inducing the development of acute pancreatitis.

Such a state is observed in case of patients, suffering from hyperlipidaemias of type I, IV and V.

Hypercalcaemia connected with the hyperactivity of the parathyroid glands, uremia and the neoplasm of bones also increases the risk of the induction of inflammatory processes in the pancreatic gland (Rau et al., 1997; Schoenberg et al., 1995).

#### **2.5 Vascular causes**

The development of acute pancreatitis may occur after cardiac-surgical operations, performed with the use of cardiopulmonary bypass, and after image-based examinations with the use of contrast, for example after abdominal aortography (Niederer & Lüthen, 1997).

In the literature, there are described cases of acute pancreatitis, occurring as a result of the complications of sclerosis such as the block of upper mesenteric artery and the block of the celiac trunk.

In the research conducted in the recent years, changes in pancreatic microcirculation are regarded as the cause of the disease in such cases (Sabater et al., 2004).

The disorders of celiac flow within pancreatic microcirculation occur in the early phase of the disease and precede changes in the digestive duct microcirculation.

The disorders of celiac flow within pancreatic microcirculation are of importance in the transformation of mild (oedemic) form in the necrotic-hemorrhagic one.

Substantial reductions in capillary perfusion and of the saturation of hemoglobin with oxygen occur.

The disorders within pancreatic microcirculation are a complex process, in which the dysfunctions of the cells of endothelial vessels occur.

Free oxygen radicals being released and cytokines participate in this process.

Important mediators causing the inflammatory reactions are: blood platelet activating factor, neoplasm necrosis factor  $\alpha$  (TNF- $\alpha$ ), cytokines (IL-1, IL-6, IL-8), interferon  $\gamma$  (INF- $\gamma$ ), thromboxane, leukotrienes and prostaglandins (Lewandowski et al., 2007; Osman & Jensen, 1999; Rau et al. 1997).

## 2.6 Genetic causes

The course of acute pancreatitis is dependent on one hand on the activity and strength of factors, damaging the pancreas, and, on the other hand, on the genetically-conditioned response of the immunological system.

Depending upon the individual properties, the self-limitation of the inflammatory process may occur, or, alternatively, its intensification and proliferation may occur.

Genetic research has differentiated a disease of the genetically-conditioned mechanism of development: *hereditary pancreatitis* – acute pancreatitis occurring within the family.

The research suggests the existence of mutation N34S in the gene responsible for coding a pancreatic inhibitor, trypsin, defined as PSTI (*pancreatic secretory trypsin inhibitor*) or SPINK1 (*serine peptidase inhibitor, Kasal type 1*).

This polypeptide constitutes one of the barriers, safeguarding against self-digestion of the cells of the pancreas.

The mutation of the gene results in the earlier activation of trypsinogen inside the cell and its destruction (Karczowski, 2002; Swaroop et al., 2004).

The premature activation of the pancreatic pro-enzymes is still regarded as the essential pathomechanism of self-digestion of the pancreatic gland which occurs in the severe form of acute pancreatitis.

Molecular researches on the mutation of trypsinogen in the course of acute pancreatitis occurring within the family have shown the superior role of the trypsin in the premature activation of proteolytic enzymes (Niederrau & Lüthen, 1997; Swaroop et al., 2004).

All it takes to activate them is a small amount of free trypsin remaining in balance with the complex: trypsin-pancreatic secretory trypsin inhibitor (PSTI) (Karczowski, 2002).

In 2000, it was found out that the gene for pancreatic trypsin inhibitor (PSTI) may contribute to the modification of the risk of pancreatitis, particularly in case of mutation N34N PSTI, wherein the risk of the occurrence of acute pancreatitis is increased ten-fold (Karczowski, 2002).

In approximately 10% cases, it proves impossible to determine the cause of acute pancreatitis. Such cases are defined as idiopathic (Kim et al., 2003; Testoni et al., 2008).

## 3. The clinical record of the acute pancreatitis

Acute pancreatitis of mild course, or, in other words, its oedemic form, does not cause complications.

In some cases, so-called liquid collections of acute phase appear.

This is the state in which effusion liquid is accumulated in the anatomical spaces of the peritoneal cavity.

The cistern of the acute phase does not have a tissue-connecting capsule and, as a rule, it is subject to resorption to four weeks from the beginning of the disease.

Sometimes, however, it is encysted and causes the formation of false cyst of the pancreas (Sabater et al.: 2004, Williford et al., 1983).

Liquid cisterns of the acute phase may occur in the pancreatitis of mild course and the severe one alike (Morgan et al 1997).

Clinical symptoms of acute pancreatitis depend above all on the form (degree of severity), spread of changes and time of the disease duration.

The main symptom of acute pancreatitis is pain.

It is described by the patients as: encircling, and sometimes as radiating to the left or to the both of shoulder blades, and to the spine.

It is frequently felt as the pressure similar to compressing with a girdle.

Initially, it is the pain of celiac character, but after some time it transforms into somatic-celiac (mixed) one.

The individuals are unable to identify its source precisely.

Celiac pain is formed as a result of the irritation of receptors (nociceptors) in a particular organ of the abdominal cavity.

Its cause is the sudden increase of wall tension or the constriction of the smooth muscles of the celiac organs.

The pain is usually dull, less frequently stabbing, with a location that is difficult to define.

It radiates to the areas of the same neural segment, which is affected by the pain of the disease-changed celiac organ.

Frequently, it is accompanied by vegetative symptoms, for example acceleration or slowing down the heart action, vomiting or decrease in arterial blood pressure.

The pain is intensified during rest, and weakens during performing movements – the individuals are restless and motor-activated.

Conducting the stimuli of celiac pain is connected with the autonomous nervous system.

Somatic pain is connected with the irritation of the sensory endings of the core nerves of the parietal peritoneum, mesentery, retroperitoneal space or the walls of the abdominal integuments.

This pain is acute or blunt, but constant, easy to describe and clearly-localized.

