Novel strategies for the treatment of acute pancreatitis based on the determinants of severity.

Okuda State-of the-Art Lecture

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Abstract:

Acute pancreatitis (AP) is a common disease for which a specific treatment remains elusive. The key determinants of the outcome from AP are persistent organ failure and infected pancreatic necrosis. The prevention and treatment of these determinants provides a framework for the development of specific treatment strategies. The gut-lymph concept provides a common mechanism for systemic inflammation and organ dysfunction. Acute and critical illness, including AP, is associated with intestinal ischaemia and drastic changes in the composition of gut lymph, which bypasses the liver to drain into the systemic circulation immediately proximal to the major organ systems which fail. The external diversion of gut lymph and the targeting of treatments to counter the toxic elements in gut lymph offers novel approaches to the prevention and treatment of persistent organ failure. Infected pancreatic necrosis is increasingly treated with less invasive techniques, the mainstay of which is drainage, both endoscopic and percutaneous. Further improvements will occur with the strategies to accelerate liquefaction and through a fundamental re-design of drains, both of which will increase drainage efficacy. The determinants of severity and outcome in patients admitted with AP, provide the basis for innovative treatment strategies. The priorities are to translate the gut-lymph concept to clinical practice and to improve the design and active use of drains for infected complications of AP.

Keywords: Clinical acute pancreatitis, Experimental acute pancreatitis, Intestinal ischemia, Organ failure , Infected pancreatic necrosis

Introduction

Acute pancreatitis (AP) is a protean disease of unpredictable course [1]. Numerous advances in clinical management over the last few decades have contributed to a decreased overall mortality. But when severe, AP has a mortality of around 30% and continues to be a significant clinical and economic burden. Strikingly, there are no specific and effective treatments for AP and certainly none that address outcome determining pathophysiology. This is despite the considerable progress in understanding the initiation of AP, and in particular the intra-acinar events and early local inflammatory responses. The disappointment, after massive funding and elegant descriptions, is that we are no closer to effective targeted therapy. Many candidate pharmacological treatments have shown promise in the experimental setting, but relatively few have been trialled in the clinical setting and none have proven effective [2]. As a result the history of clinical trials of treatments for AP has been described as a 'litany of failure' [3].

New thinking is required if novel treatment strategies are to be developed, and this needs to start with a critical look at both the timing and targets of potential treatments. In regards *timing*, most of the failed treatments have proven to be 'too little, too late' (Figure 1). By the time patients present to hospital, usually after 24 hours or more of pain, the intra-acinar events are well established as evidenced by the marked local inflammation, tissue oedema and microcirculatory injury within the pancreas. Because of the delay in patient presentation the therapeutic window necessarily starts after hospital admission and the treatments targeting intra-pancreatic proteases, endoplasmic reticulum stress, mitochondrial dysfunction, calcium influx and local cytokines are not likely to be effective. This is because they target disease drivers that appear most important before patients are admitted. These drivers may remain important after admission, and it remains possible that some treatments will have some benefit if delivered promptly after admission, with a short 'admission to needle' time. In regards *targeting*, treatments are more likely to be effective if they address events that drive disease severity and determine outcome after patients are admitted to

hospital, because the therapeutic window remains wide open. The length of time that the therapeutic window remains open depends on the particular target of that treatment. It makes sense to consider therapeutic targets that are key aspects of AP pathophysiology after admission and which are also key determinants of disease severity and outcome.

Potential treatment targets

There are multiple potential treatment targets and Figure 2 highlights important aspects of the pathophysiology in both the pancreas and the intestine and the way in which they interact to drive systemic inflammation and multiple organ dysfunction. For instance, hypovolaemia and splanchnic vasoconstriction are acknowledged targets for treatment by fluid resuscitation, but little progress has been made in defining the most effective fluid and the best way to guide this treatment [4]. Similarly, little progress has been made in preventing intestinal barrier failure or in preventing the secondary infection of pancreatic necrosis, and yet these are important aspects of pathophysiology and offer a wide therapeutic window. The identification of potential treatments in AP requires a clear understanding of what determines AP severity and outcome.

