Prevention of infection following severe acute pancreatitis

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Purpose of review
This review highlights recently reported strategies aimed at quantifying severity of illness earlier in the course of acute pancreatitis and at preventing secondary infection in pancreatic necrosis.

Recent findings
New and improved scoring models appear to suggest that the optimal interventional window is between 24 and 72 h of the onset of severe acute pancreatitis. Prospective randomized clinical trials in which patients with severe acute pancreatitis were treated with broad-spectrum antimicrobial regimens as prophylaxis, however, have demonstrated no benefit in terms of preventing late infection in pancreatic necrosis. In contrast, early enteral nutrition with various formulas and supplements, including probiotics, may confer a clinical advantage in terms of morbidity and mortality.

Summary
Continuing to advocate antimicrobial prophylaxis in severe acute pancreatitis is not reasonable, in view of the evidence now available from two large clinical trials. Current guidelines should be revised because of the potential harm to gastrointestinal ecology associated with long-term antibiotic treatment. A suitable alternative way to prevent bacterial overgrowth and secondary infection is lacking, however.

Keywords
acute pancreatitis, antibiotic prophylaxis, enteral nutrition, probiotics, scoring systems

Introduction
Secondary infection of pancreatic/peripancreatic necrosis by gut-derived bacteria is responsible for up to 80% of deaths in patients with severe acute pancreatitis (SAP). Antimicrobial prophylaxis has emerged as the cornerstone of prevention of infection in SAP. The term ‘prevention’ in this context, however, implies multilevel, institutional treatment based on the best standards of care and sound clinical management, involving a multimodal, multidisciplinary approach [e.g. early staging, haemodynamic resuscitation, enteral nutrition, monitoring and organ support, antimicrobial therapy (as opposed to prophylaxis), and timely surgical drainage with radiological guidance when needed]. This review addresses recent reports (January to March 2001) included in PubMed that are related to scoring, early patient identification, use of antimicrobial agents and enteral nutrition in patients with SAP.

Scoring systems
Two temporal peaks in mortality exist in SAP, both related to multiple organ dysfunction syndrome: an early peak (during the first week; apparently related to the progressive systemic inflammatory response as a consequence of extensive necrosis) and a later peak (2–3 weeks after the onset of SAP; related to sepsis and infection). Clinicians use every possible tool to predict and avoid the development and progression of multiple organ failure. A first and necessary step is to classify SAP. Various multifactorial scoring systems are in use to calculate severity of illness (<48 h after admission). Some of these are based on a combination of clinical, physiological and laboratory variables (e.g. Ranson, Imrie, and Acute Physiology and Chronic Health Evaluation II scores) whereas others are based exclusively on pancreatic and peripancreatic tissue perfusion as surrogate indicators of the extent of necrosis (e.g. the Balthazar score). Despite widespread use of these systems, they lack precision in predicting the behaviour and natural history of the individual case of SAP, particularly with respect to their ability to predict poor individual outcome.

For interventions designed to mitigate the impact of the early peak in morbidity/mortality, the period between 24 and 72 h after the onset of SAP may be the optimal therapeutic window. Gocmen et al. [1] compared the discriminatory ability of established scoring systems in biliary pancreatitis, and they suggested that the Mortality Probability Model II system is more robust in identifying early perfusion deficits. This supports the notion that adequate fluid resuscitation improves perfusion and
oxygenation of pancreatic tissue and mitigates progression of necrosis. Unfortunately, specific volume replacement targets have not been established for SAP, and neither have such targets been tested in clinical trials. During the early period, excessive resuscitation and progression of necrosis may result in abdominal compartment syndrome, which resembles organ dysfunction (e.g. oliguria, low cardiac output and hypoxia). Two reports explored the utility of monitoring intra-abdominal pressure (IAP) in SAP [2*,3*]. Persistent intra-abdominal hypertension during the first week after the onset of SAP predicts development of multiple organ dysfunction syndrome, an association that is stronger in nonsurvivors, but the upper threshold of IAP that differentiates survivors from nonsurvivors is not yet clear.