It is accompanied by the tension of the muscles, called muscular defense.

The individuals are calm and they avoid movement.

The pain accompanying acute pancreatitis may be of constant intensity, but it may, alternatively, be getting more intensive (Morgan et al., 1997; Dervenis et al., 1999).

In the initial period of the disease, nausea and vomiting, which do not bring about relief, occur.

They are the symptoms of the irritation of the pneumogastric nerve.

These ailments are accompanied by the integuments, excessive hyperhidrosis, increased thirst, accelerated breath and, frequently, decrease in arterial blood pressure.

Disorders for the part of the nervous system, such as anxiety developing into fear, strong psycho-motor excitation, and hallucinations may occur (Dervenis et al 1999).

The position adopted by the individuals and their outsider appearance are frequently characteristic of this disease.

The patients are lying on their side with their lower extremities bent and appear to be suffering a lot.

The initial paleness of the body integuments may be joined by the characteristic erythema of the skin of the face – the Loeffler symptom or marbleness of the skin of the abdomen and the extremities – Halsted symptom.

These are the symptoms of vessel-widening activity of mediators of inflammatory state.

What is also a quite characteristic symptom is abdominal distention, the presence of hepatitis or blue disease.

In case of acute pancreatitis with severe course, as the complication of necrosis of fat subcutaneous tissues, lividness of the skin may occur.

If it is found in the area near the navel, it is described in the literature as Cullen symptom.

If this is found in lumbar region, this is Grey-Turner symptom (Steinberg & Tenner, 1994).

Researching abdominal integuments in a palpative manner, we frequently discover tenderness, muscular defense, peritoneal symptoms and Blumberg symptom.

It is sometimes possible to discover the presence of free liquid in the peritoneal cavity or an effusion on the left pleural cavity – Clairmont symptom

### 3.1 Diagnostic investigation in the acute pancreatitis

The most frequently performed examination is determining the activity of amylase in the serum.

In order for it to be possible to diagnose acute pancreatitis, the activity of amylase ought to be three-fold larger than the norm. It happens in the course of acute pancreatitis of severe course that the activity of amylase is correct, probably as a result of a massive damage to the parenchyma of the gland.

The most sensitive marker of pancreatitis is the increase in the activity of pancreatic lipase. This is an enzyme, produced only by the pancreatic gland, and therefore the increase in its activity is the most typical of acute pancreatitis. Proinflammatory cytokines play a crucial role in the primary activation of the cells of the immunological system as a result of damage to the pancreas (Lewandowski et al. 2007).

In the x-ray chest, it is possible to ascertain the presence of the liquid in the left pleural cavity. The plain radiological picture of the abdomen is taken as a routine measure in the diagnostics of acute pancreatitis.

Ultrasonography (USG) – possesses as many as 90% of the tenderness in diagnosing acute pancreatitis. It is a non-invasive treatment, which may be repeated several times. Ultrasonography pictures the dynamics of the pathological changes course in pancreatic parenchyma and in the adjacent tissues

Computer tomography (CT) is currently regarded as a diagnostic standard the highest is a sensitivity in terms of acute pancreatitis, Magnetic resonance imaging (MRI) – is a method, alternative to CT.

Endoscopic retrograde cholangiopancreatography (ERCP) – is the most effective method of discovering the cause of acute pancreatitis. It is simultaneously possible to remove the triggering factor.

Endoscopic sphincterotomy performed within the first 24 hours after the occurrence of the first symptoms causes alleviating the course of the disease and reduces the risk of complications

Endoscopic ultrasonography (EUS) is a modern method of imagining of the cause of acute pancreatitis, however, without a possibility of procedural intervention.

## 4. Oxidative stress and antioxidative status in acute pancreatitis

Oxidative stress was defined by Sies in 1985 as a state of relative balance in a living organism between the prooxidation activity, which means the production of free oxygen radicals and antioxidative processes, which means the deactivation of free radicals (Braganza et al., 1995; Kikuchi et al., 1997; Sies H & Cadenas, 1985).

Free oxygen radicals are substances possessing one non-paired electron, or more.

Such a chemical structure determines high instability of these chemical compositions and tendency to become involved in violent biochemical reactions parts, leading to damaging cellular structures (Matkovics et al., 1995; Schulz et al., 1999).

Contemporarily, instead of the notion free oxygen radicals the Reactive Oxygen Form (ROF) is more frequently used.

The best researched ROFs are: hyper-oxygen radical, hydrogen-oxygen radical, hyper-oxide radical, hydrogen hyper-oxygen radical and nitrogen oxide (Schulz et al., 1999; Song et al., 2003; Petrov, 2010).

Non-radical form also include non-radical type substances, the derivatives of oxygen, displaying similar impact as radicals, e.g. hydrogen peroxide, hypochlorous acid, ozone or singleton oxygen (Abu-Zidan et al., 2000; Braganza et al., 1995).

The sources of ROFs are the reactions of oxidation and reduction, mainly occurring in mitochondria and cellular membranes, including the cells of the vessel perithelium.

The source of ROFs is also the process of oxidizing hypoxanthine by xanthine oxidase, and also by the reaction in which the ions of some metals, mainly iron and copper, participate (Chmiel et al., 2002).

The formation of the reactive form of oxygen takes place, among others, in the chain of changes of arachidonic acid.

Large amounts of ROFs are formed in the course of inflammatory processes.

The source of them are the cells, directly participating in immunological response and pathogens, for example bacteria (Park et al., 2003).

The oxidation of organic substances, such as proteins and lipids, is also the source of the ROFs display strong toxic impact in relation to the cells of a human organism. The effect of their impact is damaging structural proteins, enzymatic structures, lipids of cellular membranes, breaking up the threads of DNA, damage to chromosomes, degeneration of the cytoskeleton of the cell, disorders of the synthesis of collagen and neoplasm transformation, which consequently leads to the death of a cell, which is preceded by a substantial damage and disordering its functions (Winterbourn et al., 2003).

