DEPARTMENT OF CLINICAL MEDICINE, UNIVERSITY OF BERGEN

Residiverende akutt pankreatitt

Kurs i galle og pancreas, 11. mai 2022

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Lecture overview

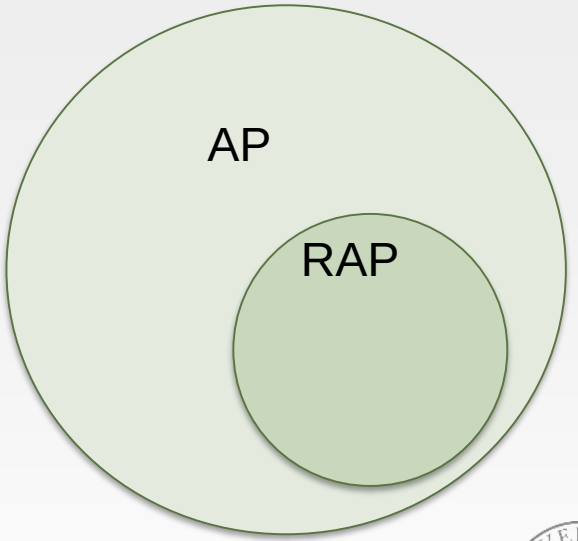
- Definitions:
  - Recurrent acute pancreatitis
  - Idiopathic recurrent acute pancreatitis
  - “True” idiopathic recurrent acute pancreatitis
- Diagnostics and diagnostic challenges
- Preventive options/treatment options

Recurrent acute pancreatitis (RAP)

- Definition:
  - ≥2 well documented episodes of acute pancreatitis
  - Resolution of symptoms between each episode*
  - Absence of morphological criteria for chronic pancreatitis

- ~20-25% of patients with AP have recurrent episodes

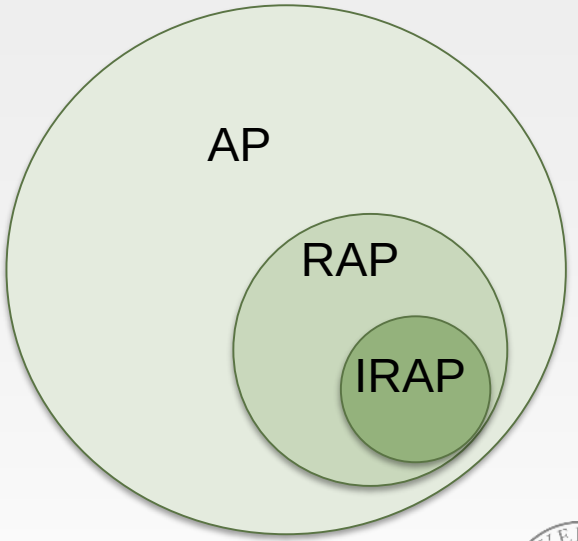
- Alcohol or gall stones still most common causes



REFERENCES: GUDA 2018, LANCET GASTROENTERAL HEPATOL. SANKARAN 2015, GASTROENTEROLOGY.

Idiopathic recurrent acute pancreatitis (IRAP)

- Idiopathic = the cause of the disease is unknown
- Cause is still unknown after typical first line investigations:
  - Patient history
  - Routine laboratory tests
  - Conventional imaging (US, CT)
- ~20-30% of recurring acute pancreatitis

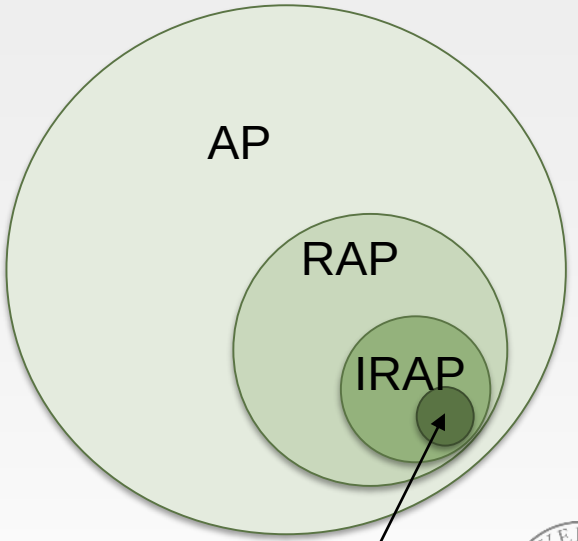


REFERENCES: GUDA ET AL, 2018, LANCET GASTROENTERAL HEPATOL. GUDA ET AL, 2018, PANCREAS. GAO ET AL, 2006, J GASTROENTEROL. GURAKAR ET AL, 2021, SCAND J GASTROENTEROL

«True» idiopathic recurrent acute pancreatitis

- No etiologic cause despite exhaustive examinations
  - Extensive laboratory tests, incl. genetic analyses
  - Advanced imaging (e.g. MRCP, EUS, ERCP)

- ~10% of patients



REFERENCES: GUDA 2018, LANCET GASTROENTERAL HEPATOL. GURAKAR ET AL, 2021, SCAND J GASTROENTEROL

Recurrent acute pancreatitis:

What causes it?

TIGAR-O: Etiology classification system for pancreatic diseases

Toxic-metabolic

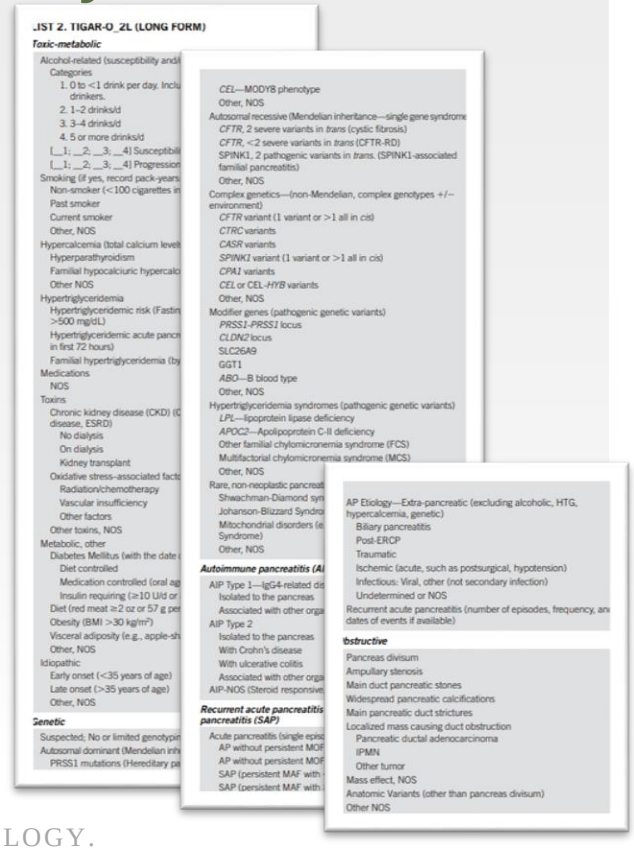
Idiopathic

Genetic

Autoimmune

Recurrent and severe acute pancreatitis

Obstructive



REFERENCE: WHITCOMB, 2018, CLINICAL AND TRANSLATIONAL GASTROENTEROLOGY.

Etiological factors

- Most common factors:
  - Gall stones
  - Alcohol
- Other factors:
  - Smoking
  - Hypertriglyceridemia
  - Hypercalcemia
  - Drugs
  - Renal failure
  - Diabetes ketoacidosis
  - Genetic variants
  - Autoimmune pancreatitis
  - Rheumatic disorders
  - Obstructive conditions:
    - Ductal anomalies
    - Tumors
  - Viral infections
  - Trauma

FIGURE: NORDAAS/BIORENDER.COM

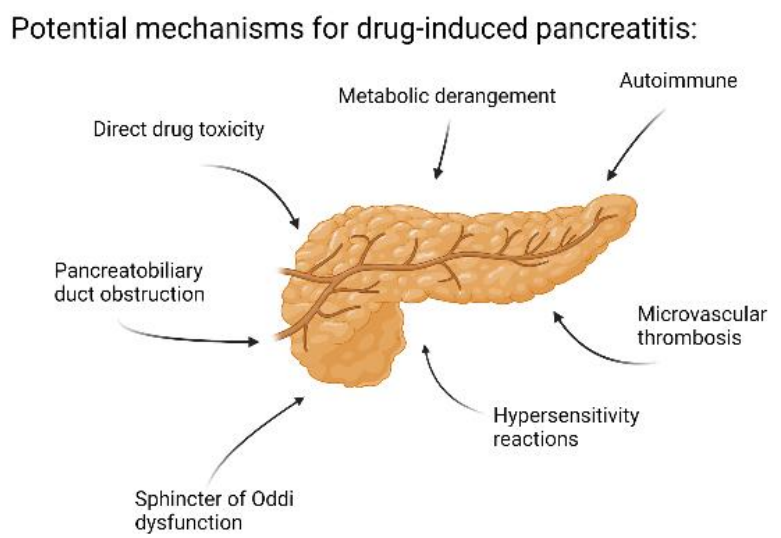
IRAP etiological factors

- Most common factors:
  - Gall stones
  - Alcohol
- Other factors:
  - Smoking
  - Hypertriglyceridemia (?)
  - Hypercalcemia (?)
  - Drugs
  - Renal failure
  - Diabetes ketoacidosis
  - Genetic variants
  - Autoimmune pancreatitis
  - Rheumatic disorders
  - Obstructive conditions:
    - Ductal anomalies
    - Tumors (not the large ones)
  - Viral infections
  - Trauma

FIGURE: NORDAAS/BIORENDER.COM

Toxic-metabolic: medications

- Several drug classes possibly related to pancreatitis
- Some examples: Statins, loop diuretics, erythromycin, azathioprine, 5-ASA, steroids



Class I	Class II	Class III
Aminosalicylates	Alkylating antineoplastics	Aminosalicylates
Anticonvulsants	Angiotensin-converting enzyme inhibitors	Antacids
Antimetabolite antineoplastics	Anticonvulsants	Antiarrhythmics
Antimicrobials	Antimicrobials	Antibacterials
Hormone replacement therapies	Antitubercular agents	Anticholinesterases
Loop diuretics	Interferons	Anticonvulsants
Non-biologic immunosuppressives	Nonopioid analgesics	Antidepressants
Nonsteroidal anti-inflammatories	Reverse transcriptase inhibitors	Antifungals
Opiates	Somatostatin analogs	Antihypertensives
Reverse transcriptase inhibitors	Thiazides	Antimetabolite antineoplastics
Steroids		Antineoplastics
		Antiplatelets
		Antivirals
		Atypical antipsychotics
		Cholesterol lowering agents
		Cyclooxygenase II inhibitors
		Estrogens
		Immunomodulators
		Nonsteroidal anti-inflammatories
		Parasympathetic agents
		Proton pump inhibitors
		Selective serotonin agonists
		Somatostatin analogs
		Steroids
		TNF-alpha inhibitors
		Vitamins

REF: WEISSMAN 2020, WORLD J GASTROENTEROLOGY

Genetics

Think genetics in young patients.

Autosomal dominant:

PRSS1, hereditary pancreatitis. Increased trypsin activation.

Autosomal recessive:

CFTR, cystic fibrosis and different pancreatitis phenotypes.
Impaired bicarbonate secretion.

SPINK1, associated with RAP. Increased damage from prematurely activated trypsin. Cofactor.

