MEDISINSK-ODONTOLOGISK FAKULTET
KLINISK INSTITUTT 1

Autoimmun pankreatitt

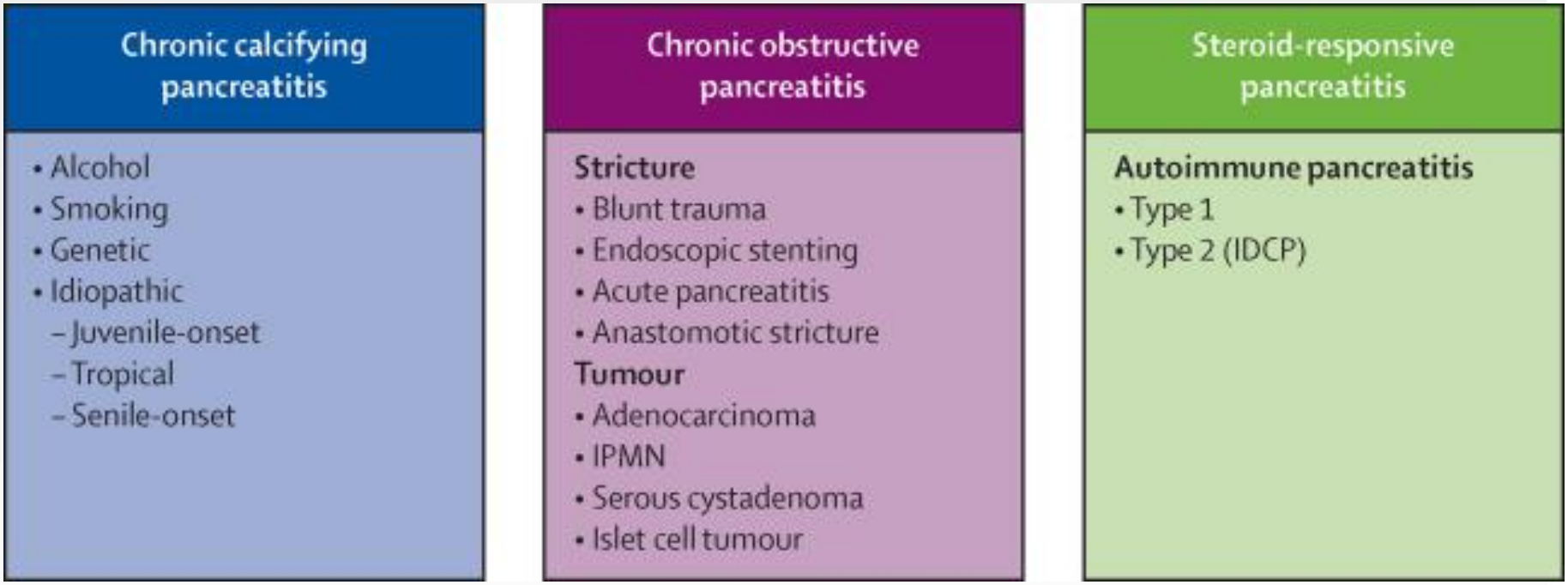
Hvordan skaffe seg venner for livet?

UNIVERSITETET I BERGEN

Læringsmål

FIM091: Ha kunnskap om diagnostikk og behandling av sykdommer i pankreas, herunder akutt og kronisk pankreatitt

Sykdomsklassifikasjon



Høy grad av overlap mellom gruppene

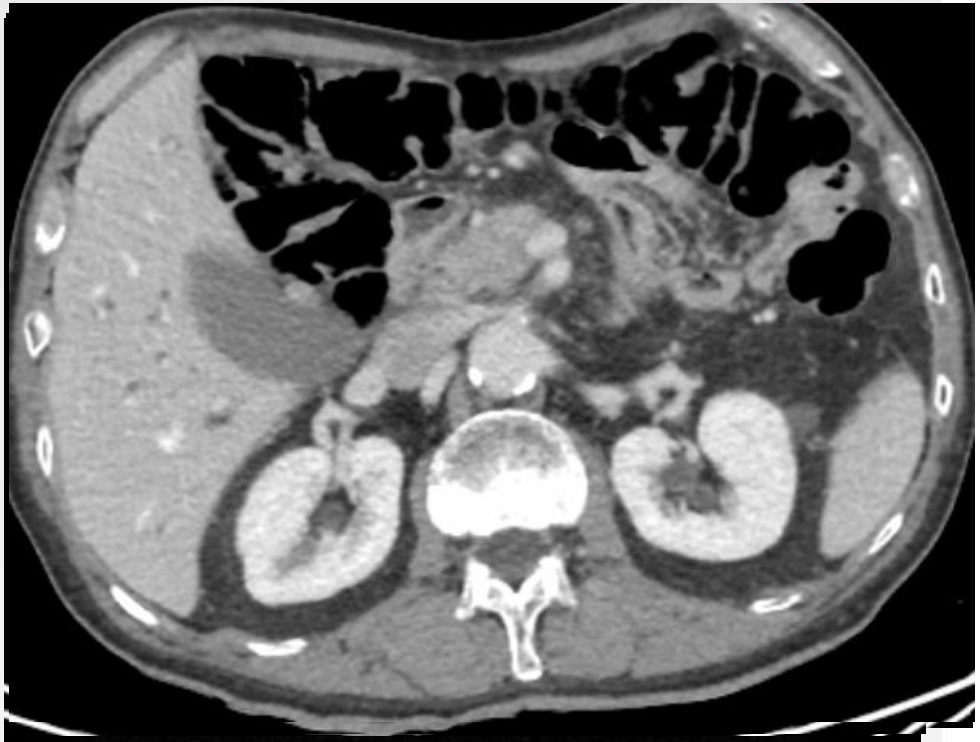
Majumder, Chari. **Chronic pancreatitis. Lancet 2016**

