Swiss Essentials in Gastroenterology

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8th edition

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Foreword

Eight years since the first edition of our handbook «Swiss Essentials in Gastroenterology and Hepatology» came out, we are pleased to present our readers with an updated and extended 8th edition.

During one advisory board meeting in 2019, we were able to gain more input from gastroenterologists to further improve on the content of the original handbook. What was also apparent from your feedback during the last years was the reassuring comments of the booklet`s usefulness in clinical routine; this reinforced our mindset to continue with this valuable project. We are very grateful to all contributing authors for their invaluable critique and efforts to help us in creating this 8th edition.
This current publication cannot and should not replace any specialty textbook. In addition, no responsibility can be taken for its completeness. The origin source data are referenced in the current tables and figures.
Any additional and critical feedback is again very welcome and should be adressed to Stephan Vavricka (stephan.vavricka@usz.ch). We will try our best to incorporate your comments into a planned updated version.

In the name of all authors

S. Vavricka
Zurich, Dezember 2019

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This book underwent critical language corrections:
we thank Melissa Wilhelmi, PhD for her invaluable feedback and input.

Sedation in endoscopy

Sedation in endoscopy

1. In Europe >80% of EGD and >85% of colonoscopies are done under intravenous sedation.
2. The preferred sedative is propofol (80%) most often used as monotherapy.
3. In 73% propofol is given as NAAPS (nonanesthesiologist-administered propofol sedation) [Heuss LT et al. Endoscopy 2012;44:504-511.]

Requirements for NAAPS

- Correct patient selection
- Willingness to deal with an individually titrated sedation
- Ability to take care of the patient even in a state of deep sedation or unintentionally reached anaesthesia
- Specific training in sedation technique, monitoring and basic life support.

Equipment

- Bag valve mask apparent and within reach
- Nasopharyngeal tube
- Oxygen
- Pulse oximetry with audible sound
- Suction device
- One endoscopist and one assistant mandatory in room. A third person immediately available from a room nearby.

[Consensus Paper SGGSSG and SGAR, 2014. http://www.sggssg.ch]

Rules for safe NAAPS
(especially for routine endoscopies in private practice)

1. assessing the patient before sedation (ASA class, comorbidities, Malampatti score)
2. pre- and permanent oxygenation with 2 l 0_2 using a nasal oxygen catheter
3. using a stable intravenous access
4. using propofol 1% as monotherapy with 5 ml syringes

5. titrating according the „2-20-20-rule“ (priming: wait 2 minutes after the first dose of 20 mg propofol. Afterwards never give a single bolus of more than 20 mg and never give a subsequent bolus faster than after 20 seconds.)
6. titrating according the patient’s reaction to a stage of moderate and only short-term deep sedation

[script on non-anaesthesiologist administered propofol sedation, SGGSSG]

Exclusion criteria for NAAPS:

1. allergy against propofol (questionable: egg or soy)
2. lack of an informed consent
3. ASA class >3 with clinical relevant cardial or pulmonal limitation

a. 2 or more active diseases (e.g. COPD and heart failure)
b. heart failure NYHA >2, instable angina, cor pulmonale
c. pneumopathy with impaired ventilation, acute pulmonal failure

Patients at risk
(a monitored anesthesia care should be considered):

- patients at relevant risk for aspiration (morbid adipositas BMI >35; functional or organic stenosis in upper GI tract)
- patients with „difficult airways“ and potentially impaired mask ventilation (morbid obesity BMI >35; severe obstructive sleep apnea syndrome (OSAS); anatomic abnormalities e.g. impaired opening of the mouth, impaired reclination, oropharyngeal tumors)
- patients with instable neurological or neuromuscular diseases (e.g. cerebral vascular insult (CVI), ALS, seizures)

Complications:
even in correct selected patients apneas and desaturations occur in a rate of:

- ERCP ~ 1: 400
- Gastroscopy ~ 1: 500
- Colonoscopy ~ 1: 2000

Endoscopists and their teams have to be aware to act with a jaw thrust maneuver (Esmarch) and a bag valve ventilation until the respiration has recovered.

[Consensus Paper SGGSSG and SGAR, 2014. http://www.sggssg.ch]

ASA physical status classification system classes according to the American Society of Anesthesiologists	
ASA 1	normal healthy patient
ASA 2	patient with mild systemic disease
ASA 3	patient with severe systemic disease
ASA 4	patient with severe systemic disease that is a constant threat to life
ASA 5	moribund patient, not expected to survive without the operation

Based on the American Society of Anaesthesiologists.