Complex genetics:

Combinations of genetic mutations, e.g. SPINK1 + CFTR → adds to the risk

REF: KUMAR, 2016, JAMA PEDIATRICS. JALANY, 2017, AM J GASTROENTEROL. GUDA, 2018, PANCREAS.
FIGURE: OOI ET AL, 2011, GASTROENTEROLOGY

Autoimmune disorders

Autoimmune pancreatitis:

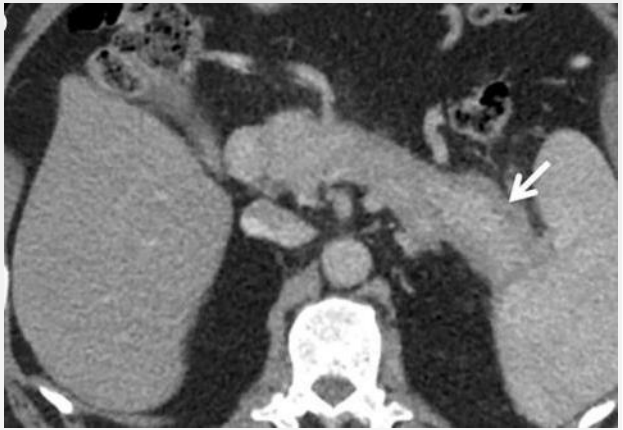
Focal or diffuse enlargement. Dramatic response to steroids.

Type 1: Systemic IgG4 disease (kidneys, bile ducts, prostate, testicles, lungs etc.). RAP not typical.

Type 2: Often focal. Presents as AP and RAP. Associated to inflammatory bowel disease.

Rheumatic diseases:

Systemic lupus erythematosus, Sjögren syndrome. Rheumatoid arteritis? Vasculitis?



AIP: CT shows diffusely enlarged and sausage-shaped pancreas

REF: KHANDELWAL ET AL, ABDOMINAL RADIOLOGY 2020. CHANG CC ET AL, 2015, PLOS ONE. CHANG CC ET AL, 2017, BMJ OPEN.
ILLUSTRATION: KHANDELWAL ET AL, ABDOMINAL RADIOLOGY 2020.

Obstructive causes

Pancreas divisum:

Congenital anomaly. Minor papilla drains the pancreas. Found in 7% of the population, but only 5% with pancreas divisum develop pancreatic disease.

Is PD alone a risk factor? Other susceptibility factors needed?

Gurakar et al, 2021:

72% of PD patients with RAP/CP had other risk factors (smoke, genetics, alcohol, biliary, high triglycerides)

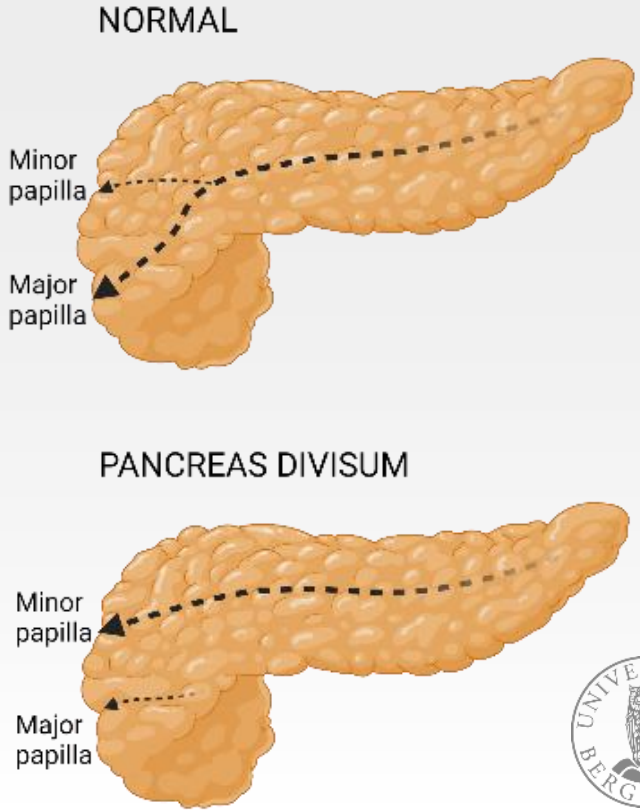


ILLUSTRATION: NORDAAS / BIORENDER.COM.

