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Reviews

Treatment revisited and factors affecting prognosis of severe acute pancreatitis

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INTRODUCTION

As stated in the author's previous articles[1-5], severe acute pancreatitis is a multifacetted disease with rapid and sometimes fulminating onset and may result in many serious complications or even death if treatment is improper or delayed. Therapeutic measures must be directed against these multifa cets simultaneously with a view to achieve the optimum results. The following regime has been practised many years since 1990 and verified repeatedly as proper and adequate.

THERAPEUTIC REGIME OF SEVERE ACUTE PANCREATITIS

Early diagnosis is based on history, symptoms and signs, elevation of serum and/ or urinary amylase and computed tomography (CT) of pancreas. Once the diagnosis is verified, treatment is immediately instituted, the treatment regime is listed in Table 1.

Octreotide (Sandostatin) and the herbal medicine, Bulpleurum Peony Cheng Qi decoction have synergistic effects, their effects are depicted in Table 2.

In Balthazar's CT grading of D and E, there are always profuse exudation peripancreatically and sometimes massive into the peritoneal cavity and retroperitoneal space, plasma is always needed to improve the hypovolemia, and human albumin for hypoalbuminemia even when hypotension or shock is absent. When the hemodynamics become stabilized, intravenous hyperalimentation should be given. Octreotide and the herbal mixture are administered simultaneously at the start, the abdominal pain and abdominal distention usually subside within 1-3 days. Usually the patients run a smooth course without much fluctuation in one to one and a half months. Another important point is that food must be restricted until one month later after abatement of all symptoms and signs.

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By the above regime, 20 cases of grade D and 10 cases of grade E recovered uneve ntfully with no mortality, almost no morbidity and no serious complications as ARDS, gastrointestinal failure and disseminated intravascular coagulopathy(DIC).

Table 1 Treatment regime of severe acute pancreatitis

CT grading	Treatment
Grade A-C	Octreotide 0.1mg q8h (H)×5-7d
	Bulpleurum Peony Cheng Qi decoction bid×5-7d
Grade D-E	Octreotide 0.1mg/25% glucose IV
	0.5mg/5% glucose in saline 1000mL/24h
	thereafter 0.6mg/5% glucose in saline 1000mL/24h
	×5-7d or more
	or Stilamin 6mg/5% glucose in saline 1000mL/24h×5-7d
	Bulpleurum Peony Cheng Qi decoction 150mL bid×5-7d
	Plasma 400mL-600mL stat, 200mL on 2nd and 3rd day each
	Human serum albumin 10-20g/d
	Low molecular weight dextran (-40)+Dan Shen liquid 16-20mL/ glucose water
	250mL×1-2d, thereafter Dan Shen liquid in glucose
	in saline ×3-5d
	Ciprofloxacin 0.2g bid+Metronidazole 100mL bid×4 weeks
	or Imipenum 0.5g q8h×4 weeks
	Compound aminoacids 500-750mL qd, Intralipid 10% 500mL qd
	Fasting for food but not the herbal medicine
	Omeprazole 40mg IV gtt. qd×7d,
	and then 20mg per oral qd×2-3 weeks
	No atropine or gastric decompression
	Calcium, potassium salts supplement with occasional magnesium salt

Table 2 Effects of Octreotide and the herbal medicinals

Drug	Effects
Octreotide (Sandostatin)[5]	Inhibits release of CCK and pancreatic enzymes
	Stimulates and activates macrophages, lowering endotoxin level[6]
	Blocks release of inflammatory cytokines[7]
	Redistributes intrapancreatic blood flow
	Attenuates the interaction of neutrophils and endothelial cells[8]
	Inhibits eicosanoid and products as PGI_2, leucotrienes
	Relaxes Oddi's sphincter
Bulpleurum Peony Cheng Qi decoction[5]	Inhibits secretion and activities of pancreatic enzymes
	Stabilizes lysosomal membrane
	Inhibits inflammatory cytokines,IL-1,IL-6,IL-8, and TNF-α;
	Inhibits vascular permeability[9]
	Increase peristalsis with purgating effect, expelling bacterial flora and endotoxin
	Protects gut mucosal barrier, preventing bacteria dislocation[10,11]
	Relaxes Oddi's sphincter
	Reduces urea synthesis, promotes urinary excretion of urea and creatinine
	Has broad antibiotic spectrum, including *B. Fragilis*
	Stimulates secretion of endogenous glucocorticoids which can inhibit cytokines and inflammatory mediators
	Decreases blood lipids, inhibits lipid peroxidation
	Inhibits TXA_2 synthase, promotes PGE_1 PGE_2 levels, inhibits transformation of fibrinogen to fibrin and prevents endotoxin induced DIC
Dan Shen *(Salvia Miltiorrhiza)*	Inhibits platelet aggregation, decreases blood viscosity, improves blood rheology and microcirculation
	Inhibits lysosomal enzymes and chemotactic neutrophils
	Blockage of calcium ion influx
	Has antioxidation effect, ameliorates inflammation and tissue damage

