

Bible Class Gallstone disease

23.09.20, M. Knecht



A bit of history

History



- Gallstones known since antiquity
 - Earliest known patient egyptian mummy 2000 B.C.
- Treatment for centuries with herbs, potions and so forth
- 1867 John Stough Boobs with first attempt at surgical treatment
 - Cholecystotomy and extraction of gallstone

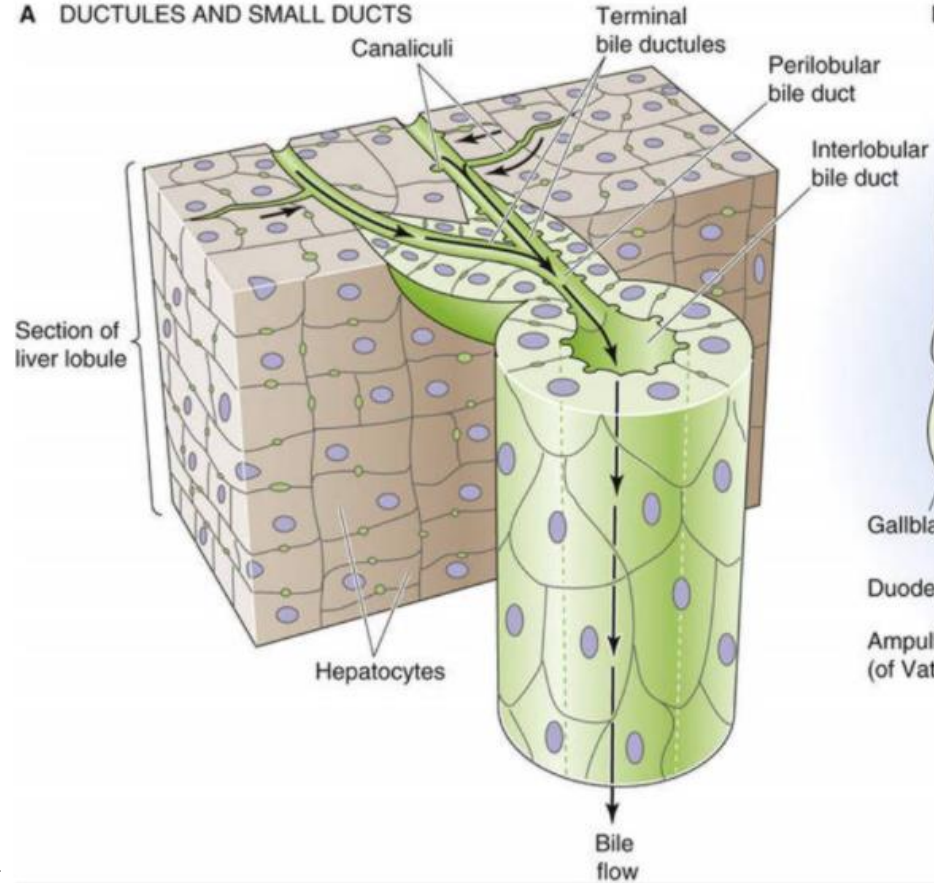
History

- 1882 Successful cholecystectomy
- 1973 Endoskopische, retrograde
Cholangio-Pankreatikographie
- 1985 Laparoscopic cholecystectomy

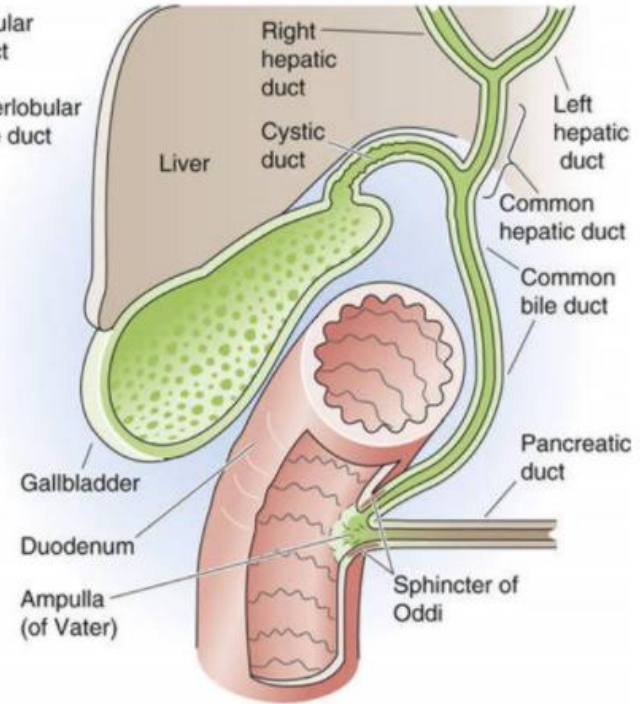


Physiology

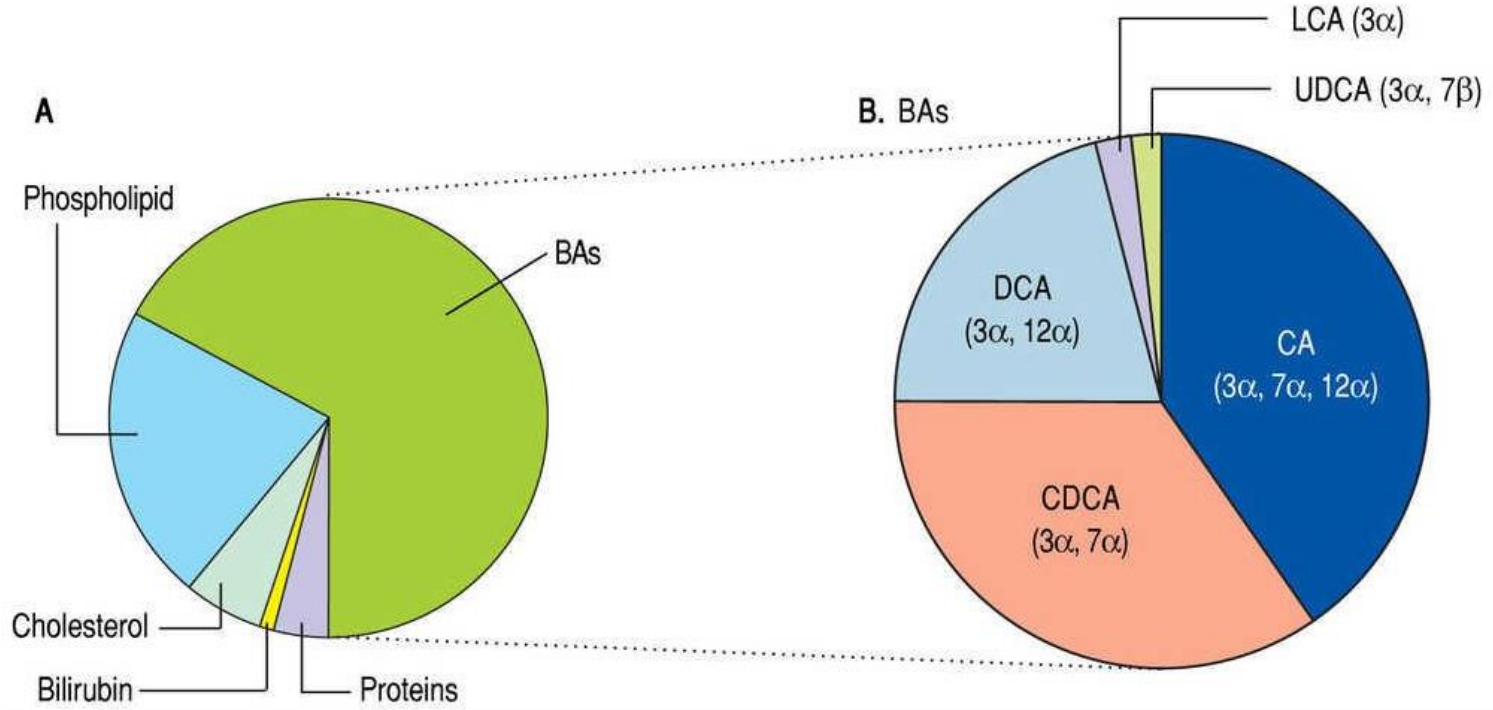
A DUCTULES AND SMALL DUCTS



B LARGE DUCTS AND GALLBLADDER



Composition



Di Caula A, *Ann Hepatol*, Nov 2017

Bile production, secretion, function



Periodical secretion via motilin, vagus nerve

Bile production, secretion, function

- Gallbladder stores and concentrates bile (5-10x)
- Filling volume ~70ml

Bile production, secretion, function



Amino and fatty acids



I-cells (Duodenum/Jejunum)



