

Pain Management in Acute Pancreatitis

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Abstract

Severe abdominal pain is a hallmark of acute pancreatitis (AP). AP-associated pain is often described by patients as a deep and penetrating type of pain with acute onset and without any prodrome. Typically, AP patients locate the maximum of pain in the upper abdomen that radiates like a belt around the trunk into their back. Pain reaches its maximum severity within hours after its onset and can last from hours up to days or even months (6, 25, 60, 74, 85). Therefore, it is not surprising that the presence of persistent epigastric pain dictates the diagnostic workup of patients suffering from AP in the clinical routine (6, 25, 29, 46, 85). Interestingly, beside its diagnostic aid (6), recent studies suggest pain as a prognostic tool to predict the severity of AP and the patients' outcome (40, 60). Nevertheless, an adequate pain therapy after patients' admission to hospital is often a challenging task, which requires interdisciplinary management. In clinical practice, the treatment of pain ranges and escalates from low-dose non-opioid analgesics to high-dose opioid analgesics and even to interventional and surgical approaches.

1. Introduction

Inflammation of the pancreatic tissue can be divided into chronic and acute inflammation depending on the degree of resolution of the tissue inflammation. Over 80% of all cases of AP

are due to gallstones or the alcohol abuse (32, 38, 50).

Severe abdominal pain is the hallmark symptom of patients suffering from AP as well as of chronic pancreatitis (61, 74, 85). In AP, the most common localization of acute pain is the epigastric region (12, 61, 74, 85). Due to the retroperitoneal localization of the pancreas, it is not unusual that patients describe AP-associated pain as deep and penetrating. Pain in AP is often associated with nausea and vomiting. Physical examination yields a pronounced tenderness of the upper abdomen with guarding, which can occur in combination with other unspecific symptoms like fever or tachycardia. Maximum pain is typically localized in the upper epigastric region and radiates like a belt around the trunk into the back (6, 12, 25). The detection of pain is a well-accepted diagnostic tool in AP. According to the modified Atlanta consensus guidelines (6, 12), AP can be diagnosed if at least two of the following criteria are fulfilled:

1. The occurrence of abdominal pain that is characterized by an acute onset and radiates to the back
2. Serum pancreatic enzymes (lipase or amylase) elevated at least threefold over the normal serum enzyme level
3. Characteristic findings of AP in imaging (contrast-enhanced-CT, MR-Imaging, transabdominal ultrasound)

2. Role of Pain in Diagnosis and Prognosis of Patients with AP

Pain is increasingly recognized as a diagnostic and prognostic factor in AP (1, 2, 6, 40, 60). Interestingly, beside its role in the diagnosis of AP, more recent studies described the interval between onset of pain and hospitalization of the patient as an adequate prognostic factor for estimation of the severity of AP (40, 60, 61). In a study by Phillip et al., patients with severe pain had shorter median pain-to-admission time when compared to patients with only moderate pain (40, 60, 61). Interestingly, the severity of pain also correlated with the severity of AP in these two cohorts, and together with serum lipase and C-reactive protein levels, pain was identified as a predictor of AP (61). The severity may also allow conclusions on the cause of AP (15, 85). Here, a genuinely severe abdominal pain preferentially

occurs in biliary AP, whereas alcoholic AP and especially autoimmune pancreatitis are predominantly accompanied by milder abdominal pain (24, 42, 44).

3. Main Arms of Pain Management in AP

The successful treatment of patients with AP has three prerequisites: 1) an adequate and early fluid resuscitation (8, 30, 31, 50), 2) proper nutritional support (48, 50, 86), and 3) an adequate pain management (5, 45, 50). An effective treatment of pain in AP ranges from the administration of simple analgesic drugs, which might be sufficient for patients with mild AP, up to the administration of potent opioid drugs, high doses of antibiotics for infected pancreatic necrosis and even to surgical or interventional procedures in cases of severe AP (1, 7, 9, 25, 27, 41, 46, 50, 51, 74, 85).

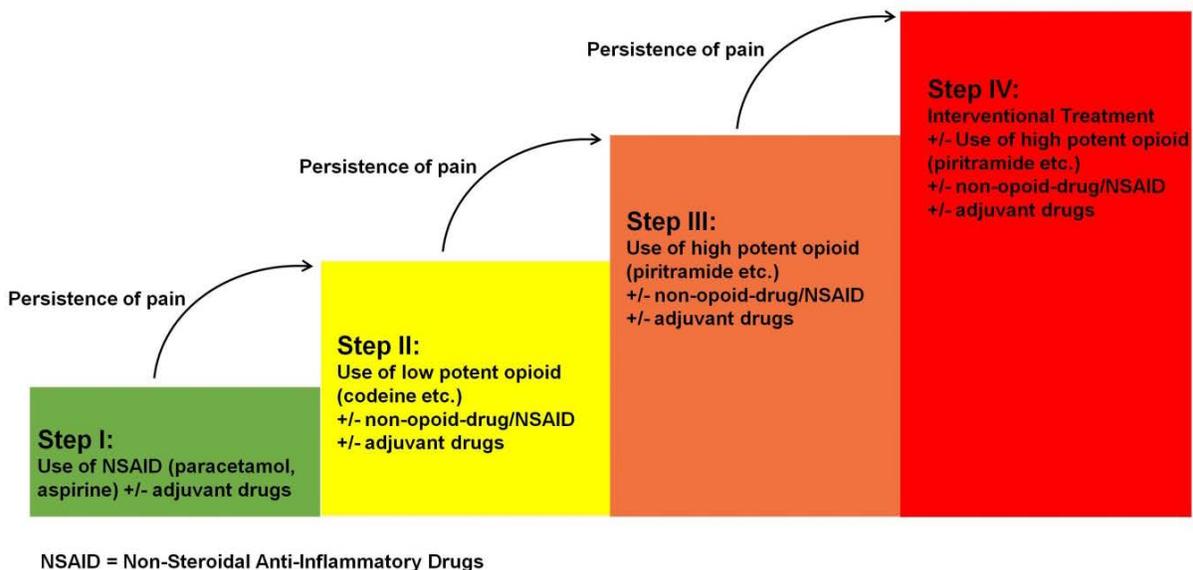


Figure 1. The modified World Health Organization (WHO) analgesia ladder after Vargas-Schaffer (84). The WHO analgesia ladder was originally developed to treat pain due to cancer. However, over time, the indications have been extended, and the medical management of pain in acute pancreatitis can similarly be grounded on a modified version of the WHO ladder. Here, persistence of pain after implementation of a measure of low potency warrants escalation of analgesia to a more potent substance, which, if there is ongoing need, can be adjuvantly combined with any measure/agent from the lower step. This modified ladder includes interventional procedures that can be indicated once medical measures have failed to provide adequate analgesia.

However, the whole spectrum of medical, interventional and surgical possibilities raises the question on how to treat AP instead of over-treating. Treatment of pain may seem to be a simple task in the clinical routine. Beside the World Health Organization (WHO) analgesic ladder (**Figure 1**), which includes the use of non-steroidal-anti-inflammatory drugs (NSAID) or their combination with highly potent opioid-analgesics in an escalating regime (1, 9, 25, 51, 56, 84), the management of abdominal pain also includes interventional strategies depending on the occurrence of AP-related complications (15, 16, 27, 29, 35, 38, 46, 64, 76, 80, 85). In fact, the adequate treatment of pain is much more complex and often needs interdisciplinary action. One reason for the challenge behind pain management is the high complexity of AP itself. Whereas mild to moderate epigastric pain is often the single symptom of edematous pancreatitis, patients with necrotizing acute pancreatitis often suffer from severe pain attacks, pleural effusion, ascites and even multiple organ failure. Importantly, whereas mild AP is rarely lethal (69), the lethality of AP reaches up to at least 30% in patients with acute, necrotizing pancreatitis and persistent multiple organ failure (13, 37, 53). Here, as discussed later in this chapter, more novel analgesic interventions like thoracic spinal analgesia receive more attention in the treatment of pain in patients with AP (3, 33).