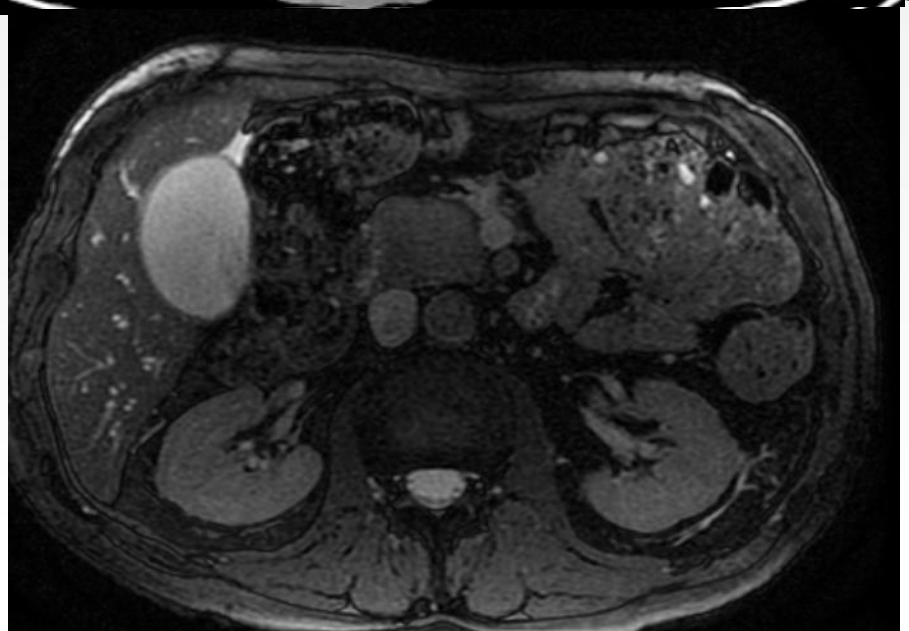
Oversikt

- Sykdomsdefinisjoner
- Diagnose
- Litt epidemiologi
- Forløp, komplikasjoner
- Behandling

Gartner f 1941

- Coloncancer, ikke pankreassykdom i familien
- Coloncancer 2015
  - Op/ cytostatica
  - HNPCC-MSS i tumor
- Ikke røyk/ alk
- Innlagt nov 19; Ikterus, hyperglykemi og vekt 80-65 kg
- ALAT 224, ALP 892, GT 1421, Bil 106
- **CT/ MR: Diffuse forandringer i caput pancreatis og dilaterte galleveier.**
- **Konklusjon: Pankreatitt eller diffust infiltrerende malignitet. Henvist EUS FNA**





