Acute Pancreatitis : Lessons Learnt Over Decades

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Disclosures

- Royalty for chapters in UpToDate – 2006
- Consultant for Cacimedica
- Full time or near full time clinician for over 32 years
- Started treating acute pancreatitis for as many years

Outline

- Magnitude of the problem
- Understanding pathogenesis
- Classification
- Severity prediction
- Identifying the cause
- Management
- Future

Initial Contributions in AP

- **Vege SS,** Clain JE, Chari ST. **JAMA 2004;291:2865.**
- **Vege SS, Baron TH. Clin Gastroenterol Hepatol 2005;3:192.**

What Is the Big Deal About Acute Pancreatitis?

- 275000 discharges of AP in 2009. Commonest GI hospital discharge diagnosis
- 30% increase from 2000 but mortality 1%
- 2.7 billion $ in health care costs

Gastroenterology 2012;143:1179

Yadav D, Vege SS, Chari ST. GI Epidemiology 2014:306

Types – Atlanta Classification 1992

- **Interstitial, edematous (mild)** – No pancreatic or peri-pancreatic necrosis. Resolves in few days
- **Necrotizing pancreatitis (severe)** – Pancreatic and peri-pancreatic necrosis.

Limitations of Atlanta Classification

- Many !

  (**Vege SS**, Chari ST. Time to revisit Atlanta classification. Gastroenterology 2005:1133-5)
- Led to a symposium in DDW 2006 at LA
- Resulted in International working group to revise the classification

Transient vs. Persistent Organ Failure

	# Patients	# Deaths (%)
Total	290	40 (14)
No Organ Failure	116	3 (3)
Transient Organ Failure	71	1 (1)
Persistent Organ Failure	103	36 (35)

Johnson et al., Gut 2004, 53: 1340

Moderately Severe AP ; A New Category. (Vege SS et al. AJG 2009;104:710)

	Mild	Moderate	Severe
Structural Alterations	Interstitial	Local complications	Interstitial or Necrotizing
Functional Effects	No Organ failure	No Organ Failure	Persistent Organ failure
Morbidity	Low	High	High
Mortality	Low	Low	High

Talukdar R, Clemens M, **Vege SS**. Validation of MSAP Pancreas 2012;41:306

Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus

Peter A Banks,[1] Thomas L Bollen,[2] Christos Dervenis,[3] Hein G Gooszen,[4] Colin D Johnson,[5] Michael G Sarr,[6] Gregory G Tsiotos,[7] Santhi Swaroop Vege,[8] Acute Pancreatitis Classification Working Group

Gut 2013;**62**:102–111

Phases of Acute Pancreatitis

- **First phase** - 1-2 weeks (Systemic inflammation dominant feature . Responsible for deaths and organ failure. No correlation with morphology at this stage)
- **Second phase** – After 1-2 weeks. Morphology of pancreatic and peri-pancreatic areas determines morbidity. Infection more common

Systemic Inflammatory Response Syndrome (SIRS) Score

- **SIRS defined by ≥ 2 of the following** :

  Pulse > 90 /min

  Resp > 20 / min or PaCO2 < 32 mm Hg

  Temp > 38 or < 36° C

  WBC count > 12,000 or < 4,000 / mm3

Types of Necrosis – Necrotizing Pancreatitis

- Usually pancreatic and peri-pancreatic or isolated peri-pancreatic. Pure pancreatic necrosis very rare
- Prognosis : Interstitial > Isolated peri-pancreatic > Pancreatic± peri-pancreatic (**Vege SS 2011**, van Santvoort et al 2011, Sakorafas et al 1999)
- **Peri-pancreatic only also included in necrotizing pancreatitis**

New Nomenclature of Pancreatic Fluid Collections

Acute necrotic collections (Peri ± pancreatic necrosis)	**4 – 6 wks**	**Walled-off necrosis**
Acute peri-pancreatic fluid collections (Resolve mostly)	**4 - 6 wks**	**Pseudocyst (very rare)**

CT : Most Frequent Imaging

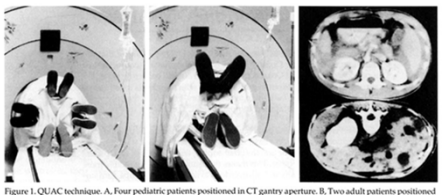
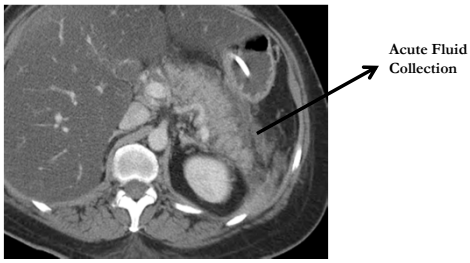
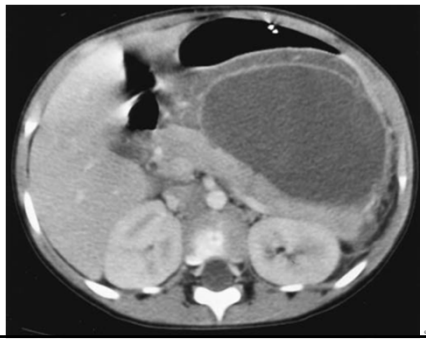