4. Role of Medical Treatment in Pain Management during AP

In 1986, the WHO presented the analgesia ladder as a framework to treat severe pain (56). This ladder was originally developed to treat pain due to cancer (56). Later, the analgesic pain regime of the WHO was also assumed to treat pain due to causes other than cancer (25, 84). According to the WHO regime, the pain treatment begins with low potent non-steroidal anti-inflammatory medication, which may be sufficient in mild or moderate pain due to AP (5, 8, 47, 50), and rises step by step up to highly potent NSAIDs alone or

in combination with opioids (56, 84). In the past, the WHO analgesic ladder was only partially useful for the treatment of AP patients because opioid analgesics, especially morphine, were long blamed to cause dysfunction of the sphincter of Oddi after systemic administration (34). However, several studies showed that morphine has no proven significantly unfavorable influence on the course of AP (57). In a comparative study on metamizole (2g/8h i.v.) versus morphine (10mg/4h subcutaneously/s.c.), metamizole resulted in somewhat more frequent and quicker pain relief than s.c. morphine (57). Earlier studies postulated pethidine as the analgesic of choice in pain due to AP (11). However, Blamey et al. could show that buprenorphine as a longer-acting analgesic has a similar analgesic capacity as pethidine, but a lower potential to cause physical opioid dependence (11).

Indeed, the latest studies including systematic reviews convincingly demonstrated that opioid analgesics could be safely administered with major benefit in AP, and that the dogma of “no opioids in AP” should be considered to be obsolete. To this end, Jakobs et al. administered 40 patients with acute or acute on chronic pancreatitis either buprenorphine or procaine as a continuous intravenous (i.v.) infusion and additional analgesics on demand (36). Here, patients who received buprenorphine had significantly less demand after additional analgesics and had lower visual analogue scale (VAS) pain scores than procaine-receiving patients, especially during the initial two days of treatment (36). In another open, randomized, controlled trial including 107 AP patients, subjects were randomized to receive either procaine (2g/24hours as continuous i.v. infusion) or pentazocine (bolus i.v. every 6 hours) (39). Here, patients being treated with procaine were more likely to demand additional analgesics when compared to patients receiving pentazocine alone (98% versus 44%) (39). Furthermore, the pain scores were much higher in the pentazocine group during the first 3 days of analgesic

treatment (39). These studies therefore provided evidence for the lack of effectiveness of procaine in AP-associated pain (47).

Overall, there seems currently to be no difference in the risk of pancreatitis-associated complications or clinically serious adverse events between opioids and other analgesic agents (9, 36, 73, 77). Particularly, opioid analgesics may be considered an appropriate choice in the treatment of AP-associated pain, and importantly, they may decrease the need for supplementary analgesia (9).

5. Role of Nutrition in Pain Management during AP

One interesting feature of AP-associated pain is potential pain exacerbation after ingestion of food or fluids (15, 46). This food-dependent progression of abdominal pain raises the question as to how far the adequate nutrition therapy also contributes to pain management. In contrast to the long-believed old paradigm on the benefits of total parenteral nutrition in AP, Sax et al. could clearly show that an early, total parenteral feeding of patients with AP does not provide any benefit with regard to the number of days to oral intake, total hospital stay, or number of AP-associated complications (66). Current literature supports the notion that the right management of nutrition is strongly dependent on the severity of AP. Importantly in patients with mild to moderate AP, nasogastric feeding seems to be well tolerated and might reduce the intensity and the duration of abdominal pain, the need of pain medication and the risk of oral food intolerance (58). However, up to now there is no evidence that it might also reduce the length of hospital stay in these patients (58, 75).

An interesting question on the interaction of pain with nutrition in AP is related to pain relapse after oral refeeding during AP. In different studies, the

incidence of pain onset or exacerbation after refeeding ranged between 21-25% and reached a maximum between 50-100% of cases within 48 h of refeeding (59). Therefore, the incidence of pain relapse after oral refeeding during AP seems to be quite high (59). Current evidence suggests that nutrition support should only be performed in patients with severe pancreatitis, whereas nutrition support is generally not needed in patients with mild or moderate disease where oral feeding should be started as soon as possible and as tolerated by patients. If nutrition support is needed in these patients, enteral nutrition should be preferred over parenteral nutrition (52). However, a clear consensus on how and when the oral refeeding should be initiated has not yet been reached. In this context, Teich et al. reported in their prospective, randomized study that patients who could decide themselves to start oral refeeding were able to start oral refeeding one day earlier compared to patients who received oral nutrition based on the serum lipase (75). Interestingly, in the self-selected eating group, oral feeding had no impact on postprandial pain and hospital stay when compared to lipase-directed decision to oral refeeding.