Gartner f 1941

Utredning HUS

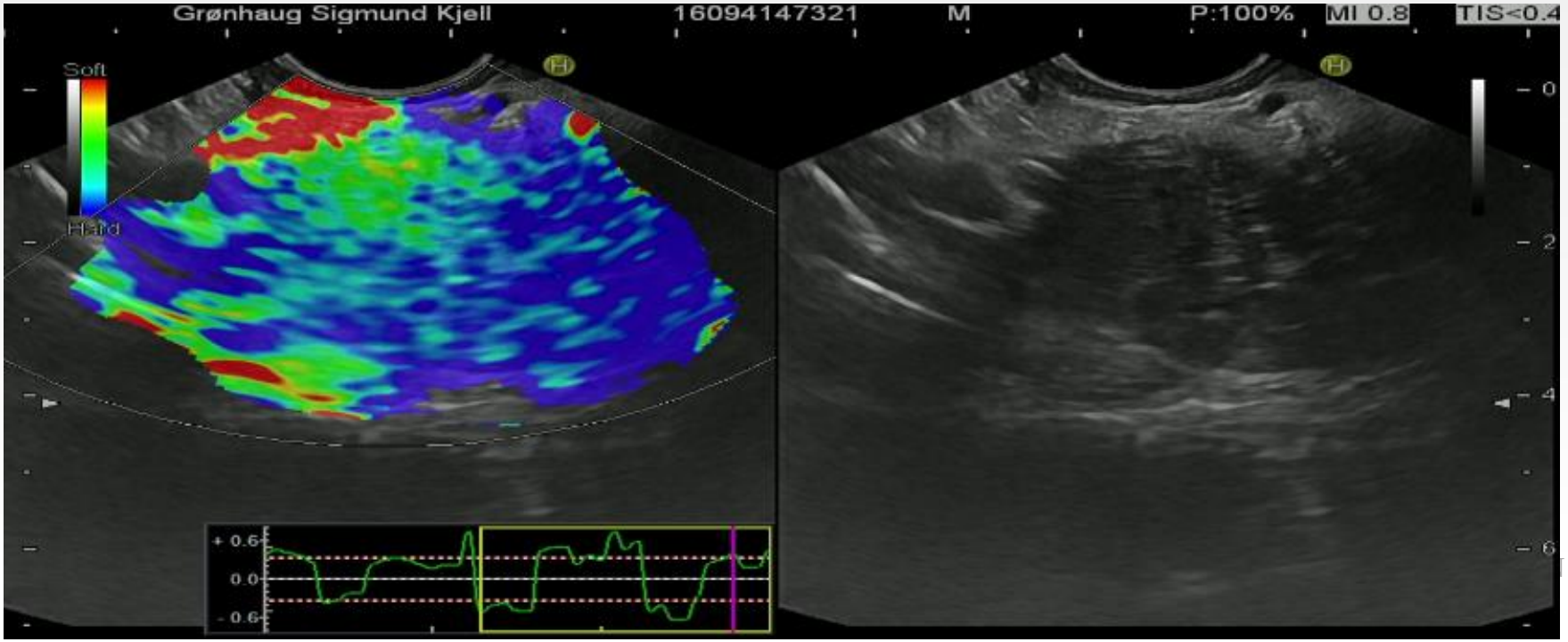
-EUS 23/12, 20/1, 14/2 og 21/2

-FNA fra tumor caput pancreatis

-ERCP med børste og stent i choledochus

Histologi: Kronisk betennelse og fibrose. IgG4 pos celler

Suppl lab: IgG4: 8,1, CA 19-9 76, FE: <15



Konklusjon og behandling

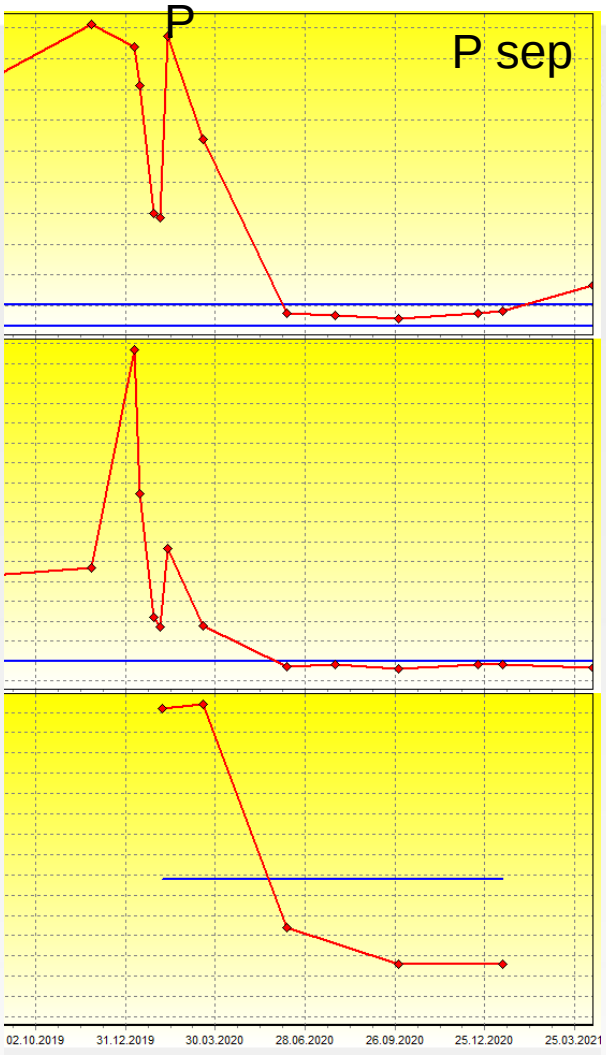
- Type 1 Autoimmun pankreatitt
- Behandling
  - Prednisolon 30 mg; nedtrapping. 6 mnd beh
  - Insulin
  - Creon
  - Ernæringsråd og næringsdrikker

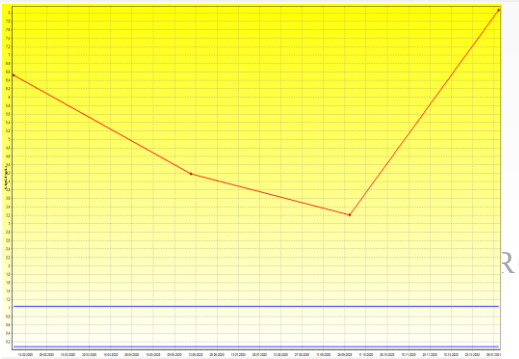
ALP

Bil

CA 19-9

IgG4





Behandlingsresultat

- Ikterus opphevet, smertefri
- Ikke dukket opp malignitet
- Vektoppgang 65-80
- I arbeid I gartneriet igjen
- Men
  - Fortsatt diabetes
  - Fortsatt eksokrin svikt
  - IgG4 stiger….

Sykdomsdefinisjon

"Autoimmune pancreatitis is a distinct form of pancreatitis characterized **clinically** by frequent presentation with obstructive jaundice with or without a pancreatic mass, **histologically** by a lymphoplasmacytic infiltrate and fibrosis and **therapeutically** by a dramatic response to steroids"

For detaljer: Se kompleks tabell med diagnostiske kriterier

Shimosegawa & Al (2011) International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 40 (3):352-358.

AIP- Sykdomsdefinisjon

Type 1

- Lymphoplasmacytic sclerosing pancreatitis (LPSP)
- IgG4 positive
- Systemsykdom (Nyrer, galleveier, prostata, testikler, lunger, peritoneum

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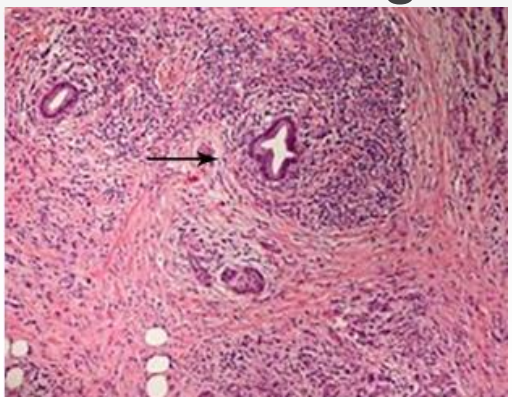
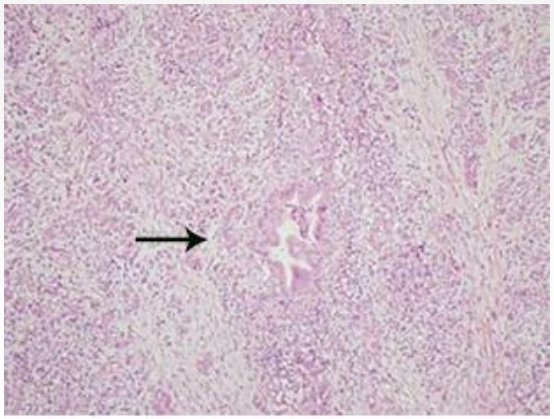


Storiform (swirling pattern) fibrosis, lymphoplasmacytic infiltration around interlobular ducts (arrow), and obliterative phlebitis

Type 2

- Idiopathic duct-centric pancreatitis (IDCP)
- IgG4 negative
- Pankreassykdom



Neutrophilic infiltration within epithelium and lumen of pancreatic duct

Type 1 vs type 2

- Imaging eller steriodrespons skiller ikke
- Typisk serologi eller involv. av andre organer: type 1
  - Fravær av serologi eller funn i andre organer avkrefter ikke type 1.

