Early multi-system organ failure associated with acute pancreatitis : a plea for a conservative therapeutic strategy

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Abstract

The mortality of severe acute pancreatitis still ranges between 10 and 20%. Nowadays, infected pancreatic necrosis is the leading cause of death. Despite advances in intensive care therapy, however, early and worsening multi-system organ failure remains a source of substantial morbidity and still accounts for 20 to 50% of the deaths. In recent years, the systemic inflammatory response syndrome and the relevant cascades of inflammatory mediators have been implicated as the key factor in the emergence of remote tissue damage. Early multi-system organ failure that supervenes in the first week is typically associated with a sterile necrotizing process. There are no pathophysiological, clinical or economical data to support the practice of debridement of sterile necrosis to prevent or to control early multi-system organ failure. This issue has never been addressed in a controlled study. Besides intensive care support, non-surgical therapeutic modalities including urgent endoscopic sphincterotomy for impacted stones, antibiotic prophylaxis for the prevention of pancreatic infection and early jejunal nutrition have been specifically developed hopefully to attenuate multiple organ failure, to obviate the need of surgical drainage and to improve survival. Fine needle aspiration of necrotic areas must be incorporated in any conservative therapeutic strategy in order to identify and not to jeorpardize those with infected necrosis that remains an absolute indication for drainage.

A specific treatment of acute pancreatitis is still lacking, so far. However, there is ample experimental and pathophysiological evidence in favour of immunomodulatory therapy in severe acute pancreatitis. The administration of one or several antagonists of inflammatory mediators possibly combined with a protease inhibitor may at last provide the opportunity to interfere with the two major determinants of prognosis : the severity of multiple organ failure and the extent of necrotic areas that creates the culture medium for bacterial superinfection. These benefits remain to be substantiated in a controlled study, however. (Acta gastroenterol. belg., **2003**, 66, **177-183**).

Key words : inflammation mediators, multiple organ failure, necrosis, acute necrotizing pancreatitis.

Introduction

About 20% of the patients admitted for acute pancreatitis (AP) run a severe course. Morphologically, severe acute pancreatitis (SAP) is characterised by the magnitude and the extent of the retroperitoneal inflammatory process, which ends up in partial or total necrosis of the gland and the surrounding tissues, usually within 96 hours after the onset of the attack (1). Severity usually manifests itself clinically soon after the onset of symptoms either through multi-system organ failure (MSOF) that typically emerges in the first week of the disease, and local complications including infected pancreatic necrosis, pancreatic abscess, retroperitoneal haemorrhage and acute pseudocyst that usually supervene later in the course of the attack (2). Thus, the severity of AP is closely associated with the extent of the inflammatory necrotizing process. The two major determinants of outcome are the volume of retroperitoneal necrosis which creates the culture medium for bacterial proliferation and the magnitude of early MSOF (3). Persistent and/or worsening MSOF beyond the first week portends the poorest prognosis (4-7).

In the last decade, advances in intensive care therapy have reduced the mortality associated with early MSOF from 90 to 20-50% (8-10). The survival of those patients with extensive areas of necrosis accounts for the 40-70% prevalence of retroperitoneal superinfection (3,11,12). Nowadays, 50 to 80% of the deaths should be ascribed to infected pancreatic necrosis (7,9,10,12,13). A conservative approach, without resorting to surgery, in case of limited and uncomplicated necrosis and a thorough surgical, radiological or endoscopic drainage in case of infected pancreatic necrosis are undisputed therapeutic issues. However, the therapeutic strategy for early and persistent MSOF associated with extensive areas of sterile necrosis remains a matter of controversy.

Early multi-system organ failure and acute pancreatitis : the role of surgery

Early and persistent MSOF occur in about 20% of acute necrotizing pancreatitis and is manifest on hospital admission in the vast majority (4,6,11,14). Although early MSOF is associated with a sterile necrotizing process in 80% of the patients, mortality exceeds 40% in this subgroup (3,4,6,15). Like pancreatic infection the incidence of early end-organ dysfunction is closely related to the volume of the necrotic areas (4,16). Even if infected pancreatic necrosis is nowadays the leading cause of death, early MSOF still remains a determinant prognostic factor, particularly in those with sterile necrosis (15). Major undisputed surgical indications in AP include infected pancreatic necrosis, massive retroperitoneal haemorrhage and acute abdomen (usually due to colonic perforation). However, there is a matter of debate as whether early debridement and drainage of extensive sterile necrotic areas may prevent or limit

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early MSOF by diverting mediators of remote organ damage and whether it may reduce the incidence of infection by removing the culture medium for bacterial proliferation.