Determinants of severity and outcome as targets for treatment

The most important determinants of AP severity and outcome have been defined by a meta-analysis[5] and showed these to be persistent organ failure (POF) and infected pancreatic necrosis (IPN). It was not possible to define the importance of the timing of POF or the importance of the number of organ systems that fail. This study provided the basis for a new classification of AP severity, the Determinants Based Classification [6], with the introduction of 4 severity categories: mild, moderate, severe and critical. Confirmation and validation of this approach has come from many retrospective studies, but the only prospective multicentre study has been from 46 intensive care units in Spain and South America [7]. In providing validation the authors raised particular concerns about the 'severe' category, considering that it actually comprised two subgroups with quite different treatment requirements and

outcomes. This prospective study described five categories of severity with distinct morbidity and mortality profiles. Specifically those with POF and no IPN had different interventions and outcomes from those with IPN and no POF (Groups 2 and 3 respectively, Figure 3). The combination of both POF and IPN, defined as 'critical' AP [6], is associated with a significantly worse outcome (Group 4 in Figure 3). Rather than use the nomenclature of Groups 1-4, and exclude those with mild AP, a working nomenclature has been proposed: 'mild', 'moderate' (Group 1), 'moderately severe' (Group 2), 'severe, (Group 3) and 'critical' (Group 4) (Figure 4)[8].

This systematic approach to classifying disease severity is essential pre-requisite for the development and evaluation of novel treatment strategies. It is important to have sufficient homogeneity in patient groups to test and accurately interpret the results of treatments [9].

The aim of this of article is to draw on these developments to propose novel but plausible treatment strategies based on the systemic treatment of POF and the local treatment of IPN.

Persistent organ failure

Two important clinical observations led to a new understanding of the role of the intestine in the promotion of systemic inflammation and end-organ dysfunction in acute and critical illness, including AP. The first was that irrespective of the particular acute disease (e.g. major trauma, haemorrhagic shock, septicaemia and AP) there appears to be similar pattern to the systemic inflammation and end-organ dysfunction [10,11]. This suggests a common mechanism. The second observation is that the intestine is subject to ischaemic injury in severe acute disease (including severe AP) as reflex splanchnic vasoconstriction occurs to response to hypovolaemia to maintain perfusion to vital end-organs (Figure 2). This intestinal ischaemic injury is often subclinical, but may manifest as intolerance to early feeding, ileus and even non-occlusive mesenteric ischaemia and infarction. Many other lines of evidence indicate that the intestine is vulnerable in AP and probably contributes to disease severity and outcome [12]. A number of models have been proposed to help explain the role of the

intestine in organ failure, including the 'gut motor'[11] and 'gut starter'[13] models. More recently, the 'gut-lymph' model was proposed by Deitch[14] and he suggested that gut-lymph is an important common mechanism in the development of systemic inflammation and end organ dysfunction [15,16].

The gut-lymph model recognizes the gut dysfunction occurs in the presence of AP. This can be seen as loss of intestinal mucus[17], endotoxaemia[18], mitochondrial dysfunction[19], increased endothelial permeability[20] and mucosal ischaemia[21]. As a result of ischaemic intestinal injury there are significant changes in the composition of lymph draining the intestine, and these changes are toxic to cells and organ systems. The gut-lymph bypasses the liver by traversing the thoracic duct and enters the systemic circulation upstream of the heart, lungs and kidneys, which are the organs that are most often prone to dysfunction and failure [15,16] (Figure 5). The gut lymph model is supported by a number lines of evidence from experimental AP and other acute diseases.

Gut lymph compositional changes correlates with disease severity. Significant changes to gut lymph composition occur in AP and other acute diseases [15]. In experimental AP the proteome of gut lymph undergoes significant change with a 40 fold increase in several pancreatic proteases and no change in anti-protease protection [22]. Lipase is known to generate free unsaturated fatty acids in gut lymph which are toxic to umbilical vein cells[23] and associated with POF[24]. Tryptophan metabolites kynurenine and 3-hydroxykynurenine are elevated in rodent gut lymph and plasma during AP and these correlate with disease severity[25].