AIP diagnose

TABLE 1. Diagnosis of Definitive and Probable Type 1 AIP Using ICDC

Diagnosis	Primary Basis for Diagnosis	Imaging Evidence	Collateral Evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1 H)
	Imaging	Typical	Any non-D level 1/level 2
		Indeterminate	Two or more from level 1 (+level 2 D*)
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or level 1 D + level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H + Rt

*Level 2 D is counted as level 1 in this setting.

Shimosegawa & Al (2011) International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 40 (3):352-358.

AIP diagnose

TABLE 2. Level 1 and Level 2 Criteria for Type 1 AIP

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical†): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
S	Serology	IgG4, >2× upper limit of normal value	IgG4, 1–2× upper limit of normal value
OOI	Other organ involvement	a or b	a or b
		a. Histology of extrapancreatic organs Any three of the following: (1) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration (2) Storiform fibrosis (3) Obliterative phlebitis (4) Abundant (>10 cells/HPF) IgG4-positive cells	a. Histology of extrapancreatic organs including endoscopic biopsies of bile duct‡: Both of the following: (1) Marked lymphoplasmacytic infiltration without granulocytic infiltration (2) Abundant (>10 cells/HPF) IgG4-positive cells
		b. Typical radiological evidence At least one of the following: (1) Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture (2) Retroperitoneal fibrosis	b. Physical or radiological evidence At least one of the following: (1) Symmetrically enlarged salivary/lachrymal glands (2) Radiological evidence of renal involvement described in association with AIP
H	Histology of the pancreas	LPSP (core biopsy/resection) At least 3 of the following: (1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration (2) Obliterative phlebitis (3) Storiform fibrosis (4) Abundant (>10 cells/HPF) IgG4-positive cells	LPSP (core biopsy) Any 2 of the following: (1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration (2) Obliterative phlebitis (3) Storiform fibrosis (4) Abundant (>10 cells/HPF) IgG4-positive cells
		Diagnostic steroid trial	
Response to steroid (Rt)*		Rapid (≤2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations	

*Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats (see text) only after negative workup for cancer including endoscopic ultrasound-guided fine needle aspiration.

†Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilatation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP, and a thorough workup for cancer is negative (see algorithm).

‡Endoscopic biopsy of duodenal papilla is a useful adjunctive method because ampulla often is involved pathologically in AIP.

AIP Diagnose

TABLE 3. Diagnosis of Definitive and Probable Type 2 AIP Using ICDC

Diagnosis	Imaging Evidence	Collateral Evidence
Definitive type 2 AIP	Typical/indeterminate	Histologically confirmed IDCP (level 1 H) or clinical inflammatory bowel disease + level 2 H + Rt
Probable type 2 AIP	Typical/indeterminate	Level 2 H/clinical inflammatory bowel disease + Rt

AIP Diagnose

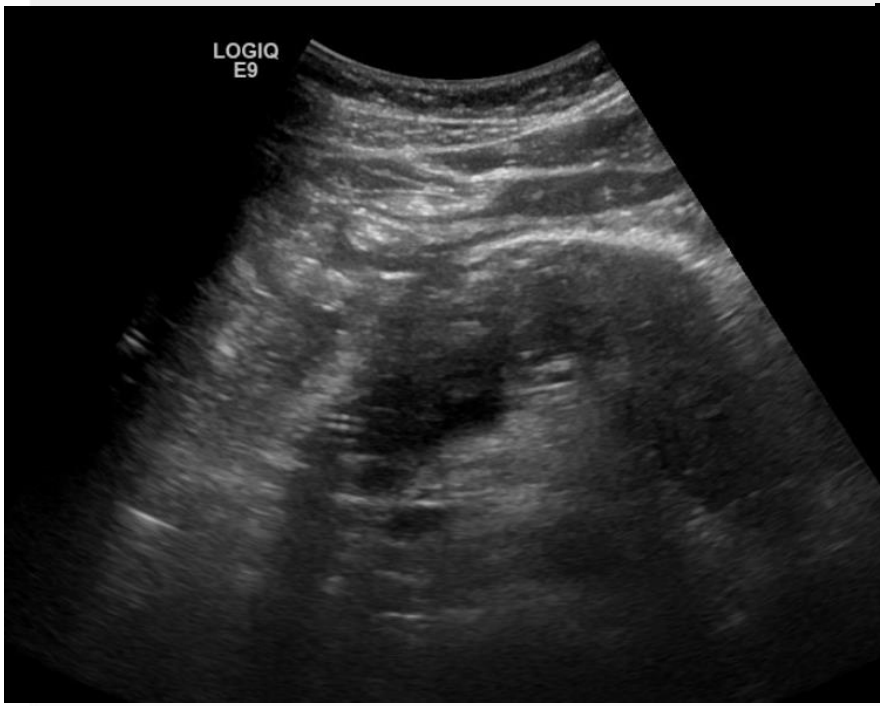
TABLE 5. Level 1 and Level 2 Criteria for Type 2 AIP