Sterile necrosis

Early surgery for sterile necrosis is advocated by some (17-22) while others favour a conservative therapeutic strategy (12-14,23-25). This issue has never been addressed nor will ever be in a controlled trial (13). Only two non-randomised studies compared these two therapeutic strategies, but imbalances between the two groups of patients preclude any definitive conclusion (13,17). Moreover, all the studies that delt with this issue were flawed. All but one trial (4) enrolled patients with AP of varying severity and only a minority studied or identified patients with early MSOF (12,14,17,24,25). Criteria of organ dysfunction were not uniform and local as well as distant tissue damage were not systematically assessed and reported. In most series (13,19,23,25) the population included patients with both sterile and infected necrosis, which further complicates data analysis. Except for the French multicentre trial (13) all the other studies were conducted in a single or at most two specialist centres. Whereas differences between local practice may be of significant concern in the multicentre trial, the relative rarity of the target population imposed a long study period in the majority of the other studies. Hence, data analysis should take into account advances in intensive care therapy, the adoption of specific therapeutic modalities (nutritional support, antibioprophylaxis, urgent endoscopic sphincterotomy, …) and new delineations/refinements of surgical techniques that accounted for a variable adhesion to the therapeutic strategy tested in the study protocol (13,23,25). Furthermore, all the series included a significant number of patients that were referred from other hospitals. This kind of enrolment was responsible for differences between operative delay in the surgical cohorts and potentially introduced a selection bias as some critically ill patients might have been considered as unsuitable for transfer because of the magnitude of early MSOF or the presence of significant co-morbidities.

In patients with sterile necrosis the results of both therapeutic strategies grossly compare. The overall mortality ranged from 5 to 15% in most series (13,14,17-19,22,23) that enrolled patients with a similar magnitude of organ dysfunction and extent of necrosis. In patients with early MSOF, a conservative therapeutic strategy was associated with a 80 to 100% survival but the number of patients was low and the severity of MSOF was poorly assessed (12,14). The early debridement of sterile necrotic areas, if motivated by a persistent MSOF, seems to be taxed with a substantial mortality which reached 100% in a small Finnish series (25). A recent report, originating from a group that favour a surgical strategy, questioned the validity of this approach in the subgroup of patients with persistent MSOF and sterile necrosis (4). Forty-seven patients with remote organ damage in the first three days after the onset of necrotizing pancreatitis were enrolled in the study. Surgical debridement/drainage of necrosis was carried out in 89% after a mean of six days from the onset of the attack. Infection of necrotic areas was previously documented in only 23% so that persistent MSOF was the primary indication for surgery in 76%. The observed mortality was 42%. In a study that evaluated the prognostic factors in sterile necrosis, mortality was primarily related to the intensity of MSOF and was not significantly different whether the patients were operated upon (46%) or not (31%) (15).

The results of the surgical approach, at best similar to those obtained by a conservative strategy, are obtained at the price of a considerable human, technical and financial burden which goes along the substantial morbidity associated with these procedures. Besides retroperitoneal haemorrhage and pancreatic/digestive fistula, secondary infection of sterile necrosis has been reported in 27 to 60%, reoperation in 40% and an hospital length of stay that was considerably longer than for those treated conservatively or even operated upon for infected necrosis (13,17,18,20). In a series of 233 patients, the mortality associated with surgery in sterile necrosis was 7% in the absence of secondary infection vs 59% in its presence (26).

In the eighties, early resection of the pancreas have been abandoned given the associated mortality and their failure to prevent or to control MSOF and pancreatic infection (27). From a pathophysiological standpoint it is hardly conceivable that debridement of sterile necrosis, days or sometimes weeks after the onset of the attack, could influence the systemic inflammatory response syndrome that underlies MSOF. Therefore, there are to date no pathophysiological, clinical or economical data to support the practice of debridement of sterile necrosis to prevent or to control early MSOF, even if the latter is severe, persistent and worsening.

Infected necrosis

Infected pancreatic necrosis is an absolute indication for drainage, either surgical, radiological or endoscopic (1). As delaying these procedures increases mortality, a conservative therapeutic strategy must incorporate a serial exploration of the bacteriological status of necrosis given the gradual increase of the incidence of infection along the course of the attack. Clinical signs (fever, organ dysfunctions), biochemical markers (white blood cell count, C-reactive protein), and CT signs (extent of necrosis) are at best indicative (1,16). The accuracy of serum procalcitonin requires confirmation in large series (28,29). CT-guided fine needle aspiration of necrotic areas with subsequent Gram stain and culture remains the gold standard for the serial bacteriological assessment of necrosis (30). Its specificity and sensitivity

Table 1. — **Controlled randomised trials of early endoscopic retrograde cholangiopancreatography/ sphincterotomy vs conventional treatment in acute biliary pancreatitis**

Authors	Patients (n)	Complications (%)		Mortality (%)	
		ES	Control	ES	Control
Neoptolemos, *et al.* (33)	121	17%*	34%	2%	8%
	SAP (44%)	24%	61%	4%*	18%
Fan, et *al.* (34)	195	18%	29%	5%	9%
	SAP (42%)	13%*	54%	3%	18%
Nowack, *et al.* (35)	280	17%*	36%	2%*	13%
Fölsch, *et al.* (36)	238	46%	51%	11%	6%
	SAP (14%)				

Control = conventional treatment ; ES = endoscopic sphincterotomy ; SAP = severe acute pancreatitis.
* : denotes statistically significant.

exceed 90% but the diagnostic accuracy of this procedure should be reevaluted in the patients that received antibiotics prophyllactically.

Early multi-system organ failure and acute pancreatitis : conservative therapeutic modalities

Advances in supportive therapy played the predominant role in swinging around the pendulum away from surgery in this indication (9). Notwithstanding, in the past decade, a better understanding of the pathophysiological mechanisms underlying local and remote tissue damage in AP has contributed to the development of specific preventive measures and therapeutic modalities. This conservative armentarium is expected also to reduce the perceived need for surgery in this indication.

Emergent endoscopic sphincterotomy in acute biliary pancreatitis

From a pathophysiological standpoint, it is firmly established that early decompression of the pancreatic duct together with the common bile duct in case of angiocholitis is a therapeutic priority in biliary pancreatitis (31). Early surgical removal of biliary stones during severe attacks was associated with a significant increase in both morbidity and mortality as compared with mild disease (32). The poor general condition of these patients as well as local factors account probably for these findings so that endoscopic sphincterotomy (ES) must be preferred in this subgroup.

Four randomised controlled trials are available (Table 1) (33-36). These four studies all compared conventional treatment with urgent (within 24 to 72 hours after admission or onset of symptoms) endoscopic retrograde cholangiopancreatography (ERCP) + ES in case of choledochal stones. However, some important differences between the studies should be highlighted. In the Chinese trial (34) the patients were enrolled in the study whatever the etiological factor. The benefit of urgent ERCP+ES was only demonstrated in the subgroup of patients with severe attacks and exclusively in terms of a decrease in the incidence of angiocholitis. Both morbidity and mortality was significantly reduced by ERCP/ES only if the 125 (65%) patients with biliary pancreatitis were considered. The study by Nowak *et al.* (35) was published only in abstract form. The German trial (36) was the single multicentre one and excluded patients with associated angiocholitis, which is a strong bias in favour of conventional treatment. Moreover, only 14% of the patients had a severe attack and unlike the other three studies an unexpected incidence of respiratory complications was associated with the endoscopic procedure. This latter finding could be ascribed to the low recruitement per centre and the attendant expertise of the operators.

In a large population of biliary pancreatitis both the morbidity (8%) and mortality (2%) associated with ES can be compared with those in a non selected population (37,38). Thus, despite the poor cardio-respiratory condition of many of these patients and a precarious local environment (duodenal edema, rigidity) early ERCP/ES in biliary acute pancreatitis is a safe procedure in hands of an experienced operator. However, the intraductal injection still carries the risk of bacterial contamination of necrosis and of worsening of the inflammatory process. As the prevalence of choledochal stones was limited to 32-48% in the studies discussed above (33-36) owing to the spontaneous transpapillary passage of stones, echoendoscopy which has a similar diagnostic accuracy as ERCP for the detection of choledochal stones enables the rapid selection of the patients with AP who could benefit from ES without jeopardizing those with a cleared bile duct through an intraductal injection of contrast (39,40). MRI cholangiopancreatography, albeit as accurate, does not allow an immediate therapeutic intervention and is not convenient for those critically ill patients.