Continuum of sedation

	Minimal Sedation (Anxiolysis)	Moderate Sedation/Analgesia (Conscious Sedation)
Responsiveness	Normal response to verbal stimulation	Purposeful* response to verbal or tactile stimulation
Airway	Unaffected	No intervention required
Spontaneous ventilation	Unaffected	Adequate
Cardiovascular function	Unaffected	Usually maintained

* Reflex withdrawal from a painful stimulus is not considered a purposeful response.

Minimal Sedation (Anxiolysis): a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate Sedation/Analgesia (Conscious Sedation): a drug-induced depression of consciousness during which patients respond purposefully* to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Deep Sedation/Analgesia: a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully* following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

Deep Sedation/Analgesia	**General Anesthesia**
Purposeful* response after repeated or painful stimulation	Unarousable, even with painful stimulus
Intervention may be required	Intervention often required
May be inadequate	Frequently inadequate
Usually maintained	May be impaired

General Anesthesia: a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Hence, practitioners intending to produce a given level of sedation should be able to rescue patients whose level of sedation becomes deeper than initially intended. Individuals administering Moderate Sedation/Analgesia (Conscious Sedation) should be able to rescue patients who enter a state of Deep Sedation/Analgesia, while those administering Deep Sedation/Analgesia should be able to rescue patients who enter a state of general anesthesia.

[Practice guidelines. Anesthesiology 2002;96:1004–1017]

Gastrointestinal Endoscopy **Checklist for home discharge after digestive endoscopy:**
Stable vital signs for at least 1 hour
Alert and oriented to time, place, and person (infants and patients whose mental status was initially abnormal should have returned to their baseline status)
No excessive pain, bleeding, or nausea
Ability to dress and walk with assistance
Discharged home with a responsible adult who will remain with the patient overnight to report any post-procedure complications
Written and verbal instructions outlining diet, activity, medications, follow-up appointments, and a phone number to be called in case of emergency
A contact person and circumstances that warrant seeking the assistance of a health care professional clearly outlined
Tolerating oral fluids not mandatory, unless specified by physician (i.e. patient is diabetic, frail, and/or elderly; not able to tolerate an extended period of NPO status)

[Dumonceau JM et al.: Endoscopy 2010 42(11): 960–974]

Quality Indicators for Screening Colonoscopy:

1. Adenoma detection rate >15% in females and > 25% in male patients (NEJM)
2. Adequate bowel cleansing: at least 90% of screening examinations should be rated as having “adequate” or better (ESGE)
3. Minimum experience for screening colonoscopists: minimum lifetime experience of 1000 examinations and a minimum annual number of 150 screening colonoscopies (UK NHS Bowel Cancer Screening, GIE)
4. Minimum standard of 90% cecal intubation rate and minimal withdrawal time of 6 minutes in at least 90% of purely diagnostic examinations (ESGE)
5. At least 90% of resected polyps are retrieved for histological analysis (ESGE)

[Kaminski MF et al., N Engl J Med 2010;362:1795-803. Corley DA et al., N Engl J Med 2014;370:1298-306. Rembacken B et al., Endoscopy 2012; 44: 957–968 (ESGE position statement) Lee SH et al., Gastrointest Endosc. 2008; 67(4):683-9]

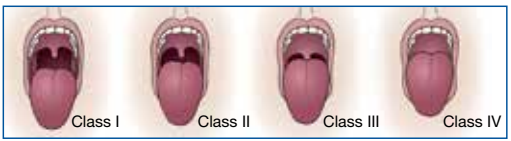
Gastrointestinal Endoscopy
Risks of complications:

	Event	Frequency
EGD	Bleeding	0% in diagnostic EGD
		<0.1% after taking biopsies
	Perforation	0.1–1% after dilatation of benign strictures
		1–5% after dilatation of malignant strictures
		1–3% after pneumatic dilatation of achalasia
Colono-scopy	Bleeding	0.2% in total
		0.3–10% after intervention
	Perforation	0.1% in diagnostic colonoscopy
		0.1–0.3% in therapeutic colonoscopy
	Morbidity	0.2% in diagnostic colonoscopy
		0.1–0.3% in therapeutic colonoscopy
	Mortality	0–0.006% in total
ERCP	Pancreatitis	1.3–6.7% post-ERCP
	Mortality	0.5% (mainly due to pancreatitis)
	Bleeding	after sphincterotomy 1.3% (mostly mild)
PEG	Leakage	up to 78%
	Peristomal infection	up to 32%
	Early mortality	8–15% mortality within 30 days of PEG insertion
	Post-PEG pneumoperitoneum	30%, but usually w/o clinical relevance
	Aspiration	0.3–1%
	Bleeding	0–2.5%
	Buried bumper syndrome	0.3–2.4%
	Peritonitis	0.5–1.3%
	Accidental removal of the catheter	1.6–4.4%
	Colo-gastrocutaneus fistula or other fistulous tracts	0.3–6.7%
	Trans- or intrahepatic PEG placement	
	Gastric volvulus	
	Tumor seeding and gastric outlet obstruction	