FACTORS AFFECTING THE PROGNOSIS OF SEVERE ACUTE PANCREATITIS

Extent of necrosis and time of treatment after onset of the disease

The extent of necrosis can be categorized into ≤30%, 30% - 50% and >50% of the surface area

of pancreas shown in CT, which is relevant to the time of treatment given. The necrotic process is dynamic in nature, if diagnosed within 24h - 48h after disease onset, the extent of necrosis is usually ≤30%, if diagnosed after 72h, it may progress to 30%-50% or even > 50% even if the treatment is proper and adequate, the pathophysiologic changes can be more complicated, the rate of infection of intestinal origin is also higher with usher in of systemic inflammatory response syndrome (SIRS), then treatment can be more difficult with worser prognosis. In America, the mortality rate of this particular disease was around 17% - 20%, because the CT report usually took three days and this delay would enable progression of necrosis to the extent of 30%-50% or even >50% with higher mortality rate.

Proper, improper and/or inadequate treatment at the beginning

The key element in determining the prognosis of the disease is the treatment given at the start, with idiopathic severe acute pancreatitis, treatment is mainly medical, if with presence of common duct stone obstruction, emergency endoscopic or surgical removal of stone is necessary.

The comprehensive medical treatment is listed in Table 1, continuous infusion of Octreotide gives better results than 0.1mg q8h given hypodermically, in the latter, sepsis occurred in 26%, and ARDS in 37%[12]. Adequate plasma, albumin, low molecular weight dextran and Dan Shen restore the blood volume and improve the microcirculation of pancreas and other vital organs. Concomitantly, Blupleurum-Peony-Cheng Qi decoction is given which has seven constituents, including: Bulpleurum, White peony, Scutellaria, *Unripe bitter orange, Magnola bark, Refined mirabilite and Rhubarb*, each 10g. It is prepared by adding 100-150 water to the first five constituents, and heated for 20min, at the 18th min, add Rhubarb (wrapped by cloth), heat only for two min, then decant the liquid and dissolve the refined Mirabilite (Na_2SO_4) crystals in it and drink. The mixture is taken twice a day by repetition of the same procedure. This herbal medicine should be taken orally for 5-7 days. No atropine, nor gastric decompression is allowed.

Combination of these measures can ameliorate the pancreatic autodigestion caused by release of pancreatic and lysosomal enzymes and ischemia-reperfusional damage significantly, it can also halt the exudation, and avoid the complications of the kidney, lung and GI tract. This herbal mixture can inhibit the excessive stimulation of macrophages; reduce the release of inflammatory cytokines, decrease the neutrophilic infiltration and its interaction with vascular endothelial cells, maintaining the gut barrier function, preventing the second attack which leads to SIRS.

Among the destructive enzymes, phospholipase A_2 (PLA_2) and lipase are most crucial, PLA_2 can destroy the phospholipid structure of cell membranes of GI tract, lung and brain. The lipase can degradate the fat which produce toxic free fatty acids injuring the capillaries and increase lipoperoxidation[13]. The cytokines damaging vital organs include IL-1, IL-6, IL-8, TNF-α, INF-γ and PAF. Among these, PAF and TNF-α increase vascular permeability which not only play important pathophysiological role in the pancreas itself but also cause complications in the lungs, brain and GI tract. By given Octreotide (Sandostatin) with concomitant herbal mixture, the damage caused by the above factors can be much reduced. Sandostatin and the herbal mixture have synergistic effects on inhibition of activated pancreatic enzymic activities and their secretion, also have complementary effect on interaction of the neutrophils and endothelial cells, and inhibition of neutrophilic infiltration in the pancreas and in the lung, thus is crucial in the treatment of severe acute pancreatitis.

When given Sandostatin or oral herb mixture singly and without given plasma, human serum albumin, but infuse large volume of balance solution or glucose in saline, these not only cannot act on simultaneously, but also may lead to cardiac and pulmonary failure, this may be one of the causes of high mortality rate and high complication rate as reported in the medical literature both domestically and abroad.

Whether preventive treatment has been instituted?