The benefits of ERCP/ES in terms of mortality and particularly morbidity have been demonstrated if this procedure is carried out within 48 hours in the patients with severe biliary pancreatitis and biliary obstruction or/and angiocholitis (33-36). Dislodgment of impacted stones, drainage of infected bile, and prevention of recurrence are the mechanisms that account for these beneficial effects. It remains to be proved that relief of

Table 2. — **Antibioprophylaxis in acute necrotizing pancreatitis : randomised controlled trials**

References	Antibiotics	Patients vs controls	Results
Perderzoli, *et al.* (42)	Imipenem	41 vs 33	Significant reduction in the incidence of pancreatic (12 vs 30%) and extrapancreatic infection in the treated group. No influence on MSOF, surgery and mortality.
Sainio, *et al.* (43)	Cefuroxime	30 vs 30	Significant reduction in urinary infection and mortality in the treated group. No difference in the incidence of pancreatic infection.
Schwarz, *et al.* (44)	Ofloxacin and metronidazole	13 vs 13	Significant improvement in the Apache II score in the treated group. No difference in the incidence of pancreatic infection nor mortality.
Delcenserie, *et al.* (45)	Ceftazidime, metronidazole and amikacin.	11 vs 12	Significant reduction in the incidence of infection (all combined) in the treated group. No difference in the incidence of pancreatic infection nor mortality.
Luiten, *et al.* (46)	Colistine, amphotericine, norfloxacin orally/6h – enema/ 24h– Cefotaxime i.v. (7 days).	50 vs 52	Significant reduction (22 vs 35%) in mortality in the treated group after correction for severity. Significant reduction in the incidence of Gram negative pancreatic infection (8 vs 33%) and surgery (0.9 vs 3.1/patient).

Apache : Acute Physiology And Chronic Health Evaluation ; MSOF : Multi-System Organ Failure.

impaction attenuates the inflammatory necrotizing process. The benefits of ES is not clearly established in the patients with severe biliary pancreatitis, but without choledochal obstruction. Similarly the systematic use of this procedure in order to clear undetected microlithiasis or to alleviate the papillary associated spasm is not recommended. Urgent (at best within 24 hours) ERCP/ES should be carried out in those with severe biliary pancreatitis and/or biliary obstruction.

Antibioprophylaxis

Pancreatic infection is a time- and extent of necrosis dependent process (3,9). Bacterial translocation from the colon is probably the dominant pathophysiological mechanism underlying infected pancreatic necrosis and accounts for the predominance of Gram negative enterobacteria in necrotic tissues (3,9,11).

In recent years several trials tested the prevention of pancreatic infection. The organisation of these trials was justified by 1) the major prognostic role of infected pancreatic necrosis ; 2) a better understanding of the pathophysiology of pancreatic infection and an improved knowledge of the microorganisms recovered from those tissues ; 3) pharmacodynamic studies which demonstrated the penetration of some antibiotics (imipenem-cilastatin, fluoroquinolones, metronidazole and cefotaxime) into the necrotic tissues at a level that exceeds the minimal inhibitory concentration of most of the bacteria responsible for the glandular infection (41).

Five randomised controlled studies are available in acute necrotizing pancreatitis (42-46). Four studies have compared the administration of a single or several antibiotics with the absence of prophylaxis and one trial tested selective digestive decontamination + i.v. cefotaxime hopefully to prevent bacterial translocation from the gut to pancreatic necrosis (Table 2). None of these studies was double blind, which could potentially had sped up surgical drainage in the control group and so have increased secondary infection of necrosis and mortality. The duration of antibioprophylaxis differed from one study to the other. The causal factor and the severity of the attack was variable in some of these trials (42,44,46). In four of these studies (42-45) the number of patients was low so that the risk of a type II error is significant. The two groups were not matched with respect to the extent of necrosis in the Italian study, which could have biased against the group treated with imipenem (42). The antibiotic tested in the Finnish study was inappropriate in terms of penetration into necrotic tissues and antimicrobial spectrum, which accounts for the high incidence (66%) of modification of the antibiotic therapy during the course of the attack (43). In the Dutch trial it is impossible to assess if the benefits of prophylaxis should be attributed to the topical or parenteral administration of the antimicrobial agents (46). No study is available which compares the two modes of administration. Notwithstanding the topical administration is by far the most labour-intensive for the nursing staff.

All these methodological flaws as well as inconsistencies between the results of these studies preclude any definitive guidelines of antibioprophylaxis in SAP. Arguments in favour of the use of antibioprophylaxis include ample and sound experimental evidence for its rationale and efficacy, the major prognostic role of infection in the clinical setting and the absence of any other reliable means to impact on the incidence of this complication. Arguments contra are the absence of hard clinical data in favour of this approach, the economical burden and the ecological impact of a prolonged broad-spectrum antibiotherapy. The latter accounts for the rising incidence of pancreatic infection by *Candida albicans* and Gram positive microorganisms (14,43,47). Moreover, bacteria cultured from necrotic tissues during antibioprophylaxis are resistant to the antibiotic administred (48). The majority of pancreatic infections which occurred despite antibioprophylaxis are usually late events and are best explained by a nosocomial hematogeneous spread of resistant bacteria (14).

If used and on the basis of the pathophysiological and pharmacodynamical data available, antibioprophylaxis should be carried out for two to four weeks as soon as necrosis and a severe course are established. Antimicrobial agents should be administrered either topically

Table 3. — **Randomised controlled studies of jejunal nutrition in severe acute pancreatitis**

References	Patients	Time interval before EN	Mortality (%)	
			EN	Controls
Powell, *et al.* (55)	13 EN vs 15 IV	72 h after admission	NA	NA
Pupelis, *et al.* (56)	30 EN vs 30 IV	24 h after surgery	3	23
Kalfarentzos, *et al.* (53)	18 EN vs 20 TPN	48 h after admission	6	10
Windsor, *et al.* (54)	16 EN vs 18 TPN	48 h after admission	0	11

EN = enteral nutrition ; IV = electrolyte solution ; NA = not available ; TPN = total parenteral nutrition.

and/or parenterally, using a carbapenem or a fluoroquinolone with an imidazole.

Early enteral nutrition

SAP is a clear-cut indication for nutritional support in order to cope with the increased protein, calorie and micronutrient requirements of those patients. Early enteral nutrition is increasingly considered as a key aspect of specific management of SAP and not only as an adjuvant therapeutic modality. The potential benefits of early enteral feeding rely mainly on the modulation of the systemic inflammatory response syndrome and on the prevention of pancreatic infection. Maintenance of the gut structural and immune barrier function, stimulation of bowel motility and preservation of the normal gut microflora are established effects of enteral feeding that may translate in the reduction of bacterial translocation (49,50). Although the concept of maintaining the pancreas at rest has never been validated, the continuous jejunal infusion of nutrients has been shown to stimulate minimally the exocrine secretion from the gland (51). There is ample clinical evidence of the feasability and the safety of this nutritional approach (52-54). There are no data on the optimal enteral formula (i.e., polymeric vs semi-elementary and immune-enhancing diets) in SAP.

Two randomised controlled studies compared starvation and early jejunal feeding with a polymeric diet. Powell *et al.* studied 24 patients with AP of moderate severity within 72 hours after admission (55). There was no benefit of early nutrition in terms of morbidity and mortality. Inflammatory markers or mediators (i.e., interleukin(IL)-6, C-reactive protein, soluble tumor necrosis factor (TNF) receptors, anti-endotoxin antibody) were not influenced by early nutrition. However, the diet only met 21% of the patients'target calorie needs, which tempers the authors'conclusions. Pupelis *et al*. enrolled 60 patients with SAP within 24 hours after surgery (56). Although the number of reoperation was significantly lower in the treated group (3% versus 27%), there was no difference in the length of hospitalisation nor mortality.

Two randomised controlled trials compared total parenteral nutrition and early jejunal feeding (first 48 hours after admission) with a continuous infusion of a semi- elementary (53) or polymeric (54) diet. The study by Kalfarentzos *et al.* included 38 patients with SAP who received an isocaloric and isonitrogenous regimen (53). The gross incidence of complications, particularly sepsis, was significantly lower in the group fed enterally. There was no difference in the nitrogen balance, the length of hospital stay and mortality. The study by Windsor *et al.* included 34 patients of whom 16 had a severe disease (54). Evaluation was carried out after a seven day-course of nutritional support. The poor digestive tolerance limited the nutritional target at the outset in the group fed enterally. Notwithstanding the latter showed a significant improvement in the Apache II score and C-reactive protein level when compared to the group treated with total parenteral nutrition. In the latter serum antiendotoxin IgM level increased and anti-oxydant capacity decreased while the group fed enterally moved in the opposite direction. The incidence of septic complications and MSOF was significantly reduced in the enteral group. Mortality and length of hospital stay were not different.

Enteral nutrition is feasible, less costly than the parenteral route, usually well- tolerated and pathophysiologically sound in SAP as it prevents protein-calorie malnutrition in a catabolic hypermetabolic disease process. The benefits with respect to local and systemic immunomodulation, maintenance of gut barrier function, occurrence of pancreatic infection and hence on prognosis remain to be substantiated in controlled studies focused on the severe form of the disease (Table 3).

The future

In part because patients seek medical attention long after initiating events have occurred, reduction of pancreatic exocrine secretion and antiprotease therapy have failed to convey any benefit in clinical studies despite encouraging results in experimental pancreatitis, and direct manipulation of the glandular microcirculation has never been attempted in humans (57). Thus, a specific treatment able to interfere early with the major determinants of outcome of these patients is still eagerly awaited.

Ample experimental and clinical evidence has accumulated that regardless of the initiating factor or etiology, excessive production of macrophage-and neutrophil-derived proinflammatory substances such as cytokines and platelet activating factor (PAF) play a key role in pancreatic damage and in the end-organ dysfunctions

accompagnying SAP. In this context, modulation of the inflammatory response to initial acinar cell injury is expected theoretically to prevent distant organ damage, to limit the extent of the local necrotizing process that besieges pancreatic infection and ultimately to improve survival. In the absence of a deep understanding of the intra-acinar cell initiating events that trigger tissue injury and, as many (if not all) patients arrived in hospital long after these events, it seems obvious that a strategy of damage prevention is impractical. Rather a logical strategy of damage control is to downregulate the inflammatory response by blocking the production or the effects of the inflammatory mediators which are believed to be responsible for most of the local and distant injury in this disease.

Although these therapeutic options provide exciting areas of investigation, today the clinical evidence in support of their benefits remains limited and controversial. So far, only three immunomodulating trials have been conducted in human AP. The first randomised placebo-controlled study tested the prophylactic administration of IL-10, given as a single bolus injection, for the prevention of post-ERCP pancreatitis (58). IL-10 was injected 30 minutes before the start of the procedure. Although no difference was observed in plasma cytokines (IL-6, IL-8 and TNF) IL-10 reduced significantly the incidence of post-ERCP pancreatitis. In the group of patients with hyperamylasemia, IL-1O pre-treatment was able to limit the increase in TNF plasma levels, which suggests that this immunomodulatory cytokine might limit local tissue damage by downregulating the production of proinflammatory mediators. These promising results could not be reproduced in another study (59). In the third randomised controlled trial, 290 patients with predicted SAP received placebo or lexipafant, an imidazolyl derivative that has an affinity for the PAF receptor seven times more avid that PAF itself, by continuous infusion for up to seven days (60). Although patients were included within 72 hours after the onset of symptoms, 44% already had organ failure on entry into the study. As the majority of organ failures had occurred before initiation of treatment, a putative beneficial effect of the PAF antagonist could not be demonstrated on the small number of new end-organ dysfunctions. In addition, at the end of the treatment period, there was no difference in organ failure score between the two groups and neither the incidence of local complications nor the mortality rate were influenced by the therapy.

Given the rapid onset of local and distant tissue injury and the inevitable delay before patient admission, a therapeutic window allowing for the antagonism of cytokines or mediators downstream in the inflammatory cascade remains to be demonstrated in clinical AP. Moreover, given the multiplicity, inherent redundancy, and pleiotropy of mediators/mechanisms involved in the attack, precise targets for specific interventions are difficult to ascertain. Although a conservative therapeutic strategy should be applied for early and even persistent MSOF as long as necrosis remains sterile, indiscriminate use or overreliance on the simplistic approach of proximal cytokine blockade may rather yield disappointing results or even harmful effects, just as protease inhibitors did in the past.

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