Gut lymph is toxic. In our laboratory the toxicity of gut lymph in AP has been assessed at an organelle (mitochondrial function[19]), cellular (endothelial and cardiac cultures) and a whole organ level (isolated perfused heart and lung[26]). Gut lymph, from a rodent model of ischaemia-reperfusion injury, infused intravenously into other rats with AP [27] caused lung injury and an increase in AP severity. A reduction in cardiac output, contractility and

impaired relaxation results from infusing gut lymph collected from an experimental model of AP into an isolated and paced heart model [28].

Preventing gut lymph reaching the systemic circulation improves outcome. In animal models of acute disease including AP, preventing toxic gut lymph from reaching the systemic circulation through either external lymph drainage or thoracic duct ligation ameliorates distant organ injury[29] and improves survival [30,31]. Pro-inflammatory cytokines (e.g. IL -1β and IL-10) are prevented from reaching the systemic circulation by external lymph drainage [32] which also improves cellular immune function [33] and reduces bacterial translocation [34]. We have demonstrated that the cardiac dysfunction associated with experimental AP can be prevented by thoracic duct ligation [35]. Thoracic duct ligation[36] and lymph diversion[37] have been shown to ameliorate lung injury in experimental AP. This is demonstrated by prevention of neutrophil priming and accumulation in pulmonary tissues[38]; reduced lung permeability[39] and histological improvement in lung injury[36]. Furthermore gut lymph is directly toxic to pulmonary microvascular endothelial cells[40] and lung injury can be reproduced when donor lymph from a rat subjected to haemorrhagic shock is infused into a naive rat [41]. Clinically these findings are supported by three non-randomised studies in AP assessing pulmonary function [42-44], one of which observed that arterial oxygenation improved immediately once drainage was instituted [42].

Inactivation of toxic factors reduces gut lymph toxicity. A number of the specific factors responsible for the toxicity of gut lymph have been identified, and these provide potential targets for therapeutic intervention. In a model of non-occlusive mesenteric ischaemia somatostatin was protective in reducing endotoxin, TNF-α and organ dysfunction [45]. Similarly both human and bovine albumin prevent in-vitro toxicity to human umbilical vein cells and in-vivo produced a dose-dependent reduction in lung injury [46]. Activation of the toll-like receptor 4 (TRL4) pathway[47] and P selectin upregulation[48] appear to be dependent on factors in gut lymph that mediate lung injury. A deep analysis of gut lymph composition is required to identify more potential targets. Clinical studies of AP have confirmed higher concentrations

of pancreatic enzymes in thoracic duct lymph than plasma[44]. The proteome of lymph in experimental AP identified that seven of the eight proteins that were significantly increased were pancreatic catabolic enzymes[22]. While intravenous anti-protease therapies have been ineffective, this data suggests that targeting proteases in gut lymph is worth exploring. It has been shown that phospholipase A2 inhibition prevents neutrophil priming[49]. Lipase in gut lymph can generate toxic free fatty acids[23]. Further the tryptophan metabolites kynurenine and 3-hydroxykynurenine which correlated with AP severity are another important potential treatment target[25].

Novel therapeutic strategies for treating persistent organ failure

This representative evidence supports the gut-lymph concept, where altered and toxic gut lymph drives that development of SIRS/MODS in severe and critical AP. Based on this there are two novel treatment strategies worth considering. The first is external drainage of thoracic duct lymph and the second is targeted drug delivery to reduce the toxicity of gut-lymph.