More recently, serum inflammatory markers were explored to evaluate their ability to discriminate, on a routine basis, between clinical recovery and persistence (interleukin-1, interleukin-6, C-reactive protein, neutrophil elastase and α1-antitrypsin) and between inflammation and infection (e.g. procalcitonin). Whereas some markers achieved their peak serum concentration as early as 24 h after the onset of SAP (interleukin-6 and C-reactive protein), others had a later zenith (interleukin-18). Macrophage migration inhibitory factor is a proinflammatory mediator isolated from human serum that has been related to the extent of SAP [4]. Removal or inhibition of macrophage migration inhibitory factor in animal models of SAP decreased acute lung injury, which suggests some therapeutic utility [5]. Whether these new markers offer any benefit in terms of bedside management remains to be determined in large clinical trials.

Radiological indices such as the Balthazar score gain accuracy after 24–48 h of the onset of SAP because true necrosis is an infrequent early event. Accordingly, severity of SAP may be underestimated early in the course. A new computed tomography based scoring system [i.e. Extra-Pancreatic Inflammation on Computed Tomography (EPIC) scoring], which is based on extrapancreatic signs of inflammation (e.g. pleural effusion, presence of ascites and extent of retroperitoneal inflammation) within 24 h after admission, was recently evaluated [6**]. The EPIC system reliably predicted outcomes such as development of severe disease and mortality. Staging of acute pancreatitis with nonenhanced magnetic resonance imaging is equally reliable and has several potential advantages over computed tomography in detecting cholelithiasis, pancreatic duct disruption and pancreatic haemorrhage [7,8].

Unfortunately, development of scoring systems is hampered by use of retrospective population-based data to identify possible variables that may serve as unequivocal outcome indicators. The methodology is generally based on cluster assay and culminates in conventional fitting of a regression model, either linear or logistic. A novel method was proposed by Mofidi et al. [9*], using artificial neural networks. It appears to adjust better the weighting of multiple variables, and so it exhibits a predictive advantage compared with conventional scoring systems. Clearly, no model in SAP is sufficiently accurate to permit prognostication in the individual patient. It may be that the problem fundamentally stems from the fact that a single snapshot of data may not provide an accurate picture in a dynamic disease state such as SAP. Future modelling solutions (possibly the ideal construct) should be based on complex and dynamic multilevel capture/recapture input, with fine individually adjusted prediction fitting.

**Antibiotic penetration into pancreatic tissue**

Any progress in the clinical management of infection with antimicrobial agents in severe pancreatitis will mandate serious reconsideration of drug distribution and penetration in both normal and infected pancreatic tissues. Predefined pharmacokinetic/pharmacodynamic targets are as important as the expected microbiology of the infected tissue. Guidelines for animal care essentially constrain acute pancreatitis models to a short study window lasting less than 8 h, a setting in which inflammation rather than necrosis is the norm. In human studies pancreatic tissue sampling has been pursued during elective pancreatectomy (cancer or chronic pancreatitis) and, exceptionally, in cases of SAP in which necrotizing tissue was obtained by one of several techniques (e.g. computed tomography guided biopsy, direct perioperative sampling, or postoperative drainage). Since the pioneering work in humans by Bassi et al. [10] and Buchler et al. [11] was reported, not much work has been done in this area except with ciprofloxacin [12], fluconazole [13] and, recently, with moxiﬂoxacin [14*] and ertapenem [15*].

Noninvasive evaluation of pharmacokinetics is a novel methodology with which to assess tissue distribution of drugs in diverse anatomic sites. Approaches include use of contrast-enhanced magnetic resonance imaging of paramagnetically labelled polymer conjugates [16] and measurement of radiolabelled ﬂuorine atoms on the drug by positron emission tomography. Thus far, the distributions of ﬂuoroquinolones (e.g. ciproﬂoxacin, trovafloxacin and ﬂeroxacin) into the pancreas of healthy individuals [17] have been examined in preclinical and phase 1 trials, although a clinical study to evaluate the controversial issue of distribution of antimicrobial agents in necrotic tissue has not yet been conducted.

**Antibiotic prophylaxis in severe acute pancreatitis**

Long-term antibiotic ‘prophylaxis’ in SAP has been accepted worldwide as standard practice for nearly a decade, in part because it is accessible everywhere but
also because it seemed rational in terms of infection control and prevention. Since the initial report by Pederzoli et al. [18] was published in 1993, supplementary articles, reviews and opinion papers have reinforced the notion that prophylaxis is meaningful in terms of preventing secondary infection of necrotic tissue in SAP. Despite the unsatisfactory quality of the underlying data, this wave of enthusiasm yielded society guidelines and hospital protocols, and meta-analyses that recommended antibiotic prophylaxis of SAP.

