

# Pancreatitis, NIET veroorzaakt door galstenen, alcohol of de endoscopist

H.R. van Buuren, MDL-arts  
Erasmus MC, Rotterdam



## Symptoms

- Upper Abdominal pain, sudden onset, sharp, severe, continuous, radiates to the back, reduced by leaning forward.

Generalized abdominal pain, radiates to the shoulder tips. Patient lies very still.

- Nausea, non-projectile vomiting, retching
- Anorexia
- Fever, weakness



**Acute pancreatitis is defined as presence of 2 of the 3 following criteria:**

- (a) abdominal pain** suggestive of pancreatitis (epigastric pain often radiating to the back)
- (b) serum amylase or lipase levels 3 or more times normal**
- (c) characteristic findings on computed tomography (CT), magnetic resonance imaging (MRI), or transabdominal ultrasound studies**

Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111

IAP/APA evidence-based guidelines for the management of acute pancreatitis *Pancreatology* 2013;13:e1-e15

# Recidiverende acute pancreatitis

- **tenminste 2 episoden van acute pancreatitis met een interval van tenminste 3 maanden**

Recurrent acute pancreatitis.  
*International State-of-the-Science  
Conference with recommendations.*  
Pancreas 2018;47:653-6

# Acute pancreatitis

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- **Veelvoorkomend probleem**
  - belangrijkste GI-opname indicatie in VS en elders
    - Gastroenterology 2013;144:1252-61
- **Incidentie neemt toe**
  - Overgewicht! Diabetes. Galstenen.
    - J Gastroenterol Hepatol 2002;17 Suppl:S15
- **10 – 30% kans op recidiverende acute pancreatitis**
  - Am J Gastroenterol 2002;97:1959-62
  - Scand J Gastroenterol 2004;39:891-4
- **10% eenmalige acute pancreatitis → chronische pancreatitis**
  - Gastroenterology 2015;149:1490-1500

# Acute pancreatitis

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# Acute pancreatitis – etiologie concept

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## Vaak meerdere bijdragende en mogelijk interactieve factoren

- Genetische predispositie
- Microlithiasis
- Alcohol
- Roken (!)
- Diabetes mellitus (type II)
- Overgewicht
- Congenitale afwijkingen (m.n. pancreas divisum)

Pancreas 2018;47: 653–666

Lancet 2015;386:85-95

# Acute pancreatitis door endoscopische procedures

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## 1. ERCP (3-4%)

## 2. Enteroscopie

- incidentie  $\pm$  0,3%

Endoscopy 2007;39:613-5

World J Gastroenterol 2010;16:2331-40

## 3. Biopteren papil van Vater

- papilla minor

Endoscopy 2009;41:E195-6

Endoscopy 2016;48:E238-9

- papilla major

[eigen waarneming]

## 4. Overige procedures

- **coloscopie**

o.a. J Clin Gastroenterol 1994;19:177-8

Case reports Gastointest Med 2019;4587371

- **gastroscopie**

o.a. J Clin Gastroenterol 2002;34:94-5

Endoscopy 1982;14:105-6

BMJ Case report 2017. pii: bcr-2017-222272

## Etiology of acute pancreatitis

<b>Mechanical</b>	Gallstones, biliary sludge, ascariasis, periampullary diverticulum, pancreatic or periampullary cancer, ampullary stenosis, duodenal stricture or obstruction
<b>Toxic</b>	Ethanol, methanol, scorpion venom, organophosphate poisoning
<b>Metabolic</b>	Hyperlipidemia (types I, IV, V), hypercalcemia
<b>Drugs</b>	Didanosine, pentamidine, metronidazole, stibogluconate, tetracycline furosemide, thiazides, sulphasalazine, 5-ASA, L-asparaginase, azathioprine, valproic acid, sulindac, salicylates, calcium, estrogen
<b>Infection</b>	Viruses-mumps, coxsackie, hepatitis B, CMV, varicella-zoster, HSV, HIV
	Bacteria-mycoplasma, Legionella, Leptospira, salmonella
	Fungi-aspergillus
	Parasites-toxoplasma, cryptosporidium, Ascaris
<b>Trauma</b>	Blunt or penetrating abdominal injury, iatrogenic injury during surgery or ERCP (sphincterotomy)
<b>Congenital</b>	Cholodochocoele type V, pancreas divisum*
<b>Vascular</b>	Ischemia, atheroembolism, vasculitis (polyarteritis nodosa, SLE)
<b>Miscellaneous</b>	Post ERCP, pregnancy, renal transplantation, alpha-1-antitrypsin deficiency
<b>Genetic</b>	CFTR, PRSS1, SPINK1, and other genetic mutations



# Kashmir – India



**Prevalentie ascariasis**  
**30% volwassenen**  
**60 % kinderen**

**acute pancreatitis n= 256**  
**- ascariasis 59/256 = 23%**

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<b>Idiopathisch ???!</b>	
<b>Autoimmuun pancreatitis ?? !!</b>	

40%

35%

4%

10 – 30% !