In the course of inflammatory process in the pancreas, the local accumulation of activated phagocytes occurs; these phagocytes are producing chemotactic factors, which cause the migration of new leukocytes to the area, invaded by inflammation.

The activated phagocyte cells release proteolytic enzymes, which damage the tissues and are the secondary source of new ROF (Wereszczyńska-Siemiątkowska et al., 1998, 2004).

Pathogenetic factors, causing handicapping of blood flow through the pancreas are the cause of ischaemia and hypoxia of the cells of this organ.

Ischaemia is a reversible and temporary process.

After this period, reperfusion occurs.

An increase in the concentration of oxygen in the blood results in the production of a very active and cytotoxic hydrogen oxide radical, regarded as the main cause of the damage to the cells of the pancreas.

As a result of reperfusion, occurring after ischaemia, deepening the damage to the endothelium of the blood vessels and activation of the components of the complement system, the activation of the mast cells, the intensification of the aggregation of blood platelets, which consequently leads to the formation of micro-thromboses occur.

The activated cells of the immunological system secondarily cause the intensified production of the reactive form of oxygen, damaging the adjacent tissues (Sweiry & Mann 1996; Telek et al., 2001).

In turn, antioxidants counteract the reactive form of oxygen in an organism.

Their function is to maintain the balance between the processes of oxidation and reduction (Curran et al., 2000; Dabrowski et al., 1999; Johnson, 2007; Satinder et al., 2011).

There are two essential defense mechanisms - non-enzymatic and enzymatic.

Non-enzymatic defense anti-oxidation system is composed of substances, so-called „sweepers“, reacting directly with the reactive form of oxygen.

They include: vitamin E, vitamin C, beta- carotene, uric acid, ceruloplasmin and glutation.



The most important enzymatic anti-oxidants include: superoxide dismutase (SOD), the system of glutathione peroxidases (GPX) and the system of catalases (Tsai et al.; Vaquero-Raya & Molero-Richard, 2005).

The disturbance of balance between the oxidation and anti-oxidation factors in case of patients with acute pancreatitis leads to oxidation stress.

The level of its intensification has a direct influence on the severity of the course of disease, the risk of complications and prognosis.

## 5. The aim of the work

The aim of the work was to examine the dynamics of oxidative (8-OHdG) and antioxidative status (TAS) in patients with mild and severe form of acute pancreatitis.

The profiles of exchanged parameters, the degree of the correlation among them and the degree of statistical significance can give certain information relating to prognosis of the course of the acute pancreas, as also he can give therapeutic and prognostic instructions.

## 6. The principles of the work

Forty patients admitted to the clinic with the symptoms of acute pancreatitis were subjected to the assessment.

All patients expressed their consent to perform the research.

Consent of the Regionale Commission of Research Ethics was obtained.

In all patients, apart from a routine examination, the following data were determined for the blood serum and the urine:

1. Oxidative activity of peroxide DNA 8- hydroxyl - 2 - deoxyguanosine (8-OHdG) in I, III, V, VII day of hospitalization.

and in the blood serum:

2. Total antioxidative status in I, III, V, VII day of hospitalization.

The patients were divided in two groups: with mild and severe form of acute pancreatitis.

In both of the groups, the dynamics of the processes of oxidation (8-OHdG) and antioxidation (TAS) were assessed; moreover, it was assessed, whether there was a correlation between separate parameters.

The obtained results were subjected to statistical analysis and the influence of the disease process on the level of the researched parameters was assessed.

## 7. Material and methods

### 7.1 Clinical material

Material for the research was obtained by means of collecting the venous blood and urine from the patients, admitted to the Department of Gastrointestinal & General Surgery Silesian Piasts` University of Medicine in Wrocław and the Department of General Surgery Railway Hospital in Wrocław during the emergency service because of acute pancreatitis between 2004 and 2006 years.

The samples of blood and urine were collected in I, III, V and VII day of hospitalization.

The research on the following parameters: 8-OHdG and TAS included patients with the acute pancreatitis of severe course and, randomly selected, with the acute pancreatitis of mild course.

In all patients, the quantitative markings of 8-OhdG and TAS respectively in I, III, V, VII day of stay at the hospital were conducted.

The patients were qualified into a research group upon the basis of the typical symptoms of acute pancreatitis.

In the group with the mild form, dominated the pain ailments of the abdomen of various intensity, bad general mood, nausea, vomiting and other symptoms.

The ailments abated most frequently after 3-4 days after the application of intravenous liquid-based therapy and treatment with analgesic and antispasmodic drugs.

This group included 20 of the patients.

In the group with the severe form, the symptoms were more serious.

The dominating ones were the pain ailments of the abdomen and the symptoms of Systemic Inflammatory Response Syndrome (SIRS), connected with the hyperstimulation of the immunological system.

In the patients, the temperature of the body increased, the action of the heart was accelerated, and the level of leukocytosis grew, while the diuresis per hour decreased.

As a result of the outflow of liquid and protein from the vascular bed, the cardiac-vascular failure, kidney failure, the respiratory system failure, necrotic changes in the parenchyma of the pancreas (visible thanks to computer tomography), thrombotic complications and enzymatic toxemia occurred.

This group encompassed 20 patients.

Altogether, 40 patients were researched in the course of the research.

Among the researched, there were 7 women and 33 men.

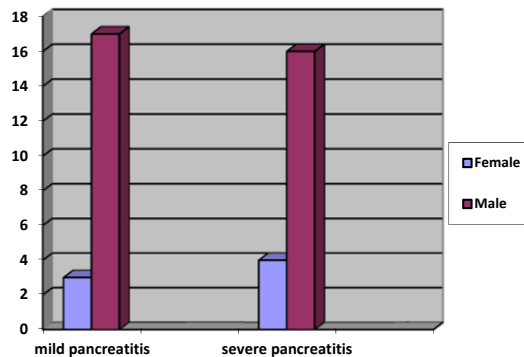


Fig. 1. Clinical material

In the group of the patients with the mild course, there were 3 women and 17 men.

In the group of the individuals with the severe course, there were 4 women and 16 men.

The oldest group member was 76 years old, whilst the youngest one 26 years old.

The average age of the patients was 51 years.

In the researched group with acute pancreatitis, women constituted 17.5%, while men 82.5%.

In the group with the mild pancreatitis, women constituted 15 %, while men 85%.

In the group with the severe pancreatitis, women constituted 20 %, whilst men 80%.

The lowest incidence rate was observed in the age groups 26-35 and 36-45.

The highest incidence rate was observed in the age groups 46-55 and 66-75.

## **7.2 Laboratory methods**

### **7.2.1 Marking oxidation activity in the serum and urine in case of the patients with acute pancreatitis**

Oxidation activity was marked in the serum and in urine upon the basis of marking 8-hydroxydeoxyguanosine (8-OhdG) with the Elis method.

The research was conducted in strict accordance with the procedure, determined by the producer – bioxtch 8-OhdG-eia kit-oxis.

The results were expressed in ng/ml.

The range of detection rate 8-OhdG in accordance with the applied methods amounted to 0.125-200 ng/ml.

The results for 8-OhdG in urine were expressed in relation to creatinine.

The norms marked in case of 15 healthy volunteers at the age of 19 to 50 years are within the range 0.00 – 0.8 ng/ml in serum and between 0,00 – 0,3 ng/ml/g/creatinine in urine.

### **7.2.2 Marking total antioxidation ability in the serum in case of the patients with acute pancreatitis**

The principle of marking according to the set produced by the Random Laboratories Company – the strict application of the regulations of the producer.

The norm marked in the serum of 30 health volunteers at the age of 20 to 65 years is within the range 1.30 – 1.75 mmol/l, and corresponding to the standard of Trolox – a substance with antioxidative properties.

## **8. The results of the serearch**

### **8.1 Clinical analisis**

Taking under consideration the aetiological factor in the entire group, the patients with biliary acute pancreatitis constituted 50% of the patients (20 patients).

The patients with alcoholic acute pancreatitis constituted 35% (14 patients).

In case of 15% (6 patients), it proved impossible to determine the causes of acute pancreatitis.

These cases were diagnosed as idiopathic.

In the group with the mild pancreatitis, patients with biliary pancreatitis constituted 40% (8 patients), with alcoholic pancreatitis constituted 35% (7 patients), while with idiopathic pancreatitis constituted 25% (5patients).

In the group with the severe pancreatitis, patients with biliary pancreatitis constituted 60% (12 patients), with alcoholic pancreatitis constituted 30%(6 patients), while with idiopathic pancreatitis constituted 10% (2 patients).

The treatment of the patients with acute pancreatitis encompassed actions in accordance with established therapeutic principles depending on the severity of the course of the disease.

In case of 20 patients with the mild pancreatitis, conservative treatment was applied. That consisted in: fasting, intravenous liquid-based therapy, pumping out the stomach contents with a pro-bang, inserted through the nose, treatment of pain, monitoring the activity of the kidneys, monitoring the pressure of the peripheral blood, monitoring arterial blood gas values and thrombotic prophylaxis.

In case of 2 patients, with biliary pancreatitis, after several weeks, cholecystectomy was performed.

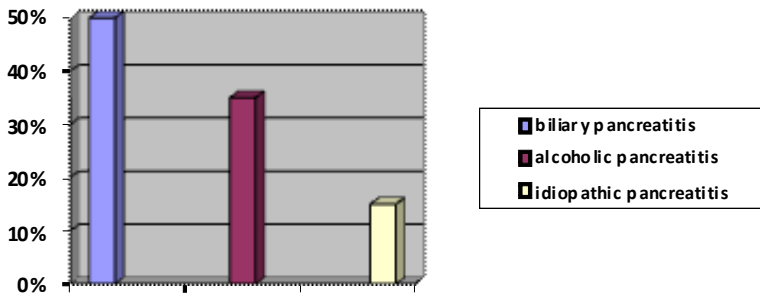


Fig. 2. The cause of the acute pancreatitis

In one patient, after 8 weeks, junction cyst of the pancreas with the jejunum was performed. In the group of patients with the mild course, the longest stay amounted was 12 days and the shortest 5 days.

Twenty patients with the severe form were divided into two sub-groups.

In the sub-group of 7 patients, ERCP with sphincterotomy was performed.

However, in one of case after three weeks an operative drainage of the abscess of the pancreas was performed.

In the sub-group of 13 patients with the severe course of acute pancreatitis, surgical procedure was required.

In case of 7 patients, cholecystectomy with the lavage of the peritoneal cavity was performed.

In case of 6 patients, the lavage of the peritoneal cavity with laparostomy was performed; in this group, in two cases- lavage was performed twice, in two cases- three times, while two other cases- four times.

In the course of further lavages, pancreatic necrectomy was performed.

All the patients were receiving antibiotics of a wide spectrum, intravenous liquid-based therapy and an analgesic drugs.

Moreover, the following were applied: gastric suction, and thrombolytic prophylaxis.

The functioning of the kidneys, the pressure of the peripheral blood and acid-alkaline economy were monitored.

Sixteen patients were fed parenterally with the supplementation of microelements.

In case of four patients, a nutritional microjejunostomy was making.

In case of 1 patient, a complication in the form of cerebrovascular accident occurred, while in case of 2 patients, the course of acute pancreatitis was made more complicated by atrial fibrillation.

These patients were treated within the framework of Intensive Care Unit.

After obtaining the stabilization of the blood circulation system, the patients returned to the surgical ward.

In one patient, massive hemorrhage from the upper digestive tract occurred, and, in spite of interventional endoscopy, the patient died.

Two other patients' death as a result of the complications of multi-organic failure.

Out of the group of 20 patients with the severe course, 3 persons died, therefore, the mortality rate in this group amounted to 15%.

The longest stay amounted to 57 days, the shortest 7 days.

