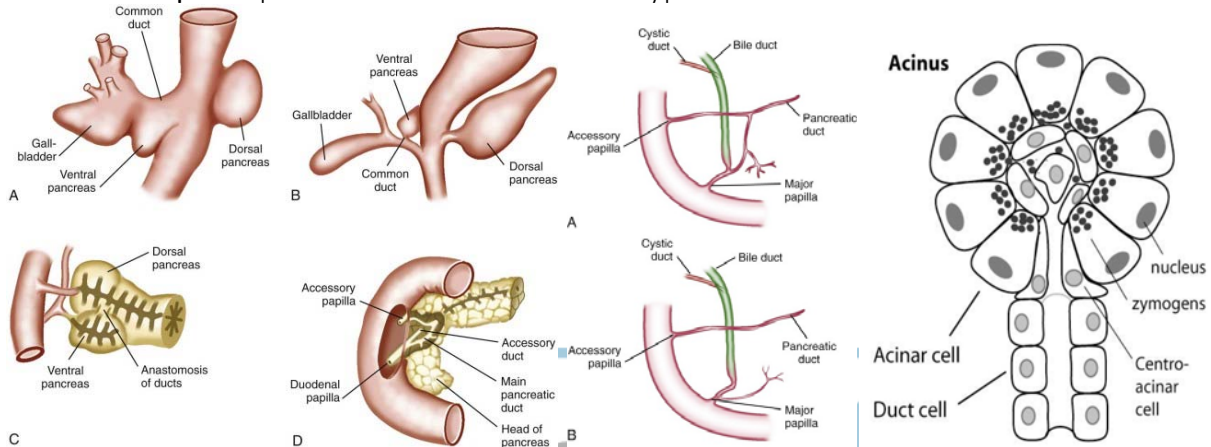


## Pancreatic Anatomy & Physiology

- Embryology

- 4<sup>th</sup> Week: ventral and dorsal pancreas bud from the endodermal lining of the duodenum
- 6<sup>th</sup> Week: dorsal portion grows to a much greater size than the ventral portion
- 7<sup>th</sup> Week: ventral portion swings around and fuses w/ the dorsal portion = dorsal portion represents tail, body and neck while the head and uncinate process is derived from the ventral portion
- Each portion develops with their own axial duct w/ the dorsal duct arising from the duodenal wall and the ventral duct from the **CBD**
- Ventral duct anastomoses with the **distal** part of the dorsal duct forming the main pancreatic duct while remaining **proximal** part of the dorsal duct becomes the accessory pancreatic duct



- Function

- General

- 80% exocrine tissue, 2% endocrine tissue, 18% fibroneurovascular septa (lobules are separated by septa that hold vessels/nerves/ducts)
- there is a portal system in which capillaries surrounding islets pick hormones and send them to the acinus via another set of capillaries
- most of the volume of pancreatic secretions is from the ducts not from the acini, non-fed state: 0.2mL/min (secretion coordinates w/ MMC) vs fed state: 4.0mL/min w/ ~2.5L/d
  - Cephalic Phase: mediated by vagus nerve by site/smell/taste of food (25% of secretion)
  - Gastric Phase: mediated by vagus nerve by gastric distension (10% of secretion)
  - Intestinal Phase: mediated by vagus nerve AND various hormones by presence of chyme in intestine (65% of secretion)

- Stimulation

- 1<sup>o</sup> Duodenal Protein → CCK → Stimulate Acinus (via Vagus thus via Ca as there are no CCK receptors!!!), Duodenal Gastric Acid → Secretin → Stimulate Duct (cAMP),

- 2<sup>o</sup> ACh-M3 (Ca), GRP (Ca), Substance P (Ca), VIP (cAMP)

- Inhibition: Sympathetic NS, Duodenal Enteric NS, Hormones (1<sup>o</sup> **Peptide YY and Pancreatic Polypeptide and Somatostatin** 2<sup>o</sup> Glucagon, Neuropeptide Y, Enkephalin, Pancreastatin, CGRP) = generally most act by inhibiting the vagus nerve

- Feedback Regulation

- free (meaning there is no food for it to act on) trypsin in the duodenal lumen binds to a receptor on the mucosa leading to hormone inhibition preventing any further pancreatic secretion
- alkalinization prevents further secretin secretion
- Endocrine: light staining Islets of Langerhans (1 million islets, B-beta 65% (insulin), PP 20% (pancreatic polypeptide), A-alpha 10% (glucagon), D-delta 5% (somatostatin))
- Exocrine: dark staining acini (grape like structure lined w/ centroacinar cells)
  - Duct Secretion (large volume)
    - Pattern: centroacinar → intralobular → interlobular → main PD (columnar/Goblet cells)
    - Electrolytes: secretes bicarb and absorbs chloride via the CFTR channel thus pancreatic secretions are isotonic and similar to plasma in all electrolytes EXCEPT bicarb (high) and chloride (low)
  - Acinar Secretions (small volume)
    - Zymogens: Protein (**trypsinogens cationic-PRSS1 (65%), anionic-PRSS2 (30%), meso-PRSS3 (5%), chymotrypsinogens A/B/C, proelastases, procarboxypeptidases A1/A2/B1/B2**), Fat (**colipsae, phospholipase A2, carboxyl ester lipase**)

- Non-Zymogens: Carb (**amylase**), Fat (**lipase**), Nucleotide (**D/RNAse**)
- Physiology: Enterokinase (peptidase) on brush border converts trypsinogen to trypsin by removing the trypsinogen activation peptide (TAP), trypsin then converts all other proenzymes into their active form
- Regulation
  - Global Enzymes Regulation
    - All enzymes are secreted as **pro-enzymes w/ activation far away in the SI**
    - Enzymes secretion is decreased when active trypsin binds **Protease Activate Receptor (PAR)** outside of the pancreas
    - **Enzymes flushed out** of the ducts by ductal fluid
  - Trypsin Catalysis
    - **Autocatalysis at R122**
    - **Chymotrypsinogen C**
  - Trypsin Inhibition
    - **Pancreatic Secretory Trypsin Inhibitor (PSTI) aka Serine Protease INHIBITOR Kazal type (SPINK1)** a peptide made by acinar cells during periods of pancreatitis that binds the catalytic site on trypsin inhibiting it
    - **Low calcium levels** are maintained around trypsin by compartmentalizing trypsin in vacuoles (calcium is at [high] in the cytoplasm and pancreatic duct)
    - **Low acid levels** are maintained in the pancreatic duct by the secretion of bicarb by duct cells
    - **Liver Alpha1-Antitrypsin and Beta2-Macroglobulin**

## Pancreatic Cancer

| Solid Tumors (98%)  | Cystic Tumors (1%)                                    |
|---|---|
| Ductal Adenocarcinoma (90%)   | Intraductal Papillary Mucinous Adenoma/Adenocarcinoma |
| Mature Cystic Teratoma (rare)   | Mucinous Cystadenoma/Cystadenocarcinoma               |
| Osteoclast-Like Giant Cell Tumor (rare)   | Serous Cystadenoma/Cystadenocarcinoma                 |
| Acinar Cell Carcinoma (rare)  | Solid Psuedopapillary Tumor                           |
| Pancreatoblastoma (rare)  |   |
| Lymphoma (rare)<br>consider the dx when you see a large pancreatic head mass but uniquely no biliary obstruction, pain, weight loss                                   |   |
| Pancreatic NETs (rare)<br>Insulinoma, Gastrinoma, Glucagonoma, Somatostatinoma<br>EUS (unlike AC they are small, along ant/post surface of pancreas, highly vascular) |   |

## Pancreatic Ductal Adenocarcinoma

- Epidemiology
  - 10<sup>th</sup> most common cancer w/ 37k cases in 2008 (2<sup>nd</sup> GI) but 4<sup>th</sup> most deadly cancer w/ 34k deaths in 2008 (2<sup>nd</sup> GI)
- RFs
  - NB no increased risk w/ alcohol aside from chronic pancreatitis
  - Familial Pancreatic Cancer (FPC) (pancreatic cancer that runs in familial and thus can be due to genetic causes, common env exposure, etc)
    - Genetic Pancreatic Cancer (10% of pancreatic cancer has a +FHx ( $\geq 2$  FDRs))
      - 75% do NOT have an identifiable causative gene
        - AD pattern w/ <80% penetrance and “anticipation” phenomenon in which pts in younger generations develop cancer 10yrs earlier than their affected parent
      - 25% have an identifiable causative gene
        - Hereditary Breast and Ovarian Cancer Syndrome (HBOCS)
          - AD Mutation: BRCA1/2
          - Cancers: premenopausal female & male breast cancer + ovarian cancer
        - Familial Atypical Multiple Mole Melanoma (FAMMM)
          - AD Mutation: CDKN2A
          - Cancers: multiple nevi/melanomas + sarcomas + lung/breast cancer
        - FAP/HNPCC/PJS (refer)
        - Ataxia Telangiectasia

|                     | Low Risk (<5x)  | Moderate Risk (5-10x) | High Risk (>10x)<br>(risk by age 70yo) |
|---------------------|---|-----------------------|--|
| <b>Demographics</b> | Old (peak 7 <sup>th</sup> -8 <sup>th</sup> decade)<br>Black<br>Male<br>Ashkenazi Jewish descent |                       |  |
| <b>Exposure</b>     | Smoking   |                       |  |

|                         |   |                            |   |
|-------------------------|---|----------------------------|---|
|                         | High Fat/Protein<br>Obesity<br>HP Infection ?<br>Benzidine and Beta-Naphthylamine<br><br>GLP-1 mimetic agent (exenatide)<br>DPP-4 inhibitor (sitagliptin) <ul style="list-style-type: none"> <li>pancreatitis (6x)</li> <li>pancreatic/thyroid cancer (3x)</li> </ul> |                            |   |
| <b>Pancreatic Dz</b>    | Cystic Fibrosis (5%)  | Chronic Pancreatitis (10%) | PRSS1 Hereditary Pancreatitis (40%)         |
| <b>Cancer Syndromes</b> | FAP/HNPCC (<5%)<br>BRCA1 (5%)   | BRAC2 (10%)                | FAMMM (20%)<br>Peutz-Jeghers Syndrome (35%) |
| <b>FHx</b>              | 1 FDR (5%)  | 2 FDR (10%)                | ≥3 FDR (25%)                                |

