Organ Failure and Acute Pancreatitis

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Since the beginning of this century, our understanding of the relationship between organ failure and acute pancreatitis has greatly improved. Organ failure is frequently observed in severe pancreatitis but it was not recognized that it is usually present early in the course of disease, often at the time of admission to hospital. We now know that this is the case. It has also become clear that a proportion of patients with organ failure improve rapidly in response to treatment and it is only those with persistent organ failure who are at risk of serious complications and death, and we are able to identify patients at risk of organ failure, and grade the severity of organ failure using objective scores.

We still do not have effective specific therapies for acute pancreatitis or for organ failure, other than general supportive measures. Our understanding of the pathophysiology remains limited, and we still lack basic and clinical research into the mechanisms of inflammation and how to manipulate them.

Diagnosis of Organ Failure

Acute pancreatitis is one of many conditions associated with organ failure. In the early 1990s, advances in critical care medicine were accompanied by descriptions of threshold values to define organ failure and systems for grading severity. Organ failure thresholds were incorporated into the definition of severe acute pancreatitis in the Atlanta classification [1], so it is not surprising that these thresholds closely match the thresholds adopted in critical care medicine. The publication by Marshall and colleagues [2] of a simple numerical scoring system to take account of the number and severity of organ failures offered the potential to categorize patients numerically. This system was modified as the SOFA score [3], which is better adapted for use in intensive care units. However, the potential application of this system to describe grades of severity in acute pancreatitis has not been widely adopted although the recent revision of the Atlanta classification published in 2013 [4] adopted the Marshall score in the definition of organ failure. See also Chap. 1. This revision does not take account of the severity of organ failure, which can be assessed and described numerically by the Marshall score (Table 2.1).

Assessment of Organ Failure in Acute Pancreatitis

Clinical research on the assessment of organ failure in acute pancreatitis has been heavily influenced by the use of a single threshold for organ failure in the original Atlanta definition. Most researchers have focused on the presence or absence of organ failure in relation to other

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Table 2.1 Modified Marshall Scoring System [2, 4] for organ dysfunction[a]

	Score				
Organ system	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal					
Serum creatinine, μmol/L	≤134	134–169	170–310	311–439	>439
Serum creatinine, mg/dL	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mmHg)[b]	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH <7.3	<90, pH <7.2

[a]A score of 2 or more in any system defines the presence of organ failure
[b]Off inotropic support

outcomes in acute pancreatitis. As the presence of organ failure was a defining feature of severe pancreatitis in the Atlanta definition, the demonstration of organ failure of any severity, and at any time, caused the patient to be allocated to the severe category. This has caused some confusion, particularly for those who failed to appreciate that the Marshall score (and Atlanta criteria) definition of organ failure included patients with lesser degrees of dysfunction, who did not require artificial ventilation, inotrope support, or renal replacement therapy.

Very few studies have attempted to explore the relationship between the severity of individual organ failures and other outcomes such as local complications and death. This may have hampered progress in our understanding of the pathophysiology of organ failure and pancreatitis, and it remains a potential research area of considerable interest. While it is clear that multiple organ failure puts the patient at greater risk of fatal outcome than a patient with only one organ failure [5, 6], I am aware of only six assessments of organ failure scores in acute pancreatitis. These mostly deal with comparisons of APACHE-II and other scores for the prediction of local complications or severe pancreatitis.

Glisic and colleagues studied 60 unselected patients and found significant correlation between the Bernard (Marshall) and the APACHE-II scores [7]. These also correlated well with C-reactive protein (CRP) levels. Dambrauskas and colleagues [8] and Mason and colleagues [9] studied 101 and 181 unselected patients, respectively. Both groups found that the Marshall score [2] or the logistic organ dysfunction score (LODS) [10] predicted outcomes such as death, pancreatic necrosis, infection, or the need for critical care equally as well as the APACHE-II score. Two reports from India [11, 12] describe 50 and 55 patients admitted to intensive care units. Both studies demonstrated the ability of the SOFA score to predict fatal outcome better than other score systems including APACHE-II and LODS.