A call for caution was issued by Barie as early as 1996 [19], acknowledging that any prophylactic regimen to prevent infection in SAP should be evaluated using key methodological benchmarks. At the centre of the debate were the selection of candidates at risk, the credit given to the pharmacokinetic/pharmacodynamic data on antimicrobial penetration into normal pancreatic tissue, the need for proven efficacy under well controlled clinical trials and, finally, whether emergence of resistance and super-infection would be among the adverse effects. Recently, well designed randomized, prospective clinical trials with fluoroquinolones [20] and carbapenems [21] documented the insubstantial role played by antimicrobial prophylaxis in terms of diminishing the morbidity and mortality resulting from infections in SAP. Furthermore, other reports have confirmed the emergence of multiresistant micro-organisms and increased incidence of fungal infection in late infected pancreatitis as consequence of long-term, prophylactic use of broad-spectrum antibiotics [22], although some authors did not identify primary fungal infections in a highly selected group of patients and in those with a short duration of antimicrobial prophylaxis [23].

Two prospective randomized clinical trials have failed to demonstrate benefit of early prophylactic antimicrobial use in patients with necrotizing SAP [20,21]. This turning of the paradigm, as has happened on many occasions in the recent history of medicine, was finally validated by two independent reviews: a modern meta-analysis [24] and an excellent Cochrane database review [25].

**Bacterial overgrowth and translocation**

Once a research pathway is abandoned, new working hypotheses arise and, frequently, old and superceded ideas are reconsidered. Selective digestive decontamination (SDD) may fall into this latter category. Originally developed to prevent radiotherapy related side effects, SDD was subsequently introduced by the late Christiaan Stoutenbeek (1947–1998) [26] into the critical care field based on hypothesis that intestinal colonization and bacterial overgrowth (by Enterobacteriaceae) in the proximal gastrointestinal tract precedes and then causes organ-specific infection (e.g. pneumonia). In SAP, the proponents of SDD support the hypothesis that infection of previously sterile peripancreatic necrotic tissue may occur either directly by bacterial translocation through a lymphatic route or indirectly by the haematological route, resulting in bacterial penetration into the portal system. Prevention of subsequent pancreatic infection by means of SDD was tested in a controlled clinical trial conducted by Luiten et al. [27] between 1990 and 1993. Although the trial’s findings were unequivocal, the potential of SDD as a standard of care in SAP was essentially ignored.

Based on similar reasoning, enteral nutrition has been implemented with the aim being to maintain the integrity of the gastrointestinal barrier and, in parallel, to prevent bacterial overgrowth and subsequent translocation. This approach is in contradistinction to the traditional one, in which fasting and total parenteral nutrition were applied in order to sustain metabolic requirements while decreasing exocrine pancreatic stimulation. Enteral nutrients can satisfy the increased metabolic requirements of SAP, but they can also provide autocrine stimulus for enterocytes; it therefore seems that enteral nutrition may be able to sustain mucosa stability more efficiently than the traditional approach. Several immunostimulatory formulas (e.g. arginine, glutamine, ω3 polyunsaturated fatty acids and vitamins) and routes of nutrition delivery (e.g. nasojejunal tube and catheter jejunostomy) have been tested. A recent meta-analysis [28] supported the benefit of the enteral approach in downregulating the stress response while enhancing immune competence and improving outcomes in SAP. The further role, if any, of parenteral nutrition, the correct timing of enteral nutrition, and the use of intra-gastric (rather than postpyloric) feeding remain subject to debate [29].

Similarly, supplementing enteral formulae with probiotics (e.g. monostrain compounds with *Lactobacillus plantarum*) may restrain bacterial overgrowth, as was suggested by the inconclusive study conducted by Olah et al. [30] in 2002. In preclinical studies, probiotics (particularly *Saccharomyces boulardii*, *Lactobacillus* spp., *Bifidobacterium breve*, *Enterococcus faecium*, *Streptococcus thermophilus*) have been found to create a niche of colonization resistance, and thus restore the intestinal microflora composition by targeting specific known aspects of this dysbiosis (e.g. recalibration of intestinal pH, reduction in local free oxygen availability, and changed fermentative enzyme activities) [31]. Results of a large randomized clinical trial in SAP with multispecies probiotics (PROPATRIA) are still pending [32,33].