Cardiopulmonary Complications

Cardio-pulmonary complications account for about 50 % of the potentially serious morbidity and approximately 50 % of all the procedure-related deaths associated with GI Endoscopy.
Aspiration with possible subsequent pneumonia, myocardial ischaemia, TIA or stroke are well-known complications of GI endoscopy.
These complications may occur up to 30 days after the procedure.

Evaluation before gastroscopy: the Mallampati classification



Modified Mallampati classification

Class 0: Ability to see any part of the epiglottis upon mouth opening and tongue protrusion

Class I: Soft palate, fauces, uvula, pillars visible

Class II: Soft palate, fauces, uvula visible

Class III: Soft palate, base of uvula visible

Class IV: Soft palate not visible at all

The assessment is performed with the patient sitting up straight, mouth open and tongue maximally protruded, without speaking or saying «ahh».

Classes I and II are associated with relatively easy intubation, classes III and IV are associated with increased difficulty.

Gastrointestinal biopsy

Upper gastrointestinal tract

Eosinophilic esophagitis:
4x distal esophagus and 4x proximal esophagus in different biopsy pots, additional biopsies from lesions such as white exsudate

Barrett's Esophagus:
Four-quadrant biopsies at 2 cm intervals (in different biopsy pots) in patient without dysplasia and 1 cm intervals in patients with prior dysplasia, additional biopsies from suspicious lesions

Helicobacter pylori:
2x antrum, 2x corpus, 1x large curvature, 1x small curvature (in total 6 biopsies)

MALT lymphoma:
10x jumbo biopsy from suspicious areal (in formalin for histological analysis and in NaCl for immunohistochemical analysis). Plus 4x biopsy from antrum, 4x corpus and 2x fundus in different biopsy pots

Vitamin B12 deficiency:
2x antrum, 2x corpus, 2x fundus in different biopsy pots

Celiac disease:
At least 6x duodenum, of which 2x from the duodenal bulb (on a gluten-containing diet)

Whipple's disease:
At least 5x duodenum (periodic acid-Schiff (PAS) reagent stain plus PCR and/or immunohistochemical analysis)

Lower gastrointestinal tract

Microscopic colitis:
≥5 biopsies, at least 1 biopsy per colon segment

IBD Surveillance:
Four-quadrant biopsies every 10 cm in different pots for different colon segments. In addition suspicious findings in different pots. Consider chromoendoscopy in patients with proven ulcerative colitis in clinical remission after at least eight years duration (full length staining of the colon with 0.4% indigo carmine and perform targeted biopsies)

Amyloidosis of GI tract:
Upper endoscopy 4x esophagus, 4x gastric, 4x duodenum (sensitivity duodenum > gastric > esophagus). Lower endoscopy 4x jumbo biopsies from rectum (congo red stain)

[References for GI biopsies: EoE, Barret, Helicobacter, Celiac, microscop. Colitis: Swiss essentials MALT: Mittwochsfortbildung (D. Flieger, Praxis 2006; 95: 1163–1168) Vitamin B12: Endoscopic-Bioptic Diagnostics, Surveillance of and Therapy for Gastrointestinal Diseases According to Guidelines; Warich-Eitel et al Z Gastroenterol.- 2010; 48 (3):414-9 Whipple: Mittwochsfortbildung (Schneider T et al Lancet Infect. Disease 2008; 8) IBD: Mixed out of "Endoscopic-Bioptic Diagnostics, Surveillance of and Therapy for Gastrointestinal Diseases According to Guidelines; Warich-Eitel et al Z Gastroenterol.- 2010; 48 (3):414-9" and Swiss Essentials Amyloidosis: USZ Richtlinien]

Percutaneous endoscopic gastrostomy (PEG)

Absolute contraindications:
- Life expectancy <4 weeks
- Active Coagulopathy
- Lack of transillumination
- Portal hypertension, gastric varices