REF: GUTTA ET AL, 2019, EXPERT REV GASTROENTEROL HEPATOL, GURAKAR ET AL, 2021, SCANDI J GASTROENTEROL.

Obstructive causes

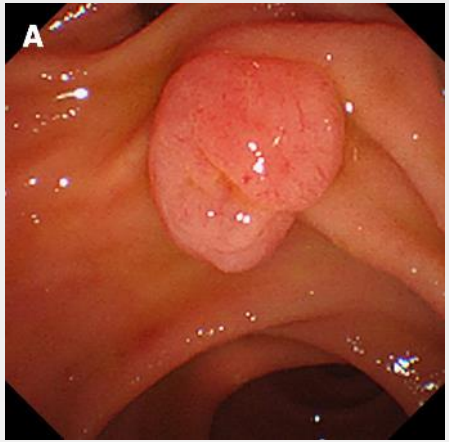
Microlithiasis:

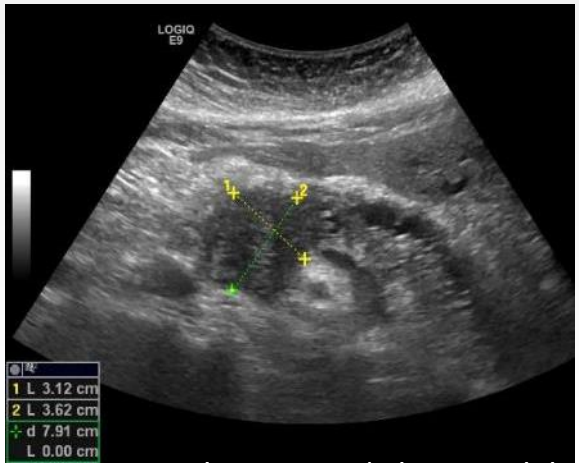
Small gallstones (<3 mm) or sludge.
Transient obstruction.

Tumors:

Ampullary tumors (benign or malignant).

Pancreatic cancer: small ones may go undetected.





ILLUSTRATIONS: DUODENOSCOPY: SAKAI ET AL, 2019, WORLD J GASTROENTEROL. US IMAGE: GILJA.

REF: GUDA ET AL, 2018, PANCREAS.

Recurrent acute pancreatitis:

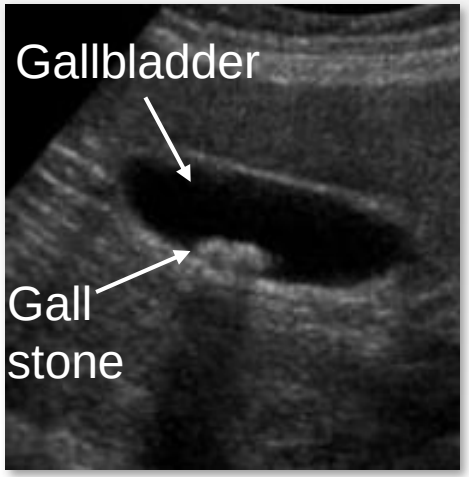
Diagnostics and diagnostic challenges

Primary diagnostics for AP/RAP

Patient history
Laboratory analyses
Imaging (US, CT)

Likely etiology based on primary diagnostics:

1) Gall stone induced
2) Alcohol induced
3) Other etiology
4) Idiopathic AP/RAP



Secondary diagnostics for IRAP

1) Patient history – again!
2) Extended laboratory examinations: triglycerides, calcium, IgG4, genetic analyses
3) Advanced imaging:
   - Computed tomography?
   - MRCP?
   - EUS? Tissue sampling?
   - Secretin stimulated MRCP?
   - ERCP?