Figure 1. QUAC technique. A, Four pediatric patients positioned in CT gantry aperture. B, Two adult patients positioned for simultaneous examination and (C) resulting image (*bottom*, liver cysts; *top*, ruptured spleen [unrelated to patient positioning within gantry]).

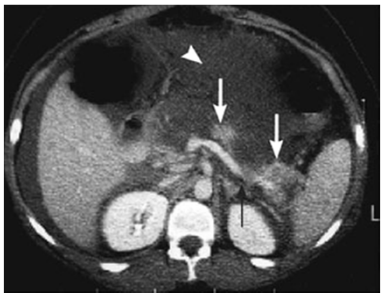
Acute Peripancreatic Fluid Collections



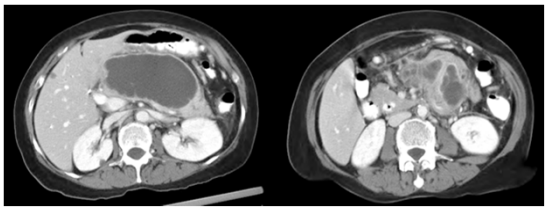
Psuedocyst with Wall and Outside the Pancreas



Acute Necrotic Collection Pancreatic and Peri-pancreatic Necrosis



Walled-off Pancreatic Necrosis (WON)



Sterile vs Infected Necrosis

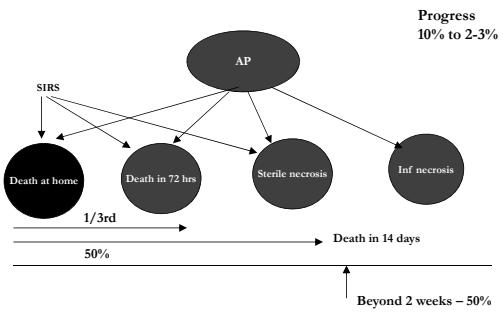
- Sterile does not need intervention usually
- Presence of gas bubbles diagnostic of infection
- **FNA not always needed** and clinical features of infection sufficient even if no gas
- FNA may help if pt not responding on antibiotics

Determinant Based 4-tier Classification

- **Critical** - Infected necrosis +Persistent organ failure
- Mortality – High (~45%)
- Determinants more important than other outcomes like length of stay, need for intervention etc.

Petrov MS, et al Gastroenterology 2010;139:813

When Do Patients with AP Die??



When, why and how do patients with acute pancreatitis die? A large experience of 910 direct (not transfer), consecutive admissions in recent years. (Yang A, Vege SS. Abstract DDW 2014)

- 24% deaths in 72 hrs, 80% deaths in 2 weeks
- Fulminant AP not the common cause of death
- Most patients with AP die due to persistent organ failure in 2 weeks
- Subsequent deaths due to infected necrosis rare
- **Need to improve persistent OF early on for any future improvement in mortality**

Management of AP

"It saves a lot of wear and tear during visiting hours."

ACG Practice Guidelines for AP

Tenner S, Baillie J, Dewitt J, **Vege SS**. AJG 2013; 108:1400

IAP/APA Evidence-based Guidelines

Pancreatology 2013;13:e1

Up-To-Date

Vege SS

Ask Mayo Expert

Vege SS

Diagnosis of AP

- **Two of the following 3 must be present** :

1. Abdominal pain consistent with AP
2. Amylase or lipase ≥ 3 times the ULN
3. Imaging consistent with AP

Be aware of at least 5 lipase systems with ULN ranging from 50 – 300 units !!

Role of Imaging in AP

- CT reserved for unclear diagnosis or no improvement in first 48 – 72 hrs. Not for all
- US indicated in all on day 1
- MRI, EUS rarely needed at presentation
- Correlation between CT nomenclature and surgical findings of collections

(**Vege SS**, et al World J Gastroenterol 2010;16:4291)

Identifying the Cause

Gallstones and Microlithiasis

- Gallstones + alcohol >60% of cases
- ALT ↑ 3× UNL has >90% PPV for biliary cause
- 3-fold ↑ALT, no stones on US :Think of microlithiasis. Go for MRCP or EUS
- < 3-fold ↑ liver tests & gallstones – cholecystectomy okay (by guide lines)
- **But** if liver tests normal, cause may be not gallstones

(**Vege SS** et al, Surgery 2012;151:199)

Acute Pancreatitis Due to Medications

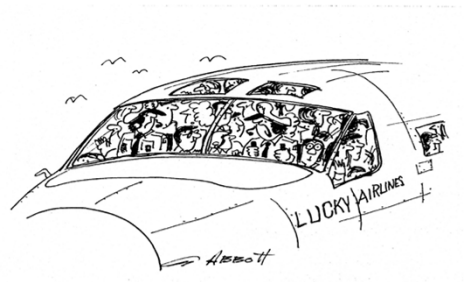
- Only Badalov class 1 & 2 (positive challenge and constant interval) need to be given importance
- Preferably started in the preceding 6 months
- One could never be very sure of a medication as the culprit; be on the lookout for other causes

Other Causes

- Be sure of TG as the cause only if > 1000 mg/dL
- Repeat TG and Ca after the attack subsides
- Don't forget cancer in pts > 50 yrs. 2% of AP due to cancer, 2% of cancers present with AP
- AIP rare cause of AP
- Main duct and side branch IPMN

  (Venkatesh PG, **Vege SS**. J Clin Gastroenterol 2011;45:755)
- Younger pts with idiopathic AP – Genes!!

Markers and Systems to Predict Severity



"I just hate it when they overbook."

At Presentation

- Age >60, comorbidities, obesity, chest Xray

  (left effusion, infiltrates)
- SIRS (simple, cheap, readily available)
- Hematocrit > 45, CRP > 150, high BUN, creatinine > 1.8 mg/dL

During the First 72 hrs

- Persistent SIRS (≥ 48 hrs)
- Persistent organ failure (≥ 48 hrs)
- BUN, creatinine, CRP ≥ 150 mg/L
- Necrosis on CT
- CT severity index (≥ 6)

SIRS at presentation, as well as for 72 hrs, simple, cheap and as good as any

Current Status of Predictors of Severity

- Not superior to expert clinical judgment
- Positive predictive value ~50%
- High negative predictive value for mortality, but one can predict that any way !!
- Urgent need for new predictors (ANN, machine learning tools and others)

Treatment

Intravenous Fluid Therapy

- Gardner TB, **Vege SS**, et al Clin Gastroenterol Hepatol 2008;6:1070
- Gardner TB, **Vege SS**, et al Pancreatology 2009;9:770
- Trikudanathan G, Navneethan U, **Vege SS**. Pancreas 2012;41:827
- Sarr MG. Ann Surg 2013;257:189

Intravenous Fluid Therapy

- 250- 350 ml /hr depending on clinical status
- **Lactated ringer** may be preferred to normal saline
- Evidence not very strong for aggressive (4.5L), method of monitoring, type of fluid
- Compartment syndrome and more intubations with mortality recent concerns
- Not of benefit beyond 24 – 48 hrs

Prophylactic Antibiotics

- No role
- May have a role in subgroup of necrosis and persistent organ failure (Vege SS. UpToDate)

Role of ERCP

ERCP for Biliary Pancreatitis

- Urgent (<24 hrs) only if cholangitis present.
- Mere biliary pancreatitis not an indication if no cholangitis and liver tests coming down even in a deteriorating patient
- In high risk patients – pre-ERCP MRCP or EUS to confirm CBD stones
- Elective before cholecystectomy

Oral Feeding in Acute Pancreatitis

- NPO passe. "Gut rousing" current concept
- If no significant ileus, vomiting, oral feeds as tolerated
- No need to wait for pain and enzymes to come down
- GI mucosa needs nutrition for integrity

Nutritional Support in SAP – When and How

- Usually between 3-5 days, when diagnosis of SAP is secure
- Early (during the first day) is under study
- **No TPN**
- 3 RCTs – nasogastric and nasojejunal no difference
- RCT NG vs NPO in mild AP - ↓ opiates,↑ gut function

Second Phase

- Infection – pancreatic, extra-pancreatic
- Intervention for collections
- Vascular and surrounding organ complications

Infection in AP

- More common after 1st week
- Pancreatic and peri-pancreatic – **infected necrosis**
- UTI, pulmonary, other
- Fungal infections in pancreas outcomes same as bacterial

  (**Vege SS**, et al. Amer J Gastroenterol 2009;104:2065)
- Prophylactic antifungals for those on abx not needed

  (Trikudanathan G, **Vege SS**. Amer J Gastroenterol 2011;106:1188)

Walled-off Necrosis (WON)

- ~15-20% of AP develop necrosis pancreatic and or peripancreatic
- 4-6 weeks later, they develop wall and become WON
- CT may misclassify them as "pseudocyst" if debris not seen
- May be sterile(70%) or infected and may be associated with persistent organ failure

When To Intervene?