External drainage of thoracic duct lymph

This is not a new idea, as there are over 70 publications relating to therapeutic thoracic duct interventions, but curiously none in the last 15 years [50]. The reasons for this drop-off includes the invasiveness of thoracic duct interventions, which entails a neck incision under general anaesthetic for thoracic duct cannulation. This intervention requires judicious fluid and electrolyte replacement and can be complicated by infection and lymph leak. Another reason for the lack of interest in thoracic duct interventions is likely to be because the results from the studies in a wide range of acute diseases have been largely equivocal, most likely reflecting inferior and under-powered clinical trial design [50]. On the basis of this literature and the experimental evidence, it has been considered that equipoise still exists that further studies are warranted. It is hypothesized that diverting toxic gut-lymph by external drainage of thoracic duct lymph during the first week will likely yield clinical benefits in severe and

critical AP. Of possible concern with this approach is the risk of immunodepletion, but this does not occur until after 3-4 weeks of thoracic duct lymph drainage [50]. It is now important to evaluate external drainage of thoracic duct lymph in the context of a randomised clinical trial to determine whether it can reduce the systemic inflammatory response, mitigate multiple organ dysfunction and improve clinical outcome in patients with severe and critical AP.

Lymph targeted drug delivery

The identification of toxic elements in AP conditioned gut-lymph (above) provides a range of potential targets for treatment that is directed at thoracic duct lymph, before it reaches the systemic circulation. Additional targets are expected with deeper compositional analysis of gut-lymph sampled from patients with AP (see above). The theoretical and experimental basis for targeting the lymph system to promote drug exposure and activity has been reviewed recently [51]. Two strategies being developed to promote the delivery of the candidate drugs to target toxic factors in gut-lymph are the *enteral administration* of drugs linked to glyceride pro-drugs and *peritoneal administration* of drugs within liposomes. The presence of lipase in thoracic duct lymph ensures the rapid release of drug from the carrier molecule [52]. The peritoneum provides a large absorptive surface and a potentially less complicated barrier for absorption than through the intestinal wall. As peritoneal lavage has some therapeutic value [53], adding a drug targeting lymph might provide stronger ethical justification for placing a catheter in the peritoneum. Most drugs have been designed to stay within the peritoneum, but in this setting there are strategies that allow enhanced absorption and an increase in the lymph to plasma concentration ratio of the drug.

In summary, the gut lymph concept provides a putative role for the gut and gut-lymph in promoting SIRS and MODS and provides a model for understanding the underlying pathophysiology of severe and critical AP. Specific treatment strategies, such as those mentioned, now need to be developed in order to translate the gut-lymph concept from the experimental to clinical setting.

Novel therapeutic strategies for treating infected pancreatic necrosis

There has been a very significant improvement in the outcomes from treatment of infected pancreatic necrosis, but it still remains an important determinant of severity and outcome in AP. The recent re-definition of the local complications of AP is an important advance [54]. This is based on the acuity of the local pancreatic complication, its content and whether it is infected or not (Figure 6). Of the four defined infected local complications, infected walled off necrosis (WON) and infected acute necrotic collections (ANC) are the ones that most often require treatment.

The PANTER trial effectively ratified the trend toward less invasive treatment of the infected pancreatic necrosis, and has validated the 'step up approach' [55]. This means that deteriorating patients who previously had an open, and often repeated laparotomy and necrosectomy (blunt debridement of infected necrotic pancreatic and peri-pancreatic tissue), are now treated by drainage first. This drainage is typically either by an endoscopic transgastric or percutaneous retroperitoneal route. These are considered complimentary, selected on the basis of the location and complexity of the target lesion and the available expertise. Sometimes a combined approach ('hybrid' or 'dual modality') is useful [56,57]. If there is a failure to respond then drainage is followed by minimally invasive debridement and there are many described approaches to this [58,59].

One of the unexpected findings of the PANTER trial was that 35% of patients who would have previously had an open necrosectomy required no further intervention beyond simple drainage. This figure is higher (43-56%) in selective non-randomised series[60,61].

There appears to be considerable variability in the way that drains are used in patients with infected ANC or WON[62,63] and significant scope for protocol standardization and technical innovation to improve the efficacy of drainage. The most common reason for drain failure is blockage from particulate matter ('necrosum'). The risk of this can be reduced by routine upsizing of the drains and by instituting an irrigation protocol. A novel strategy for the

drainage of infected ANC/WON is based on the concept of 'accelerated liquefaction' by irrigating with an active chemical or enzyme designed to breakdown the necrosum[64]. The requirements for such an approach is an understanding of the composition of necrosum, the availability of active agents that effectively break downs the necrosum and studies to demonstrate their safety and efficacy. Preliminary results using biobanked necrosum and a novel testing chamber with a range of active agents indicate that gastric juice is more effective at breaking down necrosum than many other enzymes including collagenase, streptokinase, trypsin and bromolein[65]. It is also significantly more effective than irrigation with normal saline or hydrogen peroxide[66]. There is also the opportunity to improve drainage efficacy by improving percutaneous drain design.

Conclusion

The determinants of severity and outcome in patients admitted with AP, persistent organ failure and infected pancreatic necrosis, have provided the basis for innovative treatment strategies. The priorities are to translate the gut-lymph concept into clinical practice and to improve the design and active use of drains for infected complications of AP. These of particular approaches are not the only novel therapeutic strategies being developed. Collaborative organizations designed to evaluate novel treatment strategies should be supported[67] to ensure the conduct of high quality multi-centre trials. And these strategies need effectiveness demonstrated within the available therapeutic window.

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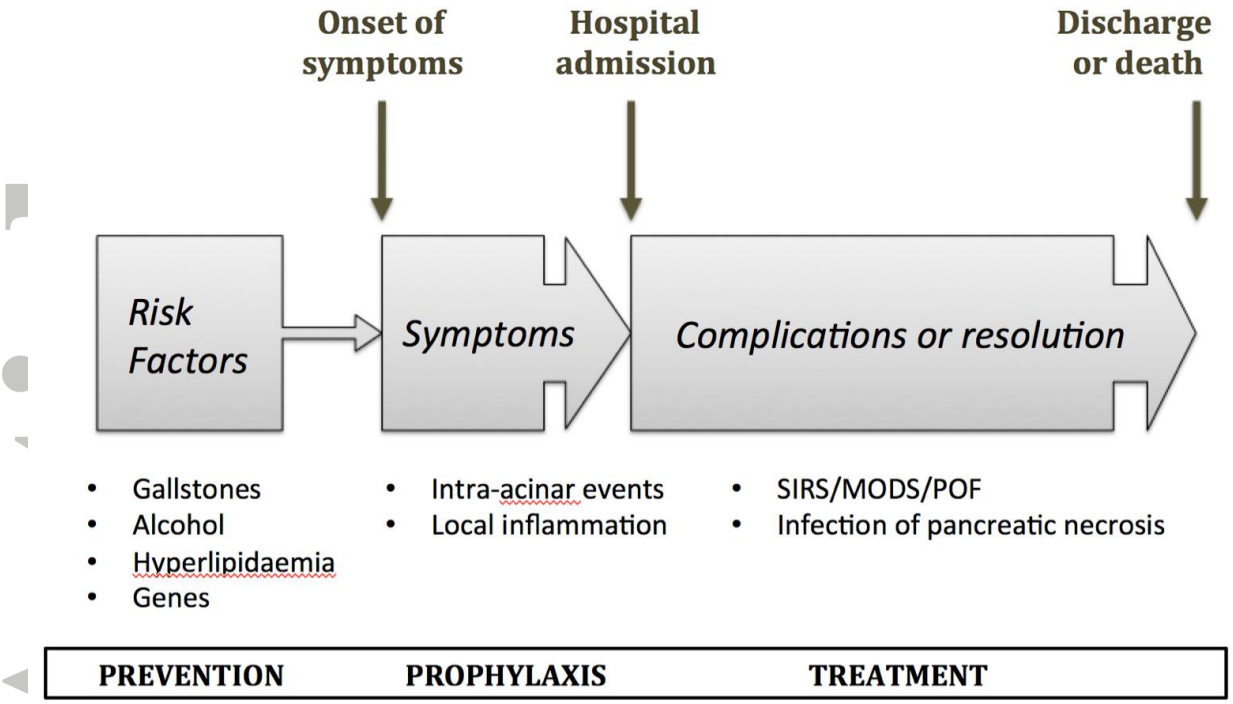

Figure 1. Schema of events before and after hospital admission in the development of acute pancreatitis, highlighting the opportunity for treatment targeting key pathophysiology responsible for severity and clinical outcome: SIRS (systemic inflammatory response syndrome), MODS (multiple organ dysfunction syndrome), POF (persistent organ failure) and infection of pancreatic necrosis.

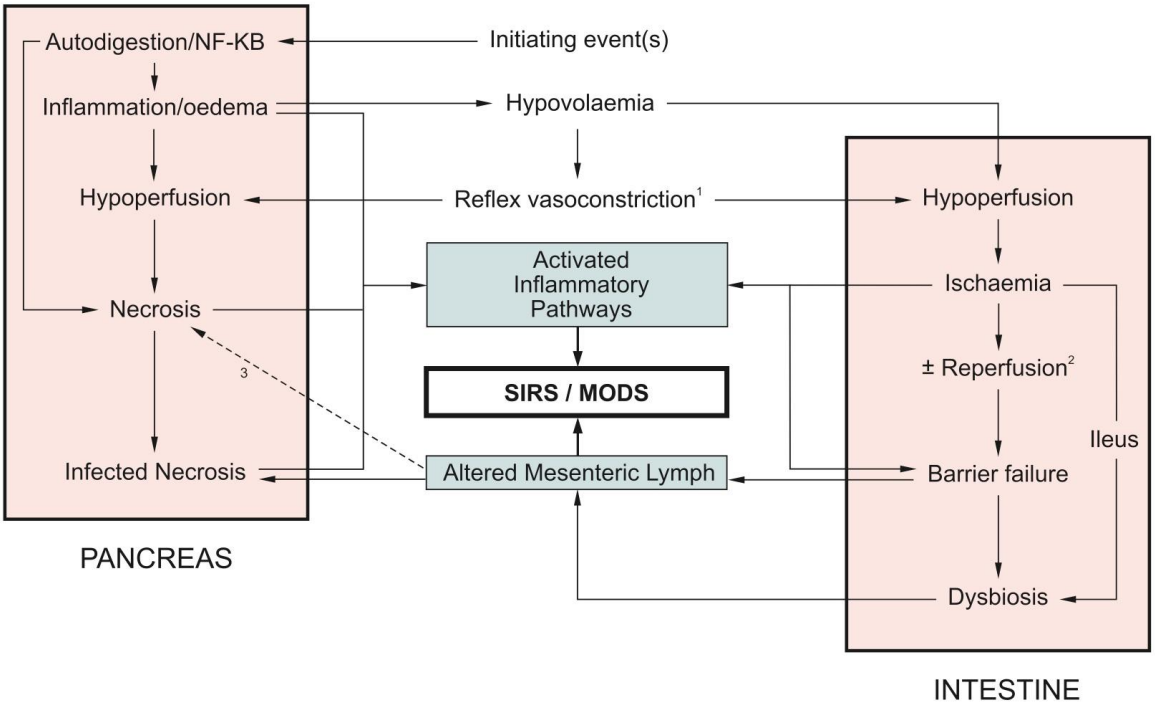

Figure 2. Schema of key loco-regional pathophysiological events in the pancreas and intestine, and how they interact to drive the severity and outcome of acute pancreatitis. Used with permission65.

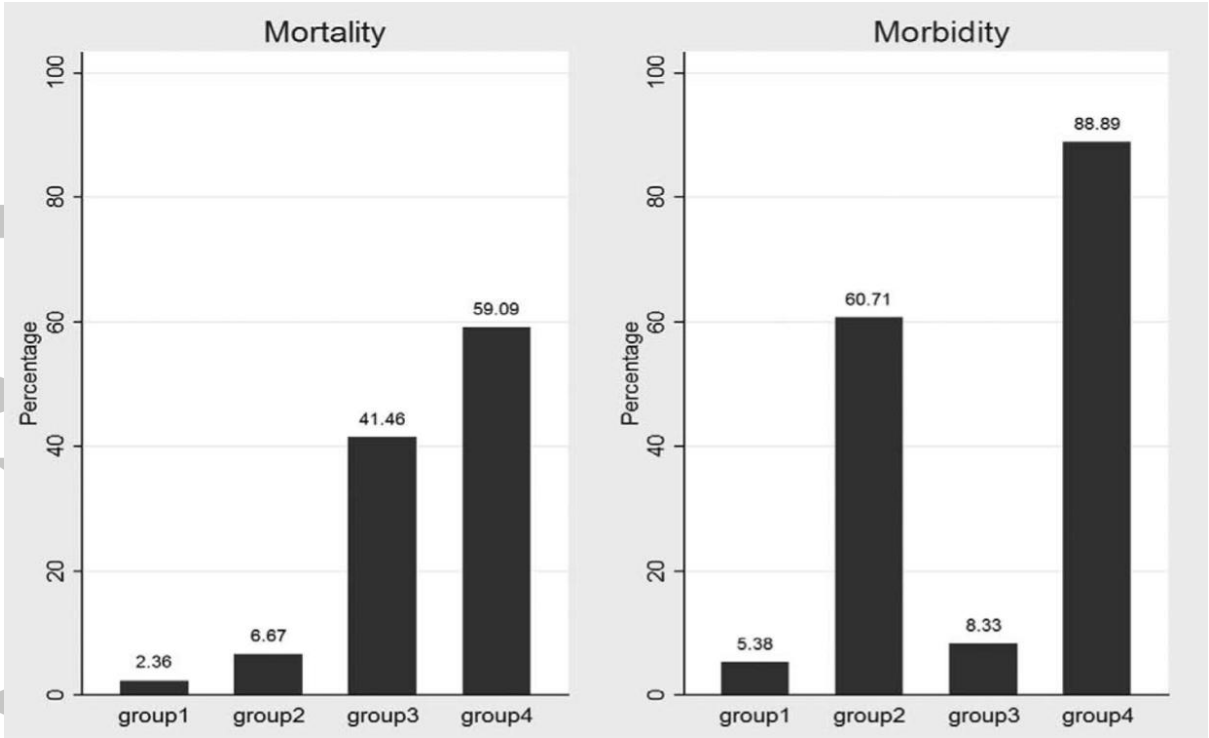

Figure 3. The four groups of acute pancreatitis severity (mild cases excluded) in the prospective multicentre study of intensive care patients highlighting the striking differences in mortality and morbidity between groups 2 and 3 (reference). The definitions of the groups and their preferred nomenclature are: These groups have been renamed as categories of severity: moderate (Group 1 - transient organ failure with or without sterile necrosis), moderately severe (Group 2 - infected necrosis without persistent organ failure), severe (Group 3 – persistent organ failure without infected necrosis) and critical (Group 4 – infected necrosis and persistent organ failure) (see Figure 4). Used with permission7.

DETERMINANTS	NO LOCAL COMPLICATIONS	STERILE LOCAL COMPLICATIONS	INFECTED LOCAL COMPLICATIONS
NO ORGAN FAILURE	**MILD**	**MODERATE**	**MODERATELY SEVERE**
TRANSIENT ORGAN FAILURE	**MODERATE**	**MODERATE**	**MODERATELY SEVERE**
PERSISTENT ORGAN FAILURE	**SEVERE**	**SEVERE**	**CRITICAL**

Figure 4. The modification of the Determinants-Based Classification of acute pancreatitis severity, based on the multicentre prospective study with the proposed nomenclature: mild, moderate, moderately severe, severe and critical acute pancreatitis, based on organ failure (none, transient or persistent) and local complications (none, sterile and infected) 8.

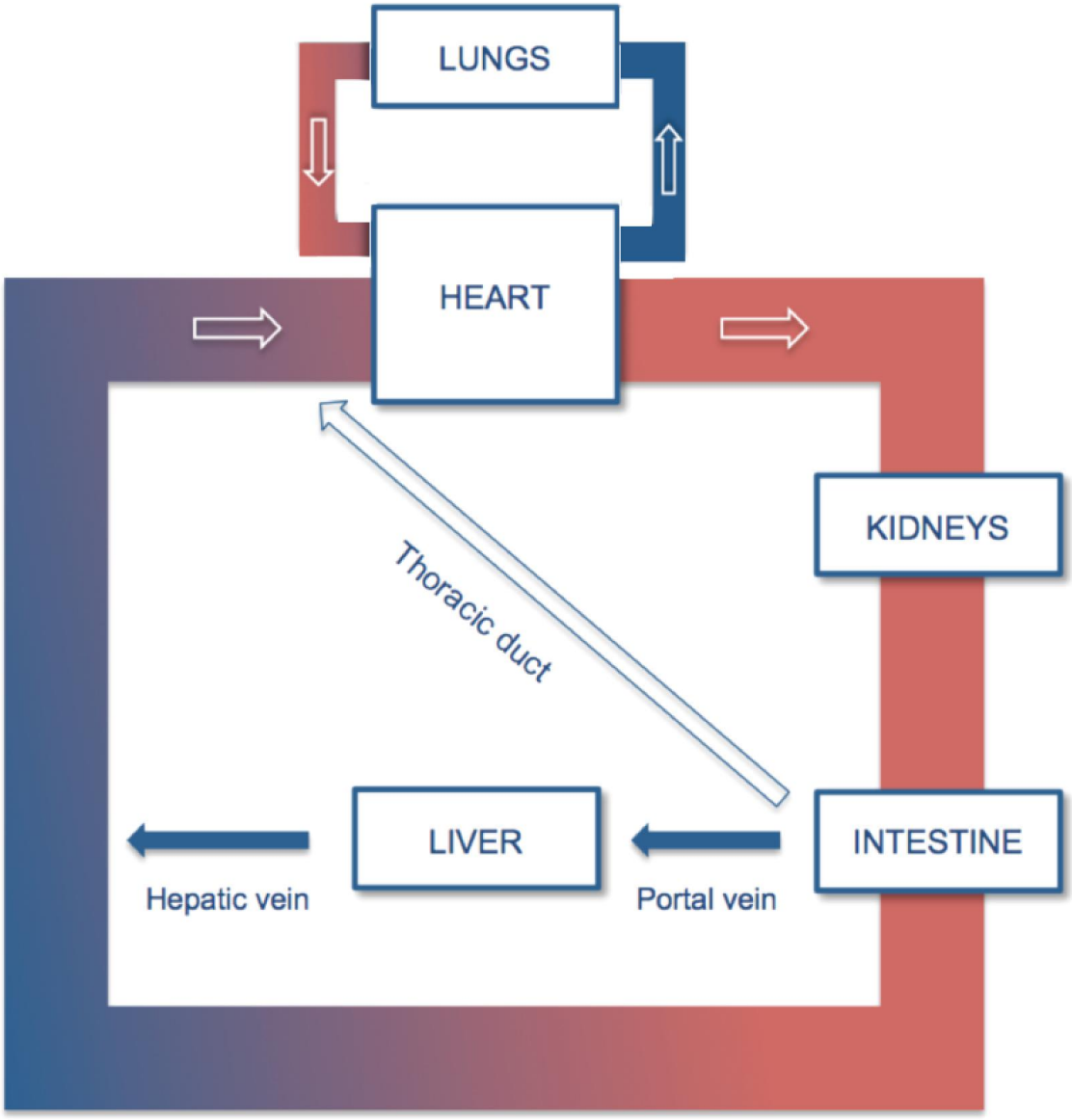

Figure 5. Schematic representation of the gut lymph concept indicating thoracic duct lymph bypassing the liver.

Content	Acute (<4 weeks, no defined wall)		Chronic (>4 weeks, defined wall)	
	No infection	Infection	No infection	Infection
Fluid	**Acute pancreatic fluid collection**	Infected APFC	**Pseudocyst**	Infected pseudocyst
Solid ± fluid	**Acute necrotic collection**	Infected ANC	**Walled off necrosis**	Infected WON

Figure 6. Definitions of the local complications of acute pancreatitis, modified from the Revised Atlanta Classification. Used with permission 3.