?? %

# Hypertriglyceridaemie

## 1% -14% oorzaak van alle acute pancreatitis

Am J Gastroenterol 1995;90:2134

J Clin Gastroenterol 2014;48:195

## Serumgehalte triglyceriden > 11 mmol/l (n= < 1,7 mmol/l)

J Clin Endocrinol Metab 2012;97:2969

## Positieve correlatie tussen triglyceridengehalte en

- kans op pancreatitis
- kans op ernstige pancreatitis

Pancreas 2008;37:13

J Clin Gastroenterol 2014;48:195

## Oorzaken

### 1. genetisch

- type I dyslipademie (fam. chylomicronemie)
- type IV (fam. hypertriglyceridemie)
- type V (primary mixed hypertriglyceridaemie)

### 2. verworven

- alcohol
- diabetes mellitus
- hypothyreoïdie
- medicatie (o.a. oestrogenen; tamoxifen)
- zwangerschap





# Acute pancreatitis en zwangerschap

**Incidentie** 2-3 /10.000 zwangerschappen

meestal 3<sup>e</sup> trimester

**Oorzaken** galstenen 66 – ≥ 80 %

Obstet Gynecol. 2008;112:1075-81

Hepatobiliary Pancreat Dis Int 2016;15:434-8

alcohol, hypercalcaëmie, idiopathisch, overige.....

zeer zelden: pre-eclampsie/HELP syndroom

## **Typische etiologie bij zwangerschap**

### **hypertriglyceridaemie**

etiologie: fysiologisch verhoging triglyceriden

o.b.v. hormonale veranderingen

tot 56% van alle gevallen

Arch Gynecol Obstet 2018;297:333-9

JOP 2012 Nov 10;13:677-80

# hypercalciëmie

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**In 1-2% oorzaak van acute pancreatitis**

**Elke oorzaak van hypercalciëmie kan leiden tot pancreatitis, op elke leeftijd**

***Snelle* stijging calcium serumspiegel waarschijnlijk belangrijker risicofactor dan  
*chronische* verhoging**

Vege et al. UpToDate® 2019

# Genetisch bepaalde pancreatitis

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## Autosomaal-dominante hereditaire pancreatitis:

- \* mutaties **PRSS1** (serine protease 1) **gen**
- \* vaak presentatie < 20 jaar
- \* recidiverende acute pancreatitis
- \* chronische pancreatitis
- \* verhoogde kans pancreascarcinoom

## Autosomaal-recessieve vorm:

- \* mutaties **CFTR** (cystic fibrosis transmembraan conductance regulator) **gen**

## Mutaties in **SPINK1** (serine protease inhibitor Kazal type 1) **gen**:

### Mutaties in **CFTR** gen:

- \* “disease modifiers”
- \* verhogen kans op pancreatitis t.g.v. andere oorzaken bv pancreas divisum

## Mutaties in **CTRC** (chymotrypsine C) **gen**

- \* geassocieerd met chronische pancreatitis
- \* vaak samen met **CFTR** en/of **SPINK 1** mutaties

overige: **CLDN2** en **CPA1** mutaties (geassocieerd met chron. pancreatitis)

# Genetisch bepaalde pancreatitis

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## indicaties voor genetisch onderzoek m.n.

- anderszins onverklaarde pancreatitis bij kinderen
- idiopathische chron. pancreatitis m.n. lft < 25 jaar
- pancreatitis met familiair voorkomen van recidiverende acute of chronische pancreatitis, of pancreatitis op kinderleeftijd
- recidiverende acute pancreatitis zonder oorzaak

Gastroenterol Clin North Am 2007;36:325  
Pancreatology 2001;1:405

## Classification system of drug-induced acute pancreatitis

<b>Class Ia drugs</b>
At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs
<b>Class Ib drugs</b>
At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out
<b>Class II drugs</b>
At least 4 cases in the literature
Consistent latency ( $\geq 75$ percent of cases)
<b>Class III drugs</b>
At least 2 cases in the literature
No consistent latency among cases
No rechallenge
<b>Class IV drugs</b>
Drugs not fitting into the earlier-described classes, single case report published in medical literature, without rechallenge



### Summary of drug-induced acute pancreatitis based on drug class

Class Ia	Class Ib	Class II	Class III	Class IV
o-methyl dopa	All-trans-retinoic acid	Acetaminophen	Alendronate	Adrenocorticotrophic hormone
Azodisalicylate	Amiodarone	Chlorothiazide	Atorvastatin	Ampicillin
Bezafibrate	Azathioprine	Clozapine	Carbamazepine	Bendroflumethiazide
Cannabis	Clomiphene	Didanosine	Captopril	Benazepril
Carbimazole	Dexamethasone	Erythromycin	Ceftriaxone	Betamethasone
Codeine	Ifosfamide	Estrogen	Chlorthalidone	Capecitabine
Cytosine	Lamivudine	L-asparaginase	Cimetidine	Cisplatin
Arabinoside	Losartan	Pegaspargase	Clarithromycin	Colchicine
Dapsone	Lynestrenol/methoxyethinylestradiol	Propofol	Cyclosporin	Cyclophosphamide
Enalapril	6-mercaptopurine	Tamoxifen	Gold	Cyproheptadine
Furosemide	Meglumine		Hydrochlorothiazide	Danzol
Isoniazid	Methimazole		Indomethacin	Diazoxide
Mesalamine	Nelfinavir		Interferon/ribavirin	Diclofenac
Metronidazole	Norethindronate/mestranol		Irbesartan	Diphenoxylate
Pentamidine	Omeprazole		Isotretinoin	Doxorubicin
Pravastatin	Premarin		Ketorolac	Ethacrynic acid
Procainamide	Trimethoprim-sulfamethazole		Lisinopril	Famciclovir
Pyritinol			Metolazone	Finasteride
Simvastatin			Metformin	5-fluorouracil
Stibogluconate			Minocycline	Fluvastatin
Sulfamethoxazole			Mirtazapine	Gemfibrozil
Sulindac			Naproxen	Interleukin-2
Tetracycline			Paclitaxel	Ketoprofen
Valproic acid			Ponatinib	Lovastatin
			Prednisone	Mefenamic acid
			Prednisolone	Nitrofurantoin
				Octreotide
				Oxyphenbutazone
				Penicillin
				Phenophthalein
				Propoxyphene
				Ramipril
				Ranitidine
				Rifampin
				Risperidone
				Ritonavir
				Roxithromycin
				Rosuvastatin
				Sertraline
				Strychnine
				Tacrolimus
				Vigabatrin/lamotrigine
				Vincristine

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Summary of

Class Ia
o-methylpapa
Azodisalicylate
Bezafibrate
Cannabis
Carbimazole
Codeine
Cytosine
Arabinoside
Dapsone
Enalapril
Furosemide
Isoniazid
Mesalamine
Metronidazole
Pentamidine
Pravastatin
Procainamide
Pyritinol
Simvastatin
Stibogluconat
Sulfamethoxa
Sulindac
Tetracycline
Valproic acid

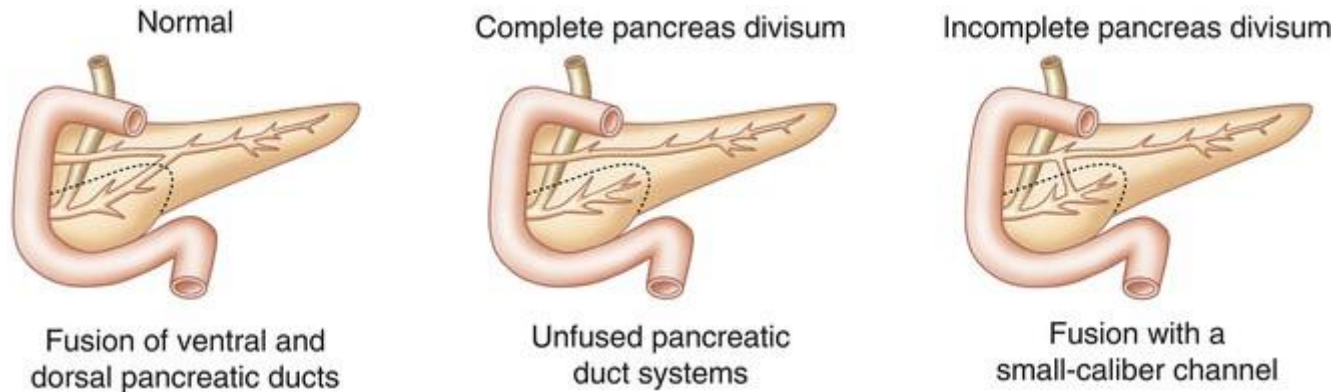
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**Furosemide**  
**Chloorthiazide**  
**Azathioprine**  
**6-mercaptopurine**  
**Mesalazine**  
**Simvastatine**  
**Enalapril**  
**Losartan**  
**Erythromycine**  
**Tetracycline**  
**Isoniazide**  
**Omeprazol**  
**Propofol**  
**Carbimazol**  
**Thiamizol**