- Mechanism
  - Genetic Progression thru PanIN (85%) or IPMN/MCN (15%) pathways creating non-mucinous or mucinous AC
- S/S
  - Head Tumors (60%, typically produce Sx earlier in course due to invasion of surrounding structures)
    - **CBD Obstruction** = painless jaundice and **Courvoisier's Sign** (palpable nontender gallbladder)
    - **PD Obstruction** = acute/chronic pancreatitis and exocrine insufficiency (always suspect PC in an elderly pt w/ no other causes)
    - **Duodenal Obstruction** = nausea/vomiting, anorexia, weight loss
    - **Celiac/SMA Neurovascular Plexus Damage w/ RP Spread** = low intensity, dull, vague, constant, mid upper ab pain w/ radiation to mid scapular back often accompanied by sitophobia
  - Diffuse/Body/Tail tumors (20%/15%/5%, typically produce Sx later in course and are often "silent" for quite sometime until extensive local growth and metastasis)
  - Other
    - **Classic B Symptoms** (weight loss, night sweats, fever)
    - **New Onset DM** (always suspect PC in an elderly pt w/ no other causes, this is actually 2/2 amyloid produced by tumor that then accumulates in beta cells causing dysfunction not so much due to tissue destruction by the cancer)
    - **Trousseau's Sign** (migratory thrombophlebitis 2/2 procoagulant production, many times this is the initial presenting symptom)
    - **Paraneoplastic Syndrome** (esp Cushing's Syndrome and Hypercalcemia)
- Dx
  - **Cancer Markers** (good at separating neoplastic pancreatic pathology from non-neoplastic pancreatic pathology and distinguishing ductal neoplasm from non-ductal neoplasm)
    - **CA 19-9** (Carbohydrate Antigen #) S/S depends on cutoff (most common 37 U/mL)
      - Sensitivity 70-90% (falsely normal in early small cancers)
      - Specificity 80-90% (falsely high in other GI cancers and obstructive jaundice, cholangitis, pancreatic duct obstruction)
      - PPV 60-90% NPV 60-90%
    - Other: CA-125, CEA, MUC1/3/4, DuPan2, Tumor M2 Pyruvate Kinase, Oncofetal Antigen
    - Pancreatic Enzymes (Amylase/Lipase) are variable
  - **Pancreas Protocol CT** (best for M of TNM staging)
    - "pancreas protocol" = thin sections, helical, dual phase IV/Oral contrast w/ an arterial phase (nl pancreas enhances vs neoplasms do not enhance) and then 70sec later a venous phase (allows assessment of mets and tumor involvement of venous structures)
    - PD dilated in cancer but not in AIP
  - **EUS w/ FNA** (best for TN of TNM staging)
    - Perform before ERCP b/c stenting can interfere w/ EUS staging and if unresectable on EUS then metal stenting should be done during ERCP but if resectable there is controversy whether you should stent or not
    - Better than CT in that it can pick up smaller lesions and is more accurate in assessing resectability esp when it comes to LN and vascular involvement esp of venous vessels but not so much arterial vessels which are better assessed by CT
    - Tissue dx is not a prerequisite to proceeding to surgery but is necessary if undergoing neoadjuvant therapy or locally advanced/metastatic dz (some say still do b/c the cancer may be not AC but something else like lymphoma, NET, etc)
    - NB CT percutaneous Bx has higher r/o seeding but there is a r/o seeding during EUS FNA therefore talk to surgeons before hand especially if body/tail cancer b/c surgery will not remove that part of the stomach while head cancers are FNA thru the duodenum and thus tract will be removed during the Whipple
    - NB a negative FNA does not exclude malignancy
  - **MRCP/ERCP**
    - "Double Duct Sign" (HOP cancer results in stricture/obstruction of distal PD and intrapancreatic CBD)
    - Allows for tissue sampling via Brush Cytology and Forcep bx w/in ducts

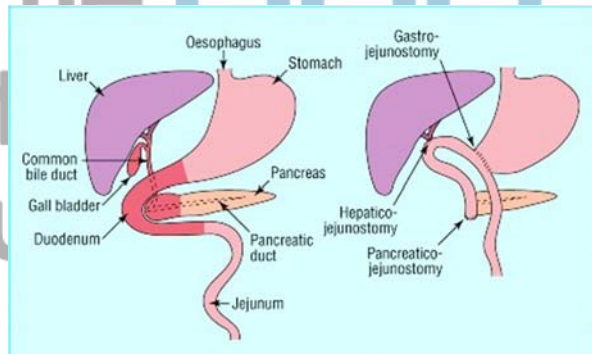
- **PET**
  - Use: (1) differentiating post-op changes and scarring from tumor recurrence, (2) assessing response to neo adjuvant chemoradiation, (3) differentiating benign from malignant masses
- **Screening & Surveillance**
  - AGA does not recommend screening general population b/c techniques lack sensitivity unless pt has high risk factors (PRSS1 Hereditary Pancreatitis, FAMMM, Peutz-Jeghers Syndrome,  $\geq 3$  1<sup>st</sup>/2<sup>nd</sup>/3<sup>rd</sup> Degree Relatives) then begin surveillance w/ alternating MRI/EUS (equally effective, CT not as effective) starting at 40yo for HP/FAMMM/PJS or 10yrs younger than the FDR w/ pancreatic cancer and then Q1yr (goal is to identify T1N0M0 and high grade precursor lesions like PanIN3 or IPMNs/MCNs) and if a suspicious lesion then total pancreatectomy is recommended
    - Problem is that it is hard to identify tissue changes suggestive of early cancer in pts w/ underlying chronic pancreatitis
    - Kras mutation analysis in pancreatic juice
  - American Cancer of the Pancreas Screening Consortium Study (CAPS 3) = 92 of 216 high risk pts were found to have a suspicious pancreatic lesion on CT-11%/MRI-33%/EUS-42% = conclusion is that MRI and EUS are complimentary and that these modalities detect curable high grade neoplasms

| AJCC Staging | Tumor  | LN | Metastasis  | NJNC Approach             | Management   | Median Survival                |
|--------------|--|----|---|---------------------------|--|--------------------------------|
| Stage I      | Tis (CIS)<br>T1 (<2cm)<br>T2 (>2cm)  | N0 | M0  | "Resectable"<br>10%       | ± NeoAdjuvant Chemoradiation then Surgery then Adjuvant Chemoradiation | 10-20mo<br>5yr survival 10-25% |
| Stage II     | T3 (extend into duodenum, bile duct, etc but no vessel involvement)  | N0 | M0  |                           |  |                                |
| Stage III    | T1<br>T2<br>T3   | N1 | M0  |                           |  |                                |
| Stage IV     | A<br>T4 (adjacent vessel involvement: arteries (CA, SMA, SA) and veins (PV, SMV, SV)<br><br>irregular vessel wall → loss of hyperechoic interface → encasement w/ venous collaterals, thrombosis, visible tumor in lumen | N# | M0  | "Locally Advanced"<br>30% | Chemoradiation   | 8-12mo                         |
|              | B<br>T#  | N# | M1 (distant mets usually first into liver, omentum, peritoneum or adjacent viscera (spleen/stomach/adrenal/colon) and then to lung, pleura, bone) | "Metastatic"<br>60%       | Palliation   | 3-6mo                          |

- Clinically everyone categorizes pts utilizing the NJNC approach b/c it is hard to accurately assess LN status w/o surgical intervention
- NB "borderline resectable" if very "little" vascular involvement
- What is the fundamental problem? 25-50% of pts predicted to have resectable dz according to CT/EUS criteria are found to have unresectable lesions on laparotomy usually visible small peritoneal/serosal/capsular implants, micromets detectable only on peritoneal washings and subtle vascular involvement all of which are missed on CT/EUS therefore staging laparoscopy (Bx of any suspicious lesions and peritoneal washings for peritoneal mets, sample ascites if present, bx liver to determine if unexpected cirrhosis is present) should be a part of our standard w/u b/c pts with these findings are found to prognosis similar to M1 dz, some centers recommend staging laparoscopy for >2cm and/or body/tail resectable tumors
- **Treatment**
  - Assess response to Tx w/ CA19-9, serial imaging and Sx
  - Palliation
    - Relieve CBD obstruction
    - Relieve gastric/duodenal obstruction with endoscopic stenting, J-tube or gastrojejunostomy
    - Treat endocrine/exocrine dysfunction
    - Psychiatric Dz Tx
    - Nutrition consult
    - Relieve pain with opioids, radiation, or percutaneous/endoscopic/surgical chemical celiac plexus block/neurolysis (CPB/N)
  - Chemoradiation
    - Neoadjuvant (unclear)
      - Done if "borderline resectable"
    - Adjuvant (unclear)
      - Gastrointestinal Tumor Study Group (GITSG) conducted b/t 1972-1984 was first to demonstrate the effectiveness of chemoradiation (43 pts after surgery were randomized to observation vs

chemoradiation w/ external beam radiation and concurrent 5-FU and it was found that median survival was 20mo in the Tx group vs 11mo in the observed group) NB several larger studies confirmed these findings but others, principally the European Organization for Research and Treatment of Cancer (EORTC) and the European Study Group for Pancreatic Cancer (ESPAC-1) demonstrated no statistical difference = conclusion is that evidence is equivocal, studies utilizing other chemo agents (gemcitabine instead of 5-FU results in a slightly higher increase in survival nonetheless we are talking in the order of a few months but there is more dramatic improvement in cancer related symptoms) may likely show benefit = here at BUMC we utilize FOLFIRINOX = 5-FU + Leucovorin + IRINotecan + OXaliplatin (NB anti-EGFR (erlotinib-Tarceva, cetuximab-Erbitux, gefitinib-Iressa), farnesyltransferase (tipifarnib-Zarnestra) and matrix metalloproteinases (marimastat))

- “Palliative”
  - National Cancer Institute for clinical trials ([www.cancer.gov/clinicaltrials](http://www.cancer.gov/clinicaltrials))
- Surgery
  - If Tail: Distal Pancreatectomy
  - If Multiple: Total Pancreatectomy (anticipate brittle diabetes and exocrine insufficiency)
  - If Head: Whipple (Head/Body Pancreatectomy, Antrectomy, Total Duodenectomy, Choledochectomy, Cholecystectomy, Truncal Vagotomy THEN Pancreaticojejunostomy, Gastrojejunostomy, Choledochojejunostomy)
    - NB Modified Whipple = pylorus-preserving pancreaticoduodenectomy (PPPD) which preserves the pylorus resulting in better gastric emptying and thus better post-op nutrition
    - NB 1-3.9% surgical mortality and 2.1-12.6% morbidity (1° fistula) even w/ experienced surgeons hence it is very important that Whipples be done at “centers of excellence for pancreatic surgery” (not sure how to find these and the definition of “excellence”) b/c they have better outcomes
    - NB b/c LN mets are common it has been advocated that retroperitoneal lymphadenectomy be done but studies indicate no survival benefit (there was actually longer hosp stays, higher rates of fistulas, higher incidence of delayed gastric emptying) therefore not done anymore



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#### Pancreatic Cysts

- Epidemiology
  - 1/2/25% of >50yo pts have pancreatic cysts on CT/MRI/autopsy based on large studies
- S/S
  - given the common use of imaging 25% of cysts are found incidentally and thus are asymptomatic
  - these tumors are often slow growing and thus if symptomatic the most common complaint is ab pain, palpable mass or obstruction resulting in pancreatitis, jaundice, GOO
    - **NB when you see a pt w/ FIRST episode of AP and has a cyst don't think pseudocyst but think of a cystic neoplasm (particularly IPMNs) that has caused AP**
- Dx
  - Approach: surgery, sample, surveillance, reassurance
  - if you find a pancreatic cyst some degree of w/u is necessary b/c CT & non-FNA EUS is not sensitive enough to differentiate non-neoplastic vs neoplastic cysts therefore w/u is dictated by (1) clinical appropriateness (eg age, comorbidities, pt wishes, etc), (2) whether there are worrisome features (eg. older pt, malignancy Sx such as weight loss, ≥3cm or growth, solid components either w/in cyst or adjacent to it, thickened/enhancing wall, etc) then start w/ **MRCP/MRI w/ secretin and EUS w/ FNA** otherwise just follow w/ MRI Q3mo-3yrs depending on size to document change in size/features and if so then w/u
    - NB a large series demonstrated that the risk of malignancy in a lesion <3cm is 3% which is equivalent to mortality from pancreatic surgery hence one should follow asymptomatic <3cm lesions
    - NB some say if <1cm then watch and if >3cm then surgery w/ controversy for cysts b/t 1-3cm and thus EUS w/ FNA may be helpful