The average time of hospitalization was 8 days for cases with the mild course and 18 days for the cases with the severe course (Fig. 3).

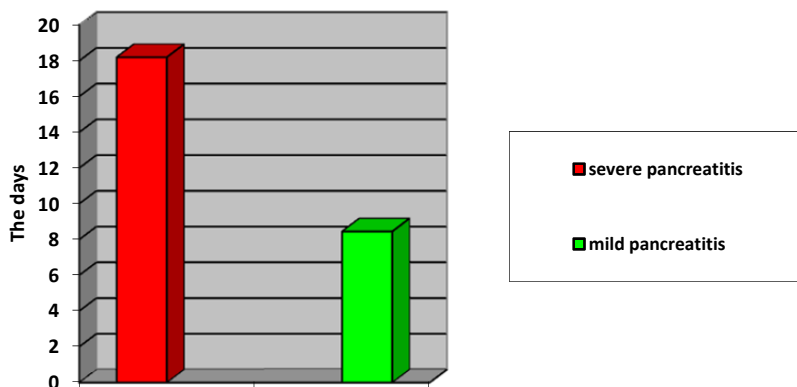


Fig. 3. The average time of hospitalization

### 8.2 Oxidation activity measured by the amount of 8-OhdG in the blood serum in patients with the mild and severe pancreatitis

In both groups of the patients, quantitative marking of 8-OhdG in the blood serum was performed.

As it is made clear by the data presented in Fig. 4, in case of the patients with the mild course of acute pancreatitis, the average value of 8-OhdG was decreasing along with the time of stay at hospital.

Therefore, on I day it amounted to, on average, 2.49 ng/ml SD $\pm$ 1,51, on III day 2.13 ng/ml SD $\pm$ 1,52, on V day 1.71 ng/ml SD $\pm$ 0,43, and on VII day to 1.59 ng/ml SD $\pm$ 0,29.

In case of the patients with the severe form of acute pancreatitis, the average value of 8-OhdG was two times higher and was growing with the time of stay at hospital.

On I day, the level of 8-OhdG amounted to, on average, 4.77 ng/ml SD $\pm$ 2,65, on III day 5.97 ng/ml SD $\pm$ 3,01, on V as much as 6.68 ng/ml SD $\pm$ 4,01, and on VII day 6.21 ng/ml SD $\pm$ 3,74, Fig. 4.

In case of the patients, in whom multi-organic complications (the abscesses of the peritoneum, circulation-respiratory failure, septic shock, thrombolytic complications) occurred, a high concentration of 8-OhdG was noticeable. These were patients from the group with the severe course of acute pancreatitis. In the group with the severe course of acute pancreatitis, the highest concentration of 8-OhdG were observed in case of the patients with complications in the form of the abscesses of the peritoneum.

For a male, aged 63, with the abscess of the peritoneum, value of 8-OhdG on V day of hospitalization amounted to 16.5 ng/ml.

For a male, aged 28, also with the abscess of the peritoneum, value of 9-OhdG on III day amounted to 16 ng/ml.

For a female, aged 69, value 8-OhdG on V day amounted to 15 ng/ml.

For a female, aged 60, value of 8-OhdG on III day amounted to 9.5 ng/ml.

In the group of patients with the severe course with other complications, for example with circulation-respiratory failure, the values of 8-OhdG were lower.

For a male, aged 33, with acute respiratory failure, requiring the use of an endotracheal tube – the value of 8-OhdG amounted to 2.8 ng/ml on V Day.

For a male, aged 70, treated at the Intensive Care Ward with respiratory failure, the value of 8-OhdG on V day amounted to 3 ng/ml.

For a male, aged 48, with acute respiratory failure and cardiac failure (rhythm disturbance) on III day, the value of 8-OhdG amounted to 7.82 ng/ml.

A male, aged 70, with circulation-respiratory failure – the value of 8-OhdG on V day amounted to 2.8 ng/ml.

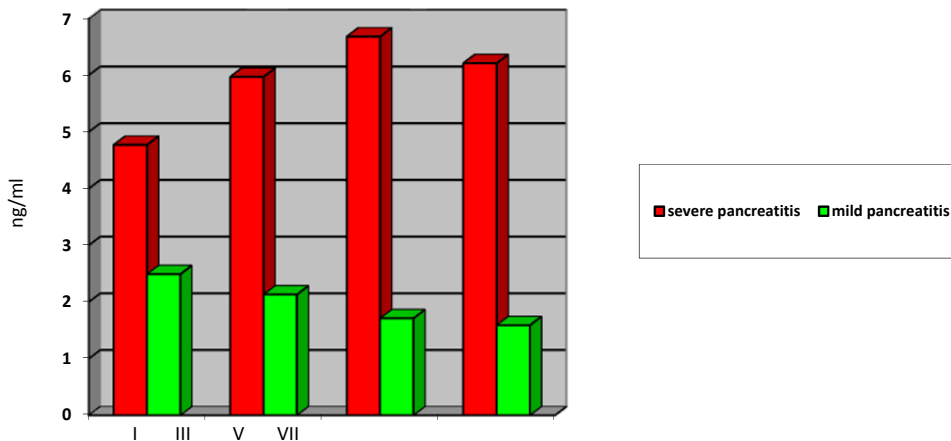


Fig. 4. The average values of 8-OhdG in the blood serum in patients with acute pancreatitis.

### 8.3 Oxidation activity measured with the amount of 8-OhdG in urine in patients with the mild and severe pancreatitis

In case of the patients with the severe form of acute pancreatitis, the average values of 8-OhdG were several times higher than in case of the patients with the mild form of acute pancreatitis.

In case of the patients with the mild form of acute pancreatitis, on I day the average value of 8-OhdG amounted to 2.69 ng/ml  $SD \pm 1, 30$ , on III day amounted to 2.14 ng/ml  $SD \pm 0, 66$ , on V day only as little as 1.87 ng/ml  $SD \pm 0, 53$ , and on VII day it amounted to 1.62 ng/ml  $SD \pm 0, 47$  (Fig. 5).

In case of patients with the severe form of acute pancreatitis, the average value of 8-OhdG on I day amounted to 7.99 ng/ml  $SD \pm 9, 75$ , on III day it increased to 8.68 ng/ml  $SD \pm 7, 16$ , on V day it amounted to as much 9.51 ng/ml  $SD \pm 7, 90$ , on VII day it reached the value of 7.55 ng/ml  $SD \pm 4, 31$  (Fig. 5).

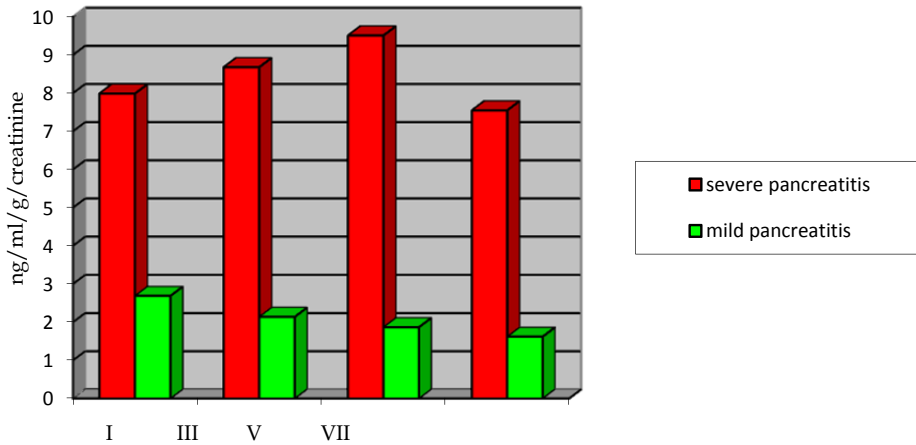


Fig. 5. The average values of 8-OHdG in urine in patients with acute pancreatitis.

#### 8.4 Results of total antioxidation ability in the blood serum in patients with the mild and severe pancreatitis

In case of the patients with the mild form of acute pancreatitis on I day of hospitalization, the average total antioxidation activity measured with the TAS, amounted to 1.19 mmol/l SD±0, 10, on III day it amounted to respectively 1.26 mmol/l SD±0, 12, on V day it insignificantly increased to 1.27 mmol/l SD±0, 10, and on VII day it reached the value of 1.26 mmol/l SD±0, 14 (Fig.6). In case of the patients with the severe form of acute pancreatitis, the average values of TAS amounted respectively to: on I day - 1.27 mmol/l SD ± 0,21, on III day - 1.27 mmol/l SD ± 0,21, on V day - 1.31 mmol/l SD ±0,16, and on VII day - 1.32 mmol/l SD±0,17 (Fig. 6).

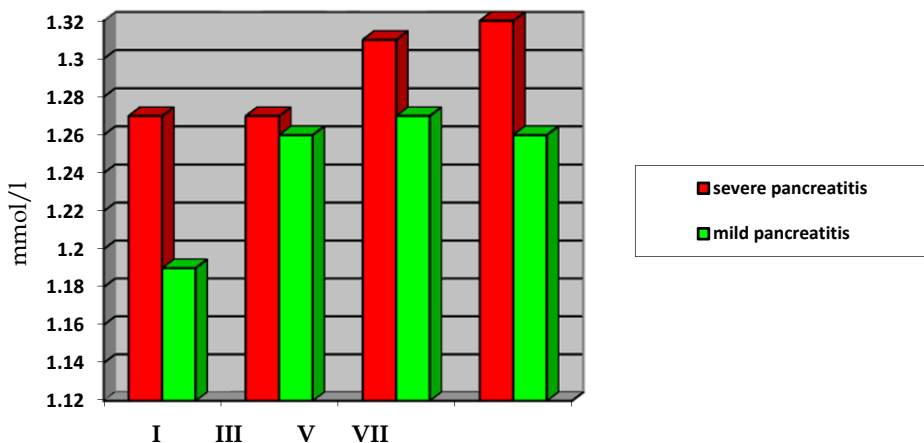


Fig. 6. The average values of TAS in case of the patients with acute pancreatitis.

### 8.5 Statistical analysis

Statistical analysis applies to the interpretation of the results of laboratory research and their mutual connections with a clinical image in case of the selected group of 40 patients, suffering from acute pancreatitis.

The analysis encompassed the results of the research on oxidation potential, anti-oxidation potential, interleukin-6 and the protein of acute phase. In this manner, the values making it possible to assess the level of advancement of the disease process and the risk of possible complications were obtained. The results of the research are the indicator of the dynamics of acute pancreatitis. In the course of the research, the analysis encompassed the influence of selected clinical parameters on the dynamics of the inflammatory process, and what was attempted, was the interpretation of the correlations between these parameters. These parameters were assessed in terms of their usefulness in the diagnostics and prognostics of the course of acute pancreatitis. At the separate stages of hospitalization, causal-result interdependencies between the researched parameters were determined. A so-called level of significance ( $p$ ) was subjected to analysis. The levels of significance ( $p$ ) for a group of patients with the mild form of pancreatitis are presented in Table 1, while for a group of patients with the severe form in Table 2.

The results of the research were correlated in both of the groups of patients, with the mild and severe forms of acute pancreatitis. The analysis of the degree of dependence of parameters was presented with the use of correlation co-efficient. Table 3 illustrates the correlations for a group of patients with the mild course of acute pancreatitis, while Table 4 for a group of patients with the severe course.

	8-OhdG I	8-OhdG III	8-OhdG V	8-OhdG VII	8-OhdG I urine	8-OhdG III urine	8-OhdG V urine	8-OhdG VII urine
8-OhdG I		0,0016	0,4371	0,1364	0,0177	0,4419	0,9263	0,9061
8-OhdG III	0,0016		0,2048	0,0859	0,0049	0,0167	0,3057	0,7938
8-OhdG V	0,4371	0,2048		0,0639	0,4399	0,0288	0,3732	0,6942
8-OhdG VII	0,1364	0,0859	0,0639		0,9844	0,4258	0,9106	0,5278
8-OhdG I urine	0,0177	0,0049	0,4399	0,9844		0,0001	0,0564	0,0696
8-OhdG III urine	0,4419	0,0167	0,0288	0,4258	0,0001		0,0013	0,1426
8-OhdG V urine	0,9263	0,3057	0,3732	0,9106	0,0564	0,0013		
8-OhdG VII urine	0,9061	0,7938	0,6942	0,5278	0,0696	0,1426	0,0088	

A group of patients with the mild form of pancreatitis.

Table 1. The levels of significance ( $p$ ) for intra-group correlations.



	8-OhdG I	8-OhdG III	8-OhdG V	8-OhdG VII	8-OhdG I urine	8-OhdG III urine	8-OhdG V urine	8-OhdG VII urine
8-OhdG I		0,0081	0,1213	0,0254	0,0059	0,0044	0,0000	0,0148
8-OhdG III	0,0081		0,0066	0,0345	0,0612	0,0097	0,0032	0,0126
8-OhdG V	0,1213	0,0066		0,0000	0,9842	0,8771	0,2748	0,3124
8-OhdG VII	0,0254	0,0345	0,0000		0,5568	0,9066	0,1522	0,4137
8-OhdG I urine	0,0059	0,0612	0,9842	0,5568		0,0017	0,0002	0,1536
8-OhdG III urine	0,0044	0,0097	0,8771	0,9066	0,0017		0,0002	0,0004
8-OhdG V urine	0,0000	0,0032	0,2748	0,1522	0,0002	0,0002		0,0002
8-OhdG VII urine	0,0148	0,0126	0,3124	0,4137	0,1536	0,0004	0,0002	

A group of patients with the severe form of acute pancreatitis.

Table 2. The levels of significance (p) for intra-group correlations.

	8-OhdG I	8-OhdG III	8-OhdG V	8-OhdG VII	8-OhdG I urine	8-OhdG III urine	8-OhdG V urine	8-OhdG VII urine
8-OhdG I	1,00	0,74	0,24	0,62	0,55	0,21	-0,03	-0,05
8-OhdG III		1,00	0,38	0,69	0,73	0,61	0,34	0,10
8-OhdG V			1,00	0,73	-0,26	-0,60	-0,32	-0,17
8-OhdG VII				1,00	0,01	-0,36	0,07	-0,29
8-OhdG I urine					1,00	0,88	0,65	0,67
8-OhdG III urine						1,00	0,84	0,53
8-OhdG V urine							1,00	0,92
8-OhdG VII urine								1,00

Marked correlations are significant, with  $p < 0.05$ .

Table 3. Intra-group correlations of a group of patients with the mild form of pancreatitis.

	8-OhdG I	8-OhdG III	8-OhdG V	8-OhdG VII	8-OhdG I urine	8-OhdG III urine	8-OhdG V urine	8-OhdG VII urine
8-OhdG I	1,00	0,57	0,36	0,54	0,69	0,67	0,86	0,68
8-OhdG III		1,00	0,59	0,51	0,51	0,62	0,71	0,69
8-OhdG V			1,00	0,89	0,01	-0,04	0,30	0,32
8-OhdG VII				1,00	0,19	0,03	0,42	0,26
8-OhdG I urine					1,00	0,76	0,83	0,49
8-OhdG III urine						1,00	0,81	0,85
8-OhdG V urine							1,00	0,89
8-OhdG VII urine								1,00

Marked correlations are significant, with  $p < 0.05$ .

Table 4. Intra-group correlations of a group of patients with the severe form of acute pancreatitis.

## 9. Discussion

Acute pancreatitis is a disease of moderate-to-severe or severe course.

In terms of anatomy, it is characterized by the reversible damage to the pancreas and the tissues adjacent to the pancreas in the form of oedema and necrosis, but sometimes by multi-organic complications as well.

Acute pancreatitis still constitutes a major problem for contemporary medicine.

It results from the fact of diagnosis-related difficulties and from the lack of an effective therapy of the severe course of acute pancreatitis.

The pathogenesis of acute pancreatitis still remains unknown.

Many researches has proved that the origins of anatomical changes, occurring in the course of the pancreatic gland, are connected with micro-circulation disorders.

What has also been confirmed is the participation of many mediators in the development of the changes of this type.

The direct factors of changes causing acute pancreatitis are: the activation of pancreatic enzymes and micro-circulation disorders.

In the cases of severe acute pancreatitis with multi-organic complications, micro-circulation disorders, mainly afflicting the lungs, liver, the digestive tract and the circulation system occur, accompanied by the development of Systemic Inflammatory Response Syndrome (SIRS) and Multi-Organ Dysfunction Syndrome (MODS).

The research showed that the increase in the value of 8-OhdG, particularly within the fifth days, was connected with the severe pancreatitis with multi-organic complications.

The increase in the values, particularly of 8-OHdG, in the serums and urine, in case of the individuals with the severe form of acute pancreatitis, may be associated with the spread and intensification of inflammatory process, damaging the cellular structures.

Those results are compatible with the research of (Szulz et al. 1999 and of Wereszczyńska-Sięmiątkowska et al 2003, 2004), who emphasize the role of oxidation stress in the processes of destruction of factors connected with them in the forecasting of acute pancreatitis.

8-OHdG is defined as a marker of the living cell DNA damage.

The reactive form of oxygen, produced in oxidation stress, may attack the biological structures of DNA and destroy them, this being the result of the oxidation of chemical compounds, contained in it.

Damage to nucleic bases or breaking up the bounds, connecting nucleotides, occur.

Lower values of 8-OHdG and reduced dynamics of its increase in the course of disease were found in the case of the individuals with the mild form of acute pancreatitis.

Those results suggest that the values of 8-OHdG reflect the activity of disease process and may be useful in the assessment of the severity of disease, as well as in the forecasting in the course of treatment.

The review of the literature (Rahman et al., 2004; Roth et al., 2004; Virlos et al., 2003) shows that the perfect antioxidation ability, marked in blood serums, in case of the individuals with the severe form of acute pancreatitis, is lowered as compensative mechanisms are being exhausted.

Therefore, TAS, as one of methods of marking the anti-oxidation properties, is a useful forecasting marker, and lowering its value may signal transfer from the mild form of acute pancreatitis into the severe form.

Own research provided no evidence for the claim that there were any substantial differences in terms of the value of TAS in the case of the individuals with the severe and mild form of acute pancreatitis.

Both in case of the severe and mild form of acute pancreatitis, no TAS growth or TAS fall tendency in separate markings of the conducted research was noticed, either.

Such results, when confronted with the research of others authors (Dziurkowska-Marek et al., 2004; Modzelewski, 2005; Rahman et al., 2004), in which lowering of the value of antioxidation potential in the individuals with acute pancreatitis – may result from the method of marking.

In own research, the behaviour of the TAS values at similar level in separate markings may be connected with the administered treatment, for it is known that some medicines may show antioxidation properties.

According to the research of (Scott et al., 1993), such is the action of vitamin C.

Anti-oxidation action of beta-carotene, vitamin A (retinol) and vitamin E (tocopherol) was confirmed by (Curran et al., 2000) in their work.

Similar reports were received from (Virlos et al., 2003), researching the properties of vitamin C, selenium and acetylcysteine (Dejong et al., 2001).

In own material, all the patients with the severe pancreatitis, apart from operational treatment, required intensive treatment.

All the patients were provided with extra-intestinal or intra-intestinal feeding (in 4 cases, with the use of microjejunosotomy) with the supply of elementary diets and of micro- and macro-elements.

The Vitalipid preparation was administered; this preparation contains, among others, vitamin A (retinol) and vitamin E (tocopherol).

As an additive to industrial diets, enriching intravenous drip, among others, with vitamin C, folic acid, biotin and pantothenic acid.

Oxidation processes exert a destructive influence on many important functions of the organism and may constitute an additional, apart from other inflammatory factors, property, destroying the cellular and tissue structures of the organism.

The potential of oxidation activity may, therefore, constitute an indication of intensified inflammatory reactivity.

Antioxidation potential (TAS) may inform about the efficiency of the systems antioxidation systems, significant in the neutralization of the intensified oxidation processes.

Currently, the pharmacological attempts of alleviating the results of acute pancreatitis are made (Curran et al., 2000; Vaquero-Raya & Molero-Richard, 2005; Virlos et al., 2003).

In the light of the most up-to-date knowledge, certain pharmacological impacts provide hope for the application of a new, effective strategy, which may significantly improve the results of the treatment of the severe pancreatitis.

The improvement in the blood flow in organs is achieved by means of using isovolemic haemo-dilution.

In this method, intravenous drips, such as 0,9% NaCl, Dextran 40 000, 10% HES and albumins, are

The application of heparin, as an anticoagulation factor, may result in the improvement in the blood saturation of organs, too.

Application of the antagonists of receptors of bradykinin B<sub>2</sub> and gabexate mesylate exerts a beneficial influence on microcirculation.

Cleansed beef hemoglobin turned out to be a safe substitute of the blood and to improve, as an oxygen carrier, the saturation of the tissues with oxygen (Panek et al., 2007).

The application of oxidizing agents, so-called plasma oxygen carriers, is currently a new strategy in the treatment of the severe pancreatitis.

Upon the basis of own research, it was determined that the high values of 8-OhdG in the serum of peripheral blood and urine alike in case of the patients with acute pancreatitis, indicate these tests may reflect the severity of the course of acute pancreatitis, as well as serve for predicting the occurrence of multi-organic complications to a degree greater than that in case of other biochemical tests.

## 10. Conclusion

1. As performed examinations show, 8-OhdG parameter, marked by means of Elisa method in the serum and urine is the sensitive parameter of acute pancreatitis inflammatory activity.
2. High values of 8-OhdG are characteristic for acute pancreatitis with severe course and are the indicator of oxidative stress. They inform also about the risk of multiorganic complications.
3. Total antioxidative status (TAS) is similar in both groups of patients and its decrease is not statistically significant for the severe form of acute pancreatitis.

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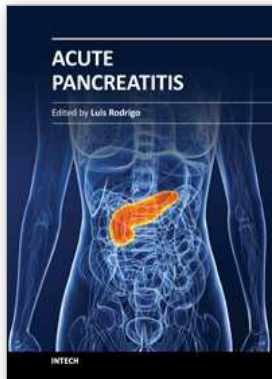
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## **Acute Pancreatitis**

Edited by Prof. Luis Rodrigo

ISBN 978-953-307-984-4

Hard cover, 300 pages

**Publisher** InTech

**Published online** 18, January, 2012

**Published in print edition** January, 2012

Acute Pancreatitis (AP) in approximately 80% of cases, occurs as a secondary complication related to gallstone disease and alcohol misuse. However there are several other different causes that produce it such as metabolism, genetics, autoimmunity, post-ERCP, and trauma for example... This disease is commonly associated with the sudden onset of upper abdominal pain that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10-25% of AP episodes are classified as severe. This leads to an associated mortality rate of 7-30% that has not changed in recent years. Treatment is conservative and generally performed by experienced teams often in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has a significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudo-aneurysm formation, or venous thrombosis, increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Andrzej Lewandowski, Krystyna Markocka-Mączka, Maciej Garbień, Dorota Diakowska and Renata Taboła (2012). Oxidative Stress and Antioxidative Status in the Acute Pancreatitis, *Acute Pancreatitis*, Prof. Luis Rodrigo (Ed.), ISBN: 978-953-307-984-4, InTech, Available from: <http://www.intechopen.com/books/acute-pancreatitis/oxidative-stress-and-antioxidative-status-in-the-acute-pancreatitis>

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