Intraabdominal sepsis: newer interventional and antimicrobial therapies for infected necrotizing pancreatitis

Joseph S. Solomkin and Konstantin Umanskiy

Purpose of review
Recent advances in interventional techniques and antimicrobial therapy have significantly affected the morbidity and mortality of infected pancreatic necrosis. This review describes elements of this progress.

Recent findings
Operative management of infected pancreatic necrosis has consisted of formal laparotomy and debridement of the pancreatic necrosis/infection. Typically, the abdominal wound has been left open and the pancreatic bed has been reexplored at frequent intervals. This staged approach has been replaced by a single definitive operative procedure. More recently, laparoscopic techniques have been used, and provide the possibility of substantially lessened morbidity. The benefits of antimicrobial prophylaxis, typically with carbapenems, have been demonstrated in several clinical trials. The use of such broad-spectrum therapy has complicated the antimicrobial management of prophylaxis failures. A resistant flora is encountered in such patients, including gram-positive cocci, yeast, and gram-negative bacilli. This has been shown to mandate empiric therapy with combination regimens based on agents not used for prophylaxis.

Summary
These findings recommend the practice of routine antibacterial prophylaxis with systemic agents. Patients receiving such treatment should be monitored for colonization by yeast; surveillance cultures do not appear to be necessary because these critically ill patients have an inflammatory disease and frequently experience temperature elevations warranting cultures to rule out infection. If infection is documented by aspiration or intervention, aggressive antimicrobial therapy directed at organisms identified by Gram stain should be started. Classes of antimicrobial agents other than those used for prophylaxis should be used.

Introduction
Perhaps the most challenging problem in intraabdominal infections has been the management of infected pancreatic necrosis [1]. During the reporting period, considerable information has become available regarding new interventional strategies, and the requirements for empiric therapy for documented infected pancreatic necrosis have been clarified. This article will therefore focus on this highly morbid disease.

Indications for intervention in pancreatitis with necrosis
The at-risk population for infection after prophylaxis are those with necrosis of approximately 30% or more of the pancreas as determined by contrast-enhanced CT scanning. Although advances in supportive and adjunctive care have resulted in decreased mortality rates, death still occurs in 10 to 20% of patients. Recent data suggest that patients with pancreatic necrosis without infection can be managed with a conservative strategy, reserving surgery or other forms of intervention for documented infection. Infection may develop late after weeks of sterility, and is diagnosed by fine-needle aspiration of pancreatic necrosis [2••]. These authors also noted that conservative management produces a subset of patients with persistent pain, malaise, and an inability to tolerate a diet or return to activities of daily life. These patients with organized necrosis do well with delayed debridement.

Evolution of interventional strategies for infected pancreatic necrosis: from repetitive laparotomy to laparoscopy
The surgical management of infected necrosis has evolved from a strategy of planned reexplorations until no further evidence of necrosis was identified [3] to a more recent approach of a single procedure with CT scan follow-up if clinical signs suggest recurrent infection [4]. In the recent past, an expanding experience with laparoscopic procedures in the management of pancreatic necrosis has been reported. These reports have detailed different approaches, including transmesocolic, transgastric transgastrocolic, and retroperitoneoscopic approaches [5,6••,7,8]. Prior to completion of the operation, placement of a postoperative lavage system has been performed, although the exact need for this is unclear.

In reading these reports, it is important to recognize that some of the cases described were encapsulated abscesses

Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

Correspondence to Joseph S. Solomkin, MD, Department of Surgery, University of Cincinnati College of Medicine, 231 Albert B. Sabin Way, Cincinnati OH 45267-0558, USA
Tel: 513 558 4427; fax 513 558 5661; e-mail: joseph.solomkin@uc.edu

© 2003 Lippincott Williams & Wilkins
1070-5295

rather than the unorganized necrosis that requires more difficult dissection. Nonetheless, these approaches likely offer management of these conditions without the added problems of a large abdominal incision. Given the relative infrequency of this condition (infected necrosis), it is unlikely that a comparative trial will be performed.