Class IV
Adrenocorticotrophic hormone
Ampicillin
Bendroflumethiazide
Benazepril
Betamethasone
Capecitabine
Cisplatin
Colchicine
Cyclophosphamide
Cyproheptadine
Danazol
Diazoxide
Diclofenac
Diphenoxylate
Doxorubicin
Ethacrynic acid
Famciclovir
Finasteride
5-fluorouracil
Fluvastatin
Gemfibrozil
Interleukin-2
Ketoprofen
Lovastatin
Mefenamic acid
Nitrofurantoin
Octreotide
Oxyphenbutazone
Penicillin
Phenophtalein
Propoxyphene
Ramipril
Ranitidine
Rifampin
Risperidone
Ritonavir
Roxithromycin
Rosuvastatin
Sertraline
Strychnine
Tacrolimus
Vigabatrin/lamotrigine
Vincristine

UpToDate: An Evidence-Based

# Pancreas divisum als oorzaak voor acute pancreatitis



## **Controverse: pancreas divisum oorzaak van (acute) pancreatitis ??**

Lancet 2015; 386-85-96

Gastroenterology 1985;89:1431

Endoscopy 1991;23:55

Endoscopy 1991; 23:88

## **Duidelijke associatie van recidiverende acute en chronische pancreatitis bij pancreas divisum met**

- cystic fibrosis gen (CFTR) mutaties/functie
- SPINK1 mutaties/polymorfismen
- PRSS1 “ ”

Am J Gastroenterol 2012;107:311-7

Am J Gastroenterol 2004;99:1557

## **Subgroup van patiënten met pancreas divisum ontwikkelt (recidiv.) acute pancreatitis en/of chronische pancreatitis**

\* suggestie: multifactorieel bepaalde ziekte

# Autoimmuun pancreatitis (AIP)

## 1. Type I. (systemische) IgG4 gerelateerde ziekte

- presentatie: icterus; gewichtsverlies; pancreaszwellung
- presentatie zeer zelden als “acute pancreatitis”
- meestal leeftijd > 60 jaar

## 2. Type II. Ook bekend als “idiopathische duct centric pancreatitis”

- zeldzamer
- ook op jongere leeftijd
- normaal IgG4
- associatie met inflammatoire darmziekte
- soms presentatie als acute of recidiv. acute pancreatitis

# pancreatitis

	autoimmune type I	non-autoimmune
<b>pain</b>	- / ±	+ / ++++
<b>amylase/lipase</b>	n / ↑	n / ↑↑↑
<b>weight loss</b>	+ / ++++	- / ±
<b>pancreatic function</b>	↓↓	± / -
<b>gender</b>	<b>male</b> +++	<b>male</b> +
<b>age</b>	> 50 - 60	30 - 50
<b>IgG/ IgG4</b>	n / ↑ / ↑↑↑	<b>normal</b>
<b>other autoimmune disorders</b>	+	-

Okazaki et al Gut 2002;51:1-4

Kim K et al Am J Gastroenterol 2004;99:1605-16

Finkelberg et al New Engl J Med 2006;355:2670-6

# Autoimmuun pancreatitis als oorzaak van acute pancreatitis ??

## *Etiology of acute pancreatitis*

UpToDate 2019

- no routine testing for IgG4
- acute autoimmune pancreatitis is rare
- extremely rare cause of recurrent acute pancreatitis