Cholecystikinin (CCK)

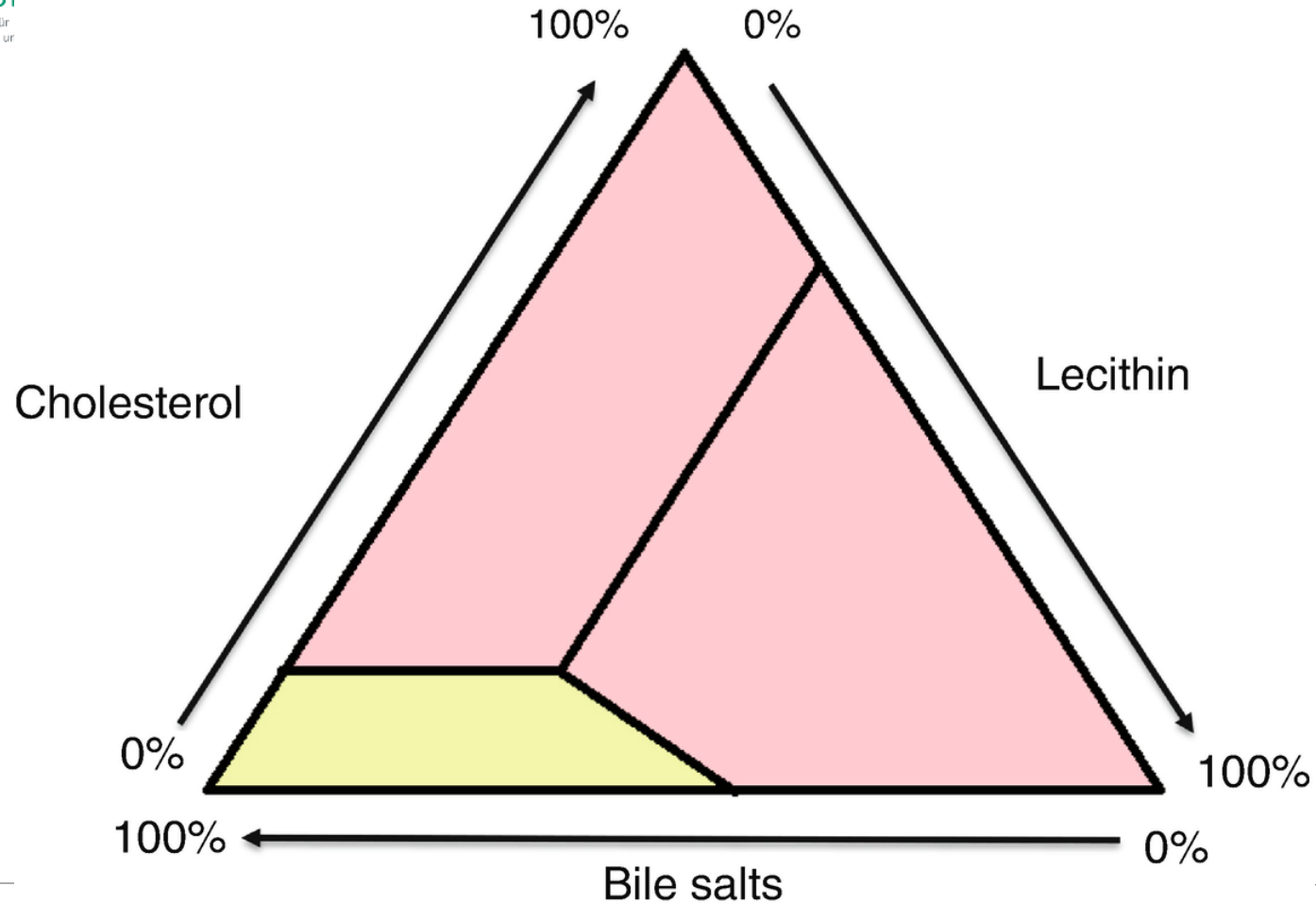


GB contraction, SOD relaxation

Bile production, secretion, function

- Elimination/carrier of excess cholesterol (BA and phospholipids)
- Absorption of Vitamin ADEK and fat in terminal ileum
 - Additionally BA with much more complex regulating mechanisms (FXR, PXR, GPBAR-1...), e.g. aiding in energy, glucose, lipids and lipoprotein metabolism and effect on microbiota
- BA absorption in terminal ileum entering entero-hepatic circulation
 - Negative feedback regulation

Pathophysiology





Stone formation

- Oversaturation of bile with cholesterol (or unconjugated bilirubin)
 - Associated with hypertriglyceridämie and low HDL
 - Insulin resistance
- Decreased BA secretion
- Concentrating bile in GB leads to increased lipids per dl and instability of uni-/multilamellar vesicles
- Altered gallbladder motility

Ahlberg J, *Acta Chir Scand* 1979

Cholesterol stones



Risk factors

- Non-modifiable
 - Age
 - Gender
 - Familial history
 - Genetics (mutations in the hepatic cholesterol transporter ABCG5/8)
 - Ethnicity (Caucasian, hispanics)

Risk factors

- Modifiable
 - Diet (high calorie/carbs, low fiber)
 - Pregnancy
 - Physical inactivity
 - Metabolic syndrome (weight, DM)
 - Rapid weight loss
 - TPN
 - Fasting
 - Drugs (estrogen, progesterone, thiazides, ceftriaxon, clofibrate)
 - HCV
 - Cirrhosis
 - Crohns

Classic mnemonic

- 6 F's
 - Fat
 - Forty
 - Female
 - Fertile
 - Family
 - Fair



Risk factors

- Estrogen → Increased cholesterol secretion and endogenous synthesis
- Progesteron → Decreased bile salts secretion, gallbladder stasis

Pigment stones



Risk factors

- Non-modifiable
 - Age

Risk factors

- „Modifiable“ (oversaturation with bilirubin)
 - Hemolysis (e.g. in sickle cell anemia, spherocytosis)
 - Ileal resection/Crohns
 - CF
- Cirrhosis

Brown pigment stones



Risk factors

- Biliary Infection (ascaris/clonorchis, enterococcus/e.coli)
 - Inflammatory stenosis
 - β -Glucuronidase converts bilirubin glucuronide to unconjugated bilirubin
 - Hydrolyse lecithin to release fatty acids

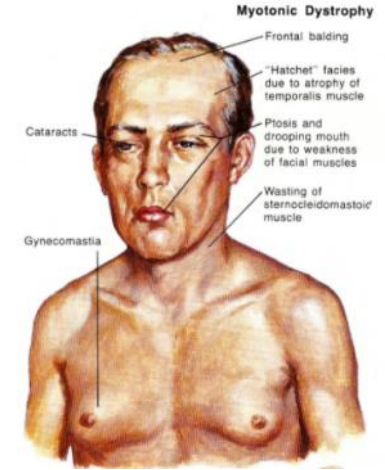
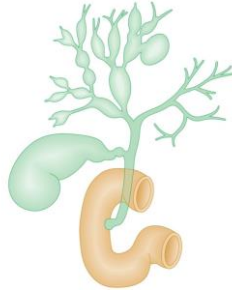
When to be suspicious



- Young patients, familial cluster, intrahepatic or recurring stones without classic RF-profile
 - think of secondary cholelithiasis

- Hemolysis?
- BAM?
- Infection (Parasites, Bacteria)?

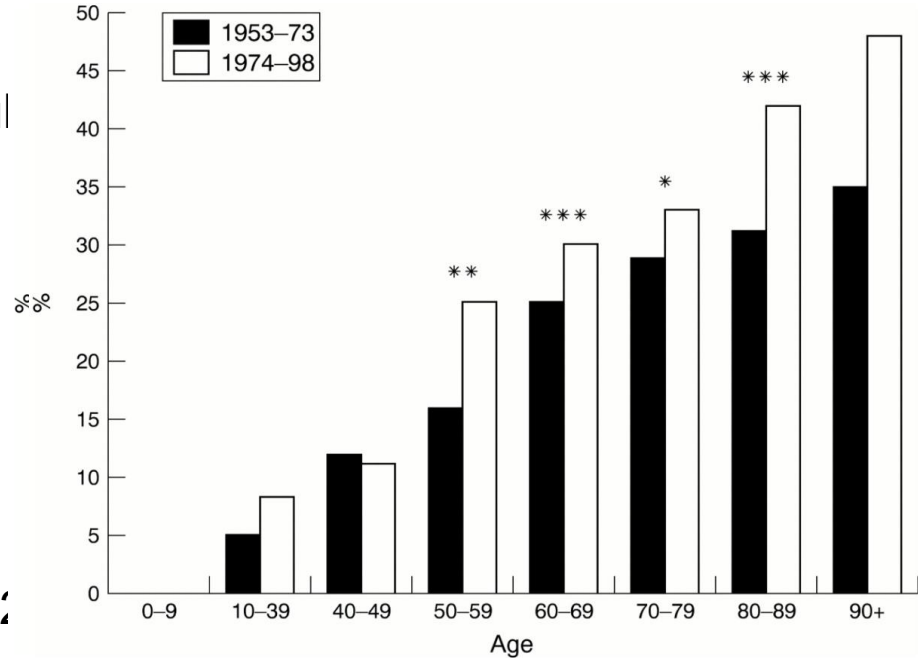
- Genetics?
 - Caroli?
 - CF?
 - Dystrophic myotonia type 1/2? (muscle weakness, cataract, fatigue)
 - Young patients?
 - LAPC: Lipid analysis duodenum/liver for phospholipid deficiency (ABCB4 and ABCB11 mutation)



Epidemiology

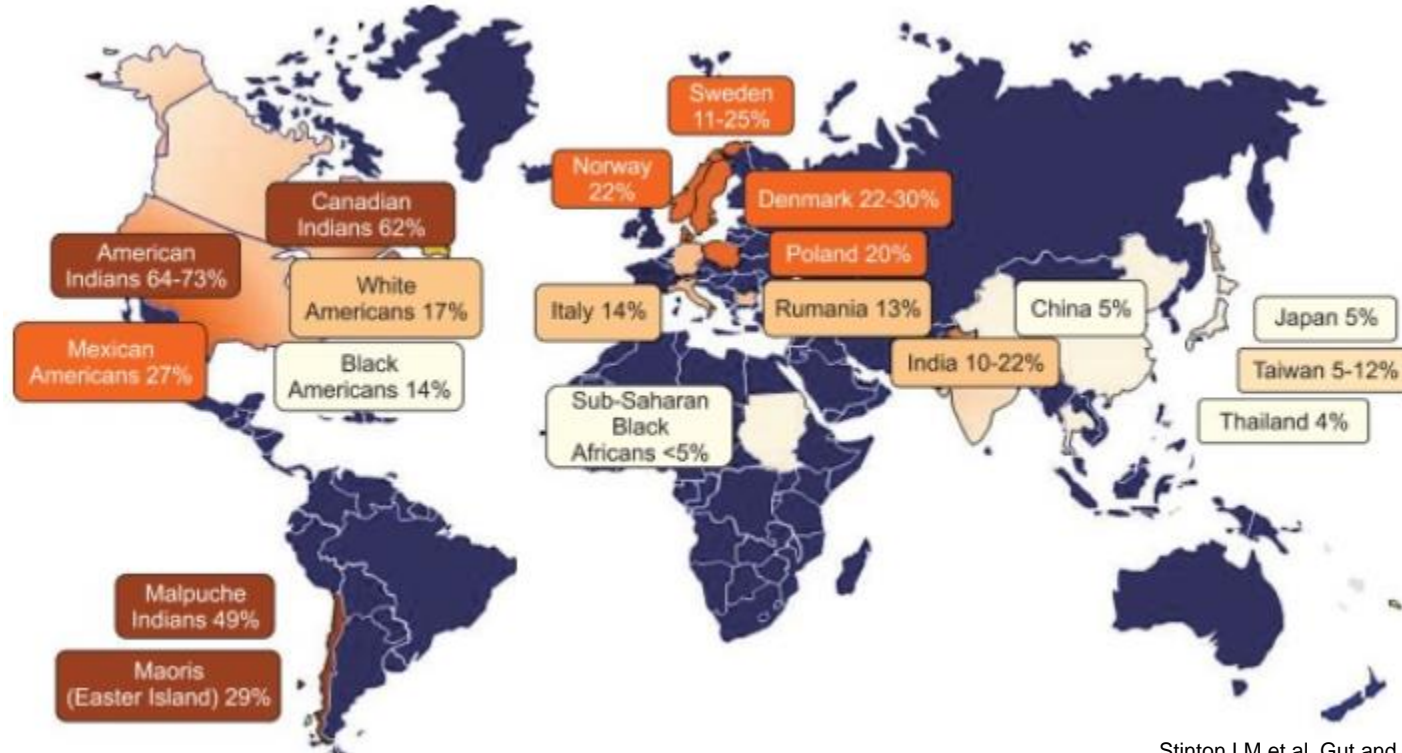
Epidemiology

- Prevalence 10-15% of popul
- ♀ > ♂ (2 fold)
- More often with age
- Increasing prevalence
 - DE: 6.0% in 1998 vs. 21.1



Malzer W, Dig Dis Sci. 1998
 Volzke H, Digestion. 2005
 Bateson MC, PMJ, Nov 2000

Prevalence (Ultrasound in female patients)



Stinton LM et al, Gut and Liver, Apr 2012

Epidemiology

- 2nd most common GI-admission after GI-bleeding in 2014
 - ~ 350'000 admissions in US per year
- ~16.3 billion US \$
- Comparison: NAFLD 32 billion US \$



Peery et al, Gastroenterology, 2018 Oct

Clinical manifestation

Clinical manifestation

- Mostly asymptomatic, i.e. incidental finding (ca. 75%)

Natural course:

- >75% remain asymptomatic
- 2-3% annual risk of symptomatic disease
- 10% mild and 10% severe symptoms
- Complication rate 2.9% (fever, jaundice, pancreatitis) Ransohoff et al, Ann Int Med, 1983
Festi et al, J Gastroenterol Hepatol, 2010
- After first episode risk of recurrence ~70%, 4% emergency CHE

Thistle JL et al, Ann Intern Med 1984

Clinical manifestation

- Classic biliary colic
 - Gallbladder contraction forcing stone in cystic duct or through bile ducts
 - RUQ or epigastric pain, dull, radiating to back/right shoulder, VAS >5
 - 30min – 6h (longer pointing towards cholecystitis)
 - Often postprandial (~1h, mostly fatty food), evening/nocturnal
 - Associated symptoms (nausea, vomiting, diaphoresis)

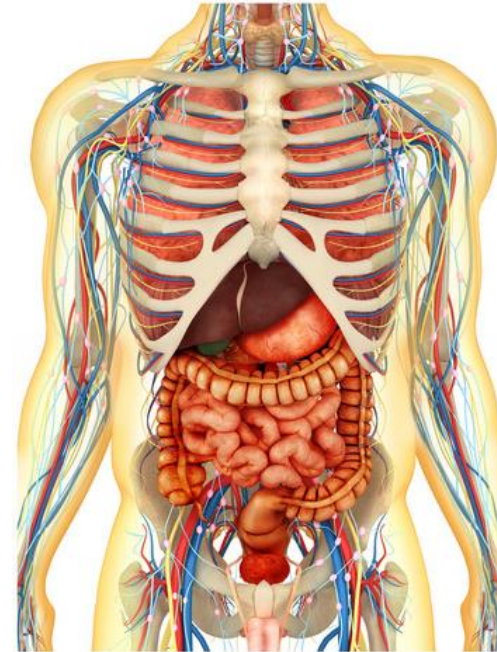


Clinical manifestation

- Atypical (rather DDs)
 - Belching
 - Fullness after meals/early satiety
 - Regurgitation
 - Abdominal distension/bloating
 - Epigastric or retrosternal burning
 - Nausea or vomiting alone
 - Chest pain, nonspecific abdominal pain

Differential diagnosis

- GERD
- Gastritis
- Peptic ulcer
- Functional (dyspepsia, biliary pain, IBS)
- Hepatitis
- Pancreatitis
- Pyelonephritis
- CAD



General diagnostics

Lab works

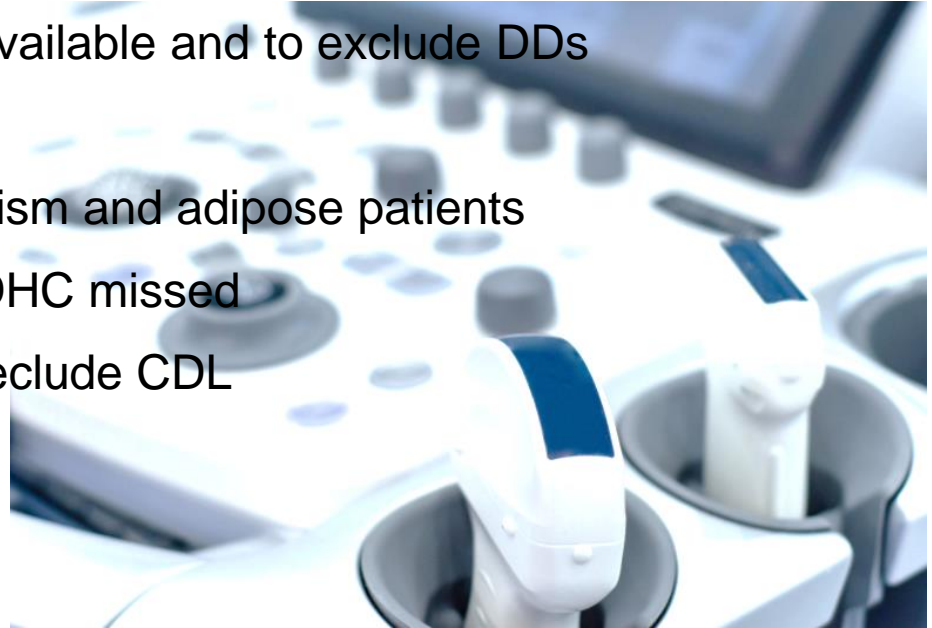


Should be normal in uncomplicated disease!

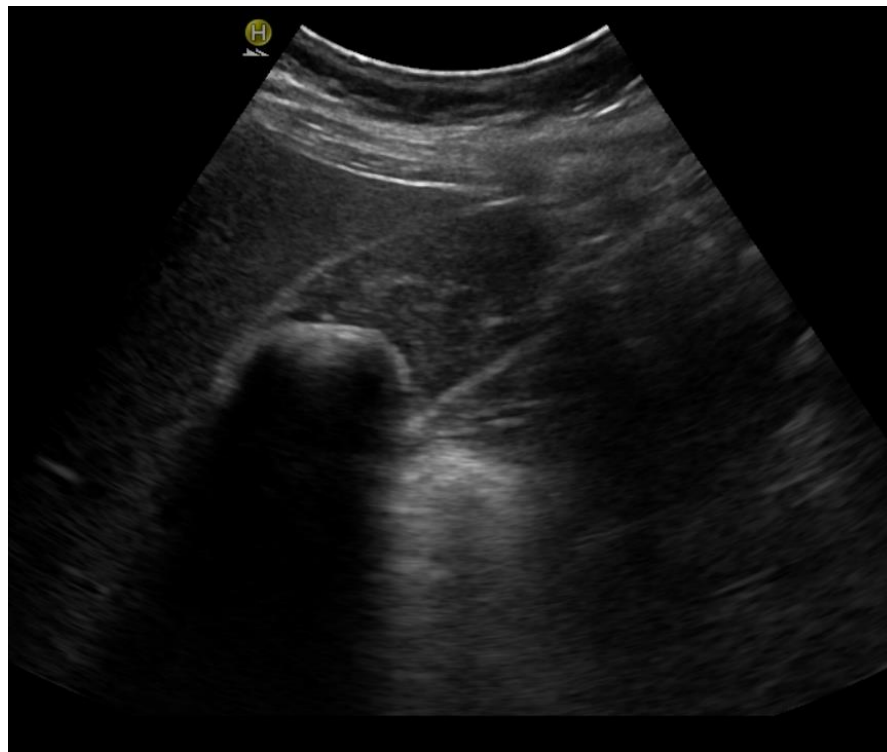
Cholestatic	- > CDL
Lc/CRP	- > infectious
Amylase/lipase	- > pancreatitis

Ultrasound

- Usually first line bc cheap, readily available and to exclude DDs
 - But observer dependent
 - Decrease visualization in meteorism and adipose patients
 - Stones in cystic duct and distal DHC missed
 - Normal examination does not preclude CDL
- Sensitivity 95-97%, specificity 97%



Ultrasound

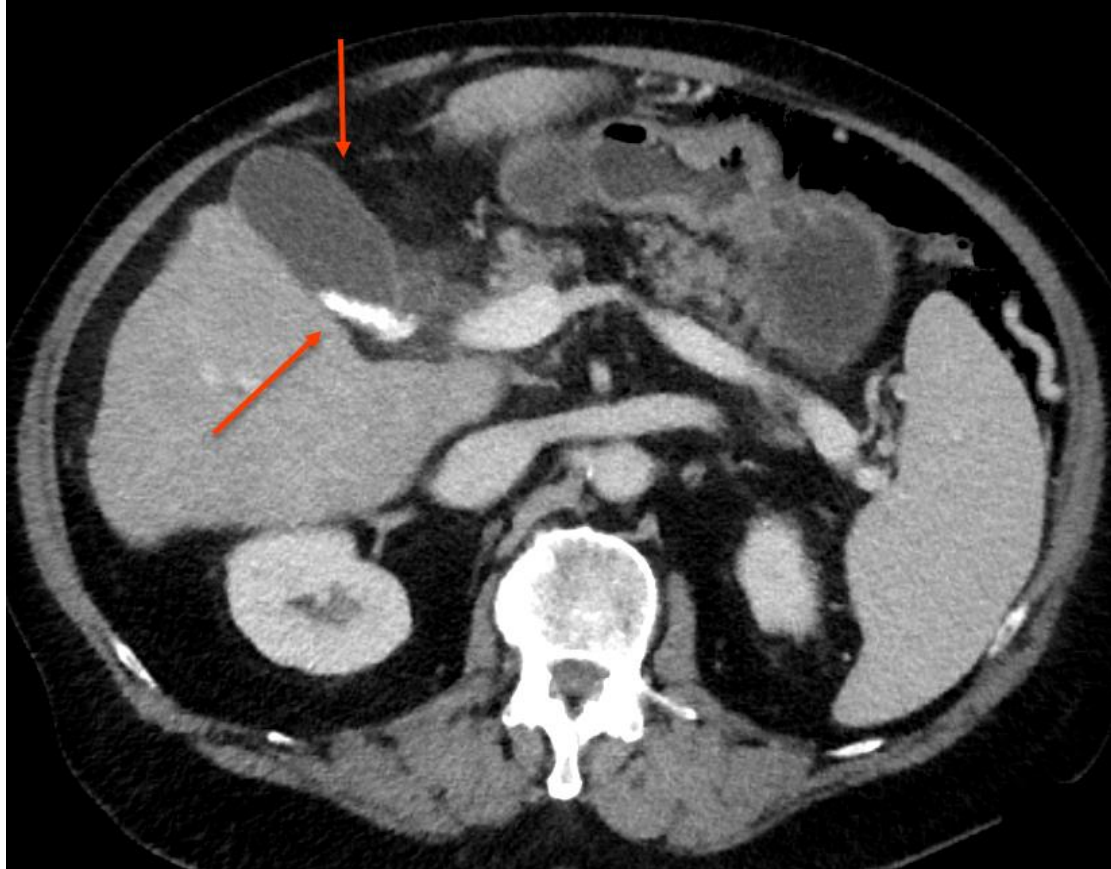


CT

- Non invasive, readily available, reproducible
- Exclusion of differential diagnosis and complications
- Radiation exposure of 10mSv without and 20mSv with contrast
 - i.e. 7y natural background radiation
- Bad yield!
 - Sensitivity 39%, specificity 93%



CT



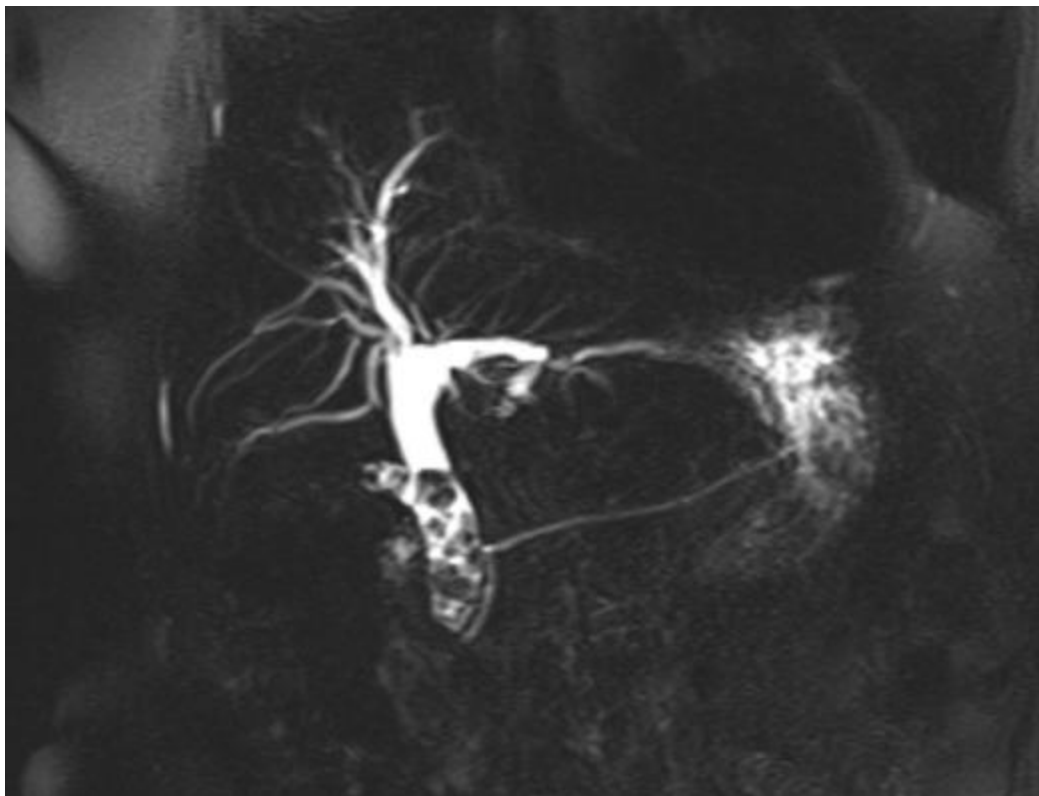
MRCP

- Visualization of intrahepatic bile ducts and pancreas
- No radiation
- Not readily available
- Rather expensive
- Can miss small stones (<5mm)
 - Sensitivity 93%, Specificity 96%



Giljaca V, Cochrane Database, 2015 Feb
Meeralam Y, Gastrointest Endosc, 2017 Dec

MRCP



EUS

- Best imaging for DHC, most of all small stones (<5mm)
 - Sensitivity 93-97%, Specificity 90-93%
 - If normal US/CT sensitivity of 94-98% to detect stones
- Exclusion of differentials (stomach, pancreas)
- Combination with therapy (ERCP)
- Invasive
- Operateur dependent



Kohut M, Endoscopy, 2002 Apr
Tae JJ, Gut Liver, 2011 Mar
Meeralam Y, Gastrointest Endosc, 2017 Dec

EUS



ERCP

- Rarely used as sole diagnostic tool, mostly therapeutic
 - Bile microscopy
 - Only visualization of bile ducts and to a lesser degree gallbladder
- Invasive, complication rate
- Radiation

ERCP



Treatment of gallstones

General recommendation

- Asymptomatic -> no treatment needed
- Symptomatic -> offer cholecystectomy

BUT: porcelain gallbladder, stones >3cm, stones + polyps ≥ 1 cm
prophylactic in oncological (esophagus/stomach) or extended intestinal
resections, bariatrics

Conservative

- UDCA (10mg/kgKG) moderately efficient
 - 60% stone free in 6 months

May GR e al, Aliment Pharmacol Ther 1993; 7: 139–148



- Only in bariatrics with rapid weight loss
 - But often prophylactic CHE with bariatric surgery
- ESWL inefficient with high recurrence (up to 80% after 10y)

Operative

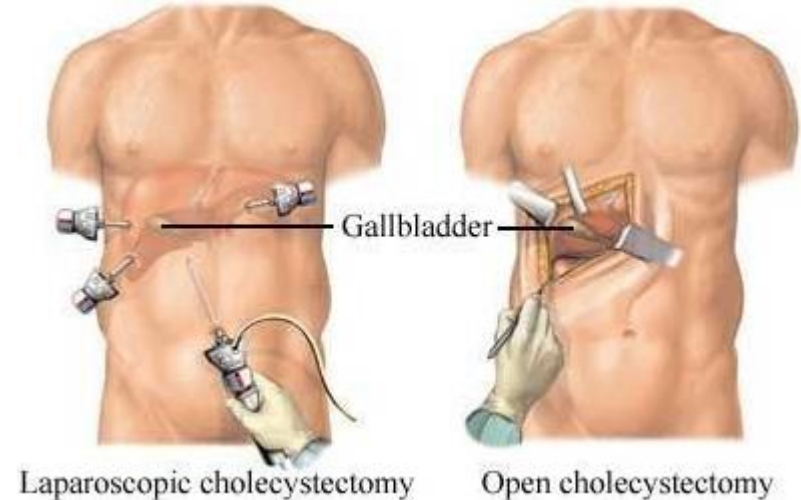
- Laparoscopic over open CHE

Shorter

hospital stay
convalescence

No difference

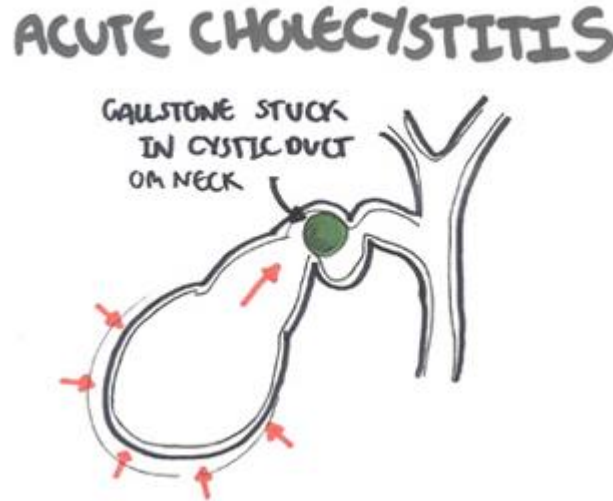
mortality
complication
operation time



Complications

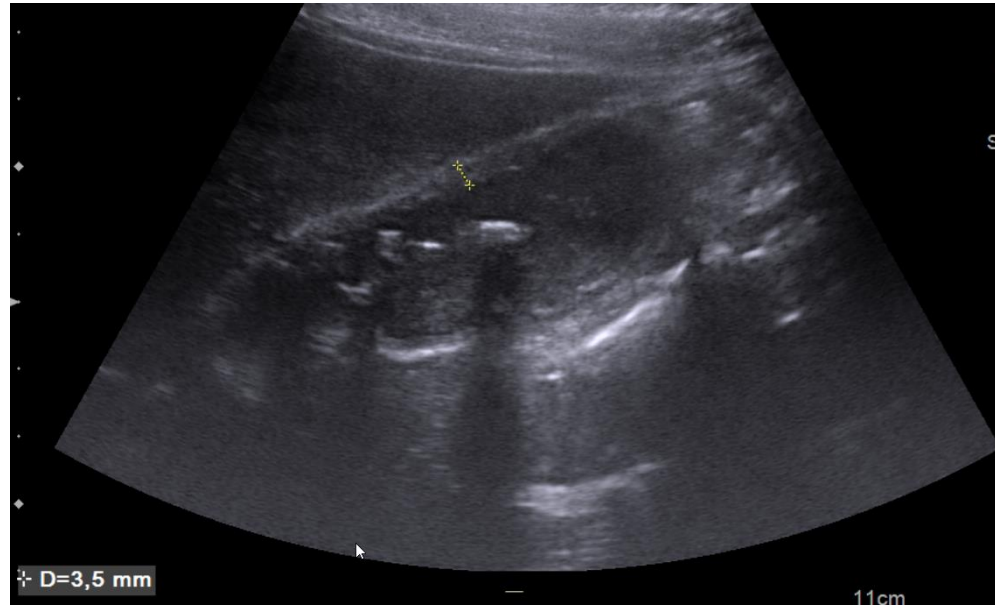
Acute Cholecystitis

- Stone occlusion -> GB distension/stasis -> superinfection (mostly E.coli)
- RUQ pain
- Fever
- Often elevated LFT



Acute Cholecystitis

- Diagnosis mostly with ultrasound
sens/spec ~80%



Acute Cholecystitis

- May lead to empyema or chronic cholecystitis/porcelain gallbladder
- Treatment:
 - Sepsis: Urgent Antibiotics + cholecystectomy within 72h
 - DGVS <24h (ACDC study), NICE <1 week
 - Uncomplicated cholecystitis: cholecystectomy <72h, antibiotics no clear data
 - Chronic/porcelain: Elective cholecystectomy

Timing of cholecystectomy

- Early CHE associated with
 - Less bile duct injuries
 - Shorter hospital stay
 - Fewer re-admissions and ED visits

Altieri MS et al, Surg Endo, Aug 2019

Acalculous cholecystitis

Mostly patients in ICU/critically ill after major trauma/surgery, sepsis

Dysfunction and hypokinesis of gallbladder
(e.g. lack of stimulation)

Concentration of bile salts increasing
pressure within the organ

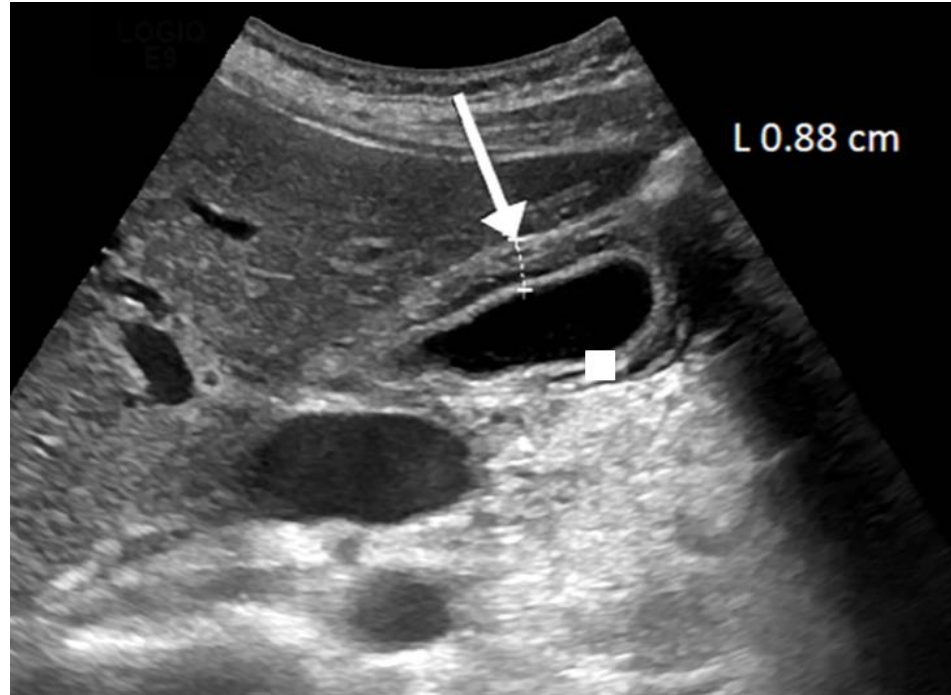


Ischemia

seeding and growth of enteric
pathogens

(*E. coli*, *Klebsiella* and others)

Acalculous cholecystitis

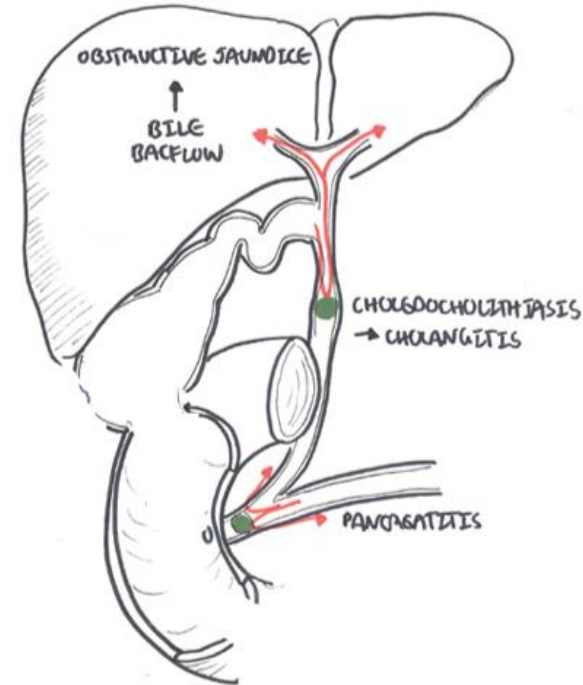


Acalculous cholecystitis

- Treatment of choice is antibiotics and cholecystectomy
- If unstable drainage (percutaneous, EUS-guided) may be considered
- Mortality remains high up to 50%

Choledocholithiasis

- Passage of stones in bile duct
- Up to 20% of all gallstone patients
- 21-34% of CBD stones migrate spontaneously

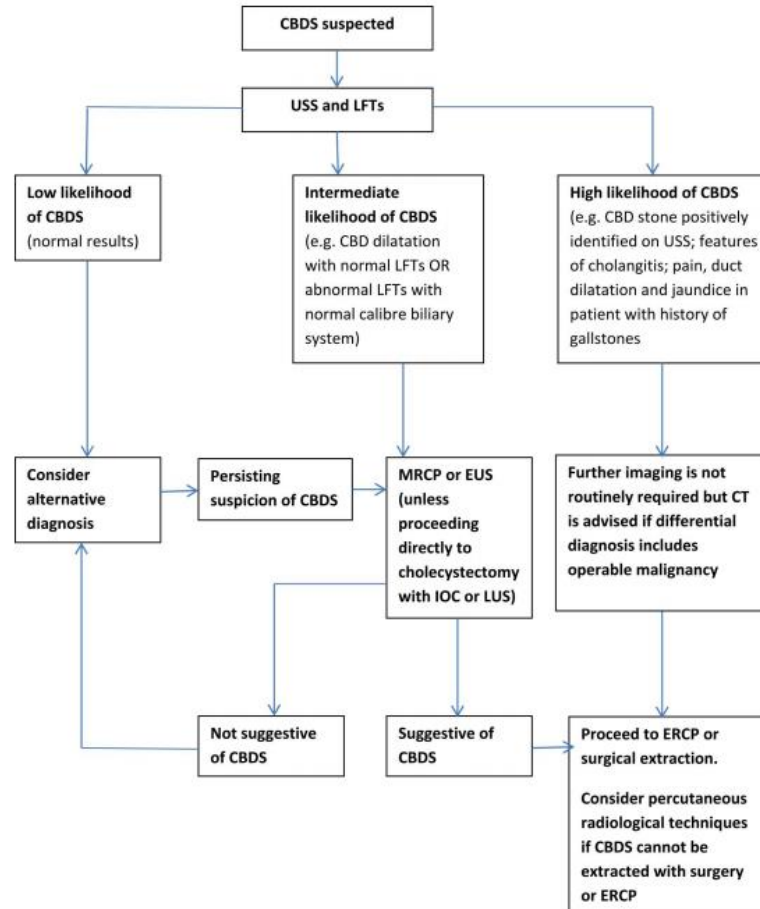


Choledocholithiasis

- Symptoms similar to biliary colic
 - Can be intermittent
 - may cause biliary pancreatitis or cholangitis
- In cholangitis „Charcots triad“: Fever, pain, jaundice
- or „Reynolds pentad“: + sepsis and confusion

Choledocholithiasis

- Lab values normal to cholestatic
 - Possibly elevated lipase/amylase or inflammatory markers
- Diagnosis with ultrasound or EUS



Choledocholithiasis



Choledocholithiasis



Cholangitis

- Grading of severity according to Tokyo Guidelines 2018

Mild	Moderate	Severe
<ul style="list-style-type: none">No criteria of moderate/severe cholangitis.	<p>Any of the following:</p> <ul style="list-style-type: none">White blood cell count $> 12\,000$ or $< 4000/\text{mm}^3$,Fever $\geq 39^\circ\text{C}$,Age ≥ 75 years,Total bilirubin $\geq 5\text{ mg/dL}$,Hypoalbuminemia	<p>Dysfunction of any one of the following (see reference for specific criteria):</p> <ul style="list-style-type: none">CardiovascularNeurologicalRespiratoryRenalHepatic, orHematological system

Timing of ERCP?

- Severe/septic cholangitis: Urgent biliary drainage (<12h)
- Non-septic cholangitis/severe pancreatitis: Drainage <72h
- If bile duct not cleared, biliary stenting and possibly EHL

ERCP complications

- Post-ERC-Pa
- But up to
- Bleeding
- Perforation
- Cholecystitis
- Mortality

Type	Description	Frequen- cy [16]
I	Duodenal wall perforation (by the endoscope)	18 %
II	Periampullary perforation (by sphincteroto- my/precut)	58 %
III	Biliary or pancreatic duct perforation (by intraductal instrumentation)	13 %
IV	Retroperitoneal gas alone	11 %

Andriulli A, Am J Gastroenterol, 2007
Kochar B, Gastrointest Endosc, 2015

ERCP

- Risk factors for post-ERCP pancreatitis?
 - Repeat manipulation of papillae
 - Cannulation/contrasting of PG
 - Pre-cut
 - Young and female
 - SOD
 - Non dilated bile ducts
 - St. n. (post ERCP) pancreatitis

ERCP

- Prophylaxis?
 - 100mg Rectal indomethacin/diclofenac
 - If contraindication Ringer's 3ml/kgKG/h
 - Prophylactic stenting of PG after contrast/guidewire
 - 5 Fr/6 cm

Timing of cholecystectomy?

- CDL/Cholangitis: within 72h after drainage

Reinders JS et al. Gastroenterol 2010

- Pancreatitis: Mild interstitial → Same hospitalisation (<72h)
Risk of recurrence 17 vs. 5%

Da Costa DW, PONCHO trial, Lancet 2015

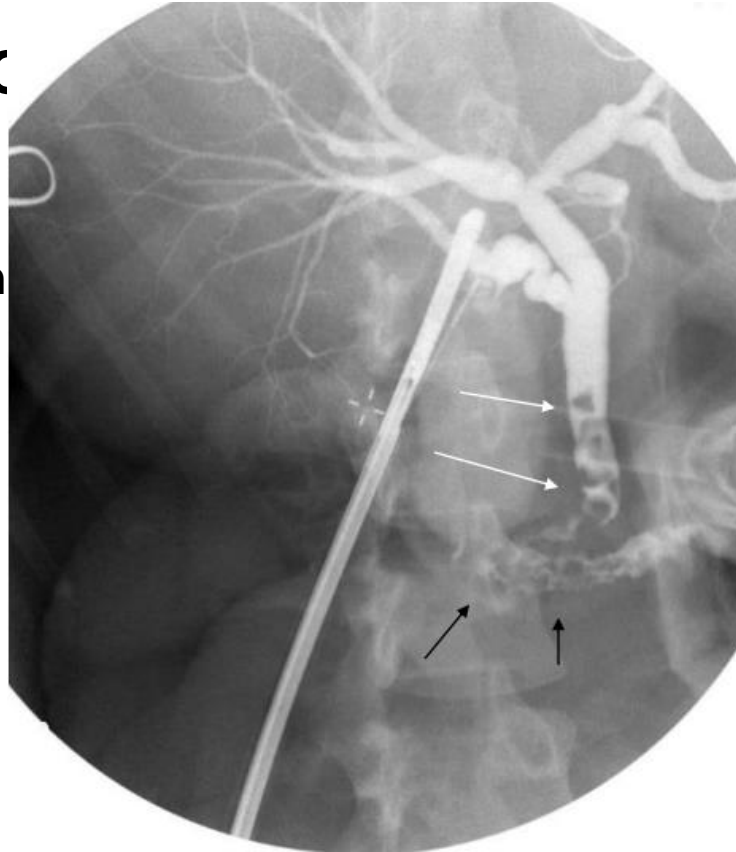
Severe necrotizing → 6 weeks delay

Splitting = pre-/post-c



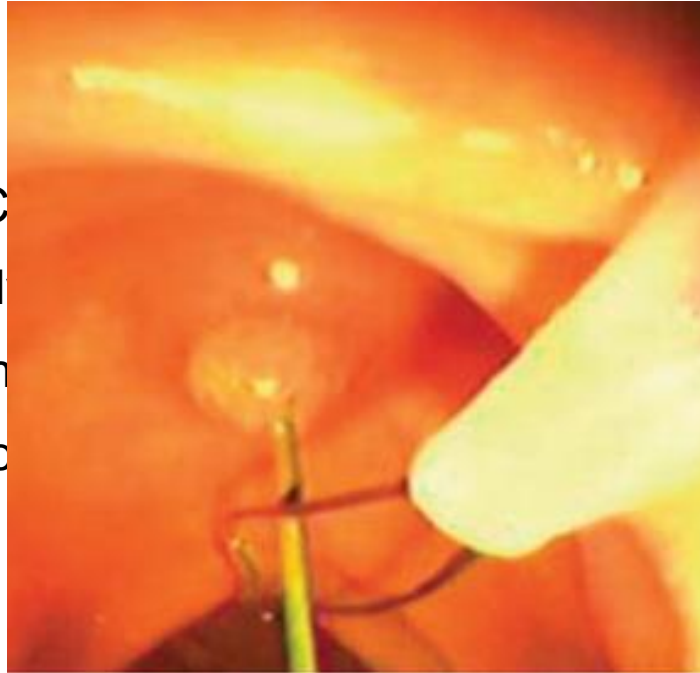
Intraoperative ERC

- Intraoperative cholangiography



Intraoperative ERCP

- Rendez-vous ERCP
 - Laparoscopically
 - Pulling wire from
 - Direct access to



and duodenum

Intraoperativ ERC

Pros

- Single intervention
- Highest success rate
- Lowest morbidity
- Shortest hospital stay
- No manipulation papilla/PG
 - **Pancreatitis risk 0.8%**

Cons

- Logistics/infrastructure
- Patient position

Limitations

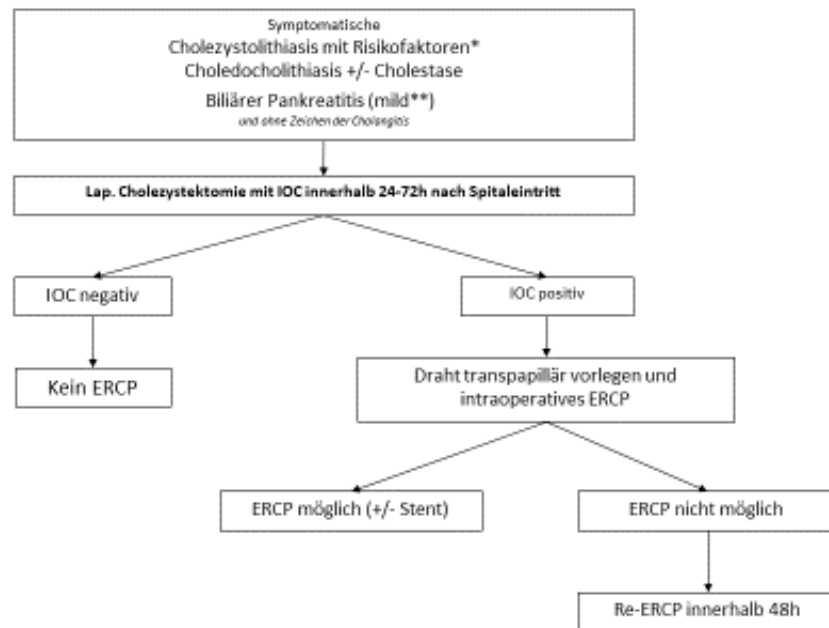
- Anesthesiological risk
- Stone burden/size/location

Gurusamy K et al. Br J Surg 2011
Mallick R, Gastrointest Endosc, 2016
Ricci C, JAMA surgery 2018

What now?

- Cholecystectomy with intraoperative ERC as treatment of choice
 - Especially with high complications/pancreatitis risk
- Pre-operative ERCP if logistically not possible
 - Aim for CHE <72h
- Try to avoid post-CHE ERCP

What now?