**Potential risks of laparoscopic intervention**

In parallel with these technical advances, considerable work continues on the immunologic consequences of insufflation of an inert gas (usually CO₂). The particular issue is that peritoneal fluid is absorbed through transdiaphragmatic stomata, in turn leading into the thoracic duct [9]. Ordinarily, flow is driven by negative intrathoracic pressure with inspiration; increased intraabdominal pressure during a laparoscopic procedure for established intraabdominal infection would be expected to increase such flow. This is a particular concern, especially in peritonitis with inflammatory mediators, bacteria, endotoxin, and other bacterial products. However, the local intraabdominal immune system behaves in a particular way when exposed to carbon dioxide pneumoperitoneum; suppression of intraperitoneal cell-mediated immunity has been demonstrated in some studies. This feature may be clinically important and should be acknowledged when considering laparoscopic surgery in patients with sepsis [5,10–13].

In a thorough study of the impact of laparoscopy with exposure to CO₂ and room air under a similar pressure on local, systemic, and distant organ immune responses, Ure et al. randomized 20 piglets into four groups: CO₂ laparoscopy, air laparoscopy, CO₂ laparotomy, and air laparotomy. Laparotomy versus laparoscopy, when performed with CO₂, significantly increased polymorphonuclear leukocytes and decreased the percentage of macrophages in peritoneal fluid at intervals up to 48 hours. There was a significant increase in plasma interleukin-6. Similar differences between the procedures were found with exposure to air. The use of air versus CO₂ in laparoscopy, but not in laparotomy, resulted in an increase of peritoneal polymorphonuclear leukocytes and a decrease of the percent macrophages in peritoneal fluid (%MF) up to 48 hours. Inflammatory responses were reduced by a laparoscopic approach and by exposure to CO₂ versus air. Peritoneal responses were affected to a larger degree than systemic parameters.

These findings cannot be directly translated into clinical meaning or relevance. Rather, they suggest elements for analysis in future clinical research projects. The more extensive reviews do not suggest the existence of a substantial clinical problem with this.

**Origin of infection in pancreatic necrosis**

Microbial translocation may represent an important cause of septic morbidity in patients with acute pancreatitis. Alterations in intestinal permeability may also predispose to translocation. The extent of gastric colonization and intestinal permeability have been examined in patients with acute pancreatitis [14]. Gastric colonization was determined by culturing a sample of nasogastric aspirate, and intestinal permeability was measured using a dual sugar probe technique (lactulose/thamnose). A total of 59 patients were studied, 24 (41%) of whom had severe disease. There was a significantly higher incidence of colonization with potentially pathogenic enteric bacteria in patients with severe disease compared with those with mild disease (57 vs 6%, P < 0.001). Intestinal permeability was neither associated with disease severity nor was it predictive of septic morbidity.

**Role of antibacterial prophylaxis in pancreatic necrosis**

There has been some further progress in understanding antibiotic therapy for pancreatitis and its complications. This area has received increasing intention because of the trend to provide prophylactic broad-spectrum antibiotic agents therapy for noninfected acute necrotizing peritonitis. Death from acute severe pancreatitis results from infection and multiple organ system failure occurring late in the course of illness. Patients with necrotizing pancreatitis involving at least one third of the organ are at highest risk of secondary infection and death. A recent review has summarized the findings of available trials [15]. Antibiotics were beneficial in four recently completed studies: imipenem significantly reduced pancreatic and nonpancreatic sepsis (P ≤ 0.01) [16]; ceftazidime reduced all infectious complications (P < 0.01) and deaths (P = 0.0284) [17]; a regimen of ceftazidime, amikacin, and metronidazole reduced all infectious complications (P < 0.03) [18]; and protocol use of imipenem significantly reduced pancreatic infection compared with nonprotocol antibiotics (P = 0.04) and no antibiotics (P < 0.001) [19]. Based on these results, early antibiotic prophylaxis in patients with necrotizing pancreatitis has been suggested, and most practitioners use imipenem for this task.

An alternative approach to preventing infections in patients with necrotizing pancreatitis is to provide oral selective digestive decontamination regimens, but this has not been rigorously evaluated in pancreatitis.

**Impact of antimicrobial prophylaxis on subsequently encountered infecting flora**

An important issue becomes the flora identified in infections occurring after antimicrobial prophylaxis, and this was addressed in a single-center prospective study, in 103 patients with necrotizing pancreatitis seen consecutively [20]. In that study, patients with proven necrotizing pancreatitis received a prophylactic intravenous antibiotic treatment. Pancreatic infection was regarded as an indication for surgery. Thirty-three patients (32%)
had infected necrosis. Gram-negative organisms were isolated from 19 patients (58%), gram-positive organisms were isolated from 18 patients (55%), fungal organisms were isolated from 8 patients (24%), and multiresistant organisms were isolated from 3 patients (9%). In 7 patients (21%), the organisms cultured from the pancreatic tissue were resistant to the antibiotics given for prophylaxis. Infection with multiresistant organisms or organisms resistant to the antibiotic used for prophylaxis, but not with fungal infection or gram-positive or gram-negative infection, was correlated with a negative outcome. Fungal infection under adequate treatment was not associated with a negative outcome. Other studies have found an increased mortality from yeast infections [21].

Established pancreatic infection remains perhaps the most difficult infection to control, in part because of a host who has already experienced one insult (the inflammatory insult of severe pancreatitis) and in part because of the more resistant microbial flora anticipated. For these infections occurring after previous antibiotic therapy, either for prophylaxis or treatment of infection, there is a sufficiently high probability that resistant organisms will be present to warrant initial empiric treatment with agents aimed at multidrug-resistant gram-negative and gram-positive organisms. The exact agents to be used will depend upon the individual hospital’s experience with nosocomial infection. There is compelling evidence, however, that higher success rates will be achieved if the initial empiric therapy covers those organisms later found to be present. The importance of appropriate and adequate cultures must be stressed.

Management of gram-negative organisms in postoperative infections

The primary issue regarding empiric therapy for gram negatives is whether there is any benefit to combination therapy when both agents are active against the identified organisms. There is a considerable mythology that combination therapy improves outcome from gram-negative infection. The available data, however, indicate that this is not so [22].

The argument in favor of combination therapy came from an era when the only effective antibiotics for *Pseudomonas aeruginosa* were aminoglycosides and semisynthetic penicillins such as carbenicillin, and later, mezlocillin and piperacillin. A rather remarkable acceptance of laboratory findings of synergy as directly relevant to clinical practice led to strong recommendations for combination therapy. There were, however, scant clinical data to support this recommendation. More recent large-scale studies in patients with bacteremia have demonstrated no benefit of combination therapy as long as the monotherapy provided was active against the infecting organism(s). In pancreatic infections harboring gram-negative organisms, single-agent quinolone or carbapenem is effective. However, if the patient has received systemic antimicrobial prophylaxis, infecting isolates must be presumed resistant to that class of agent and treated with a representative of another class.

Management of gram-positive organisms in postoperative infections

Gram-positive organisms are common and in some cases even predominant in pancreatic infections, again in part dependent upon the antimicrobial prophylaxis provided. Because of the increasing incidence of resistance to multiple agents among these organisms, empiric therapy covering β-lactam-resistant gram-positives must often be considered. Even more ominously, the appearance and increasing incidence of vancomycin-resistant organisms now being seen suggests the possible future requirement for empiric therapy with agents such as quinupristin/dalfopristin and linezolid.

Management of *Candida* infections

There are two central issues relating to *Candida*: settings where prophylactic therapy should be given and selection of therapy when infection is documented. There are substantial and convincing data available defining indications for prophylaxis for severely ill surgical patients. These center primarily around demonstration of colonization with *Candida* [23]. However, a recent study demonstrated that patients in the intensive care unit receiving selective digestive decontamination benefited from prophylaxis with low-dose fluconazole (100 mg per day) [24]. Whether this can be extrapolated to imipenem prophylaxis is unclear.

The incidence of *Candida* infection in patients undergoing operation for infected necrotizing pancreatitis is on the order of 20 to 25%. This is sufficiently high that empiric antifungal therapy should be given when patients with necrotizing pancreatitis undergo operation for infection. The presence of yeast on Gram stain of infected material obtained either by fine-needle aspiration or by direct culture at operation may be used as a guide to such therapy. Because the most common isolate is *Candida albicans*, fluconazole is a reasonable agent for initial therapy. The next most common isolate is *C. glabrata*, which has higher minimum inhibitory concentrations for fluconazole, but these concentrations can be commonly achieved with 400 mg/d. In any circumstance, the recent availability of caspofungin has obviated the need for amphotericin therapy for this infection [25]. If the patient has received fluconazole prophylaxis, caspofungin should be empirically started when yeast are identified.
References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- Of special interest
- Of outstanding interest


Infected necrotizing pancreatitis Solomkin and Umansky 427