## **Acute pancreatitis. Seminar.**

Lankisch et al. Lancet 2015;386:85-96

- autoimmuun pancreatitis niet genoemd

## **Clinical management of patient with acute pancreatitis.**

Wu BU, Banks PA. Gastroenterology 2013;144:1272-81

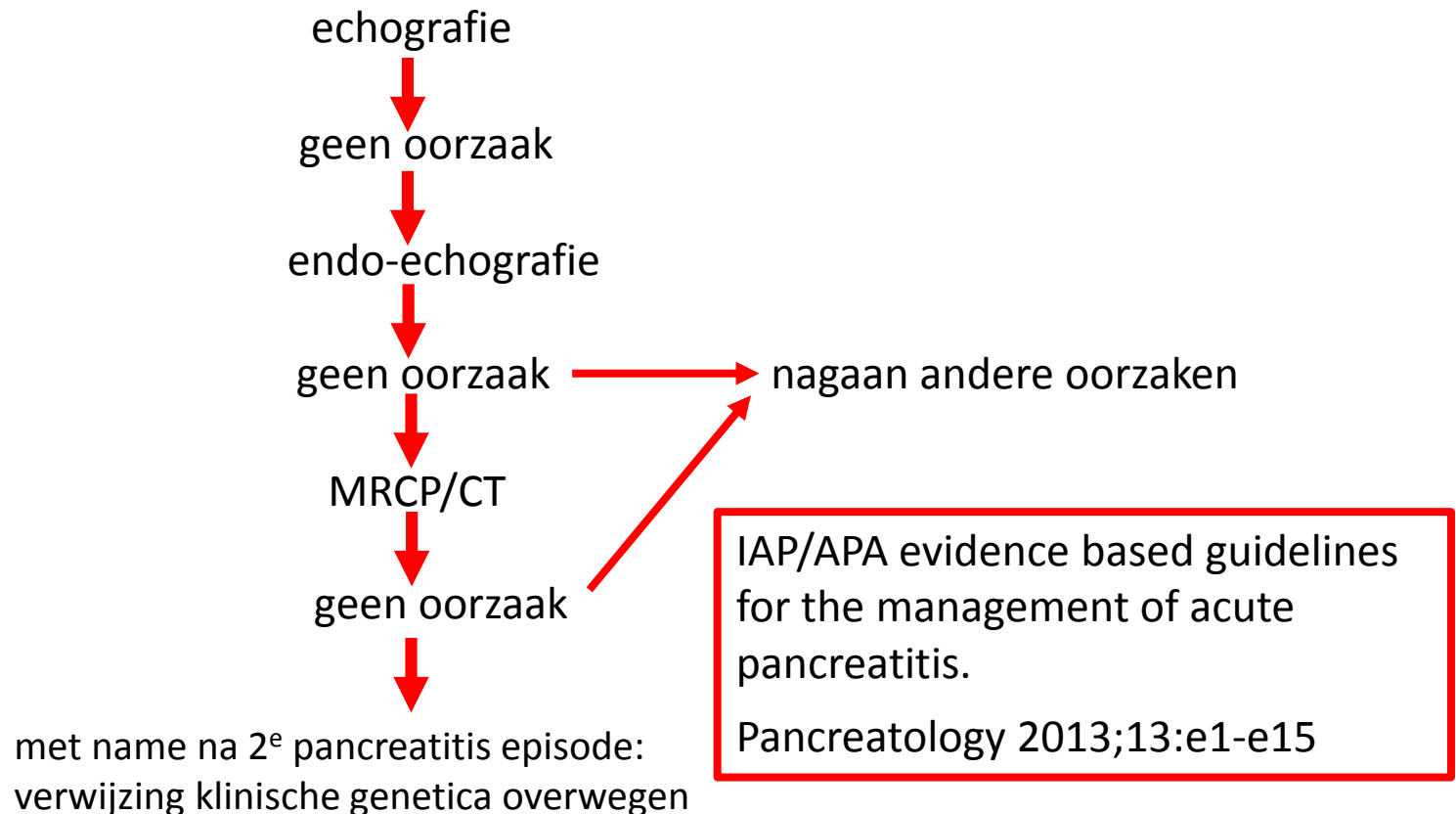
- autoimmunity rare cause of acute pancreatitis
- type II >> type 1 autoimmune pancreatitis

**Bepaal geen IgG4 bij klassieke acute pancreatitis met ++ pijn  
Wees terughoudend om acute pancreatitis te classificeren  
als mogelijk "autoimmuun pancreatitis"**

# Diagnostische benadering bij acute pancreatitis

**Anamnese:** alcohol; familie-anamnese; recente operaties/trauma's, zwangerschap; medicatie; overige aandoeningen

**Laboratorium:** amylase/lipase; CRP; levertesten; calcium; triglyceriden





# Take home messages acute pancreatitis

- **Vaak multifactoriële oorzaak !!**
- **In eerste instantie relatief simpele work-up met beperkt laboratorium onderzoek**
- **Bij recidiverende acute pancreatitis: pak er een overzichtsartikel bij!**
- **Geneesmiddelen, hypercalciemie en autoimmuun pancreatitis zijn (zeer) weinig voorkomende oorzaken**
- **Pancreatitis bij pancreas divisum wsch. multifactorieel bepaald**
- **10-20% idiopathisch**