Acute Pancreatitis Infections

GENERAL PRINCIPLES

- Acute pancreatitis (AP) is generally not caused by infection. However, secondary infection of pancreatic or peripancreatic collections in the setting of pancreatitis can occur.
- Necrotizing pancreatitis complicates 5-10% of cases of acute pancreatitis and most commonly manifests as necrosis of the pancreatic parenchyma and peripancreatic tissues.
- Infection is more likely to occur in the late stage of acute pancreatitis and in cases with necrosis. Most likely mechanism of infection is GI translocation into pancreatic tissues. Other mechanisms are possible (e.g. hematogenous or lymphatic seeding into the portal system).

Severity

1. **Mild:** no organ failure, no local or systemic complications, usually resolves in first week.
2. **Moderately Severe:** transient (<48hr) organ failure, local complications or exacerbation of co-morbid disease
3. **Severe:** persistent (>48hr) organ failure

- Severe acute pancreatitis complicates 20-30% of pancreatitis cases.
    - Mortality in severe acute pancreatitis is 15%
    - Pancreatic or peripancreatic infection complicates 20-40% of severe acute pancreatitis cases.
    - Patients with organ failure and infected necrosis have the highest risk of mortality

Local Complications of Acute Pancreatitis

Collections

	Interstitial edematous pancreatitis (no necrosis)	**Necrotizing pancreatitis**
Early (< 4 weeks)	Acute peripancreatic fluid collection	Acute necrotic collection
Late (≥ 4 weeks)	Pancreatic pseudocyst	Walled off necrosis

- **Acute peripancreatic fluid collection:** Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. No definable encapsulating wall. Most remain sterile and usually resolve spontaneously without intervention.
- **Pancreatic pseudocyst:** Encapsulated fluid collection with well defined inflammatory wall usually outside the pancreas with minimal or no necrosis. Usually occurs more than 4 weeks after onset of interstitial edematous pancreatitis to mature.
- **Acute necrotic collection:** Collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis. No definable encapsulating wall. Necrosis can involve pancreatic parenchyma and/or peripancreatic tissues.
- **Walled-off necrosis:** Mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well defined inflammatory wall. Usually occurs more than 4 weeks after onset of necrotizing pancreatitis.

Other local complications

- Other local complications of acute pancreatitis include gastric outlet dysfunction, splenic and portal vein thrombosis, and colonic necrosis.

MICROBIOLOGY

- Enterobacterales: *E. coli*, *Klebsiella spp.*, *Proteus spp*.
- *Enterococcus spp*.
- *Staphylococcus spp.*
- Anaerobes
- *Pseudomonas spp*.
- Yeast including *C. albicans*

INVESTIGATIONS

- Cultures if infection suspected:
  - Blood cultures
  - Fluid/tissue culture (if IR guided drain or debridement/necrosectomy is performed)
- Imaging:
  - CT can be used if the diagnosis of pancreatitis is uncertain. If complications of pancreatitis (necrosis, collections, infection) are suspected, contrast-enhanced CT scan after 72h of symptom onset can be considered.
  - US can help identify whether a biliary etiology for acute pancreatitis is likely
  - MRI or ultrasound may be necessary to distinguish solid from liquid content in walled-off necrosis.

DIAGNOSIS

Diagnosis of Acute Pancreatitis (2 out of 3 of the following):

1. Abdominal pain consistent with acute pancreatitis
2. Serum lipase greater than 3 times the upper limit of normal
3. Characteristic findings on abdominal imaging

Diagnosis of Infected Pancreatitis

<u>Confirmed Infected Pancreatitis</u>

1. Positive Gram stain or culture of pancreatic or peripancreatic necrotic tissue/fluid by IR, endoscopy, or surgery
   OR
2. Presence of gas in pancreatic or peripancreatic tissues on contrast-enhanced CT

<u>Suspected Infected Pancreatitis</u>

1. Persistent organ failure in patients admitted to ICU for 3 consecutive days more than 14 days after onset of acute pancreatitis
   OR
2. Elevation in 2 out of 3 of temperature >38.5°C, WBC, or CRP for 3 consecutive days more than 14 days after onset of acute pancreatitis

These clinical criteria for suspected infected pancreatitis are only considered sufficiently reliable more than 14 days after onset of acute pancreatitis.

<u>Additional Considerations</u>

- **Timing:** Infected pancreatitis is rare during the first week of acute pancreatitis.
- **Inflammatory markers:** Because acute pancreatitis is a highly inflammatory condition, elevated inflammatory markers (i.e. WBC, CRP, fevers) cannot be used on their own to make a diagnosis of infection.
- **Procalcitonin**: The PROCAP study evaluated a procalcitonin-guided approach to guide the use of antibiotics. Antibiotics were started/continued for levels ≥ 1.0 mcg/L and discontinued/not started for levels < 1.0 mcg/L. This approach was able to reduce overall antibiotic use without increasing infection or harm compared to the standard of care group. However, procalcitonin hasn't yet been validated as a diagnostic marker for pancreatitis with secondary infection.

MANAGEMENT OF INFECTED PANCREATITIS

Empiric Antibiotics for Suspected/Confirmed Infected Pancreatitis

Classification	
Non-Severe Infected Pancreatitis	ceftriaxone 2 g IV Q24H **AND** metronidazole 500 mg PO/IV Q12H **OR** amoxicillin-clavulanate 2000-200 mg IV Q8H
Severe Infected Pancreatitis *e.g., sepsis with hypotension, septic shock*	piperacillin-tazobactam 4.5 g IV Q6H *If known/suspected ESBL or severe penicillin allergy:* meropenem 500 mg IV Q6H

Doses may require adjustment for renal insufficiency

Historical literature suggesting that carbapenems have superior penetration compared to piperacillin-tazobactam had methodological flaws and have been subsequently refuted.

Antifungal therapy not recommended empirically; however, consider if ongoing deterioration despite antibacterial therapy or heavily *Candida* colonized.

Duration of Therapy

Clinical Scenario	Duration
Empiric therapy without clear evidence of infection	• Antibiotics are often started in acute pancreatitis due to the nonspecific nature of inflammatory features (e.g., fevers, leukocytosis). • In patients who remain clinically stable without features of confirmed or suspected infected pancreatitis, consider discontinuing antibiotics and monitoring (**antibiotic holiday**). • If the patient remains stable, infection is unlikely. If signs of clinical deterioration occur without alternative explanation, infected pancreatitis should be suspected.
Confirmed/suspected infection with definitive source control	• Discontinue antibiotics 4 days (96 hours) after source control. • Extending antibiotics beyond day 8 in critically ill patients with definitive source control is not likely to provide benefit.
Confirmed/suspected infection without definitive source control	• Prolonged courses of antibiotics guided by clinical and radiographic improvement may be necessary. • Definitive source control should be considered once collections mature (e.g., pancreatic pseudocyst or walled off necrosis). • Monitor clinical parameters including fever, WBC, and GI function. • Repeat imaging is often necessary.

Source Control

- Multiple source control modalities are potentially available: percutaneous drainage, endoscopic drainage, or surgical drainage/necrosectomy.
- Timing of source control intervention: For necrotizing pancreatitis, it may be beneficial to wait until the stage of walled-off necrosis is reached before performing surgical intervention/drainage. Randomized control data suggests that waiting for this stage may minimize the number of additional source control interventions. However, for refractory organ failure, source control may be required before this stage is reached.

ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis for patients with acute pancreatitis is not recommended.

- Multiple randomized controlled trials have failed to consistently demonstrate improved outcomes in patients treated with prophylactic antibiotics for pancreatitis with secondary infection.

REFERENCES

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102-111. doi:10.1136/gutjnl-2012-302779
2. Barie, P. S. (1996). A critical review of antibiotic prophylaxis in severe acute pancreatitis. *American Journal of Surgery*, *172*(6 A), 38s–43s. https://doi.org/10.1016/S0002-9610(96)00349-2
3. Bassi, C., Falconi, M., Talamini, G., Uomo, G., Papaccio, G., Dervenis, C., Salvia, R., Minelli, E. B., & Pederzoli, P. (1998). Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. *Gastroenterology*, *115*(6), 1513–1517. https://doi.org/10.1016/S0016-5085(98)70030-7
4. Bassi, C., Pederzoli, P., Vesentini, S., Falconi, M., Bonora, A., Abbas, H., Benini, A., & Bertazzoni, E. M. (1994). Behavior of antibiotics during human necrotizing pancreatitis. *Antimicrobial Agents and Chemotherapy*, *38*(4), 830–836. https://doi.org/10.1128/AAC.38.4.830
5. Berzin, T. M., Rocha, F. G., Whang, E. E., Mortele, K. J., Ashley, S. W., & Banks, P. A. (2007). Prevalence of primary fungal infections in necrotizing pancreatitis. *Pancreatology*, *7*(1), 63–66. https://doi.org/10.1159/000101879
6. Damaskos, C., Prevezanos, D., Garmpis, N., Garmpi, A., Kouraklis, G., & Dimitroulis, D. (2023). Pancreatic Pseudocyst. In Multidisciplinary Management of Acute and Chronic Pancreatitis. IntechOpen. https://doi.org/10.5772/intechopen.107320
7. Dellinger, E. P., Tellado, J. M., Soto, N. E., Ashley, S. W., Barie, P. S., Dugernier, T., Imrie, C. W., Johnson, C. D., Knaebel, H. P., Laterre, P. F., Maravi-Poma, E., Kissler, J. J. O., Sanchez-Garcia, M., & Utzolino, S. (2007). Early antibiotic treatment for severe acute necrotizing pancreatitis: A randomized, double-blind, placebo-controlled study. *Annals of Surgery*, *245*(5), 674–683. https://doi.org/10.1097/01.sla.0000250414.09255.84
8. Eggimann, P., Jamdar, S., & Siriwardena, A. K. (2006). Pro/con debate: Antifungal prophylaxis is important to prevent fungal infection in patients with acute necrotizing pancreatitis receiving broad-spectrum antibiotics. *Critical Care*, *10*(5), 8–11. https://doi.org/10.1186/cc5025
9. Isenmann, R., Rünzi, M., Kron, M., Kahl, S., Kraus, D., Jung, N., Maier, L., Malfertheiner, P., Goebell, H., & Beger, H. G. (2004). Prophylactic Antibiotic Treatment in Patients with Predicted Severe Acute Pancreatitis: A Placebo-Controlled, Double-Blind Trial. *Gastroenterology*, *126*(4), 997–1004. https://doi.org/10.1053/j.gastro.2003.12.050
10. John E. Bennett & Raphael Dolin & Martin J. Blaser. (2015). *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases* (8th ed.). Elsevier. https://doi.org/10.1016/C2012-1-00075-6
11. Leppäniemi, A., Tolonen, M., Tarasconi, A., Segovia-Lohse, H., Gamberini, E., Kirkpatrick, A. W., Ball, C. G., Parry, N., Sartelli, M., Wolbrink, D., van Goor, H., Baiocchi, G., Ansaloni, L., Biffl, W., Coccolini, F., Saverio, S. di, Kluger, Y., Moore, E., & Catena, F. (2019). Directrices WSES 2019 para el tratamiento de la pancreatitis aguda grave. *World Journal of Emergency Surgery*, *0*, 1–20. https://wjes.biomedcentral.com/articles/10.1186/s13017-019-0247-0
12. Maguire, C., Agrawal, D., Daley, M. J., Douglass, E., & Rose, D. T. (2021). Rethinking Carbapenems: A Pharmacokinetic Approach for Antimicrobial Selection in Infected Necrotizing Pancreatitis. *Annals of Pharmacotherapy*, *55*(7), 902–913. https://doi.org/10.1177/1060028020970124
13. Mowbray, N. G., Ben-Ismaeil, B., Hammoda, M., Shingler, G., & Al-Sarireh, B. (2018). The microbiology of infected pancreatic necrosis. *Hepatobiliary and Pancreatic Diseases International*, *17*(5), 456–460. https://doi.org/10.1016/j.hbpd.2018.08.007
14. Otto, W., Komorzycki, K., & Krawczyk, M. (2006). Efficacy of antibiotic penetration into pancreatic necrosis. *Hpb*, *8*(1), 43–48. https://doi.org/10.1080/13651820500467275
15. Pan, L., Li, B., Pan, X., & Sun, J. (2021). Gut microbiota in pancreatic diseases: possible new therapeutic strategies. Acta Pharmacologica Sinica, 42(7), 1027–1039. https://doi.org/10.1038/s41401-020-00532-0
16. Pederzoli, P., Bassi, C., Vesentini, S., & Campedelli, A. (1993). A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. *Surgery, Gynecology & Obstetrics*, *176*(5), 480–483. http://www.ncbi.nlm.nih.gov/pubmed/8480272
17. Ratschko, M., Fenner, T., & Lankisch, P. G. (1999). The Role of Antibiotic Prophylaxis in the Treatment of Acute Pancreatitis. Gastroenterology Clinics of North America, 28(3), 641–659. https://doi.org/10.1016/S0889-8553(05)70078-9

18. Røkke, O., Harbitz, T. B., Liljedal, J., Pettersen, T., Fetvedt, T., Heen, L. Ø., Skreden, K., & Viste, A. (2007). Early treatment of severe pancreatitis with imipenem: A prospective randomized clinical trial. *Scandinavian Journal of Gastroenterology*, *42*(6), 771–776. https://doi.org/10.1080/00365520601173855
19. Sainio, V., Kemppainen, E., Puolakkainen, P., Haapiainen, R., Schröder, T., Kivilaakso, E., Valtonen, V., Taavitsainen, M., & Kivisaarl, L. (1995). Early antibiotic treatment in acute necrotising pancreatitis. *The Lancet*, *346*(8976), 663–667. https://doi.org/10.1016/S0140-6736(95)92280-6
20. Serrablo, A., Tejedor, L., & Martínez, J. (2014). Antibiotics in severe acute pancreatitis. *Central European Journal of Medicine*, *9*(4), 565–573. https://doi.org/10.2478/s11536-013-0281-3
21. Siriwardena, A. K., Jegatheeswaran, S., Mason, J. M., Baltatzis, M., Sheen, A. J., O'Reilly, D. A., Jamdar, S., Deshpande, R., de Liguori Carino, N., Satyadas, T., Qamruddin, A., Hayden, K., Parker, M. J., Butler, J., & McIntyre, B. (2022). A procalcitonin-based algorithm to guide antibiotic use in patients with acute pancreatitis (PROCAP): a single-centre, patient-blinded, randomised controlled trial. *The Lancet Gastroenterology and Hepatology*, *7*(10), 913–921. https://doi.org/10.1016/S2468-1253(22)00212-6
22. Tellado, J. M. (2007). Prevention of infection following severe acute pancreatitis. *Current Opinion in Critical Care*, *13*(4), 416–420. https://doi.org/10.1097/MCC.0b013e32826388b2
23. Tenner, S., Baillie, J., Dewitt, J., & Vege, S. S. (2013). American college of gastroenterology guideline: Management of acute pancreatitis. American Journal of Gastroenterology, 108(9), 1400–1415. https://doi.org/10.1038/ajg.2013.218
24. Trikudanathan, G., Wolbrink, D. R. J., van Santvoort, H. C., Mallery, S., Freeman, M., & Besselink, M. G. (2019). Current Concepts in Severe Acute and Necrotizing Pancreatitis: An Evidence-Based Approach. *Gastroenterology*, *156*(7), 1994-2007.e3. https://doi.org/10.1053/j.gastro.2019.01.269
25. Villatoro, E., Mulla, M., & Larvin, M. (2010). Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.cd002941.pub3
26. Working Group IAI/APA Acute Pancreatitis Guidelines. (2013). IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology, 13(4 SUPPL. 2). https://doi.org/10.1016/j.pan.2013.07.063
27. Yang, Y., Zhang, Y., Wen, S., & Cui, Y. (2023). The optimal timing and intervention to reduce mortality for necrotizing pancreatitis: a systematic review and network meta-analysis. *World Journal of Emergency Surgery*, *18*(1), 1–15. https://doi.org/10.1186/s13017-023-00479-7
28. Zhang, H., Gao, L., Mao, W. J., Yang, J., Zhou, J., Tong, Z. H., Ke, L., & Li, W. Q. (2022). Early versus delayed intervention in necrotizing acute pancreatitis complicated by persistent organ failure. *Hepatobiliary and Pancreatic Diseases International*, *21*(1), 63–68. https://doi.org/10.1016/j.hbpd.2020.12.019
29. Gapp J, Tariq A, Chandra S. Acute Pancreatitis. [Updated 2023 Feb 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482468/