Imaging approaches

- Start with already performed examinations
  - Reevaluate? Quality sufficient? Need for a second opinion?
- Guidelines: EUS first after conventional imaging (CT, US)
- MRCP vs. EUS vs. ERCP
  - Mariani et al.:
    - MRCP + EUS highest diagnostic yield for causes of IRAP

REF: GUDA ET AL, 2018, PANCREAS. MARIANI, 2009, DIG LIVER DIS. COTTON ET AL, 2016, GASTROENTEROLOGY.

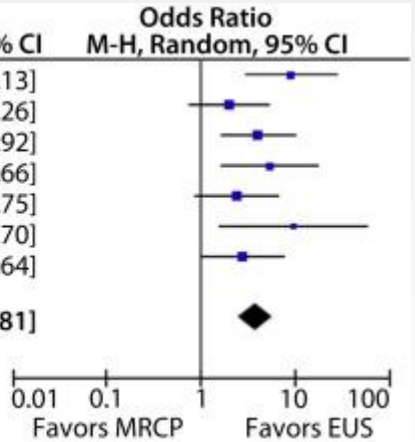
Imaging approaches

- Start with already performed examinations
  - Reevaluate? Quality sufficient? Need for a second opinion?
- Guidelines: EUS first after conventional imaging (CT, US)
- MRCP vs. EUS

Study or Subgroup	EUS Events	EUS Total	MRCP Events	MRCP Total	Weight	Odds Ratio M-H, Random, 95% CI
Bolado 2015	27	34	10	34	13.5%	9.26 [3.05-28.13]
Mariani 2009	35	44	29	44	17.4%	2.01 [0.77-5.26]
Ortega 2011	25	49	10	49	19.9%	4.06 [1.66-9.92]
Tan 2011	18	27	7	26	12.1%	5.43 [1.67-17.66]
Thevenot 2013	15	38	8	38	15.8%	2.45 [0.89-6.75]
Vila 2012	13	15	6	15	5.4%	9.75 [1.59-59.70]
Zhang 2009	20	32	12	32	15.9%	2.78 [1.01-7.64]
Total (95% CI)		**239**		**238**	**100.0%**	**3.79 [2.47-5.81]**
Total events	153		82			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 6.65$, df = 6 (P = .35); $I^2 = 10\%$

Test for overall effect: Z = 6.10 (P < .00001)



REF: GUDA ET AL, 2018, PANCREAS. MARIANI, 2009, DIG LIVER DIS. COTTON ET AL, 2016, GASTROENTEROLOGY. WAN, 2018, GASTROINTEST ENDOSC

Imaging approaches

- Start with already performed examinations
  - Reevaluate? Quality sufficient? Need for a second opinion?
- Guidelines: EUS first after conventional imaging (CT, US)
- MRCP vs. EUS
- ERCP
  - Pancreas divisum
  - Manometry (controversial)

REF: GUDA ET AL, 2018, PANCREAS. MARIANI, 2009, DIG LIVER DIS. COTTON ET AL, 2016, GASTROENTEROLOGY.

We found something – now what?

- Relevance of findings:
  - Stricture?
  - Pancreas divisum?
  - A drug potentially related to RAP?
  - Slight hypercalcemia?
  - Genetic mutations: SPINK1 or heterozygote pCFTR?

Recurrent acute pancreatitis:

Preventive options?

Preventive options – why?

- Reduce risk of:
  - Reoccurrence
  - Progression to chronic pancreatitis
  - Pain syndromes
  - Exocrine pancreatic insufficiency
  - Diabetes
  - Pancreatic cancer

Preventive options

- Remove potential triggers that may drive inflammation:
  - Alcohol
  - Smoking
  - Reduce overweight
  - Dehydration (?)
  - Opiates (?)