6. Role of Endoscopic Retrograde Cholangio-pancreatography (ERCP) in Pain due to AP

Gallstones are the most common cause of AP in Western and Asian countries with an incidence reaching up to at least 40% of all AP cases (15, 20, 72). An important question is how far the removal of pancreatitis-associated gallstones by ERCP also affects pain sensation and even more, the morbidity and mortality of AP patients. It is conceivable that ERCP contributes to adequate pain management in AP due to removal of the etiological agent. The role of ERCP in pain management for AP patients is barely described in current medical literature.

Table 1

Indications of ERCP with endoscopic papillotomy and stenting in AP	
Clear indications of ERCP in AP (must-do)	<ul style="list-style-type: none"> • Bile duct stones in patients with severe pancreatitis • Cholangitis • Poor candidates for cholecystectomy • Postcholecystectomy • Strong evidence of persistent biliary obstruction
Intermediate indication of ERCP in AP (can-do)	<ul style="list-style-type: none"> • High suspicion of bile duct stones and indication of therapy
Contraindication of ERCP in AP	<ul style="list-style-type: none"> • Low to intermediate suspicion of retained bile duct stones, • Cholecystectomy planned
Based on Banks, Freeman et al (8).	

In 2009, Chen et al. demonstrated that patients undergoing ERCP because of AP may still benefit from concerning pain management (18). Still, because of its potential complications, there is a clear consensus on the indication of ERCP in patients with AP. The single indication for primary therapy via ERCP in AP is suspected remaining pancreatic or bile duct obstructions or existing cholangitis (8, 15, 50, 54, 76, 79). Furthermore, ERCP should only be used for clearance of proven bile duct stones especially in patients who suffer from severe AP, with clear evidence of cholangitis, in those who are poor candidates for cholecystectomy, in those who are post-cholecystectomy, and in those with strong evidence of persistent biliary obstructions (**Table 1**). In contrast, ERCP should be avoided in patients with low or intermediate suspicion of retracted bile duct stones (8, 15, 50, 54, 76, 79). A large meta-analysis by Tse et al. clearly demonstrated that early ERCP has no clear benefit for patients with AP compared to an early conservative medical treatment (79).

In conclusion, in the analgesic regime of AP, other non- or less invasive procedures than ERCP should be preferred to treat pain in AP. Because

of its morbidity and mortality, ERCP should be avoided as a single analgesic procedure and should only be performed if there is strong evidence for remaining bile duct stones or co-existing cholangitis.

7. Role of Minimally-Invasive Necrosectomy and Decompressive Laparotomy in Pain due to AP

The management of necrotizing acute pancreatitis has witnessed considerable progress in recent years. Traditionally, infected pancreatic necrosis as a result of AP was considered an indication for open surgical necrosectomy. However, in recent years, an increasing number of minimally invasive approaches have emerged that could effectively limit local and systemic damage and thereby, without the need for open invasive surgery, effectively contribute to prognostic improvement that is comparable to open necrosectomy. These approaches, including repetitive percutaneous drainage via large-caliber catheters (21), endoscopic transluminal necrosectomy (68), retroperitoneal approach with percutaneous insertion of endoscopic material (19), and especially a “step-up approach” (82) have been convincingly shown to decrease the complication

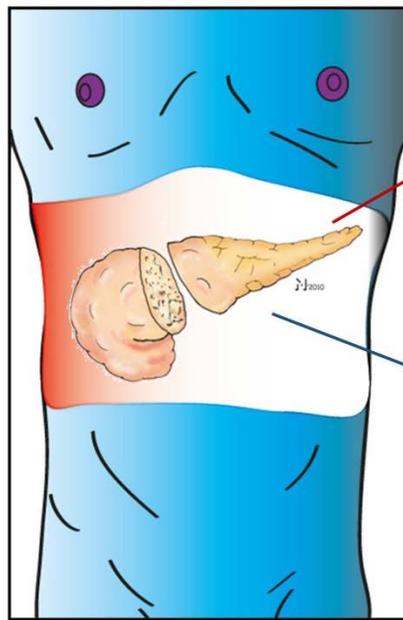
rate associated with necrotic AP. Yet, the long-term outcomes of these minimally invasive approaches have not yet been sufficiently investigated. In the GEPARD trial that studied the long-term outcome of AP patients with endoscopic necrosectomy, 81% of the patients could be freed from pancreatic necrosis and associated complications during the first hospital stay (68). From the long-term survivors, 16% suffered from secondary clinical recurrence of necrosis or emergence of pseudocysts. Importantly, all of these 11 patients with recurrence were dependent on regular intake of analgesic medication, whereas in 6 out of 11 cases, the intake of analgesics was only occasional (68). In a study that recently described the long-term outcomes of combined percutaneous and endoscopic approaches for symptomatic and infected walled-off necrosis, Ross et al. reported that only 2 out of 117 patients required late surgery for persistent pain (65). However, this study did not report on the severity and frequency of pain and on the analgesic intake of patients who did not require surgery for pain (65). Overall, these observations imply that the treatment of pain in necrotic AP via interventional techniques is also dependent on the overall success of the intervention to resolve AP-associated complications such as necrosis. On the other hand, persistent pain despite these minimally invasive approaches seems to guide the decision toward surgical intervention (62). Patients who have persistent necrotic collections or pseudocysts seem to be prone developing chronic abdominal pain, yet the long-term results of all these interventional approaches are lacking. Moreover, the impact of these promising procedures on pain sensation does not seem to be systematically recorded or reported (4).

An approach that was put forward to deal with AP-associated abdominal hypertension is decompressive laparotomy (81). Abdominal hypertension is assumed to result from a combination of pancreatic and visceral edema,

acute peripancreatic fluid collections, capillary leakage, ascites and paralytic ileus, and is encountered around 27-38% of severe AP cases (81). Abdominal hypertension is defined by the World Society of Abdominal Compartment Syndrome (WSACS) as a “life-threatening sustained elevation of the intraabdominal pressure (IAP) that is associated with new onset organ failure or acute worsening of existing organ failure” (43). Thus, elevated IAP is frequently associated with kidney dysfunction and increased peak airway pressure. However, the question whether elevated IAP is a direct cause of multi-organ failure or rather a consequence of organ dysfunction has not yet been answered (78). Furthermore, when and how to escalate percutaneous drainage to an aggressive decompressive laparotomy is also yet unclear (81). The DECOMPRESS trial as a multicenter study will compare percutaneous catheter drainage with decompressive laparotomy in patients with elevated IAP during severe AP (63). Until the results of this study are available, it should be considered that decompressive laparotomy represents a major invasive intervention with to date no convincingly proven benefit for treating elevated IAP (22, 78, 81). Accordingly, how the outcomes of these patients who undergo this aggressive surgical intervention with regard to long-term persistence of pain should be addressed in future studies.

8. Novel Strategies of Pain Management in AP

Beside the above indicated common methods of pain management in AP, clinical researchers are trying to devise novel analgesic techniques that interfere in the interaction of the nervous system with the pancreatitis (**Figure 2**). In an interdisciplinary setting, such interventions have been recently shown to be beneficial not only for pain, but also for the overall course of the disease.



Pain management strategies in acute pancreatitis:

Clinical:

- Medical (NSAIDs, opioids)
- Nutrition
- ERCP
- Epidural analgesia
- Necrosectomy?

Experimental:

- PAR2 inhibitors
- TRPV1 inhibitors
- IL-6 receptor antagonists
- Glycine
- Nitric oxide synthase (NOS) inhibitors
- Magnesium

Figure 2. Management of pain in acute pancreatitis (AP). Analgesic measures to treat AP-associated pain can be classified into clinical methods that are in widespread use in daily clinical practice. The experimental measures have been shown to be effective in numerous studies with murine or porcine AP models, yet have not been translated into clinical practice.

To this end, Bachmann et al. recently reported improved survival owing to thoracic epidural analgesia (TEA) in a porcine AP model that is based on the infusion of glycodesoxycholic acid into the pancreatic duct (3). Here, the 7-day-survival rate of animals that received bupivacaine as TEA was 82% when compared to a mere 29% in the control group. This difference was largely attributable to the improved microcirculation, tissue oxygenation and consequently preserved microscopic tissue architecture in the group of pigs that were treated with TEA, with similar results previously reported for murine AP (23, 28). In a study on 121 patients admitted to intensive care unit with AP, Bernhardt et al. reported excellent analgesia on 72% of observation days during which no systemic use of other analgesics was necessary (10). The rate of hemodynamic instability (8%) was also low. The time to normalization of serum amylase and lipase was 17.4 days (minimum one day, maximum 19 days), and the overall lethality was 2.5%. In this prospective single cohort study, epidural analgesia was thus able to produce considerable

analgesic effect without any major rate of complications (10). Therefore, based on these promising observations, the results of the three clinical trials that are currently investigating the effect epidural analgesia on the course of AP are eagerly awaited (70).

Looking at the potential benefits of analgesia, and especially epidural analgesia with its peripheral neurolytic effects, on the course of AP, it is essential to remember the contribution of “neurogenic inflammation” in the pathogenesis of AP. In this context, different noxious substances released from damaged acini, i.e. zymogens, trypsin, proteases, ions such as hydrogen or potassium can activate peripheral nociceptive sensory nerve endings. These activated sensory neurons not only signal centrally toward the spinal cord, but can also cross-activate other neurons in the neighbouring spinal cord regions that then signal into the periphery in an antidromic fashion. This antidromic reflex results in the release of substance P and calcitonin-gene-related-peptide from the peripheral nociceptive nerve endings.

These neuropeptides have the intriguing ability to chemoattract immune cells, cause vasodilatation and thereby augment local inflammation. In AP, neurogenic inflammation is recognized as a central pathophysiological event (49). Based on this premise, it is not surprising to see an analgesic and also overall beneficial effect of epidural anesthesia on the course of AP. In accordance with this strategy, inhibitors of the proteinase-activated-receptor-2 (PAR2), or of the transient receptor potential vanilloid-1 (TRPV1) have been shown to be beneficial for treating pain during experimental AP in mice (55). During experimental AP in rats, intrathecal administration of gabapentin was reported to enhance the analgesic effects of subtherapeutic doses of morphine (71). Other targets on neuronal cells to treat both the inflammation in AP and AP-associated pain are nitric oxide (NO) signaling and glycine. Treatment of rats with nitric oxide synthase (NOS) inhibitors (14) or glycine (17) reduced abdominal hyperalgesia and AP-associated histological alterations during AP in rats. Recently, blockade of interleukin-6 (IL-6)

signaling by an orally available, small-molecule IL-6 receptor inhibitor was shown to diminish abdominal hyperalgesia during AP (83). However, all these promising neuronal targets have not yet been studied in early phase clinical trials. In the clinical setting, based on its promising effects during experimental AP in rats, a promising and inexpensive agent that may be used as a novel analgesic agent is magnesium (67). The MagPEP study as a multicentre randomized controlled trial of magnesium sulphate in the prevention of post-ERCP pancreatitis shall provide data on the impact of magnesium on pain sensation during post-ERCP pancreatitis (26). Once shown to be effective, beyond its preventive usage, magnesium may be considered a novel analgesic alternative to treat pain in AP (26). Overall, the interaction of the nervous system with pancreatic inflammation may offer numerous clues for more effective treatment of both the disease itself and the associated pain. Therefore, efforts toward translating this axis into the clinical practice need to become more visible in the near future.

Table 2

Different Facets of Pain management in patients with AP	
Analgesic drugs	<ul style="list-style-type: none"> • According to the WHO analgesic ladder • No evidence of higher mortality or morbidity due to opioids • Administration of procain has no benefit for patients with AP
Supplement of nutrition	<ul style="list-style-type: none"> • Oral refeeding should be begun as fast as possible • No evidence that normalization of serum pancreatic enzymes was needed • No benefit for parenteral nutrition supplement in patients with mild or moderate pancreatitis
ERCP	<ul style="list-style-type: none"> • Only indicated if there is clear evidence of persistent biliary obstruction
Thoracic Epidural Analgesia	<ul style="list-style-type: none"> • Only few data available • Yet evidence of rapid pain relief and of reduction of the need for opiates

9. Conclusion

Abdominal pain is the earliest and a leading symptom of patients with AP. There is solid evidence that the severity of pain may also predict the clinical course of AP. Treatment of pain during AP continues to be a challenging task in the clinical routine and involves a combination of medical treatment according to the WHO analgesic ladder, adequate nutritional support and, in some cases, interventional therapy via e.g. ERCP (**Table 2**). Novel studies also suggest that the severe abdominal pain in AP could also be effectively treated by thoracic epidural anesthesia owing to the improvement of pancreatic

microcirculation and preservation of tissue architecture. Disruption of neurogenic inflammation in AP holds great promise as a novel analgesic and therapeutic strategy for AP, which yet needs to be tested in clinical early phase trials. Development of inhibitors directed against selected targets on pancreatic afferents is likely to open new paths toward more effective management of pain as an interdisciplinary challenge.

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