- Non-Neoplastic Cyst Primarily Psuedocyst (90%) = hx/imaging consistent w/ pancreatitis and non-complex cyst (refer below)
  - **Psuedocyst (85%)**
  - Other (5%)
    - **Simple/True/Epithelial Cyst** (actually very rare, only cases reports, cuboidal epithelium or benign inflammatory cells)
    - **Retention Cyst aka Dilated Side Branch**
    - **Lymphoepithelial Cyst**
    - **Adult Polycystic Disease**
    - **Dermoid Cyst**
    - **Macrocyt w/ CF**
    - **Parasitic Cyst w/ *Echinococcus* or *Taenia***
- Neoplastic Cyst (10%) = no hx/imaging consistent w/ pancreatitis and complex cyst (calcified, septa, loculations, mural nodules, thick walled, wall calcifications)
  - **Mucinous / Macrocytic = higher malignant potential**
    - **IPMN (25%)**
    - **MCN (35%)**
  - **Non-Mucinous aka Serous / Microcystic = low malignant potential**
    - **SCA (30%)**
    - Other (10%)
      - **Solid Psuedopapillary Neoplasm** (30yo females, very large, body/tail pancreas, solid but often has cystic degeneration, low viscosity, eosinophilic papillary cells, IHC is uniquely + for vimentin/CD10/beta-catenin, Tx: resect all b/c there is a risk of malignancy)
      - **Lymphangioma**
      - **Von Hippel Lindau Disease (like SCA but scattered throughout the gland)**
      - **Cystic Degeneration of Solid Malignancy esp lymphangiomas, neuroendocrine tumors, lymphomas, sarcomas, teratoma, pancreaticoblastoma, even AC and endocrine tumors**

|  | Psuedocyst  | Intraductal Papillary Mucinous Neoplasm (IPMN)  | Mucinous Cystic Neoplasm (MCN)  | Serous Cystadenoma (SCA)   |
|--|---|---|---|--|
| <b>Demographics</b>  | NA  | 65yo M=F  | 50yo F  | 60yo F   |
| <b>5yr Cyst-AC Conversion</b> <ul style="list-style-type: none"> <li>Generally less aggressive than ductal AC</li> <li>What correlates w/ malignant conversion?               <ul style="list-style-type: none"> <li>Yes: PET activity, CA 72-4, increase in size, presence of mural nodules, increasing age</li> <li>No: CEA</li> </ul> </li> </ul> | NA  | YES (MD 60% vs BD 20%)  | YES (30%)   | NO (<1%)   |
| <b>CT/EUS</b> <ul style="list-style-type: none"> <li>Can reliably differentiate SCAs from IPMN/MCNs based on their microcystic structure therefore if not SCA then do more testing</li> <li>SCA/MCN are generally more vascular</li> </ul>   | <ul style="list-style-type: none"> <li>Any Size</li> <li>Anywhere</li> <li>Unilocular Cyst</li> </ul> | <ul style="list-style-type: none"> <li>Small (1cm)</li> <li>Poorly Demarcated</li> <li>Head of pancreas</li> <li>Dilated PD or Unilocular Cyst or Macrocysts (few large loculations) separated by thick septa               <ul style="list-style-type: none"> <li>MD-IPMN: dilated main duct (intestinal type tissue)</li> <li>BD-IPMN: dilated side branch (gastric type tissue, OFTEN MULTIFOCAL)</li> </ul> </li> <li>Synchronous lesions are common</li> <li>Subtypes based on MUC Profile on Mass Spectroscopy               <ul style="list-style-type: none"> <li>Gastric: MUC1/2-, low malignancy potential</li> <li>Intestinal: MUC2+, moderate malignancy potential</li> <li>Pancreaticobiliary: MUC1+, high malignancy potential</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>Medium (5cm)</li> <li>Sharply Demarcated</li> <li>Body/Tail</li> <li>Macrocysts (few large loculations) separated by thick septa</li> <li>Thick walled w/ peripheral "egg shell" calcifications (very specific finding)</li> </ul> | <ul style="list-style-type: none"> <li>Medium (5cm)</li> <li>Sharply Demarcated</li> <li>Body/Tail</li> <li>Microcystic aka Honeycomb/Spongy (several small loculations) separated by thin septa w/ a central stellate "star/sunburst" calcified scar</li> <li>Thick walled</li> <li>Resembles VHL except unifocal area not dispersed through out the gland</li> </ul> |

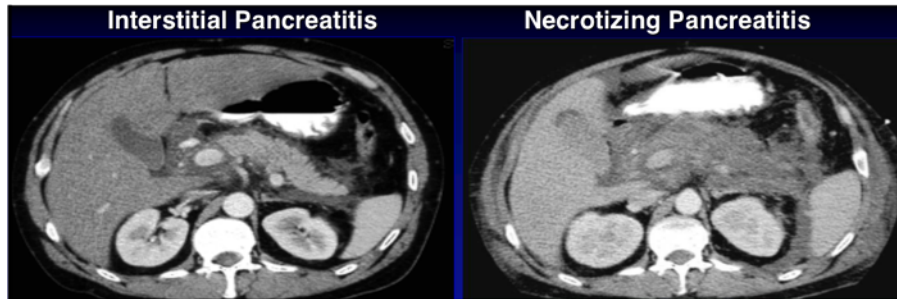
|  |   |  |  |  |  |
|--|---|--|--|--|--|
| <b>ERCP/MRCP</b>   |   | PD Communication                                     | PD communication often w/ filling defects 2/2 mucin and nodules<br><br>(mucus extruding thru papilla creating a "fish eye" appearance)   | NO PD Communication  | NO PD Communication  |
| <b>Fluid Analysis</b><br><br>(when combined together great sens and reasonably good spec - PANDA Study)  | <b>Amylase</b><br>(good way for distinguishing IPMN from MCN)   | VERY High Amylase                                    | High Amylase   | Low Amylase  | Low Amylase  |
|  | <b>Viscosity or [Mucin]</b><br>(high spec but low sens b/c contamination w/ gastric/duodenal mucin)<br>(Low: <5-20ng/mL or <1.6U/L or neg string sign vs High: >200ng/mL or >1.6U/L or pos string sign) | Low Viscosity  | High Viscosity<br><br>(they secrete lots of mucin and b/c they are part of the PD there is PD dilation w/ extrusion of mucin out of ampulla eventually resulting in PD obstruction and CP)   | (same as IPMN)   | Low Viscosity  |
|  | <b>CEA</b><br>(most accurate for differentiating mucinous from non-mucinous)<br>(Low: <5ng/mL vs High: >192ng/mL)   | Low CEA  | High CEA   | (same as IPMN)   | Low CEA  |
|  | <b>Cytology</b><br>(low sens b/c cellularity in fluid is low and contamination w/ gastric/duodenal epithelium)<br>Consider Bx or Confocal Probe   | No cytology occasionally macrophages and neutrophils | Columnar cells   | Ovarian-like subepithelial stroma w/ +ER/PR  | Cuboidal cells w/ glycogen rich cytoplasm  |
|  | <b>DNA Analysis</b><br>Three Things: (1) DNA quantity (+ if >40ng/mcl), (2) k-ras (+ if mutated), (3) LOH (+ if ≥2 genomic loci associated w/ TSG are mutated)  | Negative   | Positive   | (same as IPMN)   | Negative   |
| <b>Treatment</b><br>• No clear role for chemotherapy but there are some trials looking at ablation w/ ethanol and paclitaxel if no communication w/ the PD |   |  | Sphincterotomy to relieve mucin obstruction<br><br>Resect if <b>MD OR &gt;3cm BD OR Symptomatic OR High Risk Features (mural nodules, abnormal cytology)</b> otherwise just observe w/ MRI Q6mo-1yr depending on size (1-3cm-<1cm) | Resect <b>All</b>  | Resect if <b>Symptomatic OR &gt;4cm OR &gt;3cm growth per yr</b> otherwise just observe w/ MRI Qyr |
| <b>Follow Up</b><br>• After Tx surveillance is necessary w/ MRI/MRCP   |   |  | If resected then 5yr survival ranges from 75-100% depending on degree of malignant transformation  | If resected then 5yr survival ranges from 30-100% depending on the degree malignant transformation: if benign then no f/u but if malignant then Q6mo f/u |  |

#### Pancreatitis

- 1992 Atlanta Symposium Definition
  - Acute inflammation of the pancreas w/ variable involvement of other regional tissues or remote organ systems w/  $\geq 2/3$ 
    - (1) Sx consistent w/ dz
    - (2) Amylase or Lipase  $>3 \times \text{ULN}$
    - (3) Radiologic imaging consistent w/ dz
- Mechanism
  - obstruction w/ reflux OR direct damage  $\rightarrow$  premature conversion of trypsinogen to trypsin within acinar cells overwhelming protective mechanisms  $\rightarrow$  trypsin then activates other enzymes and the complement/kinin system which then collectively destroy local, adjacent, and systemic tissue via inflammation, microcirculatory injury, infection, etc  $\rightarrow$  extravasation of fluid  $\rightarrow$  decreased EAV  $\rightarrow$  decreased pancreatic perfusion  $\rightarrow$  increased pancreatic necrosis  $\rightarrow$  increased extravasation of fluid (vicious cycle)
- Who will develop severe disease?
  - RFs
    - Obesity w/ BMI  $>30$  (new concept!!!)**
    - Hemoconcentration**
    - AMS**
    - SIRS ( $\geq 2/4$  HR  $>90$ , WBC  $<4/$   $>12$ , PCO<sub>2</sub>  $<32$  or RR  $>20$ , Temp  $<36$   $>38$ )**
    - Age  $>55$ yo**
    - Pleural Effusion (get a CXR at admission)**
    - Comorbidities**
  - Labs
    - Urinary Trypsinogen Activation Peptide (TAP)  $>30\text{nmol/L}$  (premature activation during pancreatitis results in the release of TAP and correlates w/ severity)
    - YES Pancreatic Perfusion Markers (BUN, Cr, Hct, et al)
    - NOT Inflammatory Markers (Amylase, Lipase, ESR, CRP, et al)
  - Scoring Systems
    - Bedside Index for Severity in Acute Pancreatitis (BISAP)  $\geq 3$  BUN  $>25\text{mg/dL}$  + Impaired Mental Status + SIRS + Age  $>60$ yo + Pleural Effusion
    - APACHE-II  $\geq 9$  and Ranson's  $\geq 3$  (cumbersome and not complete until 48hrs and by then its already too late therefore don't use)
  - Important Points
    - pts dx w/ mild dz progress to severe dz indolently in the first 48hrs hence NEVER label a pt as mild during the first 48hrs
    - pancreatic complications (eg. necrosis) and extra-pancreatic organ dysfxn do NOT necessarily correlate
    - early on mortality is 2/2 organ failure while later on mortality is 2/2 local complications and infection BUT overall the most important determinant of severity is organ failure!!!
- What is severe disease based on Atlanta Symposium Classification?