Interventions for Necrotizing Pancreatitis

Summary of a Multidisciplinary Consensus Conference

Martin L. Freeman, MD, Jens Werner, MD,† Hjalmar C. van Santvoort, MD, PhD,‡*
Todd H. Baron, MD,§ Marc G. Besselink, MD, PhD,|| John A. Windsor, MD,¶ Karen D. Horvath, MD,#
*Eric vanSonnenberg, MD,** Thomas L. Bollen, MD,†† Santhi Swaroop Vege, MD,§*
and An International Multidisciplinary Panel of Speakers and Moderators‡‡

(*Pancreas* 2012;41: 1176–1194)

Do Not Intervene Early!

- Preferably **4 weeks** for a mature wall formation (less mortality, technically easier, less organ resection)
- Based on 1 RCT (surgery) and few good prospective studies (Strong rec)
- Emphasized in both recent guidelines (ACG, IAP/APA)

Am J Surg 1997;173:71,
Gastroenterology 2011;141:1254,
Arch Surg 2007;142:1194,
Arch Surg 2010;145:817

Who Needs Intervention?

WON : Indications for Intervention

- ~60% conservative treatment
- Most infected necrosis patients
- Sterile necrosis if :
  - Gastroduodenal
  - Biliary
  - Colonic

  } obstruction
  - "Persistently unwell"
- Disconnected duct with collections

What Intervention?

Options to Treat WON

- **Percutaneous catheter drainage (PCD)**
- **Endoscopic transluminal drainage (ETD)**
- **Endoscopic transluminal necrosectomy(ETN)**
- Sinus tract endoscopy (nephroscope or flex endoscope)
- Video assisted retroperitoneal debridement(VARD)
- Laparoscopic (retro, trans peritoneal, transgastric)
- Open necrosectomy (infrequent now)
- Medical (antibiotics)

WON : What Intervention?

- Open surgery very rare now (high mortality, morbidity, level 1 evidence)
- Small group with antibiotics ± PCD (stable infected necrosis)
- PCD commonest world wide and 40% don't need any other modality
- ETD, ETN becoming more common
- Laparoscopy, while has advantages, not picked up
- Step-up favored (PCD or ETD) followed by VARD or ETN
- Hybrid methods (PCD and ETD) or ETN with percutaneous necrosectomy may become the future

WON : Where Should Interventions Be Done?

- Necrotizing pancreatitis, specially if interventions required, needs **specialist center**
- **Specialist center** – High volume, multidisciplinary team (IR, ERCP, surgeon, gastroenterologist 24/7)
- **High volume** > 118/yr (Gastroenterology 2009;137:1995)

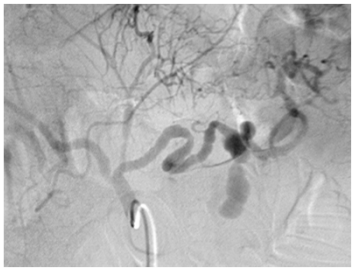
Vascular Complications of Acute Pancreatitis

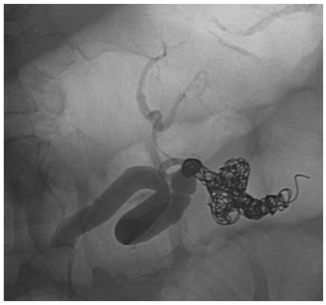
- Necrosis and bleeding from duodenum, colon
- Thrombosis of splenic, portal and/or superior mesenteric veins

  Nadkarni NA, Khanna S, Vege SS. Pancreas 2013;42:924.

  Harris S, Vege SS. Pancreas 2013;42:1251

- Splenic artery pseudo-aneurysms with bleeding





Pancreatic (Peri) Necrosis Consensus

- Try not to intervene till ~ 4 weeks
- Delay, drain and debride (minimally invasive route)
- Conservative treatment with ABX in selected group of stable patients with infected necrosis
- Minimally invasive intervention preferred to open surgery
- Know the available expertise at your center
- When in doubt ,refer !

Future

- Better methods of prediction
- Quality metrics
- We need a drug
- Pentoxifylline ? (**Vege SS**, et al RCT abstract Gastroenterology May 2013)
- Bigger trial currently awaiting review by NIH

Quality Measures in AP in the Cost-conscious Environment