* Sonographisch erweiterte Gallenwege ($>7\text{mm}$) oder laborchemisch Cholestase

** Erhöhte Pankreasenzyme und CRP $<100\text{mg/L}$ ohne Organversagen

Intrahepatic stones

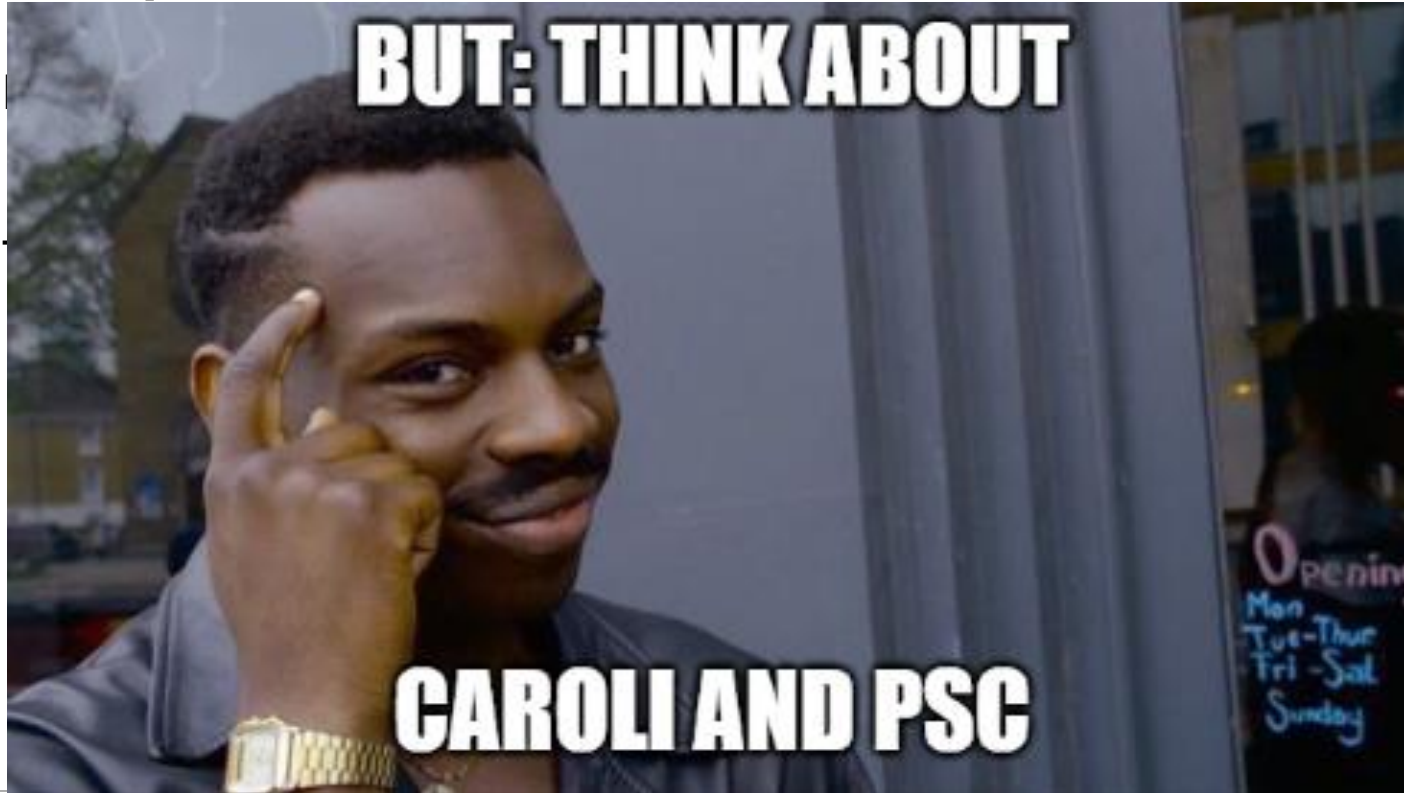
- Mostly in asia (infectious, brown pigment stones)
- Mostly asymptomatic
 - 11.5 % develop symptoms (112 patients, mean follow up 10y)
 - Median intervall to symptoms 3.4y
 - Pain, cholangitis, atrophy, strictures, abscess or CCC



Kusano T, Journal of Clinical Gastroenterology, 2001

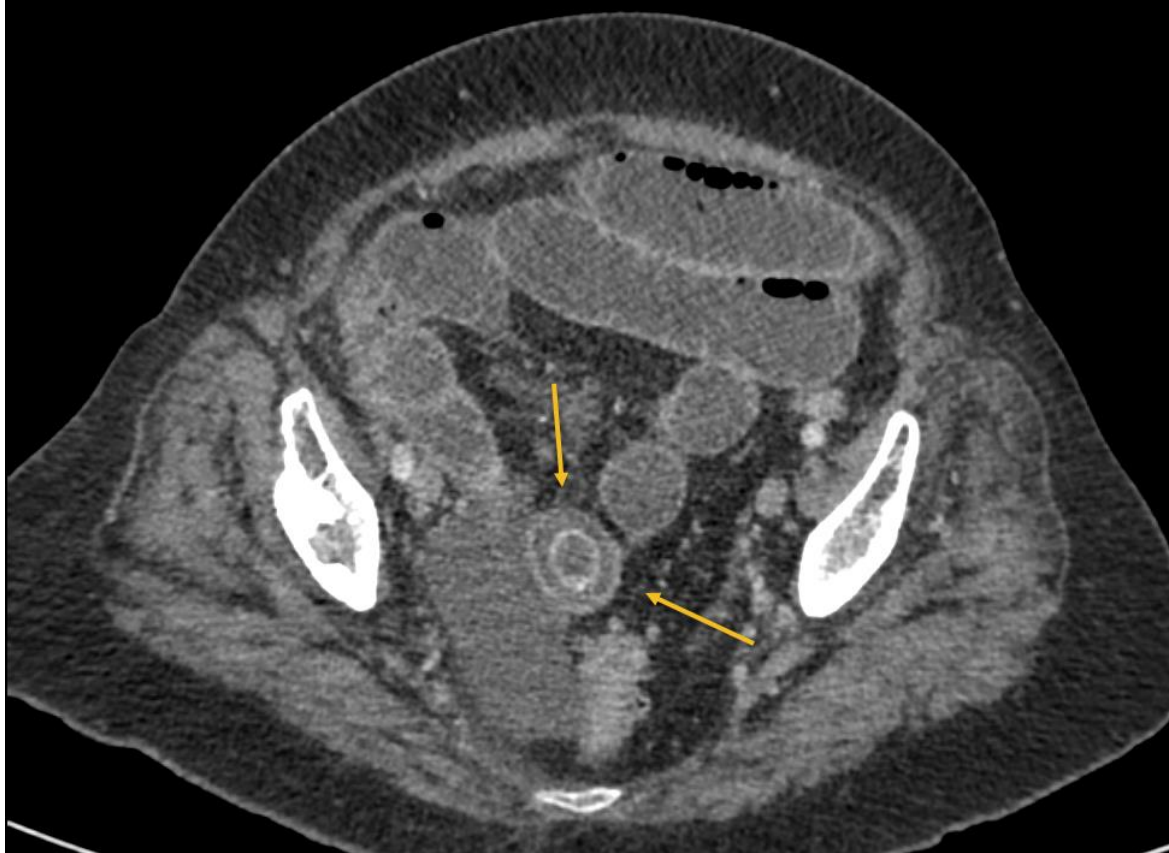
Intrahepatic stones

-
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Cholecystenteric fistula with Gallstone ileus (Bouveret-Syndrom)

- Perforation of GB-stone in Duodenum
 - Obstruction of gastric outlet/intestine
 - Pain, nausea, vomiting, fever, jaundice
- Rigler triad
- Diagnosis with CT/US (aerobilia, ectopic gallstone, small intestine ileus)
 - Treatment: Endoscopy w/ EHL, surgery



TAKE HOME MESSAGES

- Frequent problem in western population ($\pm 20\%$)
- 6 F's, but be suspicious if no clear risk factors
- 75% are asymptomatic and need no treatment, if symptomatic CHE
- If suspicion of CDL do EUS (MRCP)
- Antibiotics and urgent biliary decompression in septic cholangitis
- Rendez-vous ERCP modality of choice

Vielen Dank für die Aufmerksamkeit.