All the above reports used organ failure scores to find a cutoff between patients with or without a particular endpoint. Only one study has attempted to relate the severity of organ failure to outcomes assessed in more than two categories. Mole and colleagues [13] analyzed data from a historic cohort of 276 patients with pancreatitis who had undergone early computed tomography (CT). They showed correlation between Marshall score and the modified CT Severity Index as well as with the number and extent of local complications. However, they noted a lack of association between organ failure score and the presence of necrosis >30 % of the pancreas. It seems likely there is a complex interaction between organ failure and the causes of necrosis, which may vary between individuals.

Dynamic Nature of Early Organ Failure

While application of the Atlanta classification confirmed that organ failure often occurred in patients with severe acute pancreatitis, the

mindset of clinical researchers before 2000 was heavily influenced by the desire to identify early signs of severity, and to predict patients likely to have severe acute pancreatitis. A variety of scoring systems was used for this purpose [14–16]. See also Chap. 7. In fact, these systems all measured physiological disturbance, and they owed their effectiveness to *detection* of patients with organ dysfunction, rather than *prediction* of those likely to develop organ failure or other complications.

Publication in 2001 of a large multicentre study conducted in the United Kingdom to investigate the effect of Lexipafant in "predicted severe" acute pancreatitis [17] revealed a number of important lessons. This study included patients within 72 h of onset, with APACHE-II score >6. The proportion of patients with organ failure was the primary endpoint. However, over 40 % of patients had organ failure at the time of entry to the study, and only a further 7 % developed new organ failure during the first week. It was not possible therefore to significantly influence the primary endpoint in that trial. Until this time, it had not been appreciated that organ failure during the first week of acute pancreatitis was usually already established shortly after admission to hospital. More importantly, this trial yielded sufficient data to enable the characterization of features of organ failure associated with a high risk of death.

Using data from a similar cohort, Buter and colleagues [18] had identified the persistence of organ failure at the end of the first week as a substantial adverse prognostic factor. More than half of their patients in that category had a fatal outcome whereas patients whose organ failure had resolved by that time were unlikely to die. In our analysis [19] of 290 patients with admission APACHE-II score of >6, we found that 44 % of patients had organ failure at the time of admission. Overall just over half the patients developed organ failure during the first week. Patients with organ failure that persisted for more than 48 h, that is, it was present on 3 consecutive days, had a mortality rate of 35 %. This was true both for those with organ failure at the time of admission or organ failure which developed later during the first week (Table 2.2). Patients who had no organ failure during the first week had a very low mortality rate. Since that observation, the association between persistent organ failure during the first week of pancreatitis and at least a 1 in 3 risk of death has been confirmed by others [20–22] (Table 2.3 and Fig. 2.1) and persistent organ failure has been adopted as the primary definition of severe acute pancreatitis in the recent revision of the Atlanta classification of acute pancreatitis [4].

Table 2.2 Relationship between presence and persistence of organ failure during the first week of acute pancreatitis and death [19]

	Survived	Died	Total
No organ failure	113	3	116
Of at entry			
Transient	59	1	60
Persistent	56	32	88
New of within 7 days			
Transient	11	0	11
Persistent	11	4	15

Table 2.3 Fatal outcome in patients with persistent organ failure during the first week of acute pancreatitis

Author	Patients	Persistent organ failure (%)	Died after persistent organ failure (%)
Johnson 2004 [19]	290	103 (36)	36 (35)
Mofidi 2006 [20]	759	89 (11)	37 (42)
Singh 2009 [21]	252	13 (5)	9 (69)
Thandassery [22]	114	43 (38)	18 (42)

The observation that persistent organ failure identifies a group of patients at high risk of death has had two consequences. First, it shifted the emphasis from attempts to predict which patients would subsequently be judged to have severe pancreatitis onto the identification of patients with organ failure, and the understanding that when this persisted for more than 48 h the patient already has severe acute pancreatitis. Second, some authors have sought to identify markers already present very early after admission, which identify patients who subsequently have persistent organ failure.

