The Role of Antimicrobial Therapy in Severe Acute Pancreatitis

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KEYWORDS
- Severe acute pancreatitis
- Infected pancreatic necrosis
- Prophylactic antibiotics
- Systemic inflammatory response syndrome
- Secondary pancreatic infection
- Computed tomography-guided fine needle aspiration

KEY POINTS
- Pancreatic necrosis is prone to secondary microbial infection (infected pancreatic necrosis) with organisms found in the gastrointestinal tract (gram-negative organisms, gram-positive organisms, anaerobes, and fungi).
- Empiric broad-spectrum antimicrobial treatment of patients for clinical deterioration while awaiting final culture results is called treatment on demand.
- At this time, there is no compelling evidence that the use of prophylactic antibiotics in patients with severe acute pancreatitis is efficacious.
- Quinolones plus metronidazole or carbapenems are the initial drugs of choice to treat secondary pancreatic infections.
- Fungal organisms are found in up to 25% of cultures from infected pancreatic necrosis and are best treated with diflucan.
- When carefully applied, fine needle aspiration Gram’s stain and culture are useful for diagnosing secondary pancreatic infections.

SEVERE ACUTE PANCREATITIS

Acute pancreatitis is an inflammatory disease of the pancreas caused by a variety of etiologic factors, with alcohol, gallstones, and idiopathic factors being the most common in the United States. The pancreatic inflammation incites a complex and variable host response, resulting in a disease course can be either mild and self-limiting (80%), or severe and necrotizing (20%).

In mild acute pancreatitis, patients experience the abrupt onset of abdominal pain, nausea, and vomiting, which gradually subside over a 3- to 5-day period. Treatment consist of nothing by mouth (NPO), intravenous fluid hydration, pain control, supplemental oxygenation, and antiemetics to manage symptoms while the pancreatic inflammation subsides and the gland returns to normal structure and function. Antimicrobials play no role in this disease process. In contrast,
severe acute pancreatitis (SAP) (Box 1) results in microcirculatory disturbances within the pancreatic parenchyma, leading to tissue ischemia and regional cell death best quantified by contrast-enhanced computed tomography (CECT) as pancreatic and peripancreatic necrosis (Fig. 1). Prognostic estimates on an individual patient’s clinical course can be made by the volume, location, and infection status of the necrosis. While sterile pancreatic necrosis can be localized and compartmentalized by the body, infected pancreatic necrosis (IPN) serves as a nidus for bacteria and fungus, which is thought to be the key driver of organ failure, systemic sepsis, and death.

PATHOPHYSIOLOGY OF SECONDARY PANCREATIC INFECTIONS

Loss of both pancreatic parenchyma and its associated exocrine duct system allows leakage of pancreatic enzymes into the retroperitoneum, inciting further inflammation, fat necrosis, and fluid sequestration. It is within these areas of devitalized tissue (pancreatic and peripancreatic necrosis) and fluid (postnecrotic pancreatic fluid collections) where secondary pancreatic infections with bacteria or fungus can occur. The at-risk population for secondary pancreatic infection includes those patients with necrosis of more than 30% of their gland based on CECT, while patients with lesser volumes of necrosis have a good chance for resolution. Although the exact mechanisms contributing to secondary pancreatic infections remain uncertain, the predominant cultured pathogens imply an origin from the gastrointestinal (GI) tract. Gastric microbial colonization combined with alterations in intestinal permeability can lead to microbial translocation, which has been hypothesized as a mechanism for secondary pancreatic infections. This hypothesis, if true, might explain why both early enteral nutrition and selective gut decontamination have shown beneficial effects in decreasing secondary pancreatic infections in this setting.

CLINICAL COURSE OF SAP

The clinical course of patients with SAP can be divided into 2 phases. There is an early cytokine-mediated phase (within the first week of onset), distinguished by frequently reversible organ failure (most commonly pulmonary and/or renal) that is a consequence of the systemic inflammatory response syndrome (SIRS). In this early disease phase, deaths are attributable to MOD, mediated predominately by cytokines rather than infection. Volume resuscitation, organ support, enteral nutrition, and the search for a treatable cause of MOD (eg, bacteremia, pneumonia, ischemic colitis, or

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**Box 1**

**Definition for SAP**

- ≥30% pancreatic necrosis of CECT
  - or
- Noncontrast scans with extensive or multiple peripancreatic fluid collections and pancreatic edema (Bathazar grade E)
  - and either
- C-reactive protein (CRP) >120 mg/L
  - or
- Multiple organ dysfunction (MOD) score >2

*Data from Refs.*
If antibiotics are used in this setting, they are targeted at active infection (eg, bacteremia, pneumonia, or gangrenous cholecystitis) or started empirically (on demand) for a 72-hour course in a critically ill patient who is spiking fevers or deteriorating without an obvious source of infection. This use of antibiotics is common in critically ill patients in the intensive care unit and has been estimated to decrease mortality by up to 50% in patients with gram-negative sepsis. In this early time period following the onset of SAP, infected pancreatic necrosis is unusual, while infections in the lungs, kidneys/bladder, or bloodstream predominate. Once the source of infection is accurately identified, targeted antibiotic therapy and source control (eg, line change or cholecystectomy) can be instituted.

The second clinical phase of the disease occurs later (usually 2–4 weeks following onset), when patients develop systemic sepsis (fevers, tachycardia, or leukocytosis) combined with either persistent or new-onset MOD. Secondary pancreatic infection with bacterial and/or fungal organisms is a likely cause for this clinical deterioration. The development of infected pancreatic necrosis has been shown to peak between weeks 2 and 4. While secondary pancreatic infections (IPN and infected postnecrotic pancreatic fluid collections [IPNPFC]) are important complications in this secondary disease phase of SAP, other infectious complications can occur, requiring a thorough investigation for other possible sources of infection (blood, urine, invasive lines, or stool) (Table 1). If IPN is suspected, making a firm and accurate diagnosis is essential, as early intervention (<4 weeks after disease onset) in patients with pancreatic necrosis (particularly major open operations) has been associated with a poor clinical outcome.

**DIAGNOSIS OF SECONDARY PANCREATIC INFECTION**

IPN requires a prompt accurate diagnosis, targeted antimicrobial therapy, and a step-up approach to therapeutic intervention. Only a positive culture or Gram’s stain
from image-guided (CT or ultrasound) percutaneous fine-needle aspiration (FNA) or direct necrosectomy serves as definitive evidence of a secondary pancreatic infection. Occasionally, the presence of extraluminal gas (small air bubbles) in the non-enhancing areas of a CECT in a patient with pancreatic necrosis can be highly suggestive of infection, assuming that the extraluminal air is a consequence of gas-forming organisms in the necrosis and not localized GI tract perforation. In both instances, while the necrosis is infected, in certain situations with a localized perforation, the necrosis is able to slough into the GI tract and resolve as a consequence of an unplanned internal drainage. Although FNA can be very useful in certain situations, several caveats need to be considered. The indications for, timing of, and frequency of repeated FNA in patients with SAP are topics of considerable debate. Because of these uncertainties, specific guidelines for use of CT-guided FNA for early detection of infected pancreatic necrosis have not been clearly established. FNA is associated with a false-negative rate of approximately 10%, and although false positives can theoretically occur, they are extremely rare. Therefore, a single negative FNA should not be relied upon to rule out secondary pancreatic infection and should be repeated if the clinical suspicion for infection remains high. Lastly, FNA carries a small but real risk of contaminating sterile necrosis with bacteria. In an appropriate setting, during a single aspiration, this risk seems acceptable; however, frequent repeated aspirations should be discouraged. Given these considerations, image-directed FNA for Gram’s stain and culture should only be obtained in the situation where the result (either positive or negative) is going to directly impact treatment decisions. There are circumstances where experienced pancreatic surgeons will manage patients throughout their entire clinical course without image-directed FNA, choosing instead to follow patients clinically for resolution of symptoms and their return to wellness. In those patients who remain unwell (pain, inability to eat, organ dysfunction) despite 3 to 4 weeks of medical management and who have large volumes of retroperitoneal debris (necrosis) benefit from necrosectomy as further medical care is unlikely to result in resolution of the patient’s symptoms.

**MICROBIOLOGY OF SECONDARY PANCREATIC INFECTION**

The organisms most commonly cultured from secondary pancreatic infections include: gram-negative aerobic coliform bacteria (*Escherichia coli*, *Klebsiella*, *Enterobacteriacea*), gram-positive aerobic bacteria (*Staphylococcus*, *Streptococcus*) and fungi (*Candida* species) (Table 2). Anaerobic bacteria have been cultured in approximately 8% to 15% of patients, while fungal infections are present in 20% to 25% of

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<tr>
<th>Infectious Complications</th>
<th>Incidence of Complication</th>
<th>Timing of Complication After Onset of SAP</th>
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<tbody>
<tr>
<td>IPN</td>
<td>47% (31/65)</td>
<td>17.6 ± 2.9 d</td>
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<tr>
<td>Pneumonia</td>
<td>28% (18/65)</td>
<td>10.7 ± 2.5 d</td>
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<tr>
<td>Bacteremia</td>
<td>11% (7/65)</td>
<td>13.7 ± 1.5 d</td>
</tr>
<tr>
<td>GI tract</td>
<td>8% (5/65)</td>
<td>16.8 ± 3.9 d</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6% (4/65)</td>
<td>20.5 ± 4.8 d</td>
</tr>
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There is some evidence that following the introduction and routine use of prophylactic antibiotics in the 1990s, the bacteriology of secondary pancreatic infections shifted from gram-negative coliforms toward more gram-positive infections (ie, *Staphylococcus epidermidis*), resistant bacteria (ie, methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-resistant *Enterococcus* [VRE]), and fungi. This shift is important to note when one is selecting broad antimicrobial coverage to treat potential pathogens in an on-demand fashion before definitive culture results being available. In spite of this changing bacteriologic spectrum, there are few data to suggest that infected pancreatic necrosis with antibiotic-resistant organisms (eg, MRSA or VRE) has any worse outcome following appropriate treatment and source control than infected pancreatic necrosis with antibiotic-sensitive organisms. In contrast, there are some data to suggest that secondary bacterial infection with *Candida* is associated with an increased in-hospital mortality rate.

### PROPHYLACTIC ANTIBIOTICS IN SAP

The role of antibiotic prophylaxis in SAP has undergone a cyclical evolution. Early prospective, clinical trials in the 1970s failed to show a benefit in mortality rate using prophylactic antibiotics in patients with acute pancreatitis, although these studies were justly criticized for the inclusion of patients with mild forms of pancreatitis and the use of ampicillin, a drug subsequently shown to not penetrate sufficiently into the pancreas. With the development of powerful new antibiotics against enteric organisms in the 1990s, coupled with better laboratory and imaging methods to stratify the clinical severity of an episode of pancreatitis, use of prophylactic antibiotics in patients with SAP was again tried.

Support for this practice began to appear with the publication of small prospective randomized clinical trials showing that administration of prophylactic antibiotics in patients with SAP could reduce the incidence of pancreatic infections, reduce both infection rates and mortality, or reduce pancreatic infections, need for operation, and late mortality. These clinical trials were small, used different drugs on different schedules, measured different outcomes, and lacked appropriate placebo controls. Despite these methodological difficulties, pooling of these trials under the rubric of a meta-analysis showed a benefit for antibiotic prophylaxis.

### Table 2

**Common microbiologic isolates from IPN**

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<thead>
<tr>
<th>Gram-Negative Bacteria</th>
<th>Gram-Positive Bacteria</th>
<th>Fungal Organisms</th>
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<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td><em>Enterococcus sp.</em></td>
<td><em>Candida albicans</em></td>
</tr>
<tr>
<td><em>Klebsiella pneumonia</em></td>
<td><em>Staphylococcus aureus</em></td>
<td><em>Candida glabrata</em></td>
</tr>
<tr>
<td><em>Enterobacteriacea</em></td>
<td><em>Staphylococcus epidermidis</em></td>
<td></td>
</tr>
<tr>
<td><em>Proteus sp.</em></td>
<td><em>Streptococcus sp.</em></td>
<td></td>
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<tr>
<td><em>Pseudomonas aeruginosa</em></td>
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<td></td>
</tr>
<tr>
<td><em>Citrobacter sp.</em></td>
<td><em>Candida glabrata</em></td>
<td></td>
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<tr>
<td><em>Serratia sp.</em></td>
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<thead>
<tr>
<th>Anaerobe</th>
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<tbody>
<tr>
<td><em>Bacteroides sp.</em></td>
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<tr>
<td><em>Peptostreptococcus</em></td>
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<tr>
<td><em>Clostridia perfringens</em></td>
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*Gram-negative isolates—35%–55%.*
*Gram-positive isolates—20%–35%.*
*Anaerobic isolates—8%–15%.*
*Fungal isolates—20%–25%.*
*Data from Refs. 8,19,23–26*
In 2004 a large, prospective multi-institutional placebo-controlled double-blind trial of 114 patients with SAP randomized to ciprofloxacin and metronidazole or placebo was published showing no benefit to antibiotic prophylaxis in preventing infection in pancreatic necrosis. Following this, a second, similarly well-designed trial by Dellinger and colleagues echoed these prior findings, namely, there is no statistically significant benefit to the use of early prophylactic antibiotic in patients with SAP. One of the findings in these trials is that the equivalent outcomes between treatment and control groups in both studies spawned the idea that antibiotics given to critically ill patients on demand during the course of their hospital stay may be just as effective as continuous prophylactic antibiotics. Early and extensive use of broad-spectrum prophylactic antibiotics in critically ill patients should be discouraged unless there is compelling evidence as to their benefit. Currently, this level of evidence does not exist. The combined weight of these last 2 clinical trials will undoubtedly skew any future meta-analysis against routine prophylactic antibiotic use, making the current recommendations from the critical care society against routine prophylactic antibiotics especially prophetic.

ANTIMICROBIAL SELECTION AND TREATMENT

The spectrum of antibiotics chosen to treat IPN should include coverage for both aerobic gram-negative and gram-positive bacteria and anaerobes (see Table 1). When choosing appropriate antibiotic coverage, care should be taken to consider the classes of antibiotics that have optimal penetration into pancreatic tissue. Three groups of antibiotics have been carefully studied in this regard analyzing their penetration into the human pancreas when given intravenously in both the normal and inflamed pancreas. Aminoglycoside antibiotics (eg, netilmicin and tobramycin) in standard intravenous dosages fail to penetrate into the pancreas in sufficient tissue concentrations to cover the minimal inhibitory concentration (MIC) of the bacteria that are commonly found in secondary pancreatic infections. Acylureidopenicillins (mezlocillin and piperacillin) and third-generation cephalosporins (ceftizoxime and cefotaxime) have an intermediate penetration into pancreas tissue but are such effective bactericidal agents against gram-negative microorganisms that even with slightly lower tissue concentrations they can cover the MIC for most gram-negative organisms found in pancreatic infections. Unfortunately, these compounds as a group are much less effective against gram-positive bacteria and anaerobes. If used, they should optimally be paired with drugs used to treat gram-positive bacteria or anaerobes. Quinolones (ciprofloxacin and ofloxacin) and carbapenems (imipenem) both show good tissue penetration into the pancreas as well as broad-spectrum bactericidal activity against gram-negative and gram-positive bacteria. Carbapenems have the additional benefit of excellent anaerobic coverage. Metronidazole, with its bactericidal spectrum focused almost exclusively against anaerobes, also shows good penetration into the pancreas. Given these pharmacokinetic and microbial spectrum data, quinolones plus metronidazole or carbapenems should be the initial drugs of choice to treat secondary pancreatic infections. Prophylactic antifungal coverage should be considered in all severely ill surgical patients with multiple risk factors for invasive candidiasis due to the substantial and convincing data for its efficacy. Much less clear at present is whether these recommendations for Candida prophylaxis in surgical patients should be broadened to include their use in severely ill patients with pancreatic necrosis. Patients with yeast on Gram’s stain following CT-guided FNA or direct culture at the time of necrosectomy should receive fluconazole targeted at Candida albicans, the most common
fungal isolate in secondary pancreatic infections. *Candida glabrata*, which has a higher MIC for fluconazole than *C. albicans*, should be treated either with a higher dose of fluconazole (400 mg/d) to achieve greater concentrations in the pancreas, or caspofungin. Those patients who have been treated with fluconazole prophylactically and subsequently develop infected necrosis with yeast should be treated with caspofungin.38

Although initiation of antimicrobial therapy may be difficult, stopping antibiotics often times proves even more challenging, as there are currently no tools available to guide antibiotic therapy.39 The clinical criteria used to initiate antibiotic treatment in patients with a predicted severe course of acute pancreatitis include: newly developed sepsis or SIRS, newly developed failure of 2 or more organ systems, proven pancreatic or extrapancreatic infection, or an increase in serum C-reactive protein in combination with evidence of pancreatic or extrapancreatic infections.25 The clinical criteria to stop antimicrobial therapy in surgical patients have classically been the absence of fever and a normal white blood cell count. Secondary pancreatic infection in a patient with pancreatic necrosis in the past was considered an absolute indication for open pancreatic necrosectomy.19 Over the last decade, there has developed a more nuanced appreciation of the complex relationship between infection, the patient, and the approach and timing of intervention. Currently, in critically ill patients with early onset secondary pancreatic infection (<2 weeks), percutaneous drainage and antibiotics can be effective until the patient’s clinical course can be stabilized to allow for definitive necrosectomy. Several new minimally invasive techniques are available for necrosectomy, and these can optimally be delayed until the third or fourth week after disease onset, limiting the perioperative morbidity and mortality.39 Although there are scattered reports in the literature of patients with documented secondary pancreatic infections who have been treated successfully by antimicrobial therapy alone,40 most clinicians believe that intervention via a step-up approach is an important adjunct to antimicrobial therapy for optimal source control.18

REFERENCES