  → An overall healthy lifestyle

- Genetic counselling, family planning

Endoscopic treatment options

- Obstructive conditions
- ERCP: stenting, blocking, sphincterotomy
- Sphincterotomy in pancreas divisum?
  - SHARP trial: RCT w/ sphincterotomy or sham procedure for RAP + pancreas divisum

REF: GUTTA ET AL,2019, EXPERT REV GASTROENTEROL HEPATOL. GUDA ET AL, 2018, PANCREAS. COTÉ ET AL, 2019, SHARP TRIAL, PANCREAS

Surgical treatment options

- Obstructive conditions

- Gallstones, microlithiasis and/or transiently elevated ALP/GGT – cholecystectomy.

- Total pancreatectomy with islet autotransplantation
  - Patients with high cancer risk and progression to CP → fibrotic or cancerous tissue?
  - RAP w/intractable symptoms despite maximal medical/endoscopic therapy: Pancreatectomy → improved QoL

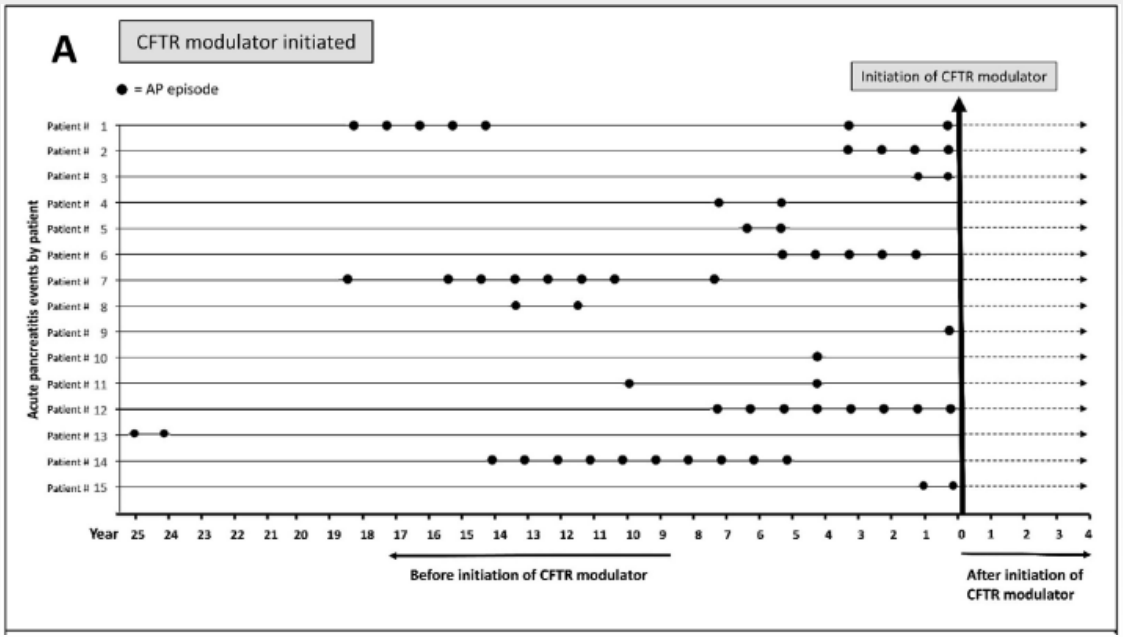
REF: BELLIN ET AL, 2016, CLIN GASTROENTEROL HEPATOL. GUDA, 2018, PANCREAS.