During admission, Omeprazole (Losec) should be given intravenously to prevent acute gastric mucosal bleeding; ciprofloxacin and metronidazole or imipenum to prevent infection, besides, the Rhuberb and Scutallaria have also antibiotic activities. Rhuberb also abolishes paralytic ileus, expel the bacteria flora together with endotoxin via the anus. The antibiotics shown above have penetrating abilities into the necrotic tissue or necrotic fluid, if other antibiotics are used instead or by rotation would not only be ineffective, but also lead to superinfection in these immunocompromized patients. Once the hemodynamic changes return to normal after correction of hypovolemia, total parenteral nutrition should be instituted to maintain positive nitrogen balance, in case with SIRS, more calories should be given regularly up to 2500-3000 Kal/d or more. Regular insulin should also be given to maintain normal blood sugar level. Supplements of calcium, potassium and magnesium salts are also required for hypocalcemia and hypopotassemia. Local fluid collection is best to be left alone without aspiration, this will be absorbed during convalescence.

During the early period, one should pay attention to avoid cardiac or renal failure, also the ARDS, in the middle period, one should notice and prevent the occurrence of pancreatic encephalopathy; late in the course, one should be aware of infection and residual infection. Food fasting but allow oral herb mixture only would take one month, early feeding can give rise to recrudescence. If one is not aware of the complicated and multifaceted nature of the disease

and has not paid great attention to the preventive measures, SIRS, multiple organ dysfunction syndrome (MODS) and eventually multiple organ failure (MOF) would be unavoidable. For SIRS, short-term hemofiltration had been adopted by the surgical pancreatology group of Shanghai Ruijin Hospital to downregulate the level of inflammatory cytokines and upregulate the antiinflammatory cytokines (IL-10) level which could shorten the course and hasten recovery[14].

Can the precipitating factors be removed or not?

The precipitating factors as microlithiasis or cholesterol crystals from the gallbladder, the high fat, high protein diet and alcohol drinking were removed after treatment and fasting, the patient usually recovered clinically in 1-1.5 months, and the pancreas showed normal texture by CT by another 1-1.5 months. But when hyperlipidemia is the inducing factor, the lipoperoxidation and pancreatic ischemia are especially severe, the reason is stated above, the course is usually fulminating, because short-acting hypolipidemic agent for intravenous use is currently unavailable, especially in those with coexistent fatty liver, the oxidation of fatty acid by the mitochondria of the liver cells cannot be augmented, the severe ischemia and lipoperoxidation would result in extensive pancreatic necrosis, and because of the persistence of free fatty acid as the stimulus, numerous complications may set in, making treatment even more difficult, fortunately this precipitating factor is rare here.

Functional status of vital organs

Aged patients usually have degeneration and deteriorating function of many vital organs, diseases as ischmic heart, hypertension, diabetes, chronic bronchitis with emphysema, chronic liver disease, impaired kidney function or even lacunar infarction of brain are common, any one or two coexisted can add further embarra ssment to the management, fortunately the severe acute pancreatitis among the aged is milder than that in the middle-aged and younger patients, they are mostly of grade C and B, whereas grade D is only occasional[15]. One must be very careful throughout the course of treatment, detailed history, physical examination, blood chemistry, blood gas analysis, electrocarcinogram should be performed on admission, fluid given must be concordant with the tolerability of patient's heart and circulation, the rate of fluid infusion shoumd be slow to avoid the unnecessary occurrence of heart failure. In case when heart failure occurs, cedilanid and dobutamine should be given to increase myocardial contractility and phentolamine to diminish the pre-and afterload. At the same time, one should also pay attention to the renal function because cardiac and renal functions are interrelated, with both cardiac and renal incompetence, the condition is usually detrimental and may be fatal.

Whether necrosectomy is timely and thorough?

With stone obstructing the pancreatico-biliary common pathway, ERCP or endoscopic sphincterotomy should be tried first, or emergency surgery to relieve obstruction with common duct T-tube drainage, but leave the pancreatic necrosis aside, operation should be as simple as possible, afterwards, comprehensive medical therapy should be instituted immediately. With nonstone obstruction where necrosis is extensive and severe, patient should be placed in ICU, given energetic medical treatment and watched carefully by dynamic CT and other measures, in case of progression of the disease, necrosectomy should be performed with thorough removal of necrotic foci. Acute peritonitis occasionally requires laparotomy for drainage, followed by short-term peritoneal lavage when there is profuse exudation and fluid collection in the peritoneal cavity and retroperitoneal space. The peritoneal exudative fluid contains PLA_2, protease, bradykinin, PAF, prostaglandins and complement component which should be evaculated. Necrosis with infection if can be controlled by antibiotics, operation may be spared, but if it is uncontrollable, surgery should be performed to remove the infected necrotic foci within the pancreas, the peritoneal cavity and retroperitoneal space thoroughly. These are the surgical viewpoints of the expertised surgeon Zhang ZT of Ruijin Hospital[16].

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