Infections in Acute Pancreatitis: A Review

Chetana Vaishnavi¹, Nikhil Bush², Rakesh Kochhar³

ABSTRACT
Acute pancreatitis (AP) is an unpredictable disease accounting for more than 50% of all hospital admissions for pancreatic diseases. The disease is generally mild and self-limiting, but about 20% of the patients develop moderate to severe AP with poor prognosis leading to high morbidity and mortality. Recently increased occurrence of AP has been noted with severe AP requiring several weeks to months for treatment. Acute pancreatitis may get complicated by pancreatic and/or peripancreatic necrosis, which may become infected through several routes. The pathogenesis of secondary bacterial pancreatic infection is still under controversy. Acute pancreatitis is the setting for most infections of the pancreas, which can complicate various stages of pancreatitis. Some patients, AP develops into necrotizing pancreatitis. Patients with AP-related infected pancreatic necrosis (IPN) are prone to develop organ failure, leading to increased mortality, further complicated by multidrug-resistant (MDR) microorganisms. The bacterial spectrum in IPN reflects the commensal flora of the intestine. Clinically, there are no reliable parameters to distinguish infected from sterile necrosis as the clinical features are indistinguishable from other infectious conditions. Infected pancreatic necrosis can be diagnosed mainly by laboratory methods like culture and radiographic scan. The management of AP has developed considerably during the past decades. The preferred choices are primary conservative and minimally invasive modalities compared to open surgical necrosectomy. Antibiotics are generally not given to patients with severe AP because of limited clinical benefits. Various aspects of infections of AP inclusive of diagnostic and management modalities have been reviewed here.

Keywords: Diagnosis, Infected pancreatic necrosis, Management, Pancreatic infections.


INTRODUCTION
Acute pancreatitis (AP) is a reversible inflammatory disease of the pancreas with acinar cell destruction¹ and characterized by pain in abdomen and increased pancreatic enzymes.² Acute pancreatitis is the most unpredictable disease of the digestive system and accounts for more than 50% of all hospital admissions for pancreatic diseases.³ The disease is generally mild and self-limiting. However, about 20% of the patients develop moderate to severe AP. Severe AP has poor prognosis because of infectious complications and leads to higher morbidity, with mortality up to 35%.⁴ Globally, AP accounts for 1–60 deaths per 100,000 person-years, with an approximate mortality rate of 2–9%.⁵,⁶ The reported incidence of AP varies from 12 to 38 per 100,000 population.⁷,8 The indicators of infection include older age group, severity of pancreatitis, and earlier antibiotic use. Significant decrease in mortality can be possible with targeted therapy that can control systemic inflammation.

In recent years, the occurrence of AP has been notably rising,⁹ and because of its impending grave nature, particularly for severe AP, there is an increased claim on healthcare resources, as it requires several weeks to months for treatment. In this review, focus shall be made on various aspects of infections of AP, inclusive of diagnostic methods and commonly used management modalities.

PATHOGENESIS
Acute pancreatitis may appear as an interstitial disease or it may be complicated by pancreatic and/or peripancreatic necrosis, which may become infected in up to 40% of cases.¹⁰ The pathogenesis of secondary bacterial pancreatic infection is still under controversy. The pathogens can get into the pancreas through several routes such as the hematogenous route, through transmural colonic migration, or through the biliary system.¹¹ Acute pancreatitis is the setting for most infections of the pancreas, which can complicate various stages of pancreatitis. About 15–20% of patients develop moderately severe or more severe disease.¹² In a small group of patients, AP takes a serious course and develops into necrotizing pancreatitis that is characterized by localized or generalized necrotic parenchymal necrosis and/or necrosis of the retroperitoneal peripancreatic fat. Patients who develop severe AP at an early stage have a high mortality rate.¹³,¹⁴ Infected pancreatic necrosis (IPN) is an independent predictor of outcome in AP.¹⁵,¹⁶ The mortality in AP ranges from 4% to 25%.¹⁴,¹⁵,¹⁷ An important role is played by translocation of microorganisms across the intestinal wall and their virulence, and dysfunction of the lymphocytes. When the pancreatic necrosis becomes infected, mortality rate may go up to 30–32%.¹⁶,¹⁸,¹⁹ There are two incidence peaks of mortality in AP.²⁰ The early phase or the first incidence peak occurs within the first week, when the immune system is enormously activated. This phase is associated with up to 50% of all deaths during the first 2 weeks of illness and mortality occurs due to multiple organ failure. In the late phase or the second incidence peak that can last for weeks to months, the mortality generally occurs due to sepsis.²¹,²² The peak of the infection ranges from the 2nd to 4th week after the onset of pancreatitis.²³ The mean duration of infection is generally after 10 days of illness and peaks during the 2nd to 4th week after the onset of pancreatitis.²⁴

© The Author(s). 2019 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
In a meta-analysis of systemic reviews comprising of 6,970 patients, the mortality rate reported was 35.2%. Jain et al. in a prospective study in 206 AP patients reported 22% overall mortality with deaths among 52% patients with severe AP, particularly in those with multiple organ failure. Higher mortality (42%) was observed among patients with infected acute necrotic collections compared to infected walled-off necrosis (33%).

Patients with AP-related IPN frequently develop organ failure and therefore IPN may be associated with increased mortality, which can be further complicated by multidrug-resistant (MDR) microorganisms. Thandassery et al. in their study of 81 AP patients reported hypotension and APACHE II score at 24 hours of hospital admission as independent predictors of occurrence of IPN. The rate of infection correlates with the extent of pancreatic necrosis and its bacterial contamination. The immunologic mechanisms to prevent the proliferation of bacteria and fungi are absent in the necrotic tissue.

**Infected Necrosis vs Sterile Necrosis**

Microbial translocation is defined as the passage of both viable and nonviable microbes and microbial products across an anatomically intact intestinal barrier. Translocation of viable microbes causes sepsis requiring antibiotic prophylaxis whereas nonviable bacterial products like pathogen-associated molecular patterns (PAMPs) cause systemic inflammatory response syndrome (SIRS) where antibiotic use is futile. In about half the number of AP patients, SIRS leads to multiple organ failure and subsequent death.

Clinically, there are no reliable parameters to distinguish infected from sterile necrosis. Microbial PAMPs such as lipopolysaccharides (LPS) activate innate immunocytes through pattern recognition receptors. The immune system also detects “danger,” through damage-associated molecular pattern (DAMP) molecules derived from other tissues. Thus, DAMPs stimulate an acute-phase response that is biologically concordant with PAMPs released during infection. This explains why it is difficult to distinguish infectious from noninfectious SIRS or to identify single molecules or molecular patterns of the host response that allow this distinction. Pathogen-associated molecular patterns cause infection when present on viable bacteria. Nonviable bacteria and microbial products (LPS), which are released spontaneously upon exposure to various triggering factors like bacterial death by antibiotics, can be accompanied by an inflammatory response. The clinical phenotype of a patient with sepsis may be similar to that of a patient with a SIRS caused by sterile inflammation like pancreatitis.

Bacterial infection of pancreatic necrosis can be seen in 30–50% of patients of necrotizing pancreatitis. Clinical indicators for sepsis like fever and leukocytosis have been found to be higher among patients with IPN. The development of new onset fever, tachycardia, worsening SIRS, or organ failure should prompt evaluation for sepsis and suspicion of infected necrosis. The presence of gas or air bubbles in the collection is highly suggestive of infection but is present only in a minority of cases. Infection rates progressively increase with duration of the disease with highest incidence in the 3rd week. A direct correlation between extent of necrosis and incidence of infection has been demonstrated in a previous study where 56% of patients with more than 50% necrosis had infection as compared to 16.7% of those with less than 30% necrosis.

**Pancreatic vs Extrapancreatic Infections**

Pancreatic infections may present itself as IPN that occurs earlier in the course of the disease or as infected pseudocysts and pancreatic abscesses that are the sequelae of acute necrotizing pancreatitis occurring more than a month after the acute episode. Infections in severe AP can be pancreatic or systemic and the prevalence usually correlates with the extent of pancreatic necrosis. The probability of super infection of necrosis increases from 24% in the 1st week of the illness to 36% in the 2nd and 71% in the 3rd week. Patients with extensive necrosis are at greater risk than those with focal necrosis. The main source of infections of the pancreas is direct translocation of bacteria from the large intestine. During such times, the intestinal barrier fails, allowing the organisms to translocate to mesenteric lymph nodes, the systemic circulation, the portal venous circulation, the peritoneal cavity, and abdominal organs, with resulting suppurating sepsis and critical complications. This could explain pancreatic infection with *Escherichia coli*, which is reported to be the most common organism in this setting. The exact mechanism of bacterial translocation however is controversial and could be via lymphatics and consecutive hematogenous spread, or transurally to the pancreas. Stress, like acute inflammation, renders the pancreas vulnerable to bacterial infections.

In the majority of patients, AP is generally mild and accompanied by minimal retroperitoneal inflammation and a peripancreatic fluid collection. In fact, AP is the setting for most infections of pancreas, which can complicate various stages of pancreatitis. In about 20% of the patients, peripancreatic fluid collection may be secondary to disruption of the pancreatic ductal system that later on develops into a pancreatic pseudocyst. In 20–40% of patients with severe AP infection, pancreatic and peripancreatic necrosis may occur, leading to deterioration of organ functions.

Infection of the (peri) pancreatic necrosis occurs in about a third of these patients, which leads to 15–39% mortality rates. Half of the mortality occurs later from complications secondary to the infection of (peri) pancreatic necrosis and the ensuing interventions. In a study by Garg et al. extrapancreatic bacterial infections were found in 31.7% of 63 patients. In a multicenter audit from Italy, 56 of 161 patients with demonstrated pancreatic necrosis developed infection. Bourgaux et al. reported extrapancreatic infections in 25% of their AP patients. In a group of 713 patients, of whom only 154 had documented pancreatic necrosis, Besselink et al. reported IPN in 98 patients, yielding an incidence of 63.3%. Petrov et al. in a meta-analysis of 14 studies comprising of 1,478 AP cases reported IPN in 314 (21%) patients, with an incidence in the individual reports ranging from 4% to 63%. Noor et al. observed pancreatic infections in 37.3% of patients and extrapancreatic infections in 62.7% of patients with severe AP with a significant increase in mortality.

Pando et al. studied the role of extrapancreatic infections in the prediction of severity and local complications in AP and found that extrapancreatic infections played a role in predicting the severity and local complications in AP and when bacteremia and IPN occur, bacteremia preceded infected necrosis in all cases. Grajales-Figueroa et al. demonstrated increased global mortality rate of 2.5% (57/2,227 AP patients) from extrapancreatic infections in hospitalized patients with AP over a period of 10 years.

**Organisms**

The bacterial spectrum in IPN reflects the commensal flora of the intestine with predominantly gram-negative organisms such as *E. coli*, *Pseudomonas aeruginosa*, *Proteus* spp., and *Klebsiella* spp. *E. coli* is also reported in many other studies to be the most common isolate in pancreatic infections, though in one study, *Klebsiella* was reported to be the most common isolate.
However, at times, gram-positive bacteria viz. *Staphylococcus aureus*, *Streptococcus faecalis*, *Enterococcus*, and anaerobes have also been found accountable for pancreatic infections. Monomicrobial infections were reported to be more common than polymicrobial. Isenmann et al. reported a polymicrobial prevalence of 15–40% among isolates. Furthermore, isolation of polymicrobial spectra should raise suspicion of fistula formation or bowel communication.

A change in the infective spectrum from gram-negative bacteria to that of gram-positive cocci and *Candida* especially in necrotizing pancreatitis patients on prophylactic antibiotics was reported by Isenmann et al., which was probably associated with increasing length of hospital stay or related to prophylactic antibiotics administration mainly targeting gram-negative bacteria. Infections with gram-positive organisms occur later due to nosocomial bloodstream spread. Noor et al. studied 51 patients with severe AP and noted pancreatic infection in 19 (37.3%) patients (14 monomicrobial, 5 polymicrobial) with *E. coli* as the predominant organism. They also reported 21 positive blood cultures in 16 patients with severe AP and *S. aureus* was the predominant microorganism followed by *E. coli*, *Enterobacter aerogenes*, *Alcaligenes xylosoxidans*, *E. faecalis*, *P. aeruginosa*, *Acinetobacter baumannii*, and *K. pneumonia*.

Resistant bacterial isolates were detected in 15.6% of the necrotic collections in a study by De Waele et al. However, more recent studies have shown an increasing incidence of MDR organisms in pancreatic infections. Jain et al. reported culture positivity in 81% of 108 IPN patients with 86% growing MDR organisms. They reported *E. coli* in 48 (32%) and *E. faecium* in 10 (7%) of 149 isolates. Mowbray et al. investigated the microbiology of 40 IPN patients and reported the most frequently identified microbes as *E. faecalis* (22.5%), *E. faecium* (20.0%), and *E. coli* (20.0%), with 19 cultures being polymicrobial. Sahar et al. investigated the microbiology of infected walled-off pancreatic necrosis in 182 AP patients of which 41% were infected. Though MDR organisms were found in only five patients, *Candida* spp. accounted for 27%. Of those, 55% were infected, most frequently with *Candida* spp., *Enterococcus* spp., and coagulase-negative *Staphylococcus*. Around 85% had symptomatic sterile walled-off necrosis treated with minimally invasive therapy, enabling judicious selection of empiric antibiotic use.

Grajales-Figueroa et al. demonstrated microbiological isolates in IPN in AP patients who died during hospitalization as *Staphylococcus* spp. (10 no.; 47.6%), *E. faecium* (9 no.; 42.8%), *P. aeruginosa* (7 no.; 33.3%), *Candida* spp. (6 no.; 28.5%), and *E. coli* (5 no.; 23.8%).

Würstle et al. analyzed the spectrum of pathogens and their resistance to antibiotics as regards to the time course of the disease and its clinical outcome in 122 patients in Germany. They isolated 309 microorganisms (26 genera, 61 species) viz. *Actinomyces* spp., *Aeromonas* spp., *Bacteroides* spp., *Citrobacter* spp., *Clostridium* spp., *Corynebacterium* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Fusobacterium* spp., *Haemophilus* spp., *Klebsiella* spp., *Lactobacillus* spp., *Morganella* spp., *Neisseria* spp., *Parvimonas* spp., *Peptostreptococcus* spp., *Prevotella* spp., *Proteus* spp., *Pseudomonas* spp., *Rothia* spp., *Serratia* spp., *Staphylococcus* spp., *Stenotrophomonas* spp., *Streptococcus* spp., and *Veillonella* spp. The authors also observed change at species level of *E. faecalis* to *E. faecium* and *Candida albicans* to non-albicans *Candida* spp. There was a 59.7% decrease in antimicrobial susceptibility in the overall number of patients with *Enterobacteriaceae* and a 46.0% increase in the incidence of MDR bacteria with increased length of hospital stay. A significantly higher mortality was observed for non-albicans *Candida* spp., *E. faecium*, and MDR bacteria suggesting that antimicrobial treatment of IPN becomes more challenging over time, due to an increase of multiresistant difficult-to-treat pathogens leading to worse clinical outcomes.

**Diagnosis**

Infected pancreatic necrosis can be diagnosed mainly by laboratory methods as the clinical signs may be sensitive but not specific. Clinically, there are no reliable parameters to distinguish infected from sterile necrosis as the clinical features are indistinguishable from other infectious conditions. Recently Qiu et al. reported that artificial neural networks can accurately predict intra-abdominal infection in moderately severe and severe AP.

Laboratory methods for diagnosis of pancreatic infections are mentioned below:

**Culture**

Identification of microorganisms can be done by culturing the pancreatic and peripancreatic fluid, which reveals the infecting bacteria that originate from the gastrointestinal tract. Isolating organisms from infectious fluid collections gives an opportunity to correlate them with the normal intestinal flora, thus helping confirm their origin. Correlation of pancreatic infection by blood culture will help to determine the hematogenous route of spread of infection. Computed tomography (CT)-guided fine needle aspiration (FNA) of necrosis for Gram staining and culture of the organisms is the diagnostic tool of choice, as it can help the clinicians in selecting the most suitable antibiotics. A positive culture or Gram’s stain of FNA fluid can confirm infected necrosis with a false-negative rate of 20%. In the past, a positive aspirate was thought to mandate surgical intervention. However, subsequent studies have refuted this claim and hence its clinical relevance in today’s scenario has diminished. The principle is to avoid early intervention to the maximum and limit tissue or fluid sampling to the time of intervention that is usually late in the course of the disease in order to avoid risk of external contamination and superinfection. Most standard guidelines recommend against this practice and hence should be avoided.

**Molecular Methods**

Molecular identification of isolated bacteria and determination of their antibiotic sensitivity require less time than conventional culture and therefore can be useful for diagnosis. It also helps to guide the clinicians about the appropriate antibiotic to be used for a particular patient, and thereby reduce drug resistance and the consequent mortality.

The molecular method for identification of the organisms via polymerase chain reaction (PCR) is better as it is more sensitive and specific, and is therefore the most widely used technique, as the organisms missed during culture can also be picked up by PCR. Polymerase chain reaction may be especially useful when antibiotics are used empirically when routine culture is negative or yield of fluid aspirate is meager. One limitation of this technique lies in its inability to differentiate between viable and nonviable cells and the resulting overestimation of microbial targets. A promising strategy to avoid this issue relies on the use of nucleic acid intercalating dyes, such as propidium monoazide (PMA), as a sample pretreatment prior to PCR for live/dead distinction. Propidium monoazide penetrates only cells with compromised cell membranes and hence its clinical relevance in today’s scenario has diminished.
membranes and once inside the cell, PMA intercalates into the DNA to which it can be covalently cross-linked upon exposure to light. This irreversible DNA modification results in suppression of PCR amplification.62–64 Although the dye is membrane-impermeable in viable cells, environmental stresses increase the permeability of PMA into the cell wall in killed bacteria.65

CT Scan: Air in Pancreas for Diagnosis
In some of the patients with severe AP, the presence of gas in the retroperitoneal area signifies infection in the pancreas.58 Radiologically contrast-enhanced CT scan is the primary imaging modality for identification of pancreatic necrosis, and the CT severity index can be useful in quantifying the extent of necrosis, which probably correlates with the possibility of developing infection.13,15 Air bubbles, if detected within the necrotic pancreas, are indications of infection (Figs 1 and 2). Positive culture from FNA is the gold standard for confirming IPN. However, Gram stain is usually positive in almost all patients with infected necrosis. The CT-guided FNA has a reported sensitivity and specificity exceeding 95%, while ultrasound-guided FNA has sensitivity of 88% and specificity of 90%.66,67

In the majority of patients with mild AP, CT scan is not necessary. However, if there is a deterioration of their symptoms or there is no improvement, CT scan would be required, which can be suspected by clinical and laboratory evaluation.68

Procalcitonin as a Marker of Infection
Investigation of biomarkers like procalcitonin (PCT) will be useful as adjunct diagnosis. Elevated PCT levels are promising markers of infection in necrotizing pancreatitis with reported sensitivity of 75–94% and specificity of 83–91% from small studies.69 Estimation of PCT may therefore be valuable in predicting the risk of developing IPN. Ji et al.70 observed that the post-percutaneous catheter drainage (PCD) serum procalcitonin level might be a respondent factor that is correlated with the necessity of necrosectomy. However, Ivanusa et al.71 reported that measurement of procalcitonin for diagnosis of IPN is inadequate and therefore many other new markers of systemic infection introduced into clinical practice such as presepsin, MID-regional pro-adrenomedullinum, CD64 neutrophil index, etc., may be more useful.

**Prophylactic Antibiotics**
All standard guidelines do not recommend routine use of prophylactic antibiotics as no significant decrease in mortality and morbidity has been found with them.72–76 This is supplemented by multiple meta-analyses that have showed no benefit with antibiotics.76 The Japanese guidelines however recommend antibiotics in the severe pancreatitis in the 1st week. Pederzoli et al.77 reported that antibiotic administration could prevent infections in patients with sterile necrosis.

Antibiotics are generally not given to patients with severe AP because of limited clinical benefits. However, antibiotics may be useful in some patients with severe AP having infected necrosis but are unfit for surgical debridement and drainage.52 Because of the use of antibiotics such as carbapenem and third-generation cephalosporins, MDR microorganisms have increased.78–80

The incidence of MDR can be as high as 50% and microorganisms that are not covered by prophylactic antibiotic regimens become pathogens in subsequent infections. The emergence of MDR may be due to longer duration of antibiotic exposure. Thus, the use of prophylactic antibiotics to prevent pancreatic infection is not recommended. In view of the growing risk of MDR bacteria, antimicrobial prophylaxis has become a real challenge.81,82 Lee et al.83 reported MDR isolates in 29 of 46 IPN patients with no difference in mortality.

Nakaharai et al.84 determined in a population-based study of 3,354 eligible patients in Japan if early prophylactic antibiotics improved the outcomes of severe AP patients and concluded that routine early prophylactic antibiotic use has no significant clinical benefit in severe AP patients but may increase the risk of hospital-acquired infections. Mowbray et al.56 reported that antibiotics with the least resistance among the microbiota were teicoplanin (5.0%), linezolid (5.6%), ertapenem (6.5%), and meropenem (7.4%), and the latter two provide good antimicrobial cover against the common microorganisms causing IPN.

**Fungal Infections**
Recently fungal infections, particularly by Candida, are more and more being identified in severe AP. Risk factors to suspect fungal sepsis in AP include use of broad-spectrum antibiotics, central
venous access, presence of renal failure, high APACHE scores, use of parenteral nutrition, diabetes mellitus, percutaneous drainage, and hospitalization beyond 4 weeks. This negatively influences the clinical course of the disease with higher incidence of systemic complications leading to morbidity and mortality. De Waele et al. reported that though the characteristics of patients with and without fungal infections as well as the mortality rate were insignificant, early treatment with fluconazole could prevent fungal infection in their patients.

Antibiotic Treatment

The spectrum of pathogens isolated from the IPN helps to decide the choice of antibiotics. Most of the bacteria are sensitive to beta lactam antibiotics, aminoglycosides, and imipenem whereas application of broad-spectrum antibiotics bears the risk for a patient of AP to develop deep fungal infections. Antimicrobial susceptibility test of selected microorganism helps determine the possible drug resistance in common pathogens and helps to assure susceptibility to drugs of choice for infections. Principles of antimicrobial stewardship include noticing changed pharmacokinetics in the critically ill, decreasing broad-spectrum therapy upon receiving culture reports, and early removal of antibiotics after establishing the source control. This will help to avoid the development of antimicrobial resistance, particularly in patients who may need frequent courses of antibiotics during the course of their disease.

Antibiotic therapy is indicated if pancreatic necrosis is suspected or confirmed on imaging. These patients have a 20–40% risk of superinfection in the retroperitoneum. The spectrum of pathogens isolated from the IPN helps to decide the choice of antibiotics. Another important deciding factor is the penetration of the antibiotic in the pancreas as selective uptake of various different classes of antibiotics occurs in the pancreas. Adequate tissue concentration in the pancreas occurs with fluoroquinolones, carbapenems, and metronidazole whereas ampicillin and gentamicin do not attain effective therapeutic levels in the pancreatic tissue. Metronidazole is suitable only as an adjunct agent for additional anaerobic coverage. The recommended antibiotics are either a combination of a quinolone (ciprofloxacin or ofloxacin) with metronidazole or, alternatively, monotherapy with imipenem–cilastatin.

In cases of infected AP, antibiotics are always recommended to treat the patients. Acylureidopenicillins and third-generation cephalosporins are effective against gram-negative microorganisms found in pancreatic infections. However, for gram-positive organisms and anaerobes, only piperacillin/tazobactam is effective. Quinolones (ciprofloxacin and moxifloxacin) and carbapenems have the extra advantage of excellent anaerobic coverage apart from good tissue diffusion into the pancreas. In terms of tissue penetration, carbapenems have the highest efficacy followed by fluoroquinolones and aminoglycosides. Hence, either of them is preferred for initial management. Appropriate application of antimicrobial treatment is required for treatment of severe AP, which is marked by organ failure and (peri) pancreatic necrosis with local complications such as infected necrosis. Leppänen et al. in their guidelines for the management of severe AP suggest that quinolones should be used only in patients with allergy to beta lactams because of their high rate of resistance and carbapenems should be used only in very critically ill patients after optimization due to dissemination of carbapenem-resistant K. pneumonia. The bactericidal antibiotic metronidazole also is capable of penetration into the pancreatic tissue. However, standard intravenous dosages of aminoglycoside antibiotics like gentamicin...
and tobramycin are unable to penetrate into the pancreas in required concentrations.\textsuperscript{100}

Longer duration of antimicrobial treatment in patients with severe AP is done in order to delay surgery. However, when the antimicrobial treatment is prolonged, there is a risk for consequent fungal infection or antibiotic resistance. Jain et al.\textsuperscript{105} observed that among those who received prophylactic antibiotics, the rate of isolation of MDR organisms was not significantly different from those who did not receive prophylactic antibiotics.

**OTHER MODES OF MANAGEMENT**

The management of AP has developed considerably during the past decades. The preferred choices are primary conservative and minimally invasive modalities compared to open surgical necrosectomy\textsuperscript{101-103} with decreased mortality.\textsuperscript{104} In patients who are asymptomatic, strong suspicion of IPN would require interventions, even though some of them may recover with antibiotics only.\textsuperscript{105} Wolbrink et al.\textsuperscript{106} advocated invasive diagnostics (e.g., through FNA) for management of IPN in the intensive care unit, prior to the start of broad-spectrum antimicrobial therapy. Surgical necrosectomy with antifungal prophylaxis is the most widely used treatment modality.

**Endoscopic or Surgical Treatment**

Patients with intra-abdominal-infected necrosis generally receive endoscopic or surgical treatment, which results in an extended hospital stay.\textsuperscript{107} Walled-off necrosis or pseudocysts, when they do not resolve, need an intervention. In a report of 178 cases with walled-off necrosis, 96% of the patients were subjected to surgical transgastric necrosectomy, with only 2% postoperative mortality and 38% morbidity.\textsuperscript{108} It is also a good option in patients with a disconnected duct syndrome.

**Percutaneous Catheter Drainage**

Open surgery is regarded to cause a more severe inflammatory response. Percutaneous catheter drainage of IPN allows delaying the later possible surgical intervention to a more favorable time.\textsuperscript{23} In a systematic review consisting of 11 studies and 384 patients, Diaz et al.\textsuperscript{109} reported PCD as primary treatment for necrotizing pancreatitis. Of these, 71% had IPN and 56% did not require surgery after PCD. Percutaneous drainage is required when a patient deteriorates.\textsuperscript{110,111} Large-bore catheters appear to be less often obstructed by the necrotic debris and therefore are more beneficial.\textsuperscript{112}

If PCD does not result in resolution of the infection, then other options such as open surgery, mini-invasive surgery, endoscopic surgery, or a combination of these can be tried. Shenvi et al.\textsuperscript{113} showed that PCD along with antibiotics was a successful line of treatment in 50% of IPN patients. Moreover, a study by Jain et al.\textsuperscript{114} in 10 patients showed that PCD prior to referral did not influence the development of MDR infection.

**Necrosectomy**

Necrosectomy can be done when the patient does not recover with drainage alone. Open necrosectomy has been largely replaced by minimally invasive techniques such as sinus tract endoscopy and video-assisted retroperitoneal debridement,\textsuperscript{114} which show decreased morbidity and mortality, especially in patients with high risk.\textsuperscript{107} An endoscopic approach to necrosectomy drastically reduces the proinflammatory response with a success rate of about 81%\textsuperscript{115} but requires repeated sessions for definitive treatment. Ji et al.\textsuperscript{70} assessed the need of surgical necrosectomy after PCD for IPN in 329 patients enrolled and concluded that both mean CT density of necrotic fluid collection and multiple organ failure are independent pre- and post-PCD risk factors for the need of necrosectomy after PCD.

**Nutritional Therapies**

Feeding by the enteric route sustains the intestinal mucosal barrier and stops the translocation of bacteria that causes pancreatic necrosis.\textsuperscript{23} It also decreases infectious complications, organ failure, and mortality as compared to total parental nutrition.\textsuperscript{116} Most institutions prefer continuous infusion over cyclic or bolus administration.\textsuperscript{23} Hsieh et al.\textsuperscript{117} reported that nutritional therapy via the nasogastric route was the most preferred therapy for AP whereas total parental nutrition was the least preferred route.

**ROLE OF PROBIOTICS**

Initially in several experimental studies, the prophylactic use of probiotics in AP was investigated. van Minnen et al.\textsuperscript{118} reported reduced overgrowth of potential pathogens, decrease in bacterial translocation, and reduced mortality with probiotics use in rats with AP. There were two randomized controlled trials (RCTs) from Hungary regarding use of probiotics in AP. The first trial in 45 AP patients showed that probiotics reduced pancreatic sepsis and the need for surgical intervention.\textsuperscript{119} In the second trial with 62 severe AP patients, Olah et al.\textsuperscript{120} concluded that nosojejunal feeding with synbiotics (inulin, beta-glucan, resistant starch, and pectin) may prevent organ dysfunction in severe AP.

Karakan et al.\textsuperscript{121} reported that supplementation of prebiotic fiber alone with enteral nutrition assessed in a randomized, double-blind study with 30 severe AP patients showed reduction of hospital stay, period of nutrition therapy, as well as overall complications compared to the usual enteral nutrition therapy. Bessink et al.\textsuperscript{122} reported a multicenter RCT where probiotics were compared with placebo in 298 patients with predicted severe AP. Probiotics were not found to reduce infectious complications, but rather increased the rate of bowel ischemia (9% vs 0%) and mortality (16% vs 6%) in the probiotics group. However, Qin et al.\textsuperscript{123} reported that the patients with probiotic therapy showed less disease severity, improved gut permeability, and better clinical results.

Cui et al.\textsuperscript{124} compared parenteral nutrition and enteral nutrition and the latter with the addition of the probiotic *Bifidobacterium* in 70 severe AP patients and reported that early enteral nutrition with *Bifidobacterium* resulted in reduced pro-inflammatory cytokines, improved gastrointestinal function, reduced complications, and shorter hospital stay. Gou et al.\textsuperscript{125} studied the use of probiotics in severe AP by including six relevant human RCTs in which a total of 14 strains of probiotic bacteria were used. In total, *Lactobacillus plantarum* was used in three trials: *B. longum*, *L. bulgaricus*, *L. paracasei*, *L. mesenteroides*, and *P. pentosaceus* were used in different combinations in two trials, and *B. bifidum*, *B. lactis*, *E. faecalis*, *L. acidophilus*, *L. casei*, *L. lactis*, *L. salivarius*, and *Streptococcus thermophilus* used in just one trial. The authors concluded that probiotics showed neither beneficial nor adverse effects on the clinical outcomes of patients with predicted severe AP. But Wu et al.\textsuperscript{126} investigated 120 patients with severe AP and found that probiotics could play a useful role in the treatment of severe AP. Bouwense et al.\textsuperscript{127} observed that currently there was no place for probiotics...
as a treatment for AP. As there was a heterogeneity in the types of probiotics and treatment strategies used, even though previous data imply the potential of single specific probiotic strains supplemented, further appraisal about the role of probiotics is required.128

**CONCLUSION**

A high index of suspicion is required for prompt diagnosis of pancreatic infections as early diagnosis and treatment can result in improved outcomes. Strict adherence to a rational antimicrobial treatment for patients with necrotizing AP is quite important. The antimicrobial therapy of IPN is more challenging with the length of the disease. Therefore, these patients can be managed well with appropriate diagnosis and identification of infection in order to improve the clinical outcome so that a change to narrow-spectrum antimicrobials can be done. Unnecessary antibiotic therapy without apparent proof of persisting infection should be avoided, as every antimicrobial treatment can lead to resistance, thereby complicating the treatment further. Other important preventive strategies include introduction of enteral nutrition and periodic change of vascular catheters. Furthermore, indications for surgical intervention should be defined and clinical trials on antifungal treatment are required.

**REFERENCES**


Pancreatic Infections

Pancreatic Infections


Pancreatic Infections