Unfortunately, bacterial translocation and overgrowth in the proximal gastrointestinal tract cannot be detected readily and speedily at the bedside of patients being treated for SAP. Detection of bacterial DNA by
polymerase chain reaction has been used to identify early episodes of bacterial translocation in digestive diseases with known breakdown of intestinal integrity (e.g. cirrhosis and SAP) [34] and its use in large SAP cohorts is warranted.

Conclusion

Continuing to advocate antimicrobial prophylaxis in SAP is not reasonable because evidence rejected the value of such practice is now available from two large clinical trials. The current guidelines should be revised, in view of the potential harm of long-term antibiotics to gastrointestinal ecology. A suitable alternative way to prevent bacterial overgrowth and secondary infection is lacking, however.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 469–470).


A novel scoring system based on early signs of systemic inflammation (aspartic, pleural effusion and retroperitoneal inflammation) on computed tomography (the EPIC score) was developed at the Gent University Hospital, which may complement the Balthazar score. An EPIC score of 4 or more had a 100% sensitivity and 70.8% specificity for predicting severe pancreatitis. The EPIC score allows accurate estimation of disease severity and mortality within 24 h of admission.


9 Mofidi R, Duff MD, Madhavan KK, et al. Identification of severe acute pancreatitis using an artificial neural network. Surgery 2007; 141:59–66. This study, conducted at the Department Clinical and Surgical Sciences (University of Edinburgh), validates a novel approach to constructing scoring systems in acute pancreatitis by means of artificial neural network analysis. A total of 684 patients with acute pancreatitis were included, of whom 27.3% had SAP. The new score was more accurate at predicting progression and the appearance of multiple organ failure (P < 0.01).


This study examined penetration of moxifloxacin (a fourth generation fluoroquinolone) into pancreas in 60 patients undergoing elective pancreas resection, who received a single oral or intravenous dose of 400 mg as perioperative anti-microbial prophylaxis. The mean tissue:plasma ratios varied from 1.8 to 0.6 to 2.6 ± 1.2.


21 Dellinger EP, Tellado JM, Soto NE, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-con- trolled study. Ann Surg 2007; 245:674–683. This multicentre, prospective, double-blind, placebo-controlled randomized study was conducted in 92 centres within North America and Europe in patients with confirmed necrotizing pancreatitis. It compared meropenem (n = 50, 1 g intrave- nously every 8 h) with placebo (n = 50) within 5 days of the onset of symptoms for 7–21 days. The primary end-point was development of pancreatic or peripancreatic infection within 42 days after randomization. Pancreatic or peripancreatic infections developed in 18% of patients in the meropenem group as compared with 12% of those in the placebo group (P = 0.401). The authors concluded that this study did not support early prophylactic antimicrobial use in patients with severe acute necrotizing pancreatitis.


The aim of this study, conducted at the Department of Medicine, Brigham and Women’s Hospital (Boston, Massachusetts, USA), was to determine the pre- valence of primary fungal infections in SAP under broad-spectrum antibiotic regimens. Sixty-four cases of SAP out of 689 consecutive acute pancreatitis cases did not acquire a primary pancreatic fungal infection. The authors indicated that limited use and short duration of carbapenem therapy may be factors that contributed to the absence of primary fungal infections.


This is a review of 27 prospective randomized trials conducted in adult patients with acute pancreatitis that evaluated interventions with nutritional therapy. A meta-analysis of seven trials showed use of enteral nutrition to be associated with significant reductions in infectious morbidity and hospital length of stay, and a trend toward reduced organ failure, with no effect on mortality when compared with use of parenteral nutrition. Insufficient data exist to determine whether enteral nutrition improves outcome over standard therapy (no artificial nutrition support) in patients admitted for acute pancreatitis. Enteral nutrition has become the new ‘gold standard’ of nutritional therapy in SAP.


The investigators showed that probiotics reduced duodenal bacterial overgrowth of potential pathogens, resulting in reduced bacterial translocation to extraintestinal sites, including the pancreas. This preclinical study supports the launch of a phase II (security and efficacy) trial in patients aiming to prevent necrotic tissue infection in SAP.