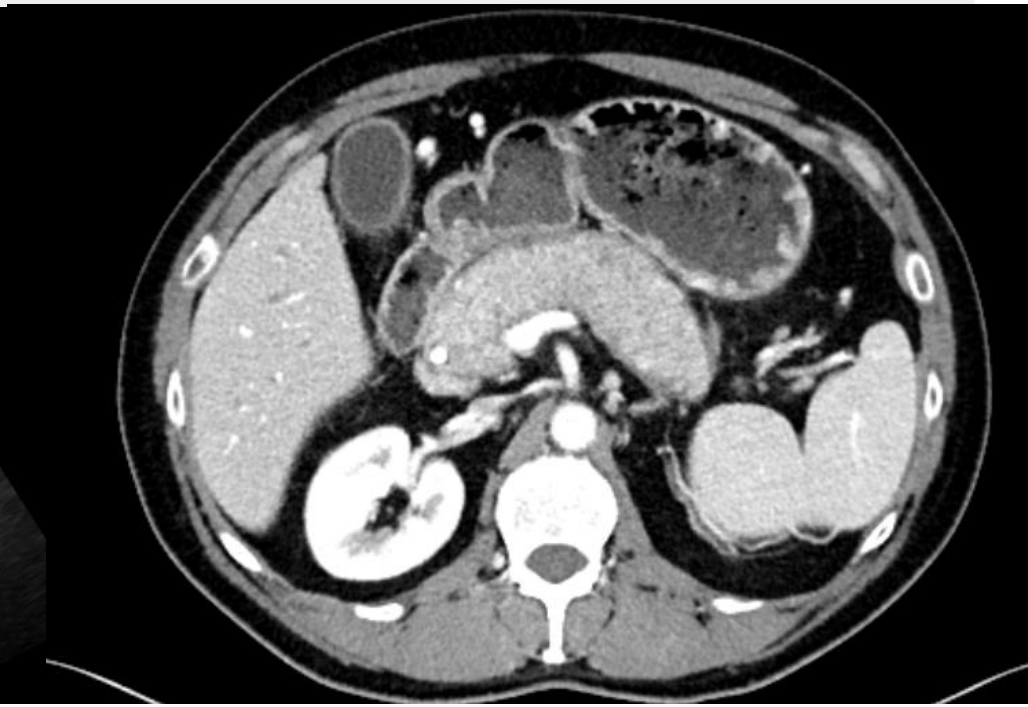
	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical†): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
OOI	Other organ involvement		Clinically diagnosed inflammatory bowel disease
H	Histology of the pancreas (core biopsy/resection)	IDCP: Both of the following: (1) Granulocytic infiltration of duct wall (GEL) with or without granulocytic acinar inflammation (2) Absent or scant (0–10 cells/HPF) IgG4-positive cells	Both of the following: (1) Granulocytic and lymphoplasmacytic acinar infiltrate (2) Absent or scant (0–10 cells/HPF) IgG4-positive cells
		Diagnostic steroid trial	
Response to steroid (Rt)*		Rapid (≤2 wk) radiologically demonstrable resolution or marked improvement in manifestations	

*Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats (see text) only after negative workup for cancer including endoscopic ultrasound-guided fine needle aspiration.

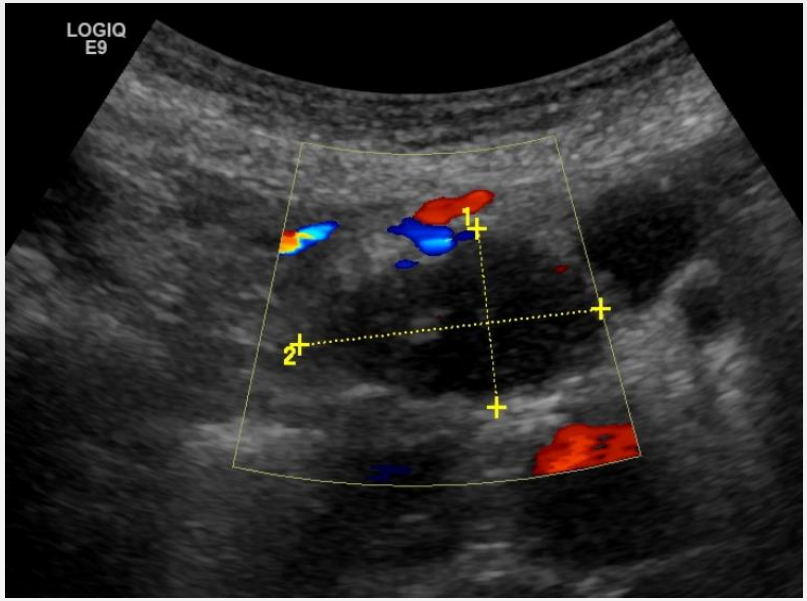
†Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilatation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP, and a thorough workup for cancer is negative (see algorithm).

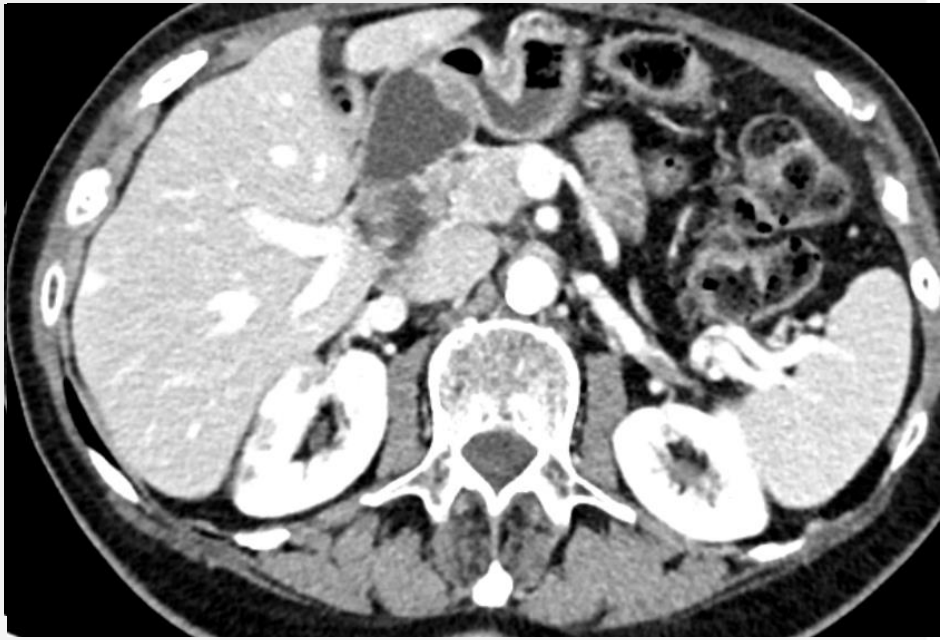
AIP billeddiagnostikk “Pølsepankreas”

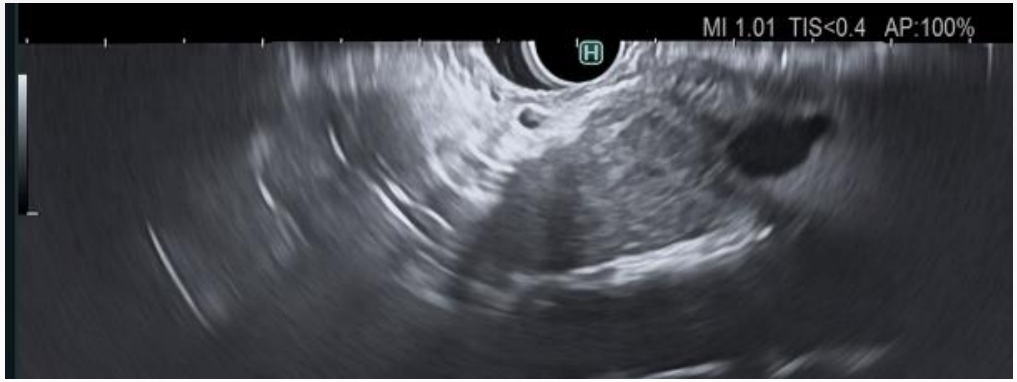




AIP Billeddiagnostikk-Fokale lesjoner







Ekstrapankreas manifestasjoner (Type 1)

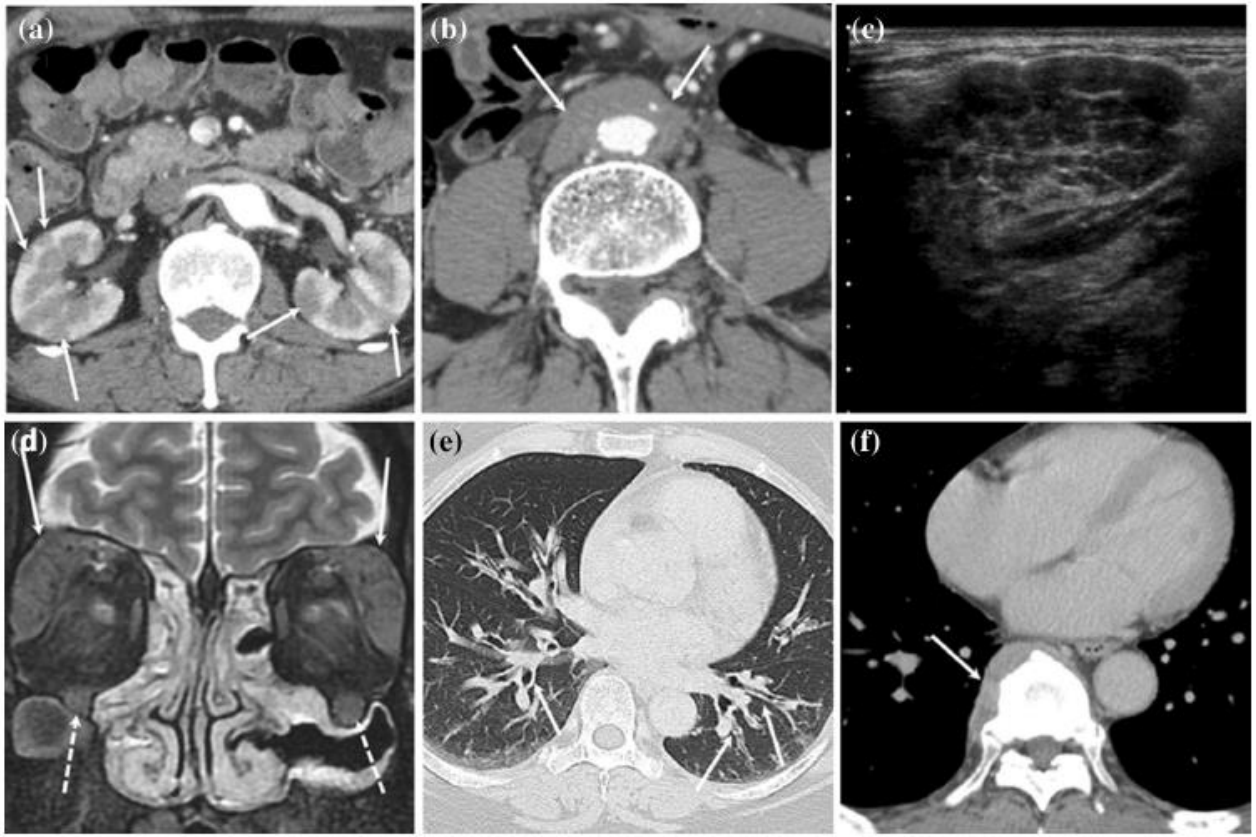


Fig. 13 Various extrapancreatic manifestation of AIP. **a** 71-year-old male with type 1 AIP. CT of abdomen shows multiple wedge-shaped low-density areas in bilateral renal cortex (arrows) consistent with IgG4-related renal disease. **b** 69-year-old male with type 1 AIP. CT of abdomen shows circumferential wall thickening of the abdominal aorta (arrows) suggestive of periaortic IgG4-related disease. **c** 81-year-old male with type 1 AIP. Ultrasonography of the submandibular gland demonstrates enlarged gland with multiple low-echoic areas surrounded by linear hyperechoic structures. **d** 62-year-old male with type 1 AIP and extrapancreatic involvement of lacrimal and infraorbital nerves. MRI (T2WI coronal) shows bilateral lacrimal glands enlargement (arrows). Bilateral infraorbital nerves are also swollen (dashed arrows). **e** 50-year-old female with type 1 AIP. Chest CT shows bronchovascular thickening in both lungs (arrows). Lung involvement is often nonspecific with IgG4-related disease. **f** 91-year-old male with type 1 AIP. Chest CT shows band-like soft tissue in right lateral aspect of lower thoracic vertebra (arrow)

