Brigham and Women's Hospital
Founding Member, Mass General Brigham

Acute and Chronic Pancreatitis

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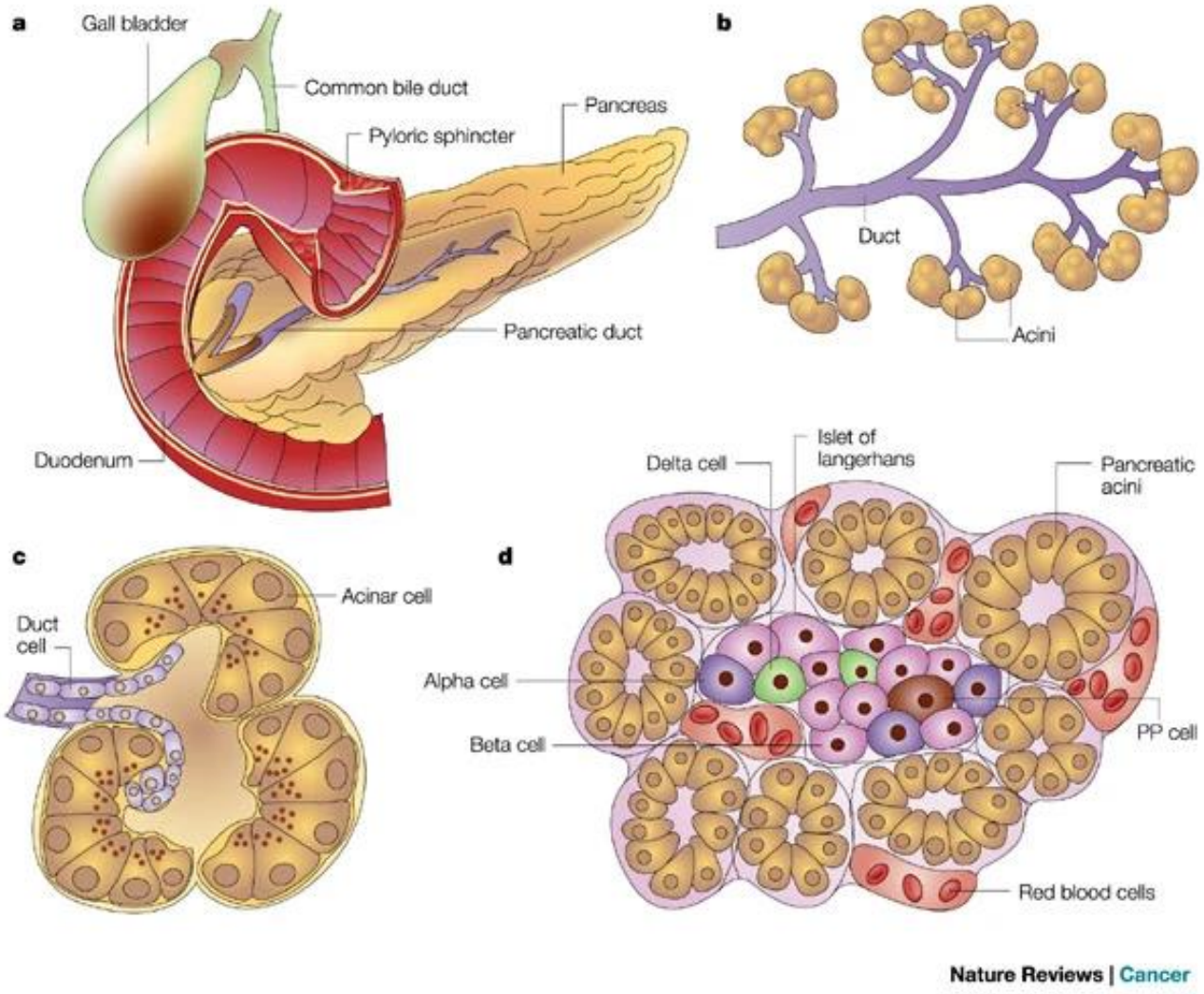
- Clinical focus: Pancreas
- Research focus: Acute Pancreatitis

I have no relevant disclosures

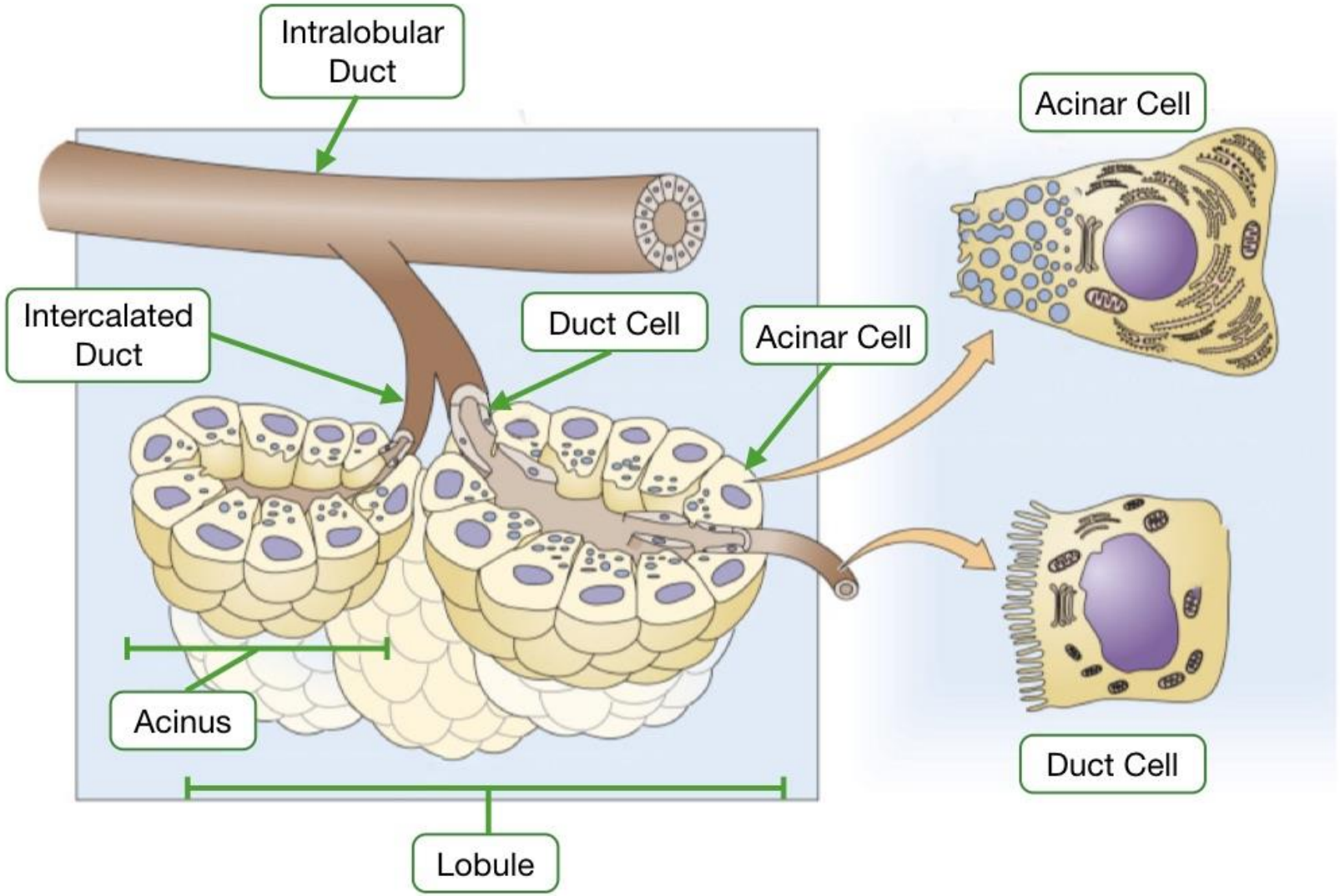
Agenda

1. **Review normal pancreas physiology**
2. **Define acute pancreatitis**
    - **Diagnosis**: *the revised Atlanta Classification*
    - **Etiology**: *gallstones, alcohol, triglycerides*
    - **Severity**: *classification, risk factors, early biomarkers*
    - **Management**: *fluids, nutrition, antibiotics, necrosis*
3. **Define chronic pancreatitis**
    - **Definition and diagnosis**
    - **Etiology**: *TIGAR-O*
    - **Natural history and symptoms**
    - **Management**: *pain, EPI*

Normal Physiology



Source: Bardeesy et al. *Nature Rev Ca*, 2002

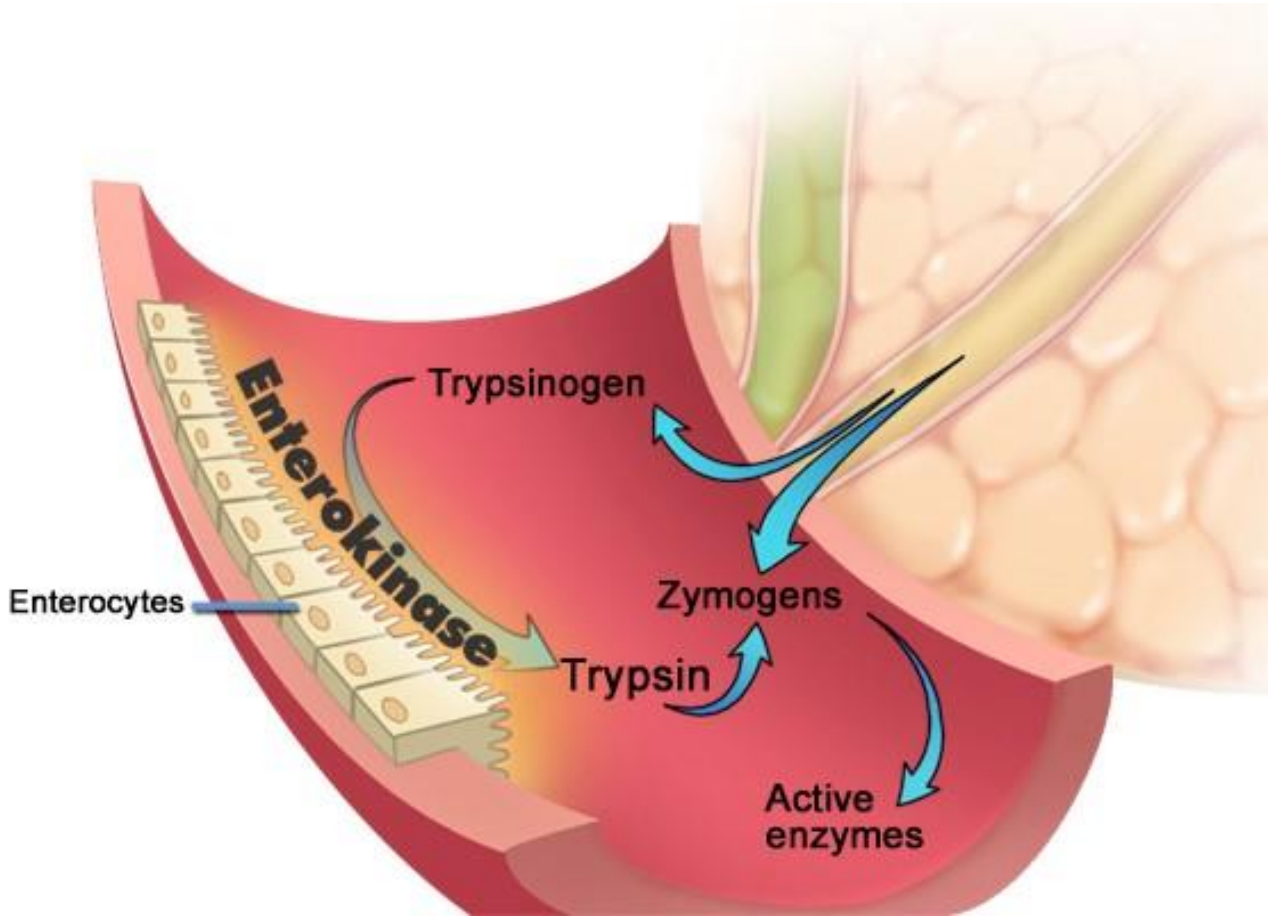


Enzymes comprise of lipases, amylases, and proteases

Source: https://medcell.org/tbl/histology_of_digestive_organs/reading.php

Protective Mechanisms

- Most enzymes are synthesized in an inactive form
- Enzymes are stored in granules, away from the rest of the cell
- Enzyme and enzyme inhibitors are co-packaged together to prevent activation
- Some enzymes can inhibit themselves
- Enzymes are rapidly flushed out of the pancreas when secreted
- Enzymes are primarily activated in the duodenum, after leaving the pancreas



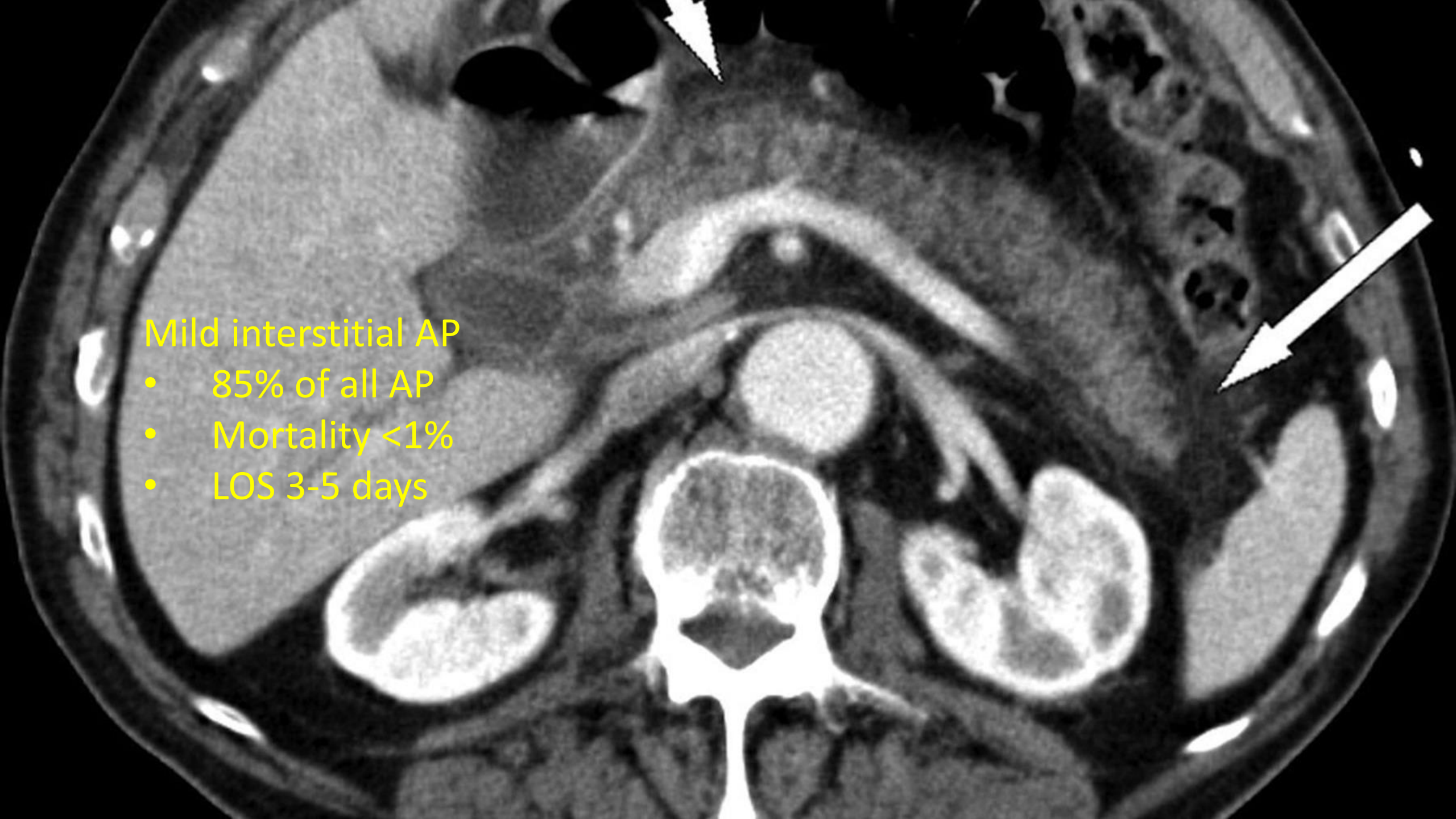
Source: Pancreapedia

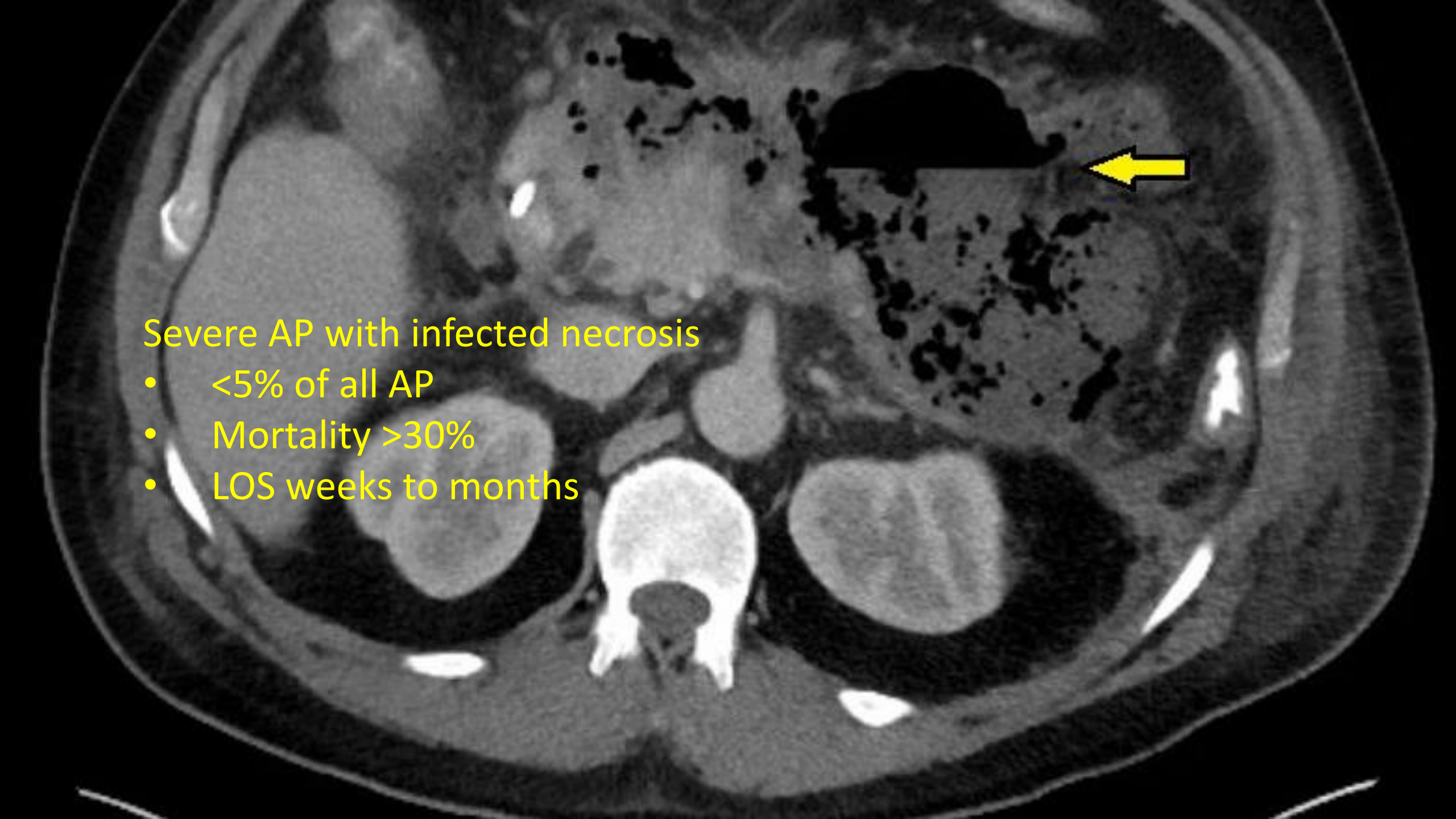
Acute Pancreatitis

Acute Pancreatitis in the United States

- Third most common GI admission diagnosis: 288,000/year
- $3 billion in aggregate costs/year
- $26,000 in charges/hospitalization
- Incidence increasing >3% /year

Source: Peery et al. *Gastroenterol,* 2021


Mild interstitial AP
• 85% of all AP
• Mortality <1%
• LOS 3-5 days


Severe AP with infected necrosis
• <5% of all AP
• Mortality >30%
• LOS weeks to months

Diagnosis

Diagnosis – Revised Atlanta Classification 2012

At least 2 of the following 3:

- Characteristic abdominal pain: acute, severe, epigastric pain, radiates to the back in 50%
- Serum amylase or lipase ≥3x upper limit of normal
- CT or MRI characteristic of AP

Source: Banks et al. *Gut*, 2013

MYTH: Elevated Lipase = Pancreatitis

55% of BWH/MGH ED with lipase > 3x ULN (>180 U/L) do NOT have AP

Humans have 12+ lipases

- Pancreatic lipase – pancreatitis, PDAC, certain medications
- Hepatic lipase – hepatitis, fatty liver, choledocholithiasis
- Gastric lipase – vomiting, gastroparesis, PUD
- Lipoprotein lipase – obesity, hyperinsulin state
- Endothelial lipase – sepsis, proinflammatory state
- Lingual lipase
- Hormone sensitive lipase
- Lysosomal acid lipase
- Phospholipase
- MAGL

Source: Jin et al. *JAMA Netw Open*, 2024

Etiology

Etiology

>75% can be explained by

- Biliary (gallstones) – ALT>150 U/L has 95% PPV
- Alcohol – chronic >50 g/day – send a phosphatidyl ethanol (PEth)
- Hypertriglyceridemia – fasting TG >1000 mg/dL

Uncommon but obvious

- Post ERCP, post traumatic

Uncommon and not obvious

- Neoplasm, hereditary, hypercalcemia, IGG4, mumps, ischemia, cholinergic toxicity
- Drugs (AZA, asparginase)

10-25% are "idiopathic"

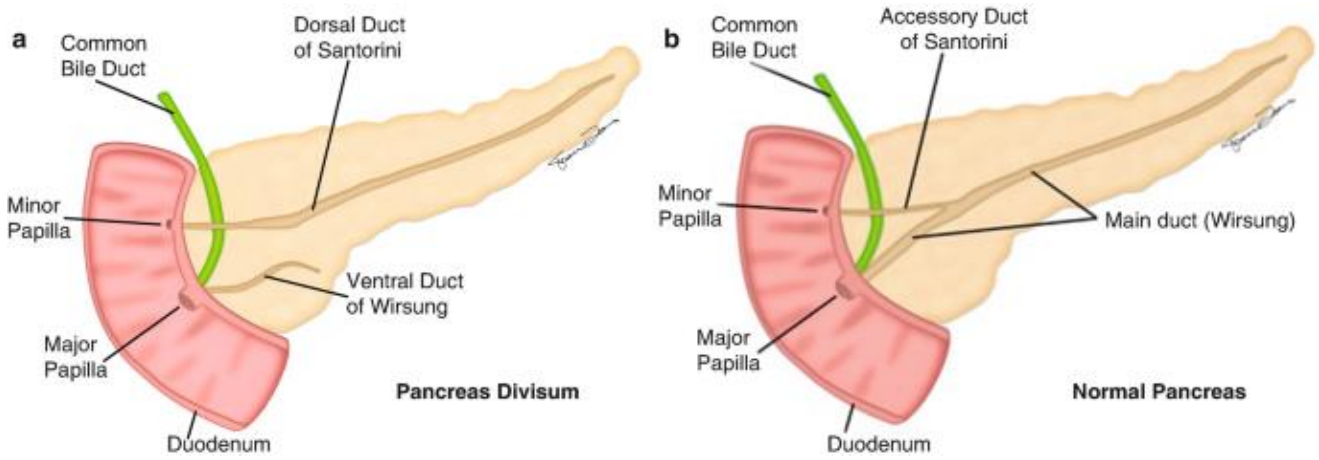
- EUS may detect an etiology (30% gallstones, 2% neoplasms)
- MRCP or EUS in all cases of idiopathic pancreatitis
- Consider CCY following 2 episodes of idiopathic pancreatitis

Source: Forsmark et al. *NEJM*, 2016 / Ulmans et al. *Endoscopy*, 2020

MYTH: Pancreas Divisum Causes Pancreatitis

SHARP trial (2026): RCT, n=148 with pancreas divisum and idiopathic RAP undergoing ERCP with minor papillotomy vs sham

- Recurrent AP: 35% ERCP vs 44% sham (aHR 0.83, 95% CI 0.49-1.41)



Source: Cote et al. *JAMA*, 2026

MYTH: GLP1-RA Causes Pancreatitis

FACT: GLP1RA cause asymptomatic hyperlipasemia

SCALE trials (pooled) – liraglutide vs placebo

- Mean lipase 31% higher
- Lipase > ULN 44% vs 15%
- Lipase > 3x ULN 3% vs 1.5%

LEADER trial – liraglutide vs placebo

- Mean lipase 28% higher
- Lipase > 3x ULN 8% vs 5%

Source: Steinberg et al. *Diabetes Care*, 2017

MYTH: GLP1-RA Causes Pancreatitis

Trial	Drug	GLP-1 RA Events (%)	Placebo Events (%)	Notes
ELIXA	Lixisenatide	5 (0.16%)	8 (0.26%)	Numerically lower with drug
LEADER	Liraglutide	18 (0.39%)	23 (0.49%)	1.1 vs 1.7 events/1,000 PYO
SUSTAIN-6	Semaglutide	9 (0.55%)	12 (0.73%)	Numerically lower with drug
EXSCEL	Exenatide QW	26 (0.35%)	22 (0.30%)	Similar between groups

Pooled analysis 4 major CVOT (n=33457)

- Pooled OR for acute pancreatitis = 0.89 (95% CI 0.63-1.27)

Pooled benefits of GLP1-RA

- 13% reduction in CV death
- 15% reduction in in MI
- 15% reduction in heart failure
- 12% reduction in all cause mortality

Source: Llu et al. *DMRR*, 2018 / Galli et al. *JACC* 2025

MYTH: GLP1-RA Causes Pancreatitis

Meta-analysis of 55 RCTs (n=106,395) evaluating GI adverse events in GLP1RA

- Cholelithiasis (RR 1.46; 95% CI, 1.09–1.97), ~ **2 additional cases / 1,000** pts treated
- GERD (RR 2.19; 95% CI, 1.48–3.25), ~**4 additional cases / 1,000** pts treated

- Pancreatitis (RR 0.95; 95% CI, 0.68–1.32)

Source: Chiang et al. *Gastro*, 2025

Etiology

Take home points:

- Gallstones > EtOH > TG explain >75%
- Idiopathic: follow up MRCP/EUS, check PETH
- Almost never due to drugs, divisum, or sphincter of oddi dysfunction
- No need to withhold (or discontinue GLP1RA)

Severity

Severity – Revised Atlanta Classification 2012

Mild: no organ failure*
Moderate: transient (<48h) organ failure or local complications
Severe: persistent (≥48h) organ failure

*Organ failure (cardiac, respiratory, renal) defined per Modified Marshall Scoring System

Source: Banks et al. *Gut*, 2013 / Marshall et all *Crit Care Med*, 1995

Severity - Local Complications

(Peri)pancreatic Fluid collections:

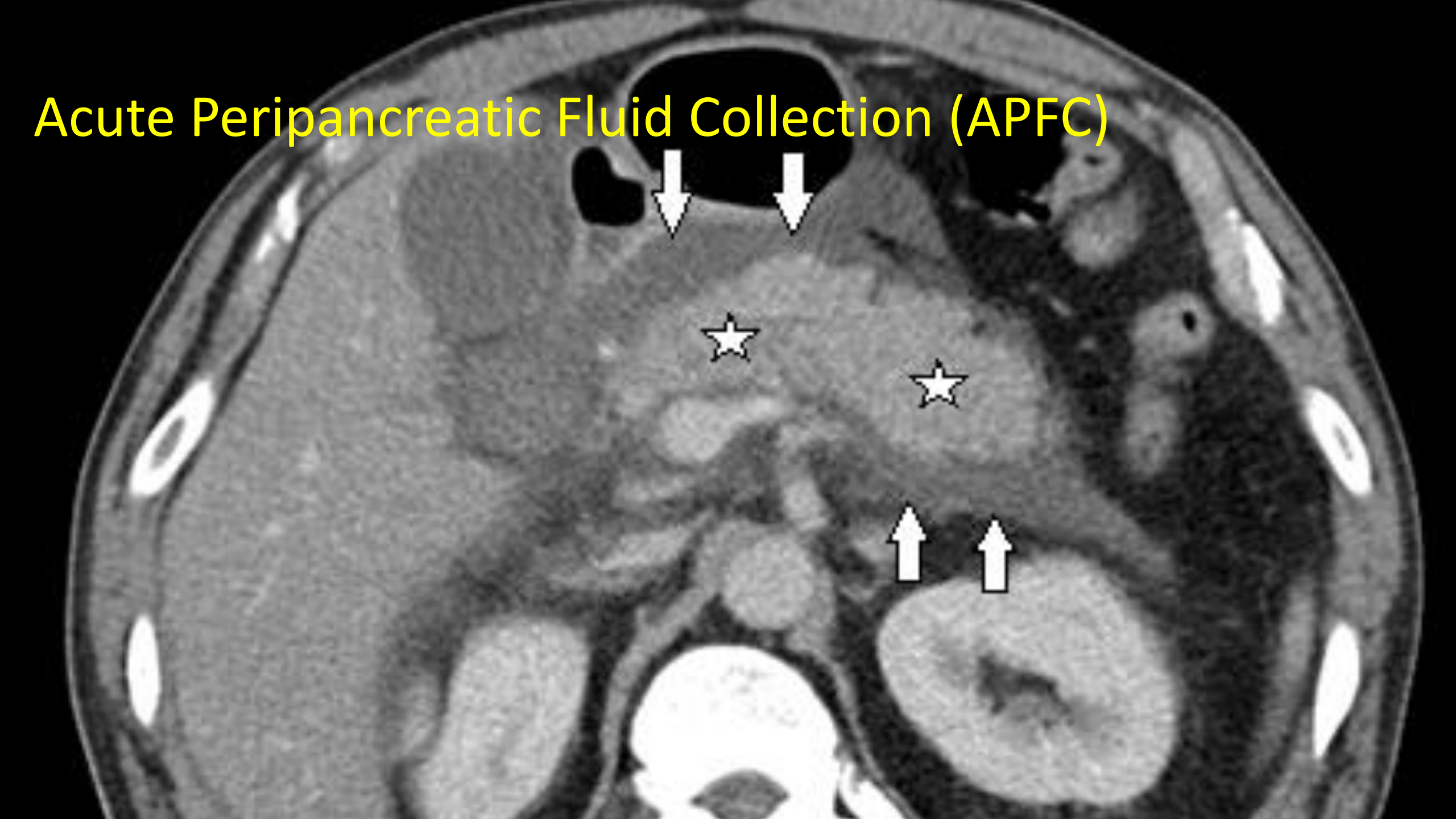
- Interstitial AP: Acute peripancreatic fluid collection (APFC) → pseudocysts
- Necrotizing AP: Acute necrotic collection (ANC) → Walled off necrosis (WON)

Other local complications:

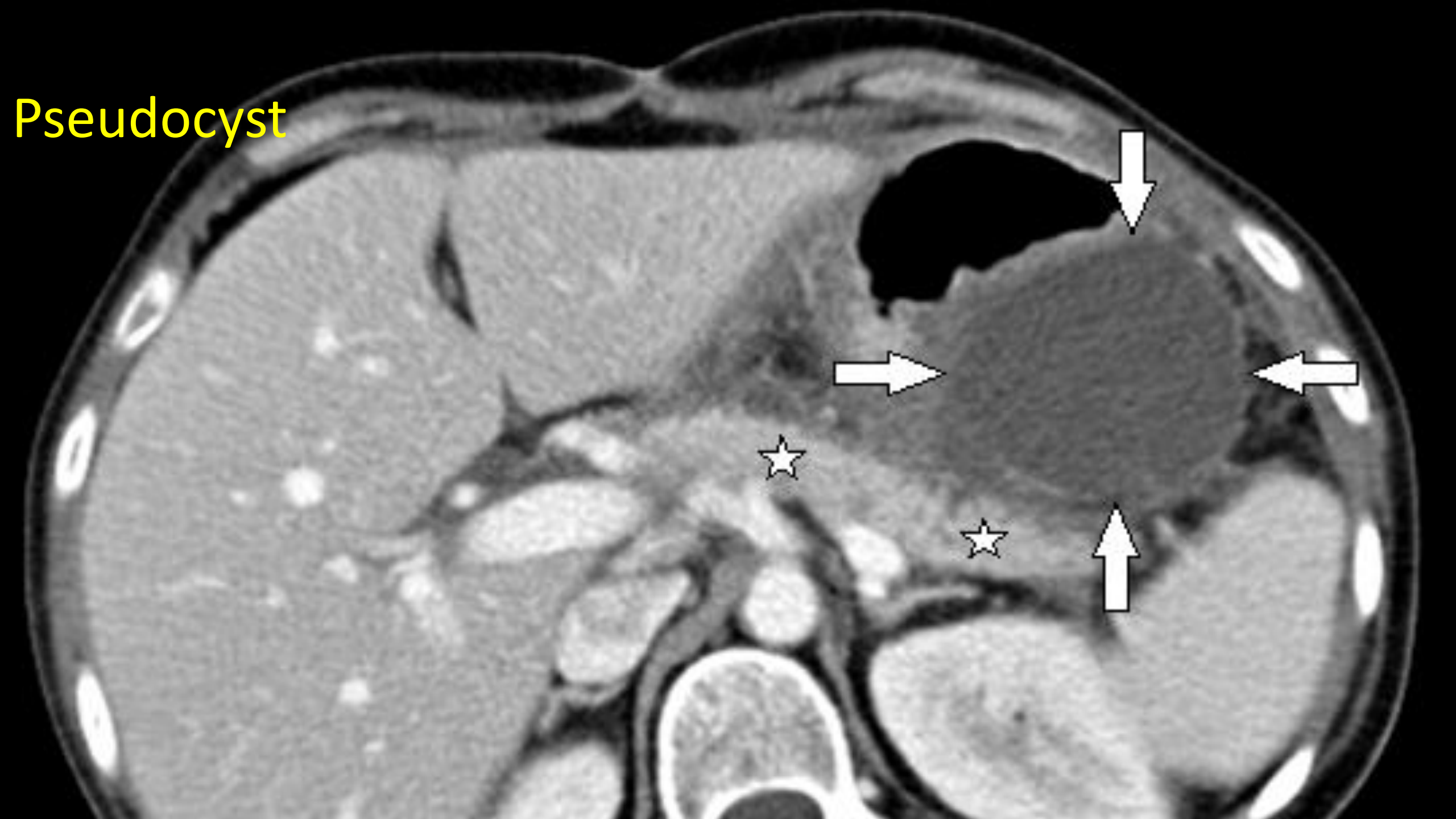
- Gastric outlet obstruction
- Splenic / portal vein thrombosis

Source: Banks et al. *Gut*, 2013

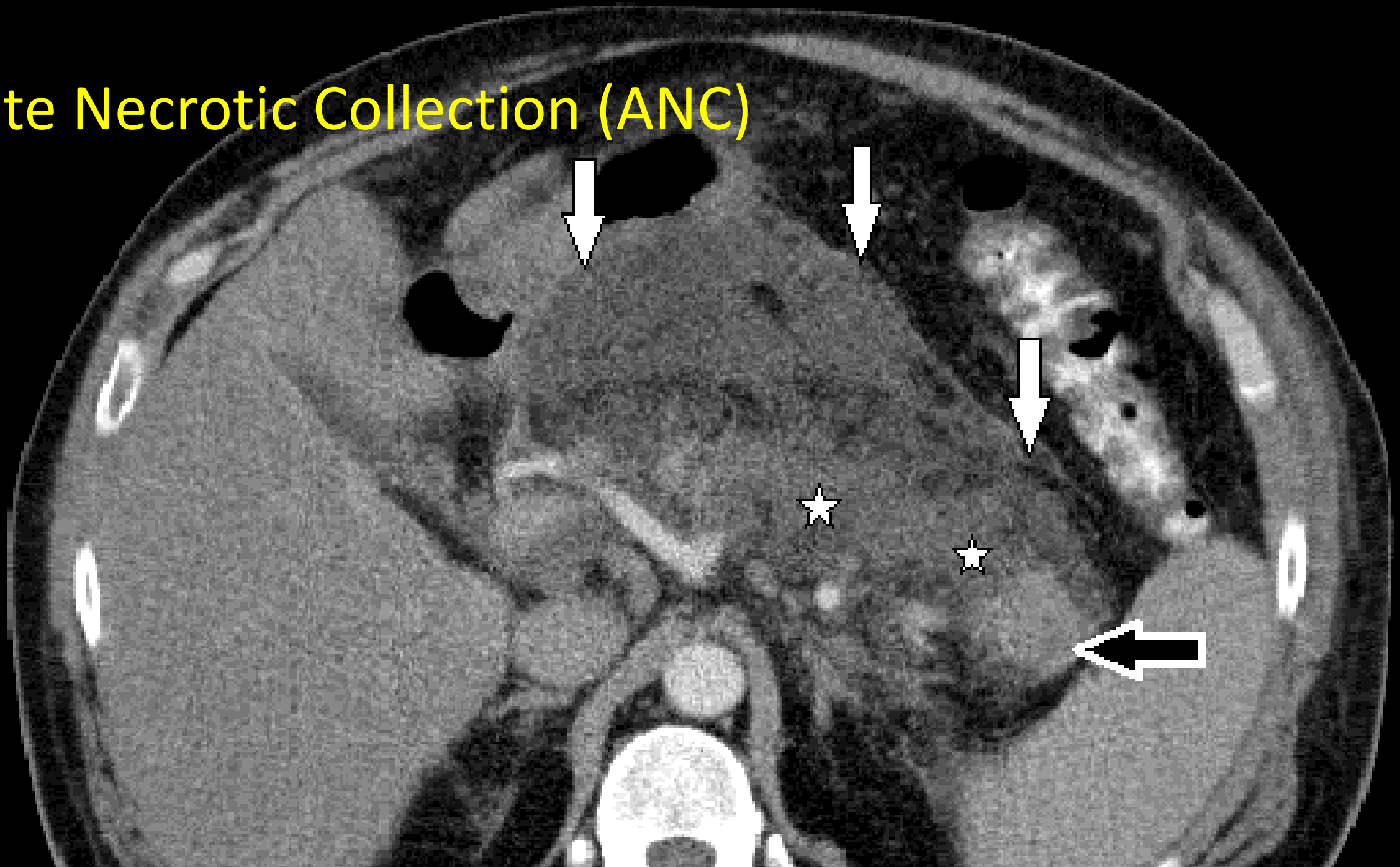
Acute Peripancreatic Fluid Collection (APFC)

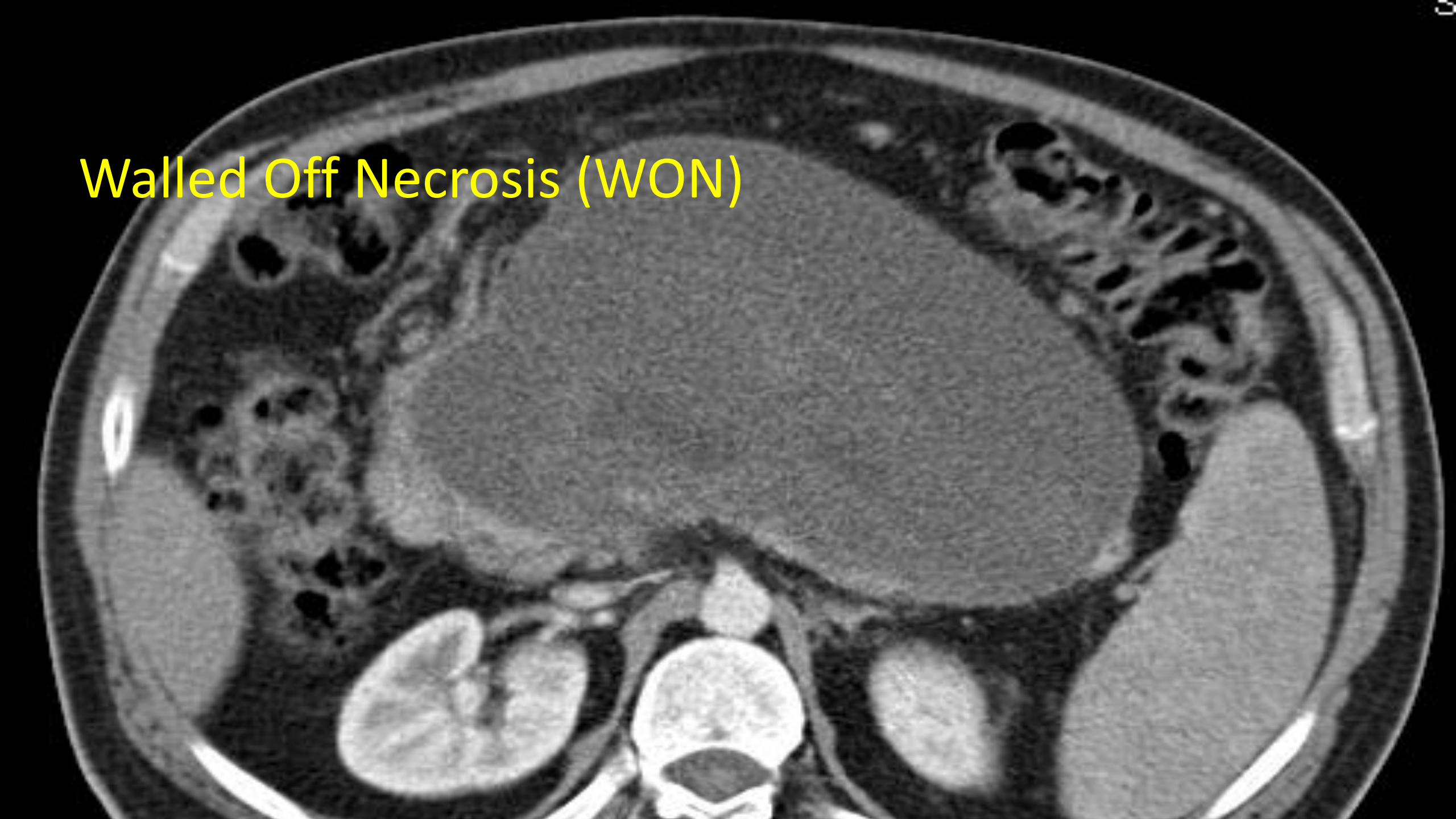


Pseudocyst



Acute Necrotic Collection (ANC)




Walled Off Necrosis (WON)

Severity - RAC 2012

Mild: no organ failure*
Moderate: transient (<48h) organ failure or local complications
Severe: persistent (≥48h) organ failure

*Organ failure (cardiac, respiratory, renal) defined per Modified Marshall Scoring System

Source: Banks et al. *Gut*, 2013 / Marshall et all *Crit Care Med*, 1995

Severity - RAC 2012

Mild (no OF): mortality 0%
Moderate (transient OF): mortality 1-3%
Severe (persistent OF):

- Single POF: mortality 20%
- Double POF: mortality 30%
- Triple POF: mortality 60%

Source: Banks et al. *Gut*, 2013 / Schepers st al. *Gut*, 2019

Severity – Predictors of Severity

- Older age
- Comorbidities
- Obesity
- First episode (0% mortality for recurrent AP)
- SIRS
- BUN > 25 mg/dl
- HCT > 44%

Severity

Take home points:

- Mortality in AP is driven by persistent organ failure
- Mortality in recurrent AP ~ 0%
- Evaluate for markers of severity (SIRS, BUN) at admission
- Monitor for signs of organ failure → ICU

Management

A 50M presents with severe epigastric pain radiating to the back, lipase 3000, ALT 300, Tbili 0.8, WBC 9. He is afebrile, HR 90, BP 120/80, RR 12, 98%. RUQUS shows gallstones, CBD 6mm. Best practice(s) are to:

A. Order CT scan for diagnostic confirmation
B. Keep patient NPO until pain has resolved
C. Administer prophylactic antibiotics to reduce risk of cholangitis
D. Proceed to ERCP for suspected choledocholithiasis
E. Consult surgery for same admission cholecystectomy
F. Bolus IVF 20cc/kg

MYTH: Aggressive IVF resuscitation improved outcomes

FACT: Moderate >> Aggressive resuscitation for mild AP

Multicenter RCT: n=249, Aggressive (bolus 20 cc/kg → 3 cc/kg/hr) vs. Moderate (bolus 10 cc/kg if hypovolemic→ 1.5 cc/kg/hr) IVF for mild acute pancreatitis (WATERFALL trial)

- Primary outcome: development of moderate/severe AP
- Safety checkpoint: fluid overload

Source: De Madaria et al. *NEJM*, 2022

Management – Fluid Resuscitation

Multicenter RCT: n=249, Aggressive vs. Moderate IVF for mild acute pancreatitis (WATERFALL trial)

	Aggressive IVF (n=122)	Moderate IVF (n=127)	
Volume first 48h	7.8 (6.5-9.8) L	5.5 (4-6.8) L	
Primary outcome (mod/sev AP)	22%	17%	RR 1.3 (0.78-2.18)
Necrosis	14%	7%	RR 1.95 (0.87-4.38)
Fluid overload	21%	6%	RR 2.85 (1.36-5.94)

Source: De Madaria et al. *NEJM*, 2022

MYTH: NPO “rests the pancreas”

FACT: AP may lead to >10% loss in body weight

- Anorexia
- Catabolic state/ negative nitrogen balance
- Gut barrier dysfunction
- Exocrine pancreatic insufficiency
- Iatrogenic malnutrition

Management – Nutrition

1. Early (< 24h) oral feeding as tolerated > NPO
   - Protects gut-mucosal barrier and reduces bacterial translocation
   - 11 RCTs: ↓ intervention for necrosis, no difference mortality, pOF, necrosis
2. Enteral > Parenteral nutrition (if cannot tolerate oral feeding)
   - 12 RCTs: ↓ infected necrosis and OF, no difference in mortality
3. NGT = NJT (predicted severe or necrotizing AP requiring enteral feeding)
   - 3 RCTs: No difference in mortality, OF (including respiratory failure), necrosis

Source: Crockett et al. *Gastroenterol,* 2018

Management – Nutrition

Take home points:

- Avoid routine NPO orders
- Feed when patient is hungry, OK to start with a solid diet
- If unable to tolerate oral feeding, use NG or NJ

Management – Antibiotics

14 RCTs assessing outcomes of antibiotic ppx – 841 patients

- No reduction in mortality, infected necrosis, non-pancreatic infections, need for surgical interventions

Take home points:

- No role for antibiotic prophylaxis
- Reserve for cholangitis or documented infected necrosis

Source: Wittau et al. *Scand J Gastro*, 2010

Management – Same Admission CCY

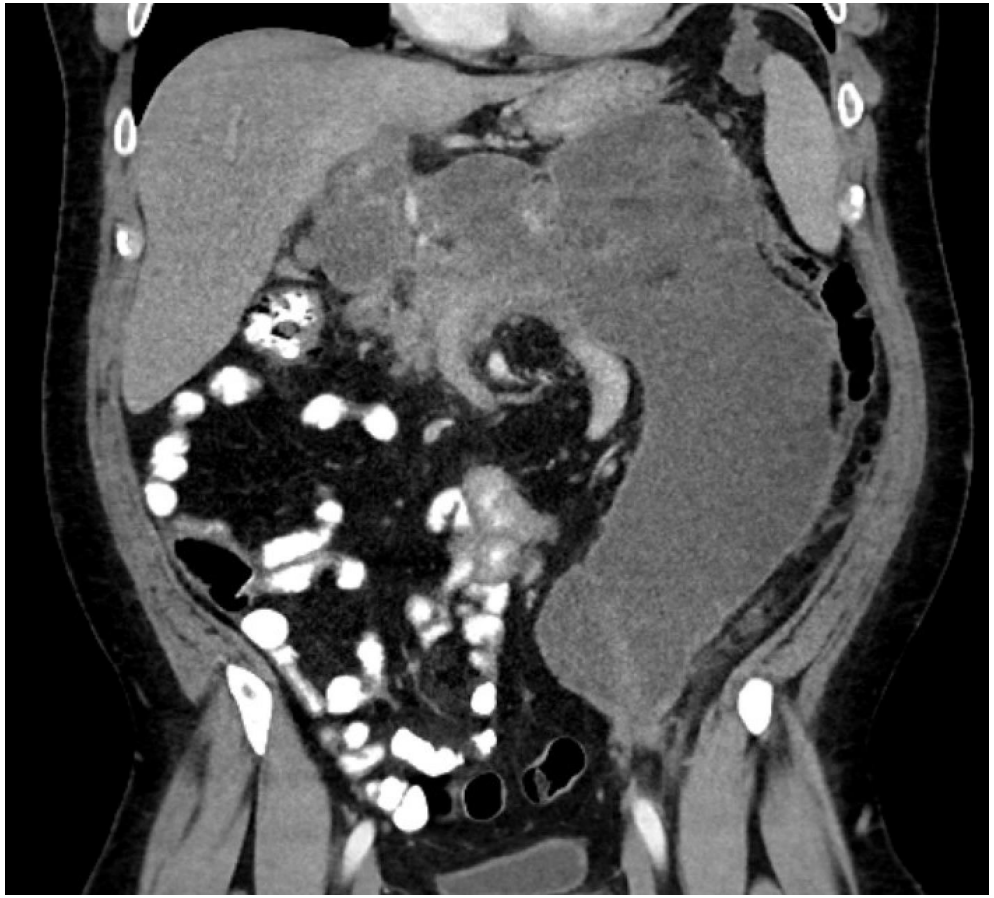
Multicenter RCT: n=266, Same-Admission vs. Interval CCY for mild gallstone pancreatitis (PONCHO trial)

- Primary composite outcome: 6 m readmission for biliary complication + mortality

	Same admission (n=128)	Interval (n=136)	
Time to CCY	1 day	27 days	
Primary outcome	5%	17%	RR 0.28 (0.12-0.66)
Reporting colic while waiting	3%	51%	RR 0.06 (0.02-0.19)
Cost to prevent 1 readmission	-€1918		

Source: Da Costa et al. *Lancet*, 2015 / Da Costa et al. *Br J Surg*, 2016

Management – Necrosis



Management – Necrosis

Sterile necrosis / pseudocysts

- Only require intervention if symptomatic (persistent pain, anorexia, nausea) later in disease course (WON, 4-6 weeks)

Infected necrosis

- Peaks 2-4 weeks after presentation
- Suspected in sepsis, SIRS, or OF >7 days after onset
- Proven by Cx/gram stain or gas within necrotic collection

Source: AGA Clinical Practice Update: Management of Pancreatic Necrosis, 2020

Management – Infected Necrosis

Meta-analysis of 5 RCTs: n=284, endoscopic drainage (n=145) vs. min invasive surgery (n=139)

	All favor endoscopic approach
Major complications	RR 0.69, (0.49-0.97)
New onset organ failure	RR 0.29 (0.11-0.82)
Fistula or perforation	RR 0.27 (0.12-0.64)
Surgical site infection	RR 0.26 (0.07-0.92)
Pancreatic fistula	RR 0.14 (0.05-0.45)
Hospital stay	6.74 days shorter

Source: Tang et al. *Ann Med*, 2023

Take Home Points (Acute Pancreatitis)

1. Pancreatitis occurs when protective mechanisms are overwhelmed
2. Do not stop or withhold GLP1RA
3. Evaluate for early markers of severity
4. Document persistent organ failure
5. Provide early, moderate, goal directed fluid resuscitation
6. Initiate early oral feeding when tolerated, regardless of severity
7. Choose enteral rather than TPN if unable to tolerate orals
8. Avoid prophylactic antibiotics
9. Drain +/- debride (EUS guided) infected or symptomatic necrosis
10. Perform early cholecystectomy for mild gallstone pancreatitis

Chronic Pancreatitis

Definition and Diagnosis

Definition - Chronic Pancreatitis

Pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.

Common features of established and advanced CP:

- Fibrosis on histology
- Pancreatic atrophy, duct distortion and strictures, calcifications on imaging
- Pain syndromes
- Pancreatic exocrine and endocrine dysfunction
- Dysplasia

Source: Whitcomb et al. Pancreatology, 2016.

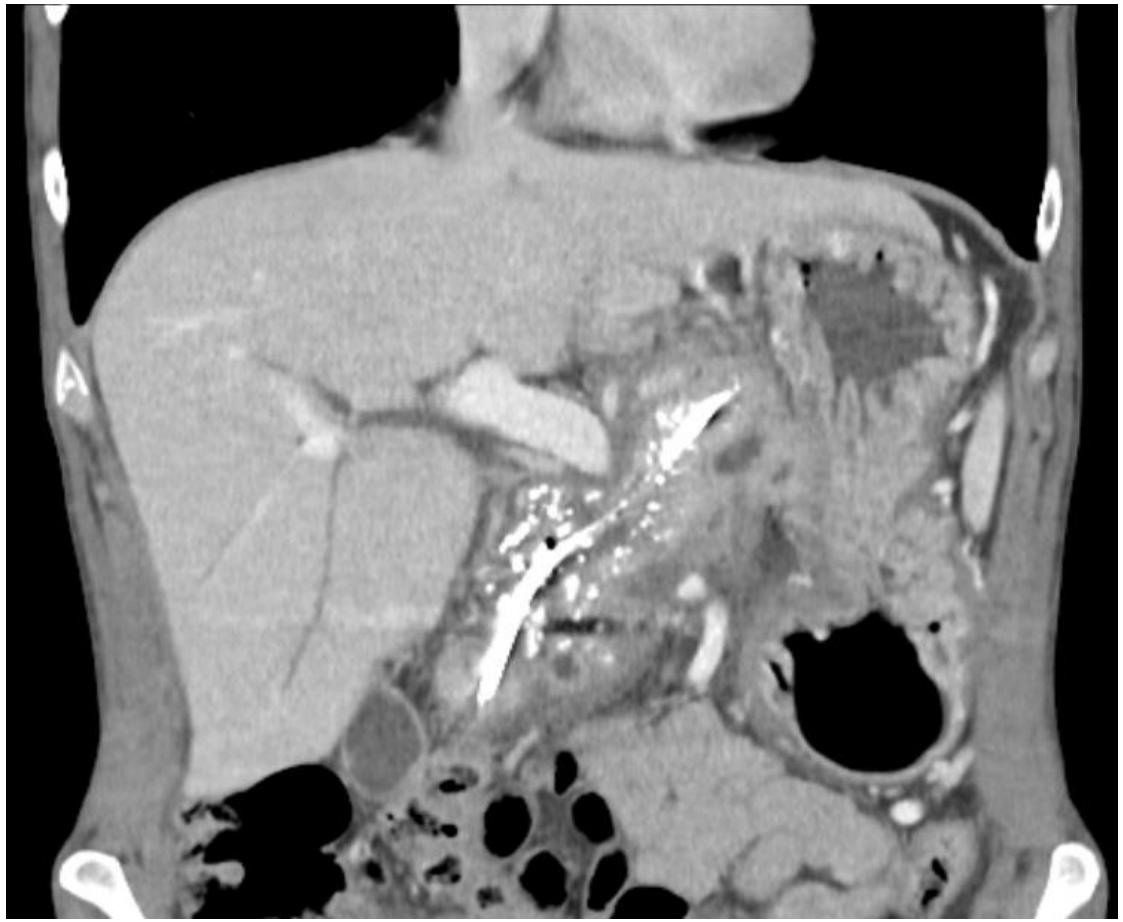
Diagnosis

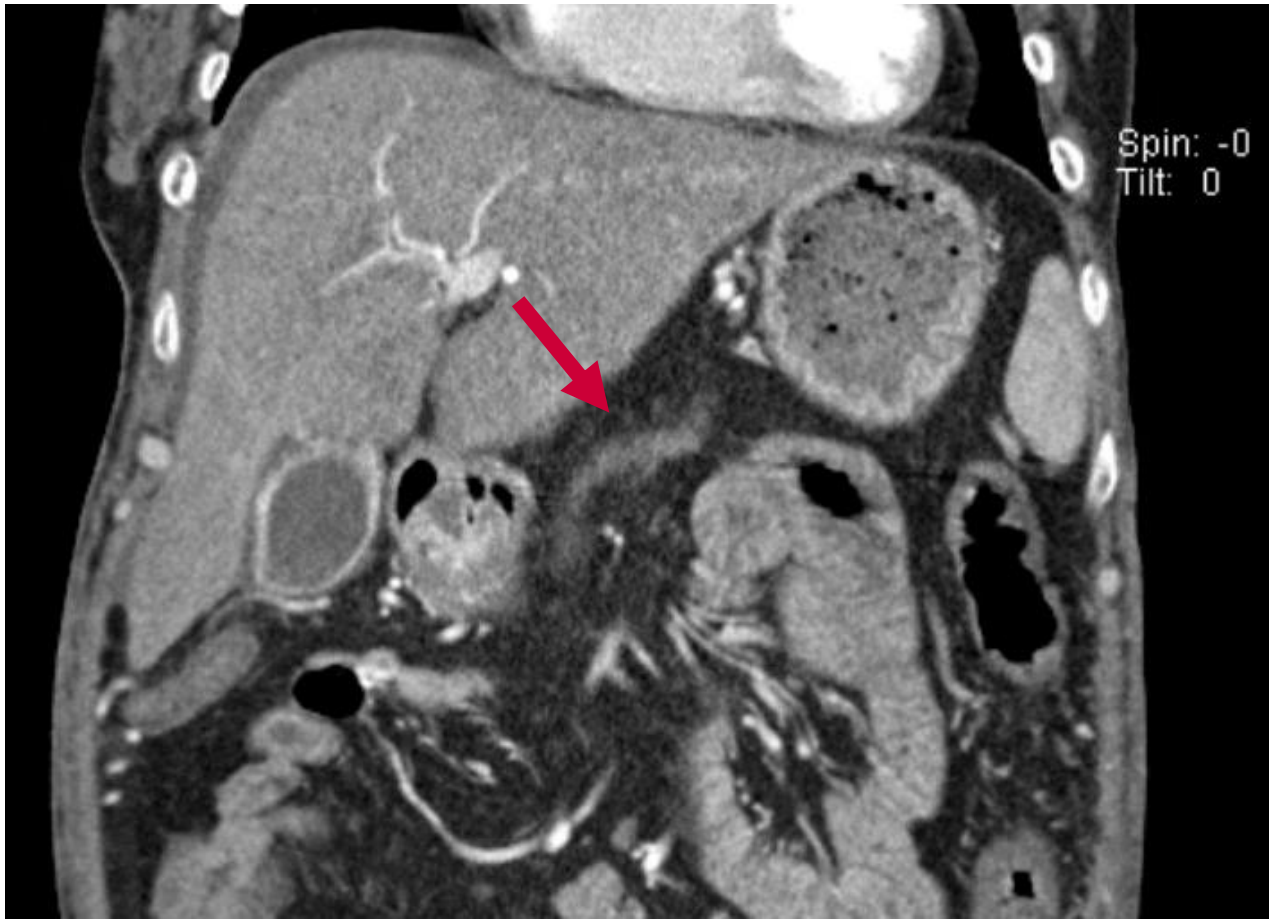
Take a history!

- History of acute pancreatitis
- Characteristic pain or maldigestion
- Genetic or environmental risk

In those with high pre-test probability, then imaging can confirm diagnosis

Diagnosis – Imaging





Etiology

Etiology – TIGAR-O

Toxic-Metabolic: Alcohol, Smoking, Hypercalcemia, Hypertriglyceridemia
Idiopathic
Genetic: *PRSS1, SPINK1, CFTR, CTRC*
Autoimmune
Recurrent/Severe AP: etiology in 60%
Obstructive: Pancreas divisum?, Duct obstruction

Source: Whitcomb et al. Gastroenterology, 2001

Natural History and Symptoms

Natural History and Symptoms

Abdominal or back pain – ETOH cessation may improve pain

Nausea vomiting

Exocrine pancreatic insufficiency (50%)

- Bloating
- Steatorrhea
- Weight loss
- Fat sol vitamin deficiency

Diabetes type 3c: duration of CP associated with islet cell loss

Pancreatic cancer: ~3-5% lifetime, higher in certain genetic conditions

Source: Gardner et al. Am J Gastroenterol, 2020

Management

Management – Pain in CP

1. Discontinue ETOH
2. Initial options: acetaminophen, NSAIDs
3. Add neuromodulator: gabapentinoids, TCAs, SNRI
4. Add antioxidants: Selenium, ascorbic acid, β-carotene, α-tocopherol, methionine
5. Pancreatic enzymes are ineffective for pain control, may improve bloating
6. Consider celiac plexus block: effective in 60%, duration 3-6 months
7. Opiates
8. Cognitive behavioral therapy may be very effective in centralized pain

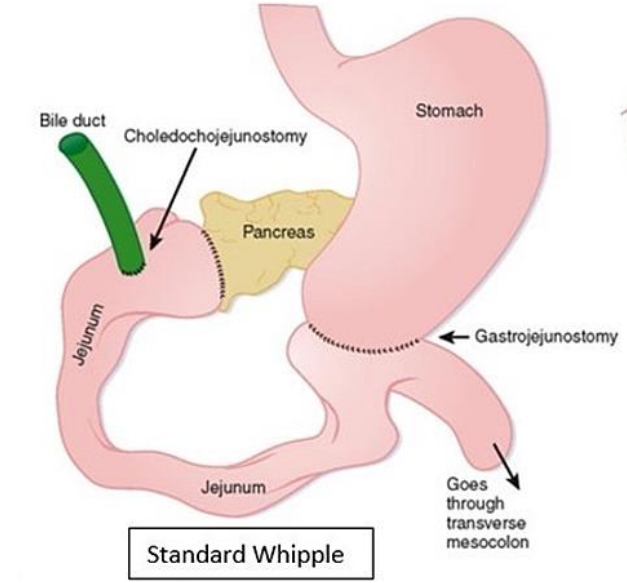
Source: Gardner et al. Am J Gastroenterol, 2020

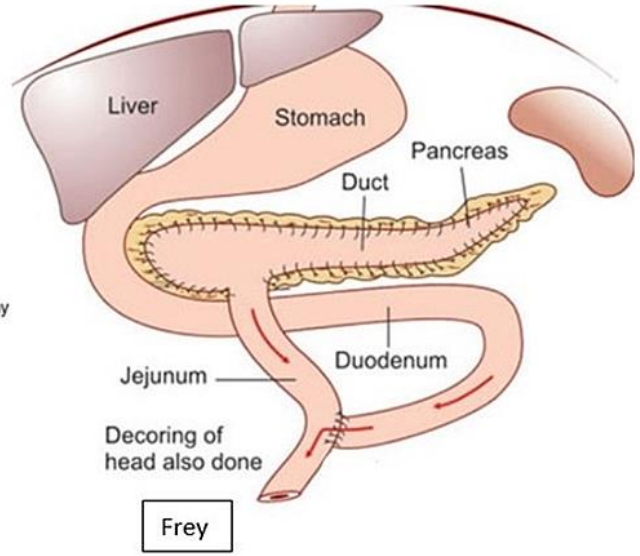
Management – Surgery leads to better long term pain relief for obstructive CP

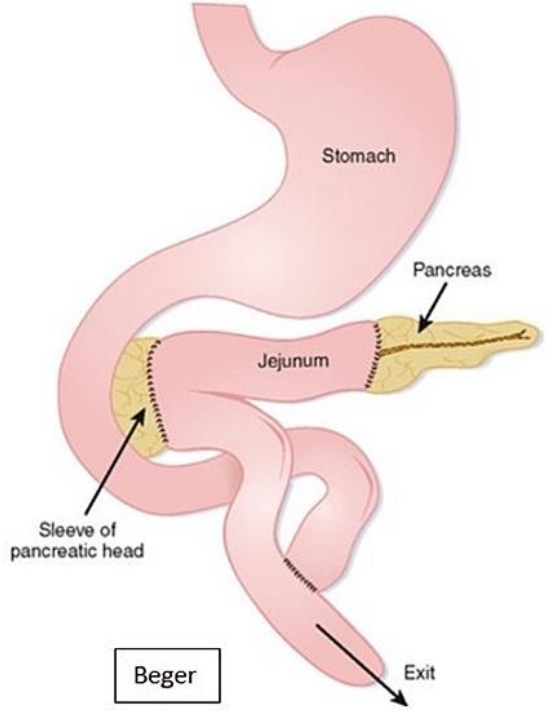
Long term outcomes of Multicenter RCT: n=61, early surgery vs. endoscopy (ESCAPE TRIAL), mean follow up 98 months

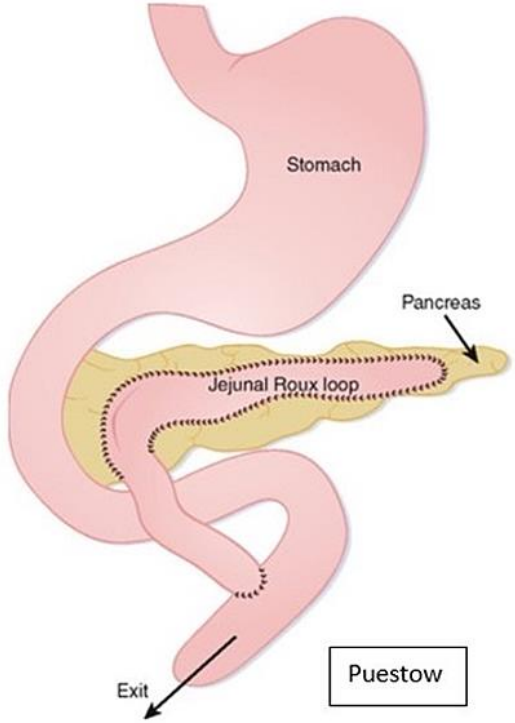
	Early surgery (n=31)	Endoscopic (n=30)	
Primary outcome (Izbicki pain score)	33	51	P = 0.03
Complete pain relief	14%	6%	P = 0.04
VAS score pain	29	47	p = 0.02
Satisfaction (very satisfied)	22%	10%	p = 0.003
No difference: SF-36 QoL score, pancreatic function, smoking or alcohol use			

Source: van Veldhuisen et al. JAMA Surgery, 2024









Source: Ashraf et al. Cureus, 2021

MYTH: Low Fecal Elastase (FE-1) = exocrine pancreatic insufficiency (EPI)

FACT: False positives (low FE-1) are very common

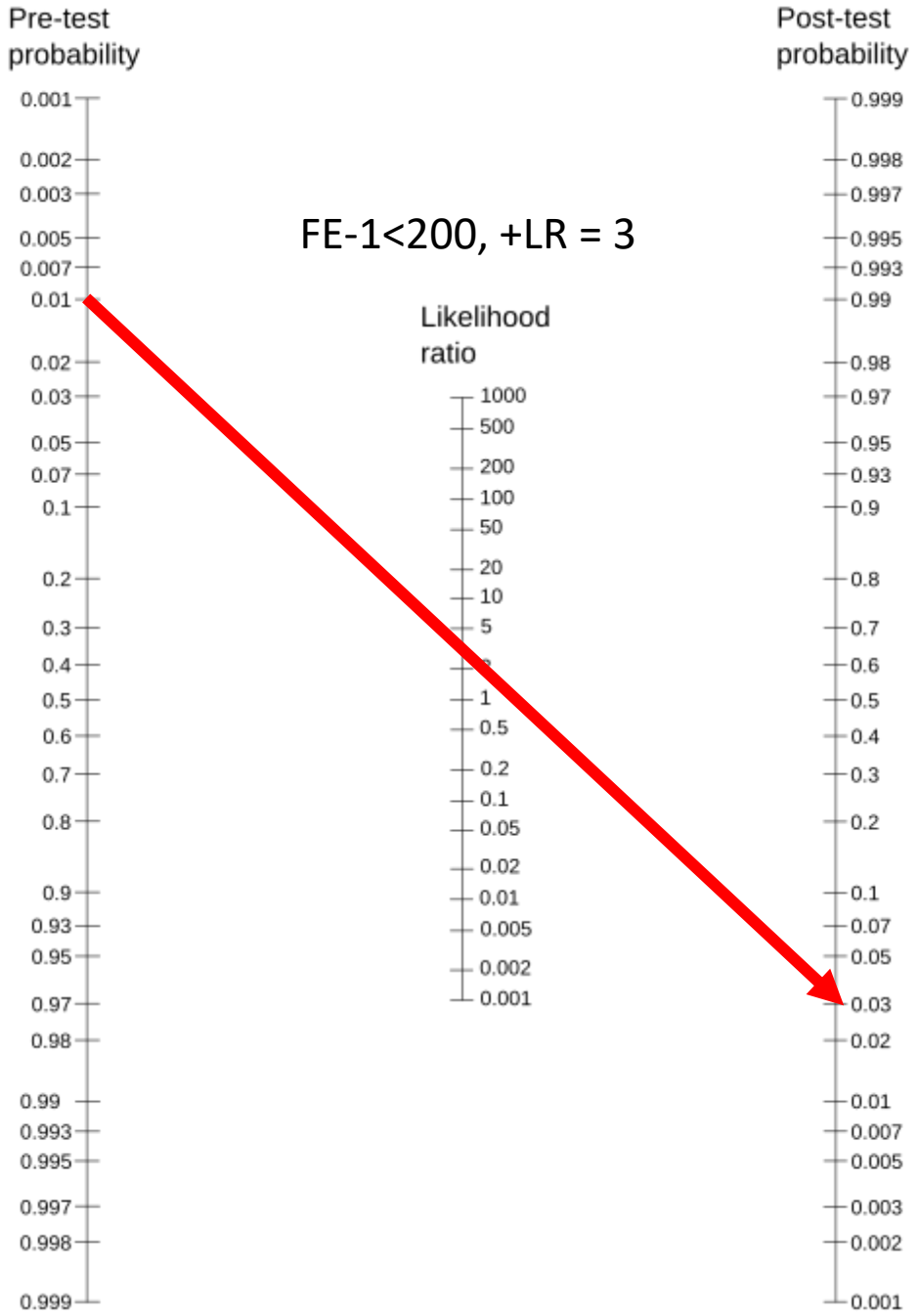
- Poorly formed/liquid stool leads to abnormal (low) results
- EPI is a low prevalence condition (~1-5%)
- The + LR of FE-1 <200 u/g = 3

Source: Vanga, et al. Clin Gastroentol Hepatol, 2018

FE-1

Pre-test probability = 1%

FE-1<200, +LR = 3



Post-test probability = 3%

Source: de la Iglesia, et al. UEG J, 2025

Management – EPI

Do not use FE-1 to screening for CP / EPI in low pre-test probability

EPI should be screened for in all CP patients

- Represents 90% loss of pancreatic acinar function
- Weight loss, steatorrhea, diarrhea, malnutrition, osteopenia
- Fecal elastase -1 most readily available diagnostic test

PERT improves fat and protein absorption, symptoms, and QoL

- Starting dose 40,000-50,000 U lipase with each meal

Evaluate periodically for

- Fat soluble vitamin (ADEK) and mineral (Zn, Mg, Cu, Se) deficiency
- Osteoporosis

Source: Gardner et al. Am J Gastroenterol, 2020

Take Home Points (Chronic Pancreatitis)

1. Diagnose chronic pancreatitis by clinical suspicion + compatible imaging
2. Treatment of pain is difficult and multimodal
3. Consider surgery > endoscopic decompression for long term pain relief
4. Interpret FE-1 judiciously
5. Dose PERT appropriately

BWH Center for Pancreatic Disease

Post-discharge follow up:

djin@bwh.harvard.edu / 617-732-6389

Clinic admin: Donna Shah

References

Banks PA, et al. Classification of Acute Pancreatitis – 2012: Revision of the Atlanta Classification and Definitions by International Consensus. *Gut*, 2013.

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