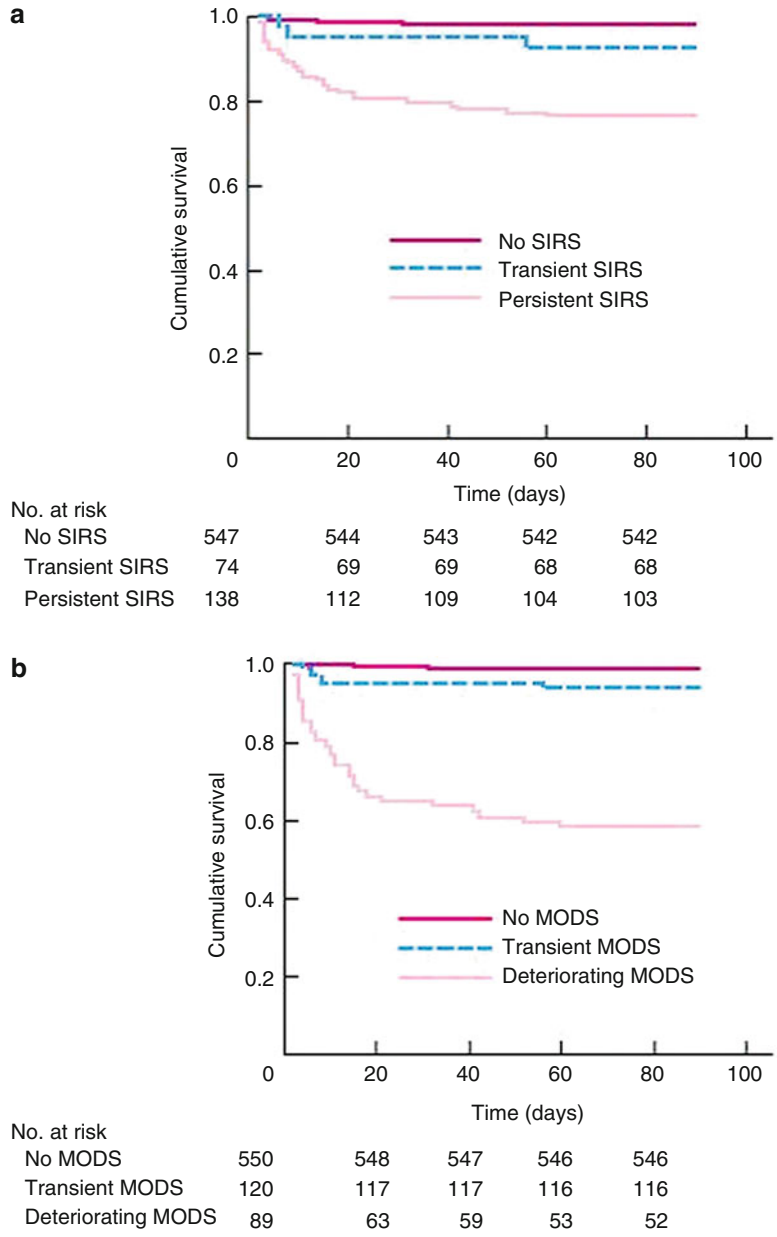

Fig. 2.1 Numbers at risk, and survival in patients with no, transient, or persistent SIRS (**a**) or organ failure (**b**). Reprinted with permission from Mofidi R., Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. Br J Surg 2006; 93(6): 738–744. Copyright 2006 British Journal of Surgery Society Ltd. Published by John Wiley & Sons, Ltd.

Significance of Persistent Organ Failure

Until 2004, early assessment of acute pancreatitis used multiple factor scoring systems during the 48 h after admission to hospital, in an effort to identify patients at high risk of complications and death. These "predicted severe" acute pancreatitis patients were in fact often already in established organ failure, and the delay of up to 48 h required to complete some of the scoring systems meant that by the time they were "predicted" to have severe acute pancreatitis they had in fact already fulfilled the criteria for severe pancreatitis that were adopted in 2012. Persistent organ failure defines severe pancreatitis immediately, often on the third day in hospital, which is a similar time scale to that required for the "prediction" given by the Ranson and Glasgow scores. The presence of organ failure based on routinely available clinical and biochemical findings immediately identifies patients at risk of severe outcome, but if the organ failure resolves within 48 h, severe pancreatitis has been avoided [4, 19]. Thus the emphasis has shifted from *prediction* of severe cases to the *identification* of those at high risk.