Khandelwal & Al. Autoimmune pancreatitis: an update. Abdominal Radiology (2020) 45:1359–1370

AIP vs cancer

Autoimmune pancreatitis	Pancreas cancer
Diffuse pancreatic enlargement but may be focal	Focal form more common
Pancreatic duct typically not dilated	Significant dilatation of the pancreatic duct
Capsule-like rim with delayed enhancement	Hyperdense rim on noncontrast CT and hyperenhancment of rim on portal venous phase
Penetrating duct sign is present	Double duct sign highly specific for PC
Side branch dilatation at the level of MPD stricture	Side branch obliteration due to tumor obliteration
Responds to short steroid course	Nonresponsive to steroids
Delayed parenchymal enhancement	Remains hypoenhancing in delayed phase
Extrapancreatic involvement of IgG4 disease	Metastasis +

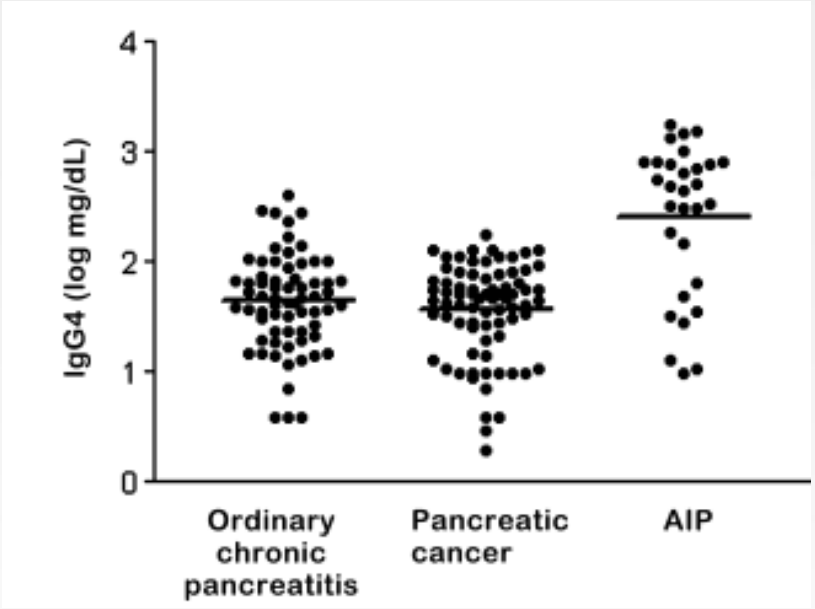
Khandelwal & Al. Autoimmune pancreatitis: an update. Abdominal Radiology (2020) 45:1359–1370

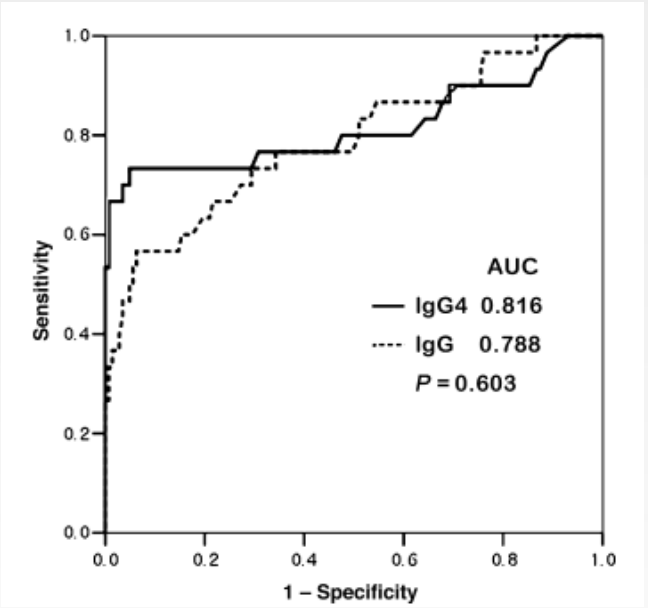
IgG4 og serologiske markører

- Type 1 AIP assosiert med øket IgG (≥ 18 g/L) og IgG4 (≥ 1.4 g/L).
  - IgG4 > 1.4 mg/dL: Sens: 86%, Spes: 90–96%
  - IgG4 > 2 X Øvre ref grense (> 2.8 g/L) svært spesifikt, mindre sensitivt (Andre studier: Kun ca 22% ved IgG > 1.4 fyller kriterier)
  - IgG4 kan være nyttig for monitorering
- Mindre økning I IgG4 sees hos 10% av pankreascancere
- Serum IgG4 normal i type 2 AIP.
- Andre serologiske markører kan sees uspesifikt (γ-globulin (> 2.0 g/dL), rheumatoid factor (20-30%), ANA (60%)

CHOI & AL (2007) THE SENSITIVITY AND SPECIFICITY OF SERUM IMMUNOGLOBULIN G AND IMMUNOGLOBULIN G4 LEVELS IN THE DIAGNOSIS OF AUTOIMMUNE CHRONIC PANCREATITIS: KOREAN EXPERIENCE. PANCREAS 35 (2):156-161.