|   | Mild (75%)                           | Severe (25%)   |
|---|--------------------------------------|--|
| <b>Complicating Features on Imaging</b> | None just Interstitial aka Edematous | Necrosis<br>Abscess, Psuedocyst, et al   |
| <b>Extra-Pancreatic Organ Dysfxn</b>    | Minimal to None                      | Shock w/ SBP $<90$<br>Pulmonary Insufficiency w/ PaO <sub>2</sub> $<60$<br>Renal Failure w/ Cr $>2$<br>GIB w/ $>500\text{mL/d}$ , et al  |
| <b>Recovery</b>                         | Uneventful Recovery                  | Death RFs/% (overall 6%) <ul style="list-style-type: none"> <li>No Organ Failure: 0%</li> <li>Interstitial: 3%</li> <li>Single Organ Failure: 3%</li> <li>Necrotizing: 17%</li> <li>Infected: 30%</li> <li>MOF: 47%</li> </ul> |
| <b>Tx</b>                               | Floor<br>General Tx                  | ICU<br>Aggressive Tx   |





- Treatment
  - **Monitor:** always look for complications esp if pt is not improving, follow labs (refer above)
  - **Pancreatic Rest:** initially keep NPO → start enteral feeds regardless w/in 36-48hrs w/ elemental NGT → once pt has an appetite and no more N/V then begin oral feeds w/ low fat diet (studies show that it is comparable to clear liquid diet)
    - **Enteral** vs Parenteral? Enteral decreases gut flora translocation while parenteral increases r/o MOF, r/o sepsis, need for surgical intervention, days in hospital, cost, mortality
    - **NGT** vs ND/JT? scientifically it makes sense to use NJ feeds b/c it skips the gastric phase of pancreatic stimulation but several studies clinically show that it makes no difference and that NGT are a lot easier and safer to pass than ND/JT
  - **Analgesia:** demerol but morphine is fine b/c there is only a theoretical r/o Sphincter of Oddi spasm based on animal studies while human studies don't show anything
  - **Etiology:** address the underlying cause
  - **Fluid Resuscitation**
    - Why? there is extravasation of protein-rich intravascular fluid into the peritoneal cavity resulting in low effective arterial volume which subsequently results in decreased perfusion pressure into the pancreas which subsequently increases ones risk of necrosis which results in more inflammation and more extravasation hence a vicious cycle
    - Hydration is most important the first 6hrs!!!
    - LR 30mL/kg x1 over 30min then 3.0mL/kg/hr ~300cc/hr (a recent studies shows that saline leads to a metabolic acidosis which can increase zymogen production hence it is now recommended to use LR which decreases metabolic acidosis)
    - Titrate based on Cardiac/Renal/Pulm Dz (it is sometimes difficult to differentiate volume overload vs ARDS), Vitals/UOP, BUN/Hct Q6hrs, consider Swan-Ganz catheter
  - **Future:** pancreatic protease inhibitor (gabexate mesylate), direct intra-arterial infusion of protease inhibitors and antibiotics, etc
- Etiology
  - Acute: 45% gallstone, 35% alcohol, 5% hypertriglyceridemia (most often missed)
  - Chronic: 75% alcohol

|               | Gallstone   | Alcoholic   |
|---------------|---|---|
| <b>Age</b>    | >40yo   | <40yo   |
| <b>Gender</b> | Greater risk in men but higher incidence in females b/c gallstones are more common  | Male  |
| <b>Hx</b>     | Usually no recurrence b/c pts often get a cholecystectomy after first diagnosis but if not then recurrence is as high as 50% at 6mo   | Recurrent h/o pancreatitis                          |
| <b>Labs</b>   | TB >1.35mg/dL on Day#2<br>ALT >150<br>Amylase >1000<br>Mild High GGT<br>NB don't forget that significant pancreatic head inflammation and edema cause some degree of biliary obstruction<br>NB sometimes CT misses stones | TB nl<br>ALT <150<br>Amylase <1000<br>Very High GGT |

- Obstruction
  - **Stones/Sludge**
    - 1° Macrolithiasis >3mm (refer)
      - Epidemiology
        - only 5% of pts w/ gallstones experience pancreatitis
        - occurs more frequently w/ medium stones (3-5mm) b/c they are more likely to pass the cystic duct but still cause obstruction
      - Mechanism

- (1) obstruction of stone at ampulla or edema from passage of stone increases pancreatic pressure thereby damaging cells or
- (2) reflux of bile into pancreatic duct 2/2 stone obstruction distal to common duct or incompetent sphincter of Oddi 2/2 recent stone passage which mixes w/ pancreatic secretions damaging cell

○ Likelihood of having CBD Stones

| Suspicion | Moderate   | Intermediate   | Strong                     |
|-----------|--|--|----------------------------|
| TB        | <1.5   | 1.8-4  | >4                         |
| AP        | <110   | 110-150  | >150                       |
| US        | Other  | CBD Dilation >6mm  | CBD Stone                  |
| Action    | EUS (95% sens)<br>MRCP (90% sens)<br>CT (80% sens) | since you are already going to take out the gallbladder with a lap chole b/c pt is symptomatic due to something (you are thinking choledocholithiasis) have the surgeons also do an IOC and if + then ERCP | ERCP followed by lap chole |

○ Tx

- controversial whether removing a gallstone emergently with ERCP vs conservative management has any effect on outcome of AP as most stones pass spontaneously and there is a risk of PEP thus most do ERCP **w/in 24-72hrs in pts w/ severe AP, ongoing obstruction signified rising bili or cholangitis**
- high recurrence rate therefore cholecystectomy

- 2° Microlithiasis <3mm and Sludge (combo of crystals (calcium bilirubinate, calcium carbonate, cholesterol monohydrate), mucin, glycoproteins, cellular debris, proteinaceous material, etc)
  - Etiology: form by a similar process to macrolithiasis BUT its important to know that pancreatitis diminishes GB contractility inducing sludge formation hence unclear what is the “chicken or the egg”
  - Mechanism: similar to macrolithiasis but also repeated exposure can lead to papillary stenosis

- NB some do not believe that microlithiasis/sludge alone causes damage but rather it is a marker for prior macrolithiasis

○ Dx

- Ultrasound
  - Finding: echogenic material w/o shadowing that layers in the most dependent part of GB
  - Transabdominal US (55% sensitivity) & Endoscopic US (96% sensitivity)
- Bile Acid Analysis (Meltzer-Lyon Test)
  - 10cc bile aspiration from duodenum during EGD following CCK administration → bile is centrifuged at 2000 revolutions/min x10min and the sediment is warmed to 37°C and examined under polarized microscopy → the presence of birefringent notched rhomboid crystals or calcium bilirubinate is consistent w/ sludge
  - 67%/83% sensitivity w/ duodenal/bile duct bile collection w/ the gold standard being direct GB bile collection

○ Tx

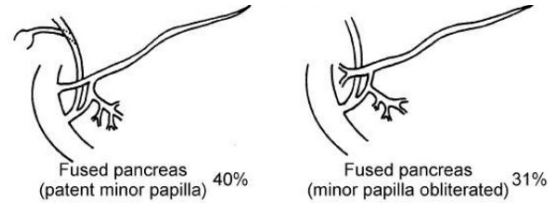
- 1° Cholecystectomy (common practice but not supported by any direct evidence)
- 2° Sphincterotomy
- 3° URSO

• Tumors (refer)

• Parasites (refer)

• Anatomic Anomalies

- Sphincter of Oddi Dysfunction (refer)
- Choledochocoele (refer)
- Periapillary Diverticula (refer)
- Duplication Cyst (refer)
- Anomalous Pancreaticobiliary Junction (refer)
- Normal Variants
  - Patent Dorsal Duct: ventral PD drains all of the pancreas thru major papilla w/ dorsal PD draining the neck BOTH into the ventral PD AND thru minor papilla (40%)
  - Non-Patent Dorsal Duct: ventral PD drains all of the pancreas thru major papilla w/ dorsal PD draining the neck into the ventral PD BUT NOT ALSO thru the minor papilla (30%, still considered normal)



- Abnormalities

- **Pancreas Divisum** (7%, can be complete if no connection exists b/t dorsal and ventral duct or incomplete if a small connection exists)
  - Definition: embryonic dorsal and ventral ducts do not fuse resulting in the entire dorsal duct becoming the main adult PD emptying the neck/body/tail thru the minor papilla while the ventral duct drains the head/uncinate process thru the major papilla
  - Epidemiology: most common congenital anomaly of the pancreas w/ incidence (general population autopsies: 5-10%, all ERCPs: 0.3-7.5%, idiopathic pancreatitis: 25%)
  - S/S: 95% of cases it is an anatomic variant w/ no clinical significance but in 5% of cases it MAY be the cause for pancreatitis though controversial
    - Theory: relative obstruction of pancreatic juice through the small minor papilla
    - Controversial

- Arguments For

- pts w/ recurrent AP have a higher Hz of PD than would be expected for the general population
- sphincterotomy or stent placement across minor papilla reduces recurrence of AP

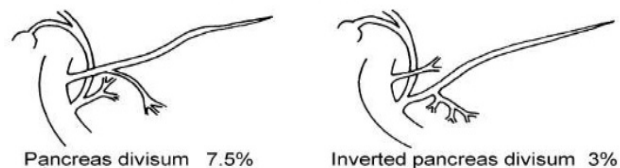
- Arguments Against

- rate of AP in PD is the same as the general population
- rate of other genetic abnormalities in PD pts is higher than the general population suggesting another cause for AP

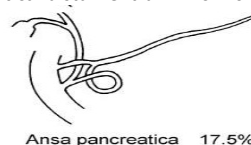
- Tx

- PD itself does not require Tx rather if Sx of AP are present then first exclude other causes of AP and if all negative then first try conservative medical therapy (abstain from alcohol, limit fat intake, pancreatic enzyme replacement, etc) and if that doesn't work then demonstrate obstruction using secretin stimulated US and intra-operative calibration w/ lacrimal probe (do this when pt has symptomatic PD w/ no dilation) and if + then consider Tx w/ minor pancreatic sphincterotomy w/ temporary stent placement
- Favorable Outcome: APR (75%) > Pancreatic-Type Pain (25%) > CP (25%)

- **Inverted Pancreas Divisum:** ventral PD drains the entire pancreas (except neck) thru major papilla w/ dorsal PD draining the neck thru the minor papilla and not into the ventral duct unlike the above normal variants (3%, significance unclear)



- **Ansa Pancreatica:** distal ventral PD forms a loop (17%)

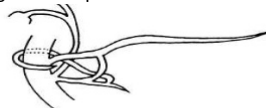


- **Annular Pancreas**

- Mechanism: ventral bud becomes fixed and fails to completely rotate and fuse with the dorsal bud → band of pancreatic tissue partially (75%) or completely (25%) encircles the 2<sup>nd</sup> part of duodenum just proximal to major

papilla w/ the annular duct draining in continuity w/ ventral duct or rarely into the dorsal duct, CBD or independently into the duodenum

- S/S: (bimodal presentation peak)
  - Neonate (complete): duodenal obstruction
  - Adult (partial): pancreaticobiliary obstruction w/ IARP or just asymptomatic
  - Other Anomalies: pancreatic divisum (1/3), Down's syndrome, duodenal atresia, tracheoesophageal fistula, cardiorenal abnormalities, malrotation
- Dx: ERCP (duct encircling duodenum), CT (pancreatic tissue encircling duodenum), CXR ("double bubble sign" w/ air in stomach and proximal duodenum)
- Complications: increased r/o ampullary/pancreatic/biliary cancer
- Tx: surgical bypass (gastrojejunostomy) not simple division or resection b/c of growth of pancreatic tissue into duodenal wall



Annular pancreas 1.5/10,000

- Toxins

- EtOH

- Epidemiology: even in heavy drinkers (what this is in terms of g/d is unclear but some say >50g/d (~3drinks) for >2yrs) only 2% develop AP and of those only 10% develop CP suggesting a genetic susceptibility esp race (black) and other environmental factors esp smoking (most important), high fat/protein diet, vitamin deficiency

- NB the classic teaching is that an alcoholic presenting w/ pancreatitis is always presenting with ACUTE ON CHRONIC pancreatitis such that if you see an alcoholic w/ acute pancreatitis but w/o chronic changes then you should actually doubt that alcohol is the cause

- NB can one heavy binge cause AP???