Currently it is not known whether treatment intervention during the 48-h window, with the aim of reducing the severity or resolving the organ failure, will have a consequential beneficial effect on mortality rates. Common sense would say that it should, but it may be that some patients recover from early organ failure because of some difference in their physiological response, rather than because of treatment given. Nevertheless, diagnosis of organ failure in any patient should of course prompt appropriate treatment to encourage resolution. At the time of writing, there is no evidence to confirm that supportive treatment can lead to resolution of organ failure and consequently reduced risk of death, mainly because treatments for pancreatitis and for organ failure are entirely supportive and it would be inappropriate to offer anything other than best supportive care. There is no specific agent that can reverse the physiological responses driving organ failure.

The physician dealing with patients with acute pancreatitis who have evidence of organ failure in the early days of the attack, must rely on basic supportive measures. These include provision of adequate inspired oxygen to maintain arterial oxygen tension, and adequate fluid infusion to maintain normovolemia, and hence normal tissue perfusion. It seems logical that this strategy should protect the respiratory, cardiovascular, and renal systems.

Early Warning, Systemic Response, and Organ Failure

The physiological response to acute injury is immediately manifest by change in parameters usually recorded as nursing observations (pulse rate, respiratory rate, blood pressure, temperature). These observations have been used in a variety of early warning scores (EWS) sometimes referred to as modified early warning scores (MEWS) [23–27]. Abnormal scores using these systems identify patients at the earliest phase of the physiological response, and therefore offer an opportunity to begin treatment before more severe irreversible changes have occurred. The value of such scores in acute pancreatitis has been investigated [28–30], and they do appear to provide an early screening tool to identify patients who ultimately develop organ failure. However this screening is relatively nonspecific, as it includes patients with minor abnormalities whose condition settles rapidly, either spontaneously or in response to initial supportive therapy.

More severe disturbance of these basic observations, with the addition of the white blood cell count as an acute marker of inflammation, has been identified in the definition of the systemic inflammatory response syndrome (SIRS) [31] (Table 2.4).

Patients who are progressing towards organ failure will first inevitably demonstrate at least

Table 2.4 Features of the systemic inflammatory response syndrome (SIRS) [31]

Core body temperature	>38 or <36 °C
Heart rate	>90 beats/min
Respiratory rate	>20/min or $PaCO_2$ <32 mmHg
White blood cell count (WBC)	>12,000 or <4,000 cells/mm^3

If SIRS is present for >48 h, the patient is likely to have severe pancreatitis

two features diagnostic of SIRS. However, patients who respond to initial treatment may not progress to organ failure and a SIRS response is less specific than the observed presence of organ failure. Mofidi and colleagues [20] have shown that an early SIRS response is predictive of subsequent organ failure in acute pancreatitis, and that if the SIRS response is present for more than 48 h, this identifies a high-risk group in the same way as persistent organ failure. In their study 25 % of patients with persistent SIRS eventually died, compared with 40 % of patients with persistent organ failure during the first week (see Fig. 2.1). We can conclude that an SIRS response, particularly if it is persistent, or if it fails to respond to initial aggressive supportive therapy, could be a useful marker for patients who will go on to persistent organ failure and who will therefore be at high risk of death.

This has important implications for the planning of therapeutic randomized trials. Most interventions designed to combat the physiological responses leading to organ failure would work better if given earlier, to prevent progression, rather than to reverse established organ failure. Depending on the proposed mechanism of action, and the anticipated effect of a new agent, it is now possible to select patients for study at a variety of time points, which will yield patient groups at different risk of organ failure and death. For example, selecting patients with SIRS, before any treatment, will include a substantial proportion that will respond to simple supportive measures and who have a relatively low mortality rate. Such criteria might be useful to select patients for a trial of an initial resuscitation strategy designed to prevent onset of organ failure. Patients who have SIRS that has persisted despite aggressive therapy represent a more selected group with a high risk of organ failure. This group might be suitable to investigate a specific agent designed to block progression towards organ failure. The percentage of patients developing persistent organ failure in each treatment group would be a suitable primary endpoint, as it is a surrogate marker for potentially fatal pancreatitis. Finally, if the agent being tested is thought to act by promoting a compensatory anti-inflammatory response, or by some other mechanism that can switch off persistent organ failure and thereby reduce the high mortality rate, it might be best to test that agent only in patients with persistent organ failure after 48 h of intensive supportive therapy.

Early Management to Minimize Organ Failure

The commonest organ failure seen in severe acute pancreatitis is respiratory, secondary to accumulation of fluid between the alveolar membrane and the capillaries in the lung. This leads to reduced gas transfer and low arterial oxygen tensions. For this reason, clinical practice is to provide oxygen supplements to patients from the time of admission until it is clear that they have mild resolving pancreatitis without evidence of organ failure. This approach is supported by expert consensus opinion [32].

Fluid Replacement

There is little good evidence to guide the administration of fluid during the first 24–48 h in hospital in patients with pancreatitis, especially those who do not have organ failure. See Chap. 8. It is sensible to ensure adequate volume replacement. Patients with severe pancreatitis may well have a fluid deficit, with loss of fluid from the circulation into the extracellular space leading to hemoconcentration. Baillargeon and colleagues [33] found that an admission hematocrit ≥47 % or failure of admission hematocrit to decrease at 24 h were risk factors for the development of pancreatic necrosis. However, these hematocrit values were not predictive of organ failure. Although the data are somewhat conflicting, others have reported similar data, with a stronger association between hemoconcentration and necrosis, than with organ failure [34–38]. Perhaps the weak association between hemoconcentration and organ failure may be due to variability in the fluid resuscitation provided to different patients.

The difficulty in evaluating descriptive cohort studies is that in the absence of a comparison group, it is impossible to know whether patients with a high volume infusion in the first 48 h have a poor outcome because they are ill and require high volume in fusion, or because the high volume infusion has been harmful. On the one hand, the most sick patients with early hypovolemia will require large volumes of fluid to restore circulatory parameters. Despite the effort to replace fluid into the circulation, these patients remain unwell and have poor outcomes. On the other hand, it may be that patients with less severe pancreatitis who receive large volumes of fluid are actively harmed by the addition of pulmonary edema to the existing tendency for fluid accumulation in the lungs. A small number of studies have tried to address this problem. For example, a study by Kuwabara and colleagues [39] in nearly 9,500 patients showed an association between higher fluid volumes in the first 48 h in hospital and fatal outcome and for the need for respiratory or renal support. The same study, however, showed that when fluid given in the first 48 h was expressed as a ratio to the total fluid given during hospitalization, a high ratio was associated with a reduced mortality. The authors concluded that either too much or too little fluid in the first 48 h can be harmful to the patient.

Warndorf and colleagues [40] in 2011 calculated the fluid volume infused on day one as a percentage of the volume infused over the first 3 days and divided their patients into three groups: those with more than 33 % infused on day 1 were designated early resuscitation and those with less than one-third on day 1 as late resuscitation. SIRS and organ failure were significantly lower in the early resuscitation group compared with the late resuscitation group, during the first 72 h in hospital.

There is evidence that too much fluid may be harmful. Mao and colleagues [41] found significantly worse outcomes in 36 patients with high volume replacement compared with 40 patients with lower volumes. However, the overall volumes infused in these groups were relatively high, and the low-volume group may in fact have been optimally replaced (Table 2.5).

Table 2.5 Outcomes in study by Mao and colleagues [41] comparing higher and lower volumes of fluid resuscitation

	Higher volume ($n=36$)	Lower volume ($n=40$)
Mean time to achieve hemodilution (h)	13.5	24
Mechanical ventilation	34 (94)	26 (65)
Abdominal compartment syndrome	26 (72)	13 (32)
Sepsis within 2 weeks	23 (64)	15 (37)
Death	11 (69)	4 (10)

Planning Fluid Therapy

Although the evidence reviewed above is difficult to interpret, there are some pointers to best practice in planning fluid replacement. There are three questions to answer in comparisons of different fluid therapies. What is the most appropriate fluid to use? What is the ideal rate of infusion and what targets should dictate infusion rate?

Choice of Fluid

Wu and colleagues [42] compared Ringer's lactate with normal saline for crystalloid infusion from the time of admission in 40 patients who received mean volume 4.3–4.5 L in the first 24 h. The group that received Ringer's lactate had significantly more patients (84 %) with reduction in SIRS and a lower mean CRP (51.4 mg/dL) compared with the saline group (0 and 104 mg/dL, respectively), but there was no difference in clinical outcomes. In another study, Du and colleagues [40] gave all patients Ringer's lactate with or without hydroxyethyl starch. There was no difference in clinical outcomes in these two groups.

Zhao and colleagues [40] used crystalloid fluid replacement with normal saline and compared

crystalloid only to a regime with additional hydroxyethyl starch. They found less intra-abdominal hypertension and improved circulatory parameters with the addition of colloid. However, general ITU experience with hydroxyethyl starch is that this fluid can increase mortality and it is not currently recommended for use in pancreatitis. Consensus recommendations at present are that fluid resuscitation early in the course of acute pancreatitis should be with Ringer's lactate [32].

How Much Fluid to Give

Because the evidence from observational studies is difficult to interpret, a causal relationship between high volume replacement and death cannot be assumed. Sufficient fluid should be given to reverse the abnormalities of circulation. In order to determine what is sufficient fluid volume, goal-directed therapy may be used. In this approach, the rate of infusion is determined by the degree of abnormality of circulatory parameters, in an attempt to restore normality as rapidly as possible.

Wang and colleagues [43] in 2013 conducted a randomized trial in patients admitted to ITU within 24 h of onset of symptoms. They allocated patients to receive Ringer's lactate and hydroxyethyl starch according to a volume replacement protocol in the control group ($n=68$), and two treatment groups that had infusion rate determined by early goal-directed therapy (64 patients had the same fluids as controls, 68 patients received control fluids plus fresh frozen plasma). The patients in the early goal-directed therapy groups were monitored and treated aggressively to achieve within 6 h a CVP of 8–10 mmHg, a mean arterial pressure >65 mmHg, urine output >0.5 mL/kg/h, and central venous oxygen saturation >70 %. Early goal-directed therapy was associated with significant reductions in number of days ventilated, number of days in ITU, and with lower numbers of patients with organ failure or fatal outcome (Table 2.6).

Table 2.6 Outcomes in a randomized trial [41] of early goal-directed therapy (EGDT) in patients who received Ringer's lactate and hydroxyethyl starch

	Control	EGDT 1	EGDT 2
Ventilated (days)	13	12.3	10.3
ITU (days)	20.6	18.6	15.4
ACS	18 (26)	14 (22)	12 (18)
MODS	20 (29)	18 (26)	16 (23)
Death	16 (23)	14 (22)	12 (18)

The critical factor to consider in circulatory resuscitation is probably to achieve adequate tissue perfusion. The circulatory parameters used to direct therapy in the above study are reasonable markers for good tissue perfusion, but this can be measured directly. Several studies have shown intestinal ischemia to be associated with poor outcome in severe acute pancreatitis. In the research setting, intestinal ischemia can be reliably identified by measurement of intestinal fatty acid-binding protein (IFABP). We have preliminary data that support a link between inadequate fluid replacement, severe pancreatitis, and higher levels of IFABP [44], and we conclude from those studies that adequate early fluid resuscitation is important. This must be carefully controlled because it is also necessary to avoid over infusion of fluid.

Ischemia of the gastrointestinal mucosa can be measured directly using gastric tonometry [45, 46]. There is little evidence to support its use in acute pancreatitis but this area deserves further investigation. Intestinal ischemia probably permits absorption of endotoxin, which contributes to excessive stimulation of the immune response, leading to SIRS and organ failure. If the intestinal mucosa can be restored to normal function by provision of adequate fluid and restoration of the circulation, then this has the potential to interrupt the cycle of progression towards organ failure. Gastric tonometry may therefore be a useful functional marker to guide the rate of fluid resuscitation.

Pain Relief

Pain relief is often neglected in discussions of the treatment of acute pancreatitis. Failure to relieve pain will have harmful effects in addition to the suffering of the patient, because abdominal pain

causes restriction of thoracic and diaphragmatic movement, with consequent impaired ventilation. This may hamper attempts to restore normal tissue oxygenation. The initial management of any patient with pancreatitis should include adequate analgesia.

With severe pain, opioid analgesia may be required. It is well established that morphine can cause increased pressure in the sphincter of Oddi. This has the theoretical risk of exacerbating the pancreatitis [47]. Many clinicians therefore choose synthetic opioids which have not been shown to stimulate contraction of the sphincter; pethidine causes less contraction, and may be safer [48]. One randomized pilot study showed better pain relief with the nonsteroidal anti-inflammatory drug, metamizole, than with regular subcuticular injection of morphine [49]. In practice at most hospitals in the United States, hydromorhpine is used, often in a patient-controlled anesthesia (PCA) approach. Ensuring adequate pain relief is the paramount concern, and it is advisable to consider the best route to deliver reliable plasma levels of analgesic agents. In patients who are nauseated or vomiting, or who have circulatory collapse, controlled intravenous infusion may be appropriate. Care should be taken to avoid respiratory depression, which could negate the benefit of good analgesia on respiratory function.

Computed Tomography and Renal Function

Current guidelines recommend avoiding early CT unless there is a positive indication. It is certainly not necessary to perform CT in all cases of pancreatitis. Indeed even in severe cases, most patients do not require CT during the first week [32]. CT may be required if there is an atypical presentation (raised amylase without pain) or delay in presentation (abdominal pain but amylase levels returning to normal). In addition, in a patient with an acute abdomen in whom there is diagnostic doubt, or when other abdominal catastrophes must be excluded, CT may be helpful. However, the intravenous contrast that may be used during CT can impair renal function, and indiscriminate use of CT increases the rate of renal failure and may prolong mean hospital stay [50]. For this reason, CT should be used with caution during the first week of admission and only for properly justified indications.

Specific Therapies

Pro-inflammatory Pathways

The pro-inflammatory pathways involved in the pathogenesis of SIRS, and its progression to organ failure, are complex. Some of the early signaling is mediated by interleukin 8 (IL-8), IL-1β, and IL-6 and the anti-inflammatory cytokines IL-2 and IL-10 [51]. These cytokine levels increase before rises in other markers of inflammation such as CRP. Platelet-activating factor (PAF) is well known as a mediator of the inflammatory response, leading to activation of platelets and neutrophils, and increasing endothelial permeability [17]. See Chap. 11.

Complement activation is involved in a variety of inflammatory diseases such as sepsis, and burns, which like acute pancreatitis have a vascular/capillary leak component. In these conditions activation of the complement and contact inflammatory cascades causes vascular leakage, tissue edema formation, and leads to hemoconcentration and hypovolemia. The activation of kallikrein plays a significant role in SIRS, and in severe cases, organ failure. Kallikrein is physiologically inactivated by complex formation with C1 inhibitor (C1INH) [52], which also inhibits activation of the complement and contact cascades at several points.