Medical treatment options

- Only relevant for subgroups of IRAP:
  - Autoimmune pancreatitis: steroids, immunosuppressants
  - Hyperlipidemic pancreatitis: control s-triglyceride levels, plasmapheresis, fibrates
  - Drug-induced: discontinue drugs

REF:YANG & MCNABB-BALTAR, 2020, PANCREATOLOGY

CFTR modulators



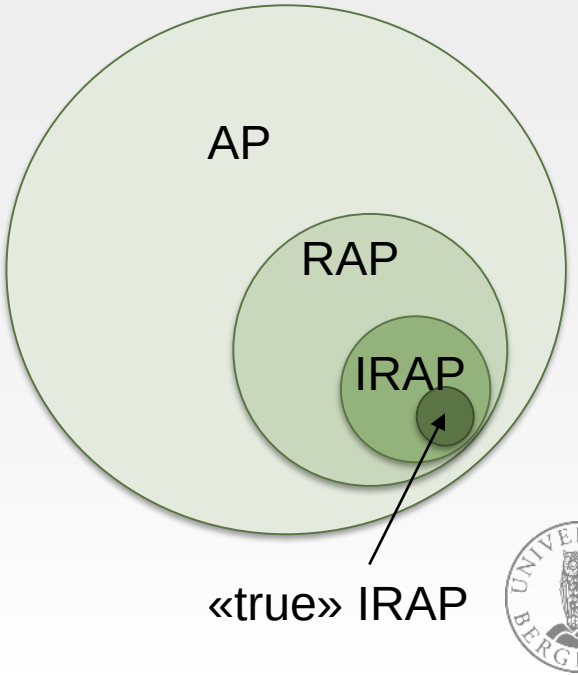
Ivacaftor

REF: AKSHINTALA ET AL, 2019, PANCREATOLOGY.

What about the truly idiopathic?

When do we stop our investigations?

- True idiopathic disease:
  - Anatomy is sufficiently mapped
  - Not known genetic variants
  - Not drugs
  - Not autoimmunity



Do we stop?

Continue monitoring: If changes, consider new examinations.

1) Pancreatic adenocarcinoma? IPMN?

2) Burden of disease, admissions, pain, nutrition..

3) Chronic pancreatitis?

	Pancreatic cancer				
Follow-up time	0–2 years		>2 years		
	Number of events/ person-years	HR (95% CI)[a]	Number of events/ person-years	HR (95% CI)[a]	HR (95% CI)[a]
Recurrent acute pancreatitis					
None	354/75,391	17.82 (13.66–23.26)[b]	83/172,183	1.92 (1.47–2.51)[b]	1.53 (1.16–2.02)[b]
1	35/8,823	20.80 (13.60–31.83)[b]	6/14,732	1.54 (0.67–3.52)	0.81 (0.33–1.98)
2	17/3,852	28.16 (16.14–49.14)[b]	4/5,263	2.96 (1.10–7.94)[c]	1.25 (0.40–3.92)
≥3	24/3,999	44.44 (27.51–71.80)[b]	13/7,847	7.47 (4.16–13.42)[b]	4.44 (1.81–10.89)[b]
Individuals without acute pancreatitis	66/247,401	1 (Reference)	167/652,242	1 (Reference)	1 (Reference)

[a]Cox regression analyses including age (18–39, 40–49, 50–59, 60–69, 70–79, ≥80 years), sex, calendar period (1997–1999, 2000–2004, 2005–2009, 2010–2013), education level (<10, 10–12, >12 years), country of birth (Sweden, other), the Charlson Comorbidity Index (0, 1, 2, ≥3 comorbidities) and alcohol abuse (no, yes).
[a]Censoring for a diagnosis of chronic pancreatitis
[b]*P*-value<0.01
[c]*P*-value<0.05

REF: SADR-AZODI ET AL, 2018, AMERICAN J GASTROENTEROL

Conclusions

Conclusions

- Most common causes: gall stones and alcohol
- The devil is in the details: extensive investigations are needed
- Cofactors may be present
- Genetics in the young and malignancies in the old
- Determining the etiology is necessary to plan preventive options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