- Mechanism: unclear but includes relaxation of sphincter of Oddi w/ reflux, spasm of sphincter of Oddi, increased permeability of pancreatic duct, sudden release of large amounts of enzymes, higher calcium-protein concentration in pancreatic juice resulting in small tubule obstruction, formation of GP-2 and calcium carbonate stones, direct damage to acinar cells via the formation of fatty acid ethanol esters (FAEEs)

- Smoking (emerging as a true independent RF)

- Other Alcohols

- Trinidad Scorpion Venom

- Organophosphorous Insecticides

- Drugs

- Drugs (120 implicated so far based on poor case reports b/c they did not meet the criteria above)

- Dx

- 1<sup>st</sup> all other causes of AP have been ruled out (DOE)
      - 2<sup>nd</sup> the interval b/t drug use and pancreatitis should be consistent w/ hypersensitivity reaction vs toxicity
      - 3<sup>rd</sup> pancreatitis is reproduced upon drug rechallenge at appropriate time period
        - NB remember pts w/ IAP also have recurrent attacks and it may be that during the rechallenge the recurrent attack is actually due to something else that happens to recur at the same time (eg. microlithiasis)

- S/S: pancreatitis is usually mild and self-limited

- Mechanism

- (1) **hypersensitivity reaction** (most common, occurs 4-8wks after starting drug and hrs-days after rechallenge, not dose related, additional eosinophilia, rash, LAD) eg. 6-MP, 5-ASA, metronidazole, tetracycline
      - (2) **drug metabolite toxicity** (dose related, occurs several months after starting drug) eg. estrogens, BB, HAART (hypertriglyceridemia w/ the last three), sulfa (Lasix, HCTZ, hypoglycemic, Bactrim), valproic acid, didanosine, isotretinoin

- Metabolic

- \*\*\* a new concept is that metabolic syndrome (dyslipidemia, obesity, glucose intolerance) can cause AP \*\*\*

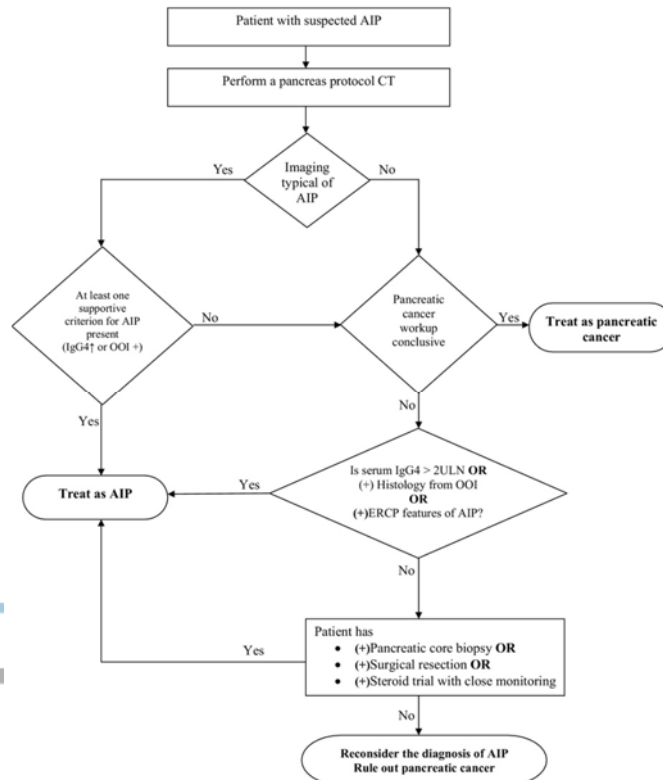
- Hypertriglyceridemia

- Epidemiology: 5% of AP (3<sup>rd</sup> most common cause!!!)
    - RFs (most pts actually have a mild form of a familial dyslipidemia and an additional acquired condition)
      - Primary (Familial Dyslipidemia esp apolipoprotein C-II deficiency)

- Secondary (refer but includes DM, EtOH, obesity, hypothyroidism, nephrotic syndrome, high estrogen state, glucocorticoid excess state, meds (estrogens, BB, HAART))
      - NB diabetes (DKA causes pancreatitis b/c insulin deficiency leads to lipolysis in adipose tissue with release of FFAs which travel to liver stimulating release of TGLs resulting in hypertriglyceridemia AND pancreatitis causes DKA by decreased insulin production by damaged pancreas)
  - Mechanism: unclear but possibly pancreatic lipoprotein lipase hydrolyzes TGL into toxic FFA w/in the pancreas which damage acinar cells OR chylomicrons occlude pancreatic capillaries causing ischemic injury
  - Dx: TGL >1000 mg/dL w/ lactescent milky serum
    - TGL greatly fluctuate
      - AP itself can mildly raise TGL levels therefore must be >1000 to make dx and always recheck levels when episode has resolved
      - Fasting TGL may be lower while post-meal TGL may be higher
    - Amylase is falsely low/normal b/c TGL interferes w/ assay
  - Tx: lower TGL to <200 mg/dL
    - Acute: some evidence that insulin and heparin activates lipoprotein lipase lowering TGL but unclear, lastly plasma exchange can be used
    - Chronic: first address LDL (**Statin, add bile acid sequestrant or cholesterol uptake inhibitor or switch statin to fibrate**) then if still high then **Ω-3FAs** (OTC supplements or the highly concentrated prescription form Lovaza/Omacor, SEs: interference w/ plt fxn, upper GI distress, taste bad, eructation) then if still then **Niacin**
- **Hypercalcemia**
  - Mechanism: deposition of calcium in the pancreatic duct, calcium is the main secondary messenger for stimulating the acinar cells to release zymogen, calcium activates trypsin
  - What causes intracellular acinar hypercalcemia?
    - Any Cause of Systemic Hypercalcemia (refer)
    - Acinar Cell Hyperstimulation
    - Luminal Bile Salts
    - Alcohol
    - Drugs
  - During any cause of AP there will be hypocalcemia (2/2 hypoalbuminemia, hypomagnesemia, decreased PTH release, calcium soap formation (saponification) from binding to FA/albumin complexes, intracellular translocation of calcium) therefore always recheck levels when episode has resolved
- **Significant Weight Change: Uremia, Malnutrition, Rapid Feeding, Bulemia**
- **Infection**
  - Viruses (1° Mumps, Coxsackie, Echovirus 2° Rubella, HAV/HBV/HEV, CMV, VZV, HSV, EBV, HIV often along w/ meds like PI and other infections esp Toxo, MAC, Candida)
  - Bacteria (Mycoplasma, MAC, Legionella, Leptospira, Campylobacter, TB, Salmonella, Brucellosis)
  - Fungi (Aspergillus, Candidiasis)
  - Parasites (Toxo, Crypto, Ascaris, Clonorchis)
    - Definite Infection: organism is found in the pancreas through stain or culture
    - Probable Infection: organism is found in the pancreatic juice or blood via stain, culture, or serology in the appropriate clinical setting in which the characteristic syndrome due to the bug is also present
    - Possible Infection: organism is found in other body site
    - NB b/c an infectious agent can be found in the pancreas w/o pancreatitis routine search for an infection in idiopathic pancreatitis is not recommended b/c of the false+ result
- **Vascular**
  - Vasculitis
  - Transabdominal Angiography (2/2 embolization of cholesterol plaques from the aorta to the pancreas)
  - Shock
  - Ergotamine Overdose
  - HCC Transcatheter Arterial Embolization
  - Long Distance Runners
  - Cardiopulmonary Bypass (2/2 hypotension and perioperative admin of calcium chloride)
  - Liver Transplantation
- **Trauma**
  - Penetrating and Blunt Trauma (penetrating trauma is obvious but blunt trauma can also cause pancreatitis by contusion or duct transection as pancreas is compressed against L2-4 (often seen in deceleration injuries in MVC, domestic/child abuse, et al), remember that amylase can be high in ab trauma regardless of whether the pancreas is injured or not)
  - Post ERCP Pancreatitis – PEP (refer)
- **GI**

- **Celiac Dz** (papillary inflammation and subsequent obstruction)
- **Crohn's Dz** (similar to Celiac Dz vs 5-ASAs/AZA/6-MP can cause drug induced pancreatitis)
- **Peptic Ulcer Disease** (if severe can penetrate into the pancreas)
- **Miscellaneous**
  - **Tropical Calcific**
    - Epidemiology: Southeast Asia, India, South Africa, Brazil
    - Mechanism: genetic predisposition (likely SPINK1) + environmental insult (low protein diet, trace element deficiency, cyanogenic glycosides in tapioca, cassava melon ingestion, parasitic infections, etc)
    - S/S: childhood CP w/ many calcifications and high r/o DM
  - **Autoimmune**
    - History
      - Various terms have been used to describe this disease entity: "nonalcoholic duct-destructive chronic pancreatitis, lymphoplasmacytic sclerosing pancreatitis with cholangitis, chronic sclerosing pancreatitis, pseudotumor pancreatitis, duct-narrowing chronic pancreatitis" but the term "autoimmune pancreatitis" was coined by Yoshida in 1995
    - Epidemiology
      - Gender and age predominance depends on the type of AIP
      - rare but accurate prevalence and incidence is not known nonetheless pancreatic cancer is more common!!!
      - some authorities quote that AIP represents 10% of CP, 10% of AIRP and 10% of pts undergoing pancreatic resection for suspected cancer
    - Mechanism
      - Pathogenesis is unclear but there are interesting immunologic and genetic associations
        - (1) distinctly associated w/ elevated IgG4 which normally constitutes the smallest fraction of total IgG and only a few other disorders have an associated elevated IgG4 (eg parasitic infections)
        - (2) autoimmune targets: UBR2 (Ubiquitin protein lipase E3 component n-Recognin 2) found on acinar cells and PBP (plasminogen binding protein) found on *Helicobacter pylori*
        - (3) HLA-DRB1\*0405-DQB1\*0401
    - S/S
      - Isolated Pancreatic Dz
        - painless obstructive jaundice 2/2 pancreatic mass
        - acute on chronic pancreatitis 2/2 PD stricture
        - **often asymptomatic**
      - Various Extrapancreatic Dz
        - Most Common
          - biliary stricture resembling PSC
          - mediastinal/hilar/inguinal LAD resembling lymphoma/sarcoidosis
          - RP fibrosis w/ hydronephrosis
          - tubulointerstitial nephritis w/ AKI
          - salivary/lacrimal duct strictures w/ dry eyes/mouth resembling Sjogren's (Kuttner's Tumor or Mikulicz's Dz)
        - Case Reports
          - lung/heart/liver/lung/pituitary
        - unlike PSC, Sjogren's, etc the response of these complications to steroids is dramatic
  - Dx
    - Classic Case: elderly male p/w obstructive jaundice 2/2 pancreatic mass w/ inconclusive histology for cancer
    - Before embarking on a dx it is important to remember that AIP is less common than pancreatic cancer and b/c AIP can mimic cancer a thorough w/u to rule out cancer must be done unless multiple levels of evidence supporting a dx of AIP
    - International Consensus Diagnostic Criteria 2010 melds all these approaches into one unifying approach combining Histology + parenchymal/ductal Imaging + Serology + other Organ involvement + Response to Tx (HISORT)
    - NB a dx of Type II AIP requires histology
    - Algorithm