Anti-inflammatory Treatments

Development of specific treatments has been hampered by a lack of effective agents for clinical trials. To date there have been no clinical studies of blockade or antagonists of the interleukins known to be involved in SIRS in acute

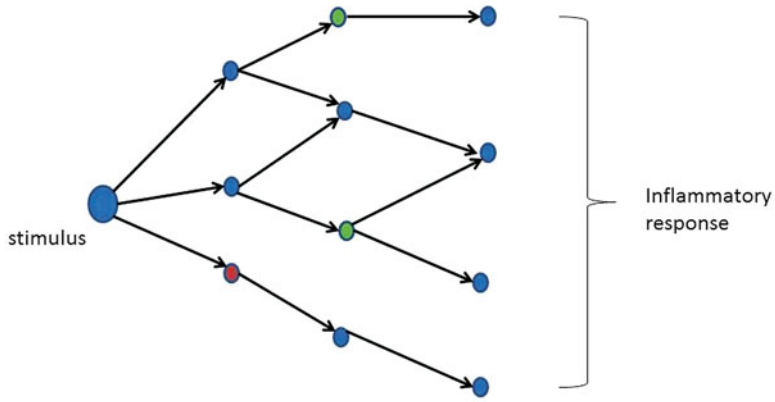

Fig. 2.2 Schematic representation of complex pathways in inflammation. The inflammatory stimulus (*blue*) activates a number of pathways. Blockade of one pathway (*red*) will have minimal effect. An agent with multiple sites of action (*green*) may be more effective. Combination of both agents will produce maximal effect

pancreatitis. This is true not only in pancreatitis but in the sepsis field in general.

Even when inhibitors of inflammatory mediators have been identified, it has proven difficult to demonstrate effectiveness in clinical trials. The most promising agent last evaluated in acute pancreatitis was the PAF antagonist, Lexipafant. This showed well in phase II studies, but a phase III study in the United Kingdom [17] failed to demonstrate effectiveness in patients recruited within 72 h of onset of symptoms. That trial showed some encouraging data with reduction in IL-8 levels in patients receiving active treatment and a reduction in mortality in a post hoc analysis of patients treated within 48 h of symptoms. However, for a variety of reasons a large multinational study of this agent failed to reach a conclusion, and further investigation has been abandoned.

It seems likely that in the complex physiological disturbances of severe acute pancreatitis, it will prove difficult to demonstrate effectiveness of single agent anti-inflammatory treatment. The multiple pathways involved in the inflammatory response suggest that blocking a single pathway may not be enough to prevent stimulation of the response via alternate routes (Fig. 2.2). This leads to the conclusion that combined therapies may be required, although such research is difficult to set up because of the many conflicting scientific and commercial interests that have to be reconciled.

However, as noted above, complement activation occurs in the SIRS response, and the inhibitor C1INH can block multiple sites in these complex pro-inflammatory pathways. The use of C1INH in other inflammatory conditions has been encouraging, without significant adverse effects [53], but there is only sparse uncontrolled evidence that this agent might affect the course of severe acute pancreatitis. In a pig model of experimental pancreatitis, C1INH improved hemodynamics and increased survival in treated animals compared to untreated controls [54–56]. Four clinical case reports describe resolution of severe acute pancreatitis within a few hours of treatment with C1INH [57–59].

In the only randomized evidence available, consecutive patients undergoing endoscopic sphincterotomy for common bile duct stones or benign papillary stenosis were randomly allocated to receive either C1INH (20 cases) or placebo (20 cases) 30 min before the procedure. The C1INH group had significantly lower serum amylase levels during the first 8 h after sphincterotomy [60]. A phase II study is now in progress to investigate the possibility that C1INH could ameliorate the inflammatory response and prevent progression from SIRS to organ failure in patients with pancreatitis who fail to respond to initial treatment.

Conclusion

The identification of organ failure is now central to the definition of severe acute pancreatitis. We know that some patients with organ failure improve rapidly in response to initial treatment, and these patients have a low mortality rate. Transient organ failure is a marker of moderately severe disease. If organ failure persists for more than 48 h, the patient has severe pancreatitis, and is at high risk (at least 35 %) of a fatal outcome.

Organ failure is preceded by a period of illness with a marked inflammatory response. If the criteria for SIRS are present, the patient is at risk of progression to organ failure, and every attempt should be made to restore normality as soon as possible. Unfortunately, there are no specific anti-inflammatory treatments currently available, and management relies entirely on supportive measures.

Development of effective treatments for SIRS and early organ failure will require targeting of multiple pathways, either with a versatile agent which can block multiple receptors, or by combinations of agents active at different sites.

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