Relative contraindications:
- Pharyngeal or esophageal obstruction
- Esophageal malignancy (no PEG if esophagectomy is planned, discuss with surgeon)
- Ascites
- Peritoneal carcinomatosis, neoplastic or inflammatory disease of the abdominal wall
- Ventriculoperitoneal shunt
- Chronic ambulatory peritoneal dialysis
- Prior gastrointestinal surgery
- Any other general contraindication to endoscopy as morbid obesity

PEG tube placement technics:
- Pull-PEG
- Push-PEG (for example in patients with neck cancer)
- Others like radiologically/laparoscopically inserted PEG

PEG size (Fresenius as an example):
- PEG Fresenius 9, 15, 20 Charrière/French (1 Charrière = 1 French = 1/3 mm).
- Jejunal prolongation: 9 French for 15 French PEG
- Button Fresenius: 15 Charrière/French, length 1.1 – 4.5 cm

Practical guidance:
- 30 minutes before intervention give a single shot of antibiotic as Amoxicillin and Clavulanic acid 2.2 g i.v. or Rocephin 2 g i.v. or Cefazolin 2 g or Cefuroxim 1.5 g. In case of Penicillin allergy late type reaction consider Cephalosporin; in acute type reaction consider Vancomycin or Clindamycin. It may not be necessary in patients already treated with antibiotic because of other reasons.
- Use of PEG: start feeding after 4 hours (organize dietary advice).
- Never remove PEG before 3–4 weeks after insertion.
- Longtime care of Pull-PEG: when changing the bandage 2–3/week put the tube 1–2 cm in the gastric and turn 360° to protect from "buried bumper".
- Care of Push-PEG: gastropexy suture removal after 3 weeks. Change to a Button-PEG after 3 weeks (cosmetic). Change the Button-PEG every (3–) 6 month. Control balloon weekly.
- Care of button PEG tube / GastroTube: change balloon fluid (Aqua dest) every 1–2 weeks, change button every 6 months. Give the patient a disposable urinary catheter for woman in case of accidental removal of PEG tube.
- In case of blocked tube: flush with warm water, vitamin C, Coca Cola (prevention from blocking: flush tube before and after using the tube).

After intentional removal of PEG: Start with fluid after 4 hours. Normal nutrition when the bandage stays dry (gastrocutaneous fistula is closed). No bath for 48 hours.

Gastric emptying before emergency gastroscopy:

- Consider 250 mg Erythromycin mixed in 50 ml NaCl 0.9%
- Short infusion over 15 minutes
- 20 minutes before gastroscopy

[Frossard, et al. Gastroenterology. 2002; 123 (1):17-23]

Risk category	Histology/most advanced finding	Interval of surveillance colonoscopy	Interval as soon as endoscopy does not show polyps
I	Hyperplastic polyp • In rectum or sigmoid **and** <1cm	Screening colonoscopy every 10 years	
	Hyperplastic polyp • >1cm **or** above sigmoid	5 years	Screening colonoscopy every 10 years
	Tubular adenoma • ≤2 polyps **and** • ≤1cm **and** • Without high grade dysplasia		
	Sessile serrated polyps • <1cm **and** without dysplasia	5 years	5 years
II	Tubular adenoma • ≥3 polyps **or** • >1cm **or** • High grade dysplasia	3 years	5 years
	(Tubulo-) villous adenoma		
	Traditional serrated adenoma or Sessile serrated polyps • ≥1cm **or** with dysplasia		
III	pT1-carcinoma in sessile polyp • Complete endoscopic polypectomy **and** • Resection margins free of carcinoma (histological) **and** • G1–G2 **and** • No angioinvasion **and** • <1000 micrometre invasion pT1-carcinoma in pedunculated polyp • Complete endoscopic resection **and** • Stalk free of tumor (Haggit level 1–2) • G1–G2 • No angioinvasion	≤3 months to control of polypectomy site, 3 years afterwards	5 years
IV	pT1 carcinoma in polyp • Not meeting all criteria of risk class III	Presentation at tumorboard, surgical resection indicated	

[Polypectomy surveillance recommendations of the sggssg]

Chromoendoscopy in the GI tract

Chromoendoscopy aims at a facilitated detection of dysplastic and malignant lesions in the GI tract. Mainly with flat, intra-epithelial neoplasias, chromoendoscopy is superior to standard white light endoscopy. The additional time needed for preparation of tissue surface, dye spraying, washing off excessive dye and inspection varies from 2 to 20 minutes – depending on the targeted lesion or organ (e.g. esophageal lesion vs. entