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EDITORIAL

Infected pancreatic necrosis: Not necessarily a late event in acute pancreatitis

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Abstract

It is widely believed that infection of pancreatic necrosis is a late event in the natural course of acute pancreatitis. This paper discusses the available data on the timing of pancreatic infection. It appears that infected pancreatic necrosis occurs early in almost a quarter of patients. This has practical implications for the type, timing and duration of preventive strategies used in these patients. There are also implications for the classification of severity in patients with acute pancreatitis. Given that the main determinants of severity are both local and systemic complications and that they can occur both early and late in the course of acute pancreatitis, the classification of severity should be based on their presence or absence rather than on when they occur. To do otherwise, and in particular overlook early infected pancreatic necrosis, may lead to a misclassification error and fallacies of clinical studies in patients with acute pancreatitis.

Key words: Acute pancreatitis; Classification; Enteral nutrition; Infected pancreatic necrosis; Pancreatic infection

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INTRODUCTION

Mortality in patients with acute pancreatitis is determined by both local and systemic factors[1,2]. The local factor is infection of pancreatic and peripancreatic necrosis/collections. The systemic factor is organ dysfunction, especially when it persists and/or when multiple organ systems are involved. The timing of these local and systemic factors is thought to be important, and thus acute pancreatitis is generally regarded as having an early and late phase[3,4]. Infected pancreatic necrosis (IPN) is considered the cardinal feature of the late phase[5-7]. This view is, however, challenged by a body of evidence that demonstrates that IPN also occurs early in some patients with acute pancreatitis. The present editorial will examine the time course of IPN and consider the clinical implications of the timing of pancreatic infection.

EARLIER SURGICAL STUDIES

The incidence and significance of early IPN can be reliably examined as there are published series that include operations performed during the first and second week. In 1986, Beger and colleagues published a seminal prospective clinical study from Germany that evaluated the bacteriological status of pancreatic necrosis in relation to the timing of surgery for acute pancreatitis[8]. Overall, 39% (45/114) of the consecutive series of patients had a

Table 1 Timing of pancreatic infection in the referred clinical studies *n* (%)

Study ID	Setting	No. of patients with confirmed IPN	Duration of disease at the time of diagnosing IPN		
			Day 1-7	Day 8-14	Day 15 +
Beger *et al*[8], 1986	Germany	45	5 (11)	8 (18)	32 (71)
Rattner *et al*[9], 1992	USA	44	2 (5)	10 (23)	32 (72)
Gerzof *et al*[10], 1987	USA	36	8 (22)	12 (33)	16 (45)
Tsui *et al*[16], 2009	China	65	1 (2)	15 (23)	49 (75)
Besselink *et al*[17], 2009	Netherlands	98	5 (5)	13 (13)	80 (82)
Overall		288	21 (7)	58 (20)	209 (73)

IPN: Infected pancreatic necrosis.

positive bacteriological culture of the debrided necrosis. Although pancreatic infection was most often detected after the second week, it is pertinent to note that 11% and 29% of the patients developed IPN within the first 7 and 14 d after onset of acute pancreatitis, respectively (Table 1). Another study, from the Warshaw group, looked back at 44 patients with proven IPN and demonstrated a similar incidence of early IPN with 5% and 28% within the first 7 and 14 d, respectively[9].

FNA STUDIES

Further evidence regarding the timing of development of IPN comes from studies that evaluated the utility of fine-needle aspiration (FNA) for the diagnosis of pancreatic infection. The first rigorous study was reported in 1987 by Gerzof and colleagues who performed computed tomography (CT)-guided percutaneous FNA and Gram staining in 60 patients with suspected pancreatic infection[10]. Overall, 60% (36/60) had pancreatic infection confirmed, with 22% (8/36) within 7 d of the onset of acute pancreatitis and 56% (20/36) within 14 d (Table 1). Similarly, in a study from Germany (1988-1996) on the utility of ultrasound-guided FNA in 98 patients with CT-proven pancreatic necrosis, it was shown that the overall incidence of IPN was 34%. During the first week, 21% (7/33) of patients had a positive FNA, and this was confirmed by bacteriological culture of the debrided necrosis[11].

BIOMARKER STUDIES

Another potential source of evidence regarding the timing of IPN in acute pancreatitis comes from studies that evaluated different serological markers of infection, for instance procalcitonin[12,13]. These studies used FNA as the gold standard to diagnose IPN but they did not formally report on the timing of the onset of IPN. However, it is interesting to note that in some cases FNA yielded a positive result as early as day 2[14] and day 3[15].

MOST RECENT STUDIES

The timing of diagnosing of IPN has been specifically examined in two recent studies, both published in 2009. In a study from China (2000-2008) there were 336 patients with predicted severe acute pancreatitis and all received intravenous antibiotic prophylaxis for 14 d from admission[16]. Infected pancreatic necrosis was confirmed by FNA in 19% (66/336) of patients overall and 25% (16/66) of these patients had proven IPN within the first 14 d (Table 1). In a study from the Netherlands (2004-2007) there were 154 patients with pancreatic necrosis and all received enteral nutrition (EN)[17]. Infected pancreatic necrosis was confirmed in 64% (98/154) of patients overall. In 5% (5/98) of these patients, IPN was proven within the first 7 d and in 18% (18/98) within the first 14 d (Table 1). These modern studies are in accordance with earlier studies, which showed that IPN occurs early in a notable proportion of patients. Furthermore, the two most recent studies may have underestimated the incidence of early IPN for three reasons. The first is that they were carried out in an era when there was a waning enthusiasm for the liberal use of FNA[18-20] and it is probable that some patients with early IPN were overlooked. The second is that there is a reported false negative rate for FNA of up to 10%[9,11]. The third reason is that the use of antibiotics and EN in the two studies may have prevented or postponed the clinical manifestation of IPN beyond the first two weeks after onset[21-23].

TRENDS IN THE INCIDENCE OF PANCREATIC INFECTION

Comparison of earlier studies with more recent studies reveals an apparent reduction in the incidence of early IPN from 29% in the 1980s[8] to 18% in the 2000s[17], but not in the overall incidence of IPN during the same time period. The explanation for this reduction is a matter of speculation, but it is worth noting that both studies[8,17] included patients with pancreatic necrosis and all patients had intra-operative confirmation of IPN. What was different between the two studies is the employed management strategies: "nil-by-mouth" and early surgery in the 1980s[8] in contrast to EN and late surgery in the 2000s[17]. The observation that there is a reduction in the early incidence, but not overall incidence, of IPN raises the questions as to whether standard EN is only able to prevent early IPN, whether it is delivered for long enough to prevent late IPN, and which criteria ought

Table 2 The new classification of severity of acute pancreatitis (Modified from[2])

Severity category	Local determinants		Systemic determinants
Mild	No (peri)pancreatic necrosis	and	No organ failure
Moderate[1]	Sterile (peri)pancreatic necrosis	or	Transient organ failure
Severe[1]	Infected (peri)pancreatic necrosis	or	Persistent organ failure
Critical	Infected (peri)pancreatic necrosis	and	Persistent organ failure

[1]Severity is graded on the basis of more severe local or systemic determinants (e.g. sterile pancreatic necrosis without organ failure has to be graded as moderate; sterile pancreatic necrosis with persistent organ failure has to be graded as severe).

to be used to stop EN. If standard EN cannot prevent late IPN then it is important to evaluate more advanced enteral formulations, including those supplemented with glutamine, antioxidants, and/or other targeted treatments[24-27].

CONCLUSION

With the main focus on the diagnosis and treatment of late IPN it appears that early IPN may have been overlooked. There are two important practical clinical implications that derive from giving due recognition to the importance of early IPN. The first is that more effective prophylactic strategies are required, as it would appear that the overall incidence of IPN has not decreased, and may even be increasing. The cornerstone of this prophylactic strategy must be EN[22,23,26], but there remain questions about when to start, what to give and when to stop. The second implication relates to the importance of IPN in determining the severity of acute pancreatitis and how this might be reflected in any classification of severity. More specifically, the severity of acute pancreatitis relates to the presence or absence of IPN rather than whether it occurs early or late in the disease course. The timing of IPN varies widely between patients and, as discussed above, occurs during the first two weeks after onset of acute pancreatitis in almost a quarter of patients. The recently proposed classification of the severity of acute pancreatitis (Table 2) takes this into account as it is based on the presence or absence of local and systemic complications[2]. It also recognizes the dynamic nature of these complications allowing for the transition from sterile to infected pancreatic and peripancreatic necrosis, and transient to persistent organ dysfunction. Furthermore, the new classification of severity takes into account the interaction between the local and systemic determinants as it has been shown that mortality rate is significantly worse in patients with both IPN and organ failure, than either alone[1]. This new severity classification system is based on actual determinants of severity and will prove useful to practicing clinicians managing individual patients through the early and late phases of acute pancreatitis and will provide a more reliable way of selecting and matching groups of patients for clinical trials, including those seeking to prevent or treat IPN in patients with acute pancreatitis.

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