IgG 4





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AIP forekomst

- Eksakt forekomst ukjent
  - Japan: Prevalens: 4.6/100,000, Incidens:1.4/100,000
    - Ca 5-6 % av pas med KP
    - Ca 4% av pankreasreseksjon pga tumor
- Type 1 (60-80%): >60år, 2/3♂. Hyppig residiv
- Type 2 (20-40%): Median 40 år, ♂=♀, 30% IBD. Vanligere I vesten, Ofte debut AP. Sjeldnere residiv

KANNO & AL NATIONWIDE EPIDEMIOLOGICAL SURVEY OF AUTOIMMUNE PANCREATITIS IN JAPAN IN 2011. PANCREAS 44; 535-539

AIP behandlingsindikasjon

- Alle symptomatiske pasienter (Smerte, icterus)
- Asymptomatiske ved
  - Mistenkelig solitær masse
  - Persisterende cholestase
  - For å beskytte mot organsvikt(?)

AIP behandling

- Prednisolon 30-40 mg / d i 4 uker
  - Trappe ned over 3-6 mnd

- Stenting av galle- eller pankreasgang er ikke absolutt nødvendig, da steroidbehandling ofte gir bedring i ikterus og pankreassvikt som følge av obstruksjon.

AIP behandling- Tilbakefallsprofylakse

- **Når?**
  - Ved raske og symptomatiske residiv
  - Ved multiorgansaffeksjon
- **Hvordan?**
  - Ny prednisolonkur uten vedlikehold
  - Ny prednisolonkur fulgt av lavdose (<10mg) I 1-3 år: Reduserer tilbakefall fra 60-23%
  - Rituximab: Induksjon (1000mg X 2 med 15 dager mellom + evt vedlikehold etter 6 mnd
  - Imurel/ cellcept/metotrexat/ tacrolimus er alternative steroidsparende regimer.

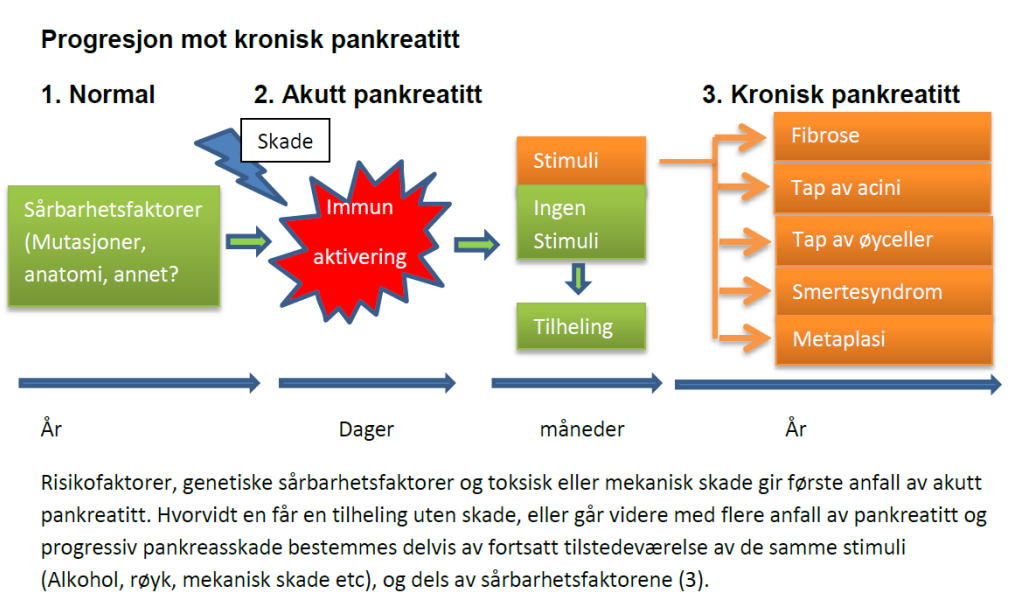
AIP prognose

- Ca 10-25% går i spontan regresjon
- Ca 97-100% responderer på behandling.
- Residiv omtrent halvparten
  - Type 1: 60%, Type 2: 5 %
- Vedlikeholdsbehandling ved type 1 reduserer residiv mot 25%

Komplikasjoner over lang tid:

- 19-67% får diabetes
- 36-85% får EPI
- Og noen hadde cancer likevel…..

Utkomme i en nordisk populasjon



Figur: T Engjom. Courtesy: The sentinel pancreatitis model, DC Whitcomb

71 svenske pasienter. 81% behandlet:

- Treatment outcome: Median follow up: 46 months, 97% were still alive, 92% in clinical remission, 70% had a radiologically complete response and 89% were treatment-free.
- **Complications:** , 47% PEI, of whom 76% had a severe form (FE < 100 µg/g) 21% diabetes mellitus, of whom 73% required insulin.

Vujasinovic & Al Diagnosis, treatment and long-term outcome of autoimmune pancreatitis in Sweden. Pancreatology. 2018 Dec;18(8):900-904. doi: 10.1016/j.pan.2018.09.003. Epub 2018 Sep 13. PMID: 30236651.

Oppsummering

- Symptomer: Smerter, Ikterus, nyoppstått diabetes, ernæringssvikt
- Funn: Diffus pancreas forstørrelse, solitære pankreaslesjoner, gallestase, annen organaffeksjon
- **Type 1:** IgG4, systemsykdom, residiv etter beh
- **Type 2**: IBD, pankreassykdom, sjelden residiv
  - Histologi: Klassiske funn, IgG4 positive?
- Behandle hovedsaklig symptomatiske
- Autiommun pankreatitt er steroidfølsom.
- Forlenget behandling/ Rituximab eller immunsuppresiva ved residiv.
- Mange får likevel EPI/ diabetes.

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