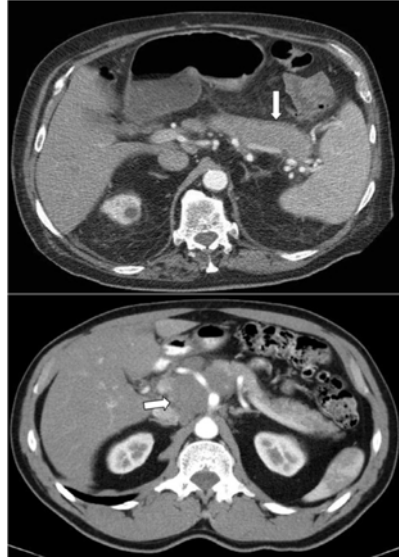




- Histology
  - Histology has confirmed suspicions that there are actually two different types of AIP suggested by epidemiology, IgG4 levels, Sx, relapse rate and IBD associations despite imaging being the same
  - EGD Bx Ampulla (easiest to obtain) vs EUS Tru-Cut Needle Bx Pancreas (rarely done)

|                                  | Type I (80%)  | Type II (20%)   |
|----------------------------------|---|---|
| <b>Histology</b>                 | Diffuse/Focal Collar-Like <b>Periductal Lympho-Plasmocytic Infiltration</b> (which is not seen in any other type of pancreatitis) |   |
|                                  | <b>LPSP = "Lympho-Plasmocytic Sclerosing Pancreatitis"</b>  | <b>IDCP = "Idiopathic Duct Centric Pancreatitis"</b>  |
|                                  | <b>IgG4</b> positive cells (>10/hpf)  | NOT   |
|                                  | Storiform <b>Fibrosis</b> w/ Atrophy  | NOT   |
|                                  | Obliterative <b>Phlebitis</b> of Veins  | NOT   |
|                                  | NOT   | <b>GELS = "Granulocyte Epithelial Lesions"</b> = Dense Periductal Neutrophils w/ Duct Destruction |
| <b>Epidemiology</b>              | ~60yo M>F   | ~40yo M=F   |
| <b>IgG4</b>                      | <b>High</b> (20% have nl IgG4 but one should not consider these Type 2)   | Normal  |
| <b>Systemic</b>                  | <b>Yes</b> (2/3 of pts, AIP is simply a pancreatic manifestation of a systemic process)   | No  |
| <b>Association w/ IBD</b>        | Some (2-6%)   | <b>Yes</b> (16-18%)   |
| <b>Mass w/ Jaundice</b>          | 2/3   | 1/2   |
| <b>Stricture w/ Pancreatitis</b> | 1/3   | 1/2   |
| <b>Dz Relapse After Tx</b>       | Possible  | Rare  |

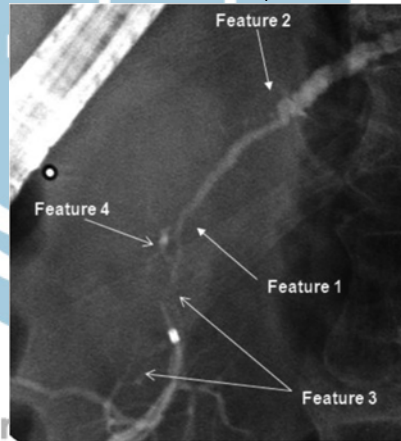
- Imaging (can also see AP/CP changes)
  - Parenchyma
    - CT (40% diffuse "sausage shaped" isodense enlargement (first image) vs 60% focal isodense enlargement aka pseudotumor (second image) w/ a hypodense rim and delayed enhancement of the pancreas during the arterial phase)



○ Ductal

- ERCP (1 - long stricture >1/3 of the PD or 3 - multiple non-contiguous strictures, 2 - lack of up stream narrowing, 4 - side branches present at level of stricture)

- NB focal is more consistent w/ cancer



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○ EUS

- Hypoechoic Enlargement



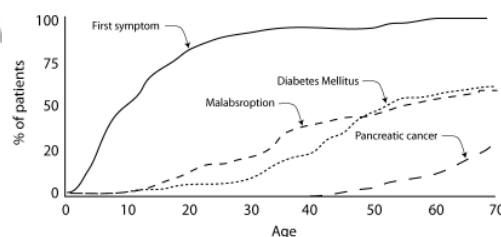
○ Serology

- **High Ig esp IgG4 >2xULN (nl 1-112mg/dL)**
  - 76% sensitivity and 93% specificity based on histology as gold standard
  - specificity is not 100% b/c high IgG4 can be seen in pancreatic cancer (10%), atopic disorders, parasitic infections, pemphigus
- **Other: High ANA, RF, ASMA, AMA** (all are not as sensitive nor specific as IgG4)
- **New: anti-lactoferrin and anti-carbonic dehydratase**

- Tx

- General: both subtypes are exquisitely sensitive to corticosteroids w/ a response rate of near 100% (therefore if pt fails to respond then one should reconsider dx)
  - Regimen: prednisone 40mg (0.6mg/kg) PO QD w/ repeat CT/Sx at 4wks to check for "rapid" response so as to determine if you Tx for 4 more weeks or begin taper decreasing by 5mg Qwk until completely off (total of 12wks)
    - NB some also follow labs (A/L/IgG4) to assess response b/c it is reassuring to see these improve but this is not always the case despite improvement in CT/Sx
  - Relapse Rate: 30-50% of Type I AIP relapse, same Tx but add azathioprine for maintenance x2yrs (some studies show that rituximab may be helpful), the definition of relapse is unclear (Sx vs Serology vs Biochemical vs Imaging), most occur w/in 3yr of dx, relapse is particularly common in those w/ biliary dz (HR 2.12,  $p = 0.03$ ) and diffuse pancreatic dz (HR 2.00,  $p = 0.04$ ), IgG4 elevations is not predictive on relapse
  - Steroid Diagnostic Tool: if the dx of AIP is not firm and cancer has not been thoroughly ruled out steroid Tx can be used diagnostically but remember that pancreatic cancer will initially respond to steroids due to the desmoplastic reaction that occurs in these cancers therefore there must be a rapid and dramatic response (some also follow CA 19-9 to see if rising)
- Familial Pancreatitis (any type of pancreatitis that runs in a familial thus can be due to genetic causes, common environmental exposure, etc)
  - Genetic Pancreatitis
    - **Hypercalcemia Syndromes (refer)**
    - **Hypertriglyceridermia Syndromes (refer)**
    - **Cystic Fibrosis**
      - Impaired CL/bicarb secretion into pancreatic duct results in less flushing of the enzymes
      - Some variants (R75Q) have nl Cl sweat tests and no lung dz BUT develop pancreatitis
    - **Hereditary Pancreatitis** (20% of pts have clinical Hx and FHx consistent w/ HP but PRSS1 is normal)
      - Mechanism: AD mutation of PRSS1 (1° R122H 2° N29I, 3° A16V, 30 total, most accurate collection [www.uni-leipzig.de/pancreasmutation](http://www.uni-leipzig.de/pancreasmutation)) w/ 80% penetrance of the Protease Serine 1 (PRSS1) gene (7q35) that codes for cationic trypsinogen → (1) Increased activation via increased autocatalytic activity AND (2) Decreased Inactivation via the formation of abnormal trypsin that is unable to be regulated by calcium and unable to be degraded
      - Complications (Big Question: Why are 20% asymptomatic?)
        - 80% IARP (children, ~10yo, interestingly severe cases are rare)
        - 50% Chronic Pancreatitis (young adult, ~20yo, interestingly severe endo/exo insufficiency is rare)
        - 40% Pancreatic Cancer (adult, ~40yo, 10/20/40% lifetime r/o by age 50/60/70, 50% of pts already have Pan-IN-3 lesions by age 30yo, RFs: 2x paternal inheritance, 2x smoking)

Hereditary Pancreatitis: Time to symptom development



- Dx: HP Mutation Panel (check in pts w/ IARP/CP w/ a +FHx or early onset AP)
  - Tx: no specific Tx just symptomatic Tx, screen for pancreatic cancer, alcohol/smoking cessation and family counseling, consider total pancreatectomy w/ islet auto-transplant for intractable Sx or if high r/o pancreatic cancer (very controversial)
    - NB mutations cluster in the calcium associated regulatory regions of PRSS1 therefore blocking calcium stimulation w/ CCB (eg. amlodipine) might in theory help but studies poor
- Other (do not solely cause AP rather they increase one's risk when other factors are present)
  - **Serine Protease Inhibitor Kazal Type I (SPINK1)**
    - N34S mutation is present in 1% of the world population
    - codes for Pancreatic Secretory Trypsin Inhibitor which normally inhibits prematurely activated trypsin that forms during pancreatitis
  - **Monocyte Chemoattractant Protein 1 (MCP1)**
  - **Chymotrypsinogen (CTRC)**
  - **Calcium Sensing Receptor (CaSR)**

- **Idiopathic Acute Recurrent Pancreatitis (IARP)**
  - Epidemiology
    - etiology of 90% of AP cases can be identified thru a routine w/u (H&P, labs including post AP TGL/Ca, transabdominal US) therefore 10% have no etiology identified and of these 50% will have a recurrent episode w/in 5yrs and of these 75% after an "extensive" w/u (ERCP + EUS) will be dx w/ true "IARP" = 3.75%
  - Approach (thorough hx, EUS, ERCP w/ SOM and Minor Papilla Cannulation but remember that PEP is much higher in this population of pts, genetic testing, labs when not in acute state including Ca, TGL, overall approach is debatable, approach should depend on severity of attacks, unique qualities of presentation, patient characteristics) = most recommend extensive w/u after a severe or >40yo 1<sup>st</sup> episode or any 2<sup>nd</sup> episode
    - 1<sup>st</sup> assess for missed common etiologies
      - surreptitious alcohol use
      - passed gallstones: why? sensitivity of TA-US for cholelithiasis/choledocholithiasis is 90/50% hence not perfect
    - 2<sup>nd</sup> check for chronic pancreatitis
      - if pts p/w recurrent idiopathic pancreatitis one must consider that the pt has now developed CP at which time the etiology becomes moot and the focus should be placed on Tx of pain and endocrine/exocrine insufficiency
      - it is important to know that early CP is NOT associated w/ abnormal structural/functional testing
    - 3<sup>rd</sup> consider more rare causes
      - DDx: Sphincter of Oddi Dysfunction (30%), PD (20%), Sludge (10%), Familial (10%), Choledochocoele, Anomalous PBJ, Annular Pancreas, Cancer, CP Flare, Autoimmune, Meds, TGL, Hypercalcemia
      - Consider a multi hit process in which individual factors do not cause AP alone but if present collectively may cause AP (eg. carrier/heterozygous genotypes (eg. heterozygous for CFTR and SPINK1) and some subsequent environmental exposure or other factor (eg. smoking, incomplete pancreatic divisum)
      - Genetic Testing: unclear to what extent, range from full CFTR analysis, A1AT, PRSS1, SPINK1 to just PRSS1
    - Tx
      - recurrent episodes are Tx like any other AP
      - experimental Tx like pancreatic enzymes, antioxidants, et al (refer below)
      - empiric cholecystectomy and/or biliary/pancreatic sphincterotomy
- S/S
  - Dull, Chronic, Severe, Mid Epigastric Pain that radiates to back, alleviated when leaning forward and worsening when supine
    - NB pain is absent in 5-10% of cases signifying VERY SEVERE pancreatitis
  - N/V/Anorexia
- Labs (Why do we measure amylase and lipase even though they represent only a fraction of the enzymes in the pancreas aka why not measure trypsin? all enzymes are secreted as zymogens except amylase and lipase therefore its easy to measure their activity when present in the blood)
  - **Amylase** (more sensitive and quicker to rise BUT less specific and rapidly clears w/ t1/2 of 10hrs (usually elevated for 3-5d in an uncomplicated attack), if it remains high after 3d consider leak)
    - 40% from pancreas vs 60% from salivary glands, tests exist which can separate pancreatic amylase (P-isoamylase) vs salivary amylase (S-isoamylase) but rarely ordered
    - Sensitivity 90% w/ False Negatives seen in hyperTG and alcoholic pancreatitis (VERY IMPORTANT TO KNOW), fatal pancreatitis, very mild pancreatitis, recovering pancreatitis, acute on chronic pancreatitis
    - Specificity 40% w/ False Positive (levels are usually only mildly high) seen in GI Dz (Ischemia, Perforation), non-GI Dz (Salivary Gland, Fallopian Tube and certain tumors secrete S-isoamylase including Papillary Cystadenocarcinoma of the Ovary, Carcinoma of the Lung), Renal Failure (decreased clearance), Macroamylasemia (amylase is bound to Ig forming a complex that is too large to be filtered by kidney therefore no hyperamylasuria but chronic hyperamylasemia), Familial Pancreatic Hyperamylasemia, Manhausen's Syndrome (saliva in urine therefore only hyperamylasuria)
  - **Lipase** (most specific and remains elevated for longer period of time (usually elevated for 10d in an uncomplicated attack) BUT less sensitive and slower to rise)
    - 90% from pancreas vs 10% from stomach
    - Sensitivity 80% w/ False Negative (same)
    - Specificity 90% w/ False Positive seen in GI Dz (Ischemia, Perforation), non-GI Dz (DKA, HIV), Renal Failure (decreased clearance)
- Imaging
  - **Double Contrast Helical CT**
    - Types of Pancreatitis

- Mild: interstitial pancreatitis (no necrosis therefore circulation is intact resulting in uniform contrast enhancement indicating flow of contrast throughout the gland) NB 25% of AP has a normal CT
  - Severe: necrotizing pancreatitis (circulation is compromised such that there is necrosis resulting in compromised circulation resulting in contrast perfusion defects) NB necrosis may not appear until 2-3d after onset and early contrast has a theoretical r/o increased necrosis therefore some wait a few days but controversial
    - NEW: serum Resistin levels (>11ng/mL) are predictive of development of necrosis (Resistin is an adiponectin that is released from adipocytes surrounding pancreas when the pancreas is necrotic)
  - CT Severity Index (CTSI) = Balthazar Score + Necrosis Score (min: 0 – max: 10) w/ Mortality: 0-6 = 4% vs 7-10 = 18%
- **KUB/CXR**
  - localized ileus of a segment of SI (“sentinel loop”) or LI (“colon cutoff sign”), pancreatic calcification if acute on chronic, blurred psoas shadow 2/2 pancreatic necrosis, RP gas if pancreatic abscess, hemidiaphragm elevation, pleural effusions (L>R)
- **Complications**
  - **Ab Organs: other -itis, obstruction from surrounding edema, fistulas (amylase >1-4k U/L), hypoactive bowel sounds 2/2 ileus, gastric dysmotility, splenic infarction/necrosis/rupture/hematoma**
  - **Ab Vessels: pseudoaneurysm w/ peritoneal/retroperitoneal hemorrhage, splenic/portal vein thrombosis, vessel rupture into pseudocyst creating hemosuccus pancreaticus, ecchymosis 2/2 extravasation of hemorrhagic pancreatic exudates**
    - Grey Turner’s Sign (flank)
    - Cullen’s Sign (periumbilical)
    - Fox’s Sign (inguinal ligament)
  - **Systemic Inflammatory Response Syndrome (SIRS) w/ MOF**
    - Kidney (AKI)
    - Heart (CHF, MI, Dysrhythmia) NB dopamine is the best pressor b/c it does not impair pancreatic microcirculation unlike others
    - Lungs (ARDS, pleural effusion w/ high amylase usually responding spontaneously, atelectasis, pneumonia)
    - Heme (DIC)
    - Leg Thrombophlebitis
    - Subcutaneous Nodular Fat Necrosis (tender red nodules over distal extremities, peritoneum, mediastinum, pleura)
  - **Chronic Pancreatitis (CP)**
    - Definition: permanent and irreversible damage to the pancreas with histologic evidence of chronic inflammation, fibrosis and atrophy/destruction of exocrine (acinar cells) and endocrine (islets of Langerhans) tissue → varying degrees of permanent clinical, morphologic and functional derangements
    - Etiology
      - Alcohol (75%)
      - Idiopathic (20%) likely unrecognized Alcohol, Autoimmune, Hereditary
        - Type (1) Early Onset: 20yo, significant pain, little structural/functional changes
        - Type (2) Late Onset: 60yo, little pain, significant structural/functional changes
      - Autoimmune
      - Hereditary
      - Tropical
      - Chronic obstruction of any cause
      - Following severe post-necrotic (esp if requiring necrosectomy) AP or following several episodes of AP of any cause
    - S/S
      - Recurrent Acute Pancreatitis → Continuous Pancreatitis w/ Exacerbations
        - Mechanism of Pain
          - (1) Compartment Type Syndrome: PD Stricture & Interstitial HTN → increased PD/Parenchymal pressure during periods of stimulation
          - (2) Neuropathic Syndrome: increased pressure on nerves w/ subsequent ischemia from fibrosis, perineural inflammation w/ damaged neural sheath + sensitized CNS → hypersensitive/responsive peripheral nociceptive nerves → allodynia/hyperalgesia
            - NB the role of the CNS is critical b/c it explains why CP pain is so hard to treat and why it is still present even after a total pancreatectomy
        - Important Points
          - other things cause pain: pseudocysts, PVT, pancreatic cancer, etc
          - some pts never have pain





- Consistent: 2 Major A or 1 Major A + 1 Major B or 1 Major A +  $\geq 3$  Minor
- Suggestive: 1 Major + 1-2 Minor or  $\geq 5$  Minor or 1 Major B +  $\geq 3$  Minor
- Indeterminate: 3-4 Minor + 1 Major B + 1-2 Minor
- Normal:  $\leq 2$  Minor

| Parenchyma   | Ducts   |
|--|---|
| <b>Major</b> <ul style="list-style-type: none"> <li>• A: <math>\geq 2</math>mm Hyperechoic Foci w/ Shadowing aka Calcifications</li> <li>• B: <math>\geq 5</math>mm Lobularity w/ Honeycombing (aka <math>\geq 3</math> contiguous lobules)</li> </ul> <b>Minor</b> <ul style="list-style-type: none"> <li>• Hyperechoic Foci w/o Shadowing</li> <li>• Lobularity w/o Honeycombing</li> <li>• <math>\geq 3</math>mm Hyperechoic Stranding</li> <li>• Cysts</li> </ul> <b>Other (atrophy, heterogenous echotexture)</b> | <b>Major</b> <ul style="list-style-type: none"> <li>• A: Stone in MPD</li> </ul> <b>Minor</b> <ul style="list-style-type: none"> <li>• Irregular/Ectatic MPD</li> <li>• <math>\geq 3</math> <math>\geq 1</math>mm Dilated Side Branch Ectasia (usually side branching should not be seen)</li> <li>• Dilated MPD</li> <li>• Hyperechoic MPD Wall</li> </ul> |

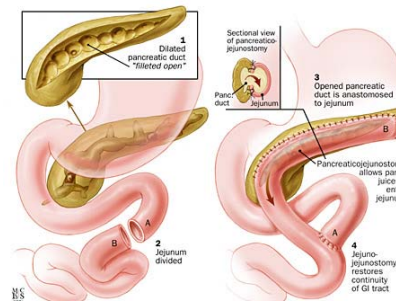
- **Endocrine/Exocrine Function**

- Why is a functional definition bad? functional tests do not become + until >40% of gland is damaged and clinical insufficiency does not occur until >90% of gland is damaged
  - usually only proteins and fats are malabsorbed NOT carbs b/c of the reserves of amylase
- Proof of Clinical Insufficiency
  - **Fecal Fat, etc** (refer to diarrhea)
  - **HbA1c, Fasting Glucose, etc** (refer to diabetes)
- Proof of Low Pancreatic Secretion
  - **MRCP w/ Secretin Stimulation:** fluid output can be semi-quantitatively assessed before and after secretin (regardless secretin alone helps improve visualization of ducts)
  - **Low Enzymes** (not very sensitive nor specific)
    - **Fecal Elastase/Chymotrypsin** (<200mcg/g)
    - **Serum Trypsinogen** (<20mg/dL)
    - **Serum Amylase/Lipase** (?)
  - **Hormone Stimulation Test:** intubate duodenum w/ OD tube or endoscope and measure pancreatic secretions (**Enzyme / Bicarb + if >80mEq/L**) while directly stimulating the pancreas w/ IV secretagogue (**CCK / Secretin**)
    - Problems: tests are not standardized b/t institutions, only a few centers perform the test, invasive test, accuracy is variable, false + in BII, DM, CD, cirrhosis, recent AP
    - Most sensitive test (60-90%)!!! (Board Question)
  - **Old Historical Tests**
    - **Lundh Test:** requires duodenal intubation, measure trypsin secretion after PO ingestion of 300mL liquid meal consisting of dried milk (5% protein), vegetable oil (6% fat), dextrose (15% carb)
    - **Serum/Urine NBT-PABA (Bentiromide) or Fluorescein-Dilaurate (Pancreolauryl) Test:** measure PABA/Fluorescein in serum/urine after PO ingestion of NBT-PABA/ Fluorescein-Dilaurate therefore the lower the level in serum/urine the less enzyme you have available b/c enzyme is need to separate NBT-PABA and Fluorescein-Dilaurate

- **Treatment**

- 1<sup>st</sup> Confirm dx of CP and rule out complications
  - **Ab Organ/Vessel Complications similar to those in AP** (refer)
  - **Pseudocyst w/ Complications:** do not develop b/c of necrosis that then results in PD leak as in AP rather it develops b/c of chronic PD obstruction that then results in PD blow out and leak, Tx is same as in AP pseudocysts but recurrences are more common
  - **Pancreatic AC** (refer)
  - **Death:** 10/20yr survival is 70/45% w/ cause of death usually from smoking related dz, continued alcohol use, pancreatic cancer, post-op complications
- 2<sup>nd</sup> Medical Management
  - Lifestyle Changes
    - decrease fat intake
    - avoid triggers including alcohol and smoking

- involve other disciplines including pain doctors, psychiatrists, social workers
    - have pts join the National Pancreas Foundation
  - Medical Analgesia
    - Start w/ propoxyphene and tramadol
    - Remind pts that goal is not total pain relief but reducing it to a level that does not interfere w/ fxn
    - 20% risk of addiction w/ narcotics
    - many pts are depressed which can lower the pain threshold therefore depression meds
    - b/c there are CNS changes leading to hyperalgesia/allodynia then NT modification is helpful (eg. TCAs/SSRIs/SNRIs, new studies indicate that voltage gated N-type calcium channel inhibitors (eg pregabalin increased over 2 weeks to 300mg PO BID) are helpful)
  - Decrease Oxidative Damage
    - Anti-oxidants (eg. selenium, beta-carotene, vitC, vitE, methionine)
  - Decrease Pancreatic Secretion
    - Pancreatic Enzymes
      - Mechanism: active proteases IN THE DUODENUM destroy intestinal CCK releasing factor → decreases CCK from the I-cells of the duodenum → decreases vagal output on pancreas → decreases pancreas secretion and thus PD pressure → decreases pain = therefore only effective if pain is from hyperstimulation not from inflammation, neuropathy, duct obstruction, etc
      - Problem: (1) this effect is minimal and studies show that it is only really effective in **small females w/ early idiopathic chronic pancreatitis** and (2) intestinal CCK releasing factor exists in the duodenum therefore only uncoated enzymes are effective but Viocase w/ PPI is no longer available
    - Anticholinergics (?)
      - Somatostatin Analogues (?) Octreotide 100-200mcg SC TID then depot form if it works, remember complications of biliary stasis and gallstone formation
  - Restore Endocrine/Exocrine Insufficiency (refer to med notes)
    - b/c glucagon is also lost these pts are at risk for hypoglycemic episodes therefore don't be aggressive w/ insulin
- 3<sup>rd</sup> Endoscopic Management (consider when medical management has failed)
  - If Abnl Duct then ERCP Tx
    - PD Sphincterotomy
    - Stone Removal (generally very difficult to use standard CBD stone removal maneuvers b/c the stones are often large, calcified and impacted in side branches therefore consider ESWL followed endoscopic removal or intraductal lithotripsy under pancreatoscopic guidance)
    - Stricture Dilation (dilation w/ stent exchange Q2mo for 6-12mo then stop)
  - If NI Duct then Denervation (CPB/CPN or PSN)
    - does not actually work and should only be done for pancreatic cancer
    - percutaneous splanchnic neurolysis by pain doctors via injection thru skin
- 4<sup>th</sup> Surgery Management (consider when medical/endoscopic management has failed)
  - If Big Duct Dz then Drainage
    - Partington & Rochelle Modification of the Puestow & Gillesby Operation (lateral pancreaticojejunostomy) = duct is opened longitudinally and anastomosed to jejunal limb of a roux-en-Y anastomosis



- Frey Operation
  - If Small Duct Dz then
    - Denervation
      - Thorascopic Bilateral Splanchnicectomy

- Spinal Cord Stimulation
- Transcranial Magnetic Stimulation
- Resection
  - Partial Pancreatectomy (many different kinds)
    - Whipple
    - Pylorus Preserving Pancreaticoduodenectomy
    - Duodenum Preserving Pancreatic Head Resection (DPPHR) aka Beger Operations
    - Burne Operation
    - Distal Pancreatectomy
  - Total Pancreatectomy w/ Islet Auto Transplantation (TPIAT) (cells are injected into portal vein and then take hold in liver, no immunosuppression is needed, 70-90% pain improvement and 20-40% insulin free at 6mo)
    - Because the pt is in an apancreatic state there is a combination of hypoinsulinemia and hypoglucagonemia thus daily requirements of insulin are actually less than that of T1DM and T2DM HOWEVER these pts also have an attenuated autonomic response to hypoglycemia resulting in diabetic unawareness and this unique feature is termed "brittle diabetes"
- **Pancreatic Fluid Collections (PFCs)**
  - 1<sup>st</sup> Rule Out Overt Pancreatic Duct Leak w/ MRCP or pancreatogram by injecting contrast JP drain
    - if low output then percutaneous drain (other: paracentesis, thoracentesis, etc) b/c they often spontaneously close
    - if high output/symptomatic/enlarging/presence of external fistula: endoscopic drainage in which you place a transpapillary stent across leak which changes the ductal drainage gradient promoting flow to the duodenum
    - if refractory then surgical repair b/c likely overt duct damage
  - 2<sup>nd</sup> Rule Out Complications
    - **symptomatic** (compression on surrounding structures (viscera, vessels, CBD), pain, early satiety, N/V 2/2 GOO, infected, hemorrhage (60% mortality, consider someone who gets really worse!!! several weeks later), rupture w/ ascites, fistulize)
    - **vascular digestion w/ pseudoaneurysm resulting in GIB w/ hemosuccus pancreaticus and hemorrhage into the cyst**
    - **spontaneous infection** from hematogenous spread or translocation from colon thru lymphatics
      - Epidemiology
        - occurs in 1/3 of WOPN and ? in pseudocyst
        - 100% mortality if not treated, 30% even if treated, represents 80% of deaths from acute pancreatitis
        - infection only occurs 10-14d after pancreatitis **never** earlier
        - NB never use the term abscess (infection triggered collection of inflammatory cells) or phlegmon (non-infection triggered collection of inflammatory cells) rather there is an infection of below
      - Px
        - **Fluid Resuscitation**
        - **Enteral nutrition** (actually decreases r/o developing infection b/c it decreases gut permeability to intestinal flora)
        - Antibiotics (very controversial b/c studies that show benefit were not DBRPCT and the few studies that were DBRPCT showed that Px was NOT effective in any type of pancreatitis and there is concern that superinfections or fungi will occur therefore presently not recommended)
        - Gut Decontamination (controversial)
      - Dx/Tx
        - If you suspect infection (persistent organ failure, systemic toxicity, gas, fistulas, delayed improvement in Sx) then obtain a CT-guided FNA and if + then abx w/ **Imipenem or FQ + Metronidazole** (only ones that penetrate pancreas) and drainage (below) and if no improvement at 4wks then prompt surgical debridement but if - then repeat FNA in 5-7d if still suspicious

|  |  |
|--|--|
| Fluid leaking from PD ( <b>homogenous</b> material meaning no solid debris AND located <b>near</b> pancreas)<br>VERY DIFFICULT TO DIFFERENTIATE FLUID LEAK FROM NECROSIS (HOMO/HETERO MATERIAL CAN SOMETIMES BE APPRECIATED ON MRI/EUS BUT NOT CT) HENCE DISTINCTION IS BASED ON | Necrosis ( <b>heterogeneous</b> material meaning some solid debris AND located <b>w/in</b> pancreas) |
|--|--|

|   | LOCATION   |   |
|---|--|---|
| Early                                       | <b>Acute Peripancreatic Fluid Collection – APFC</b> (no wall, low attenuation, early in dz, seen in 40% of AP, most resolve spontaneously and thus do not require any Tx but some turn into pseudocysts)   | <b>Acute Necrotic Collection – ANC</b> (no wall, low attenuation, early in dz, never drain b/c thick, sometimes there is peripancreatic fat necrosis)   |
| Late<br>(maturation of a wall after 4-6wks) | <p><b>Pancreatic Pseudocyst – PP</b> (thin walled (non-epithelium rather fibrotic tissue), can be found in distal places like chest and pelvis)</p> <p>Drainage</p> <ul style="list-style-type: none"> <li>Indications: <b>only if symptomatic or infected</b> <ul style="list-style-type: none"> <li>NB not size, it used to be that pseudocysts &gt;6cm or progressively enlarging cyst should be drained but not anymore b/c most actually resolve spontaneously, some follow w/ US but not needed</li> <li>Even location doesn't matter, even if in mediastinum!!!</li> <li>Approaches (ultimately based on hospital expertise and cyst location/communication)</li> <li>What is symptomatic?</li> </ul> </li> <li>1<sup>st</sup> Percutaneous Catheter Drainage by IR (except for those from CP b/c very high rate of fistula formation)</li> <li>2<sup>nd</sup> Endoscopic Drainage by GI (do ERCP first to see if it communicates w/ PD and if not then EUS) <ul style="list-style-type: none"> <li>NB make sure not pseudoaneurysm</li> <li>if they clear communication w/ PD and more fluid than solid then transpapillary drainage w/ ERCP <ul style="list-style-type: none"> <li>make sure that the PD does not have a stenosis b/c if it does then dilating it will reduce r/o pseudocyst recurrence, place a flapped stent past cyst branch or place a pigtail stent into the cyst itself</li> </ul> </li> <li>If they DON'T clear communication w/ PD but they are adherent to GI luminal viscera and more solid than fluid then transmural cystgastrostomy/duodenostomy w/ EUS <ul style="list-style-type: none"> <li>EUS scope w/ endoscopic/fluoro/US pictures, site is punctured w/ 19G FNA needle, aspirate fluid for analysis, 0.035in angled wire is fed thru into cyst, needle knife is fed over wire and the hole is enlarged, Balloon 8-18mm dilator is used depending on thickness of fluid, consider necrosectomy if needed by feeding an endoscope thru and using a snare/net to clear out necrotic material, feed another wire using a cannula, place two double pig tail stents (15cm x 7F, 12cm x10F), CT in 48hrs, remove stents at 3-4wks</li> </ul> </li> </ul> </li> <li>3<sup>rd</sup> Surgical Drainage by GS <ul style="list-style-type: none"> <li>if not PD obstruction then Resection</li> <li>if PD obstruction then Roux-en-Y Cystjejunostomy</li> </ul> </li> </ul> | <p><b>Walled Off Pancreatic Necrosis – WOPN</b> (thick walled, material liquefies allowing for drainage)</p> <p>Drainage</p> <ul style="list-style-type: none"> <li>Indications: <b>the threshold to Tx WOPN is much higher b/c much harder to Tx compared to PP therefore even if symptomatic or infected most do conservative Tx for 4wks and if still no improvement then consider more aggressive approaches</b></li> <li><b>Sterile but Symptomatic: keep NPO x3-6wks while on enteric feeds and minimize IV lines and if unable to advance oral intake after then then consider more aggressive tx</b></li> <li><b>Infected:</b> <ul style="list-style-type: none"> <li>1<sup>st</sup> Conservative Tx (above Tx for sterile + abx and if no improvement in a few days then more aggressive Tx below)</li> <li>2<sup>nd</sup> Endoscopic drainage is more technically difficult (contents are like cement), has higher rate of complications, tends to involve more severely ill pts than those w/ PP, if you do endoscopic drainage you can't transpapillary rather the only approach is a modified transmural drainage approach (nascystic irrigation lavage tubes + pigtail stents) or endoscopic necrosectomy/debridement (dilate transmural tract w/ 20mm balloon, pass a forward viewing scope into WOPN and snares/forceps are used to remove necrotic debris) but generally percutaneous drainage or surgical necrosectomy/debridement are the most common Tx used</li> </ul> </li> <li>NB percutaneous drainage is nearly impossible b/c the material is so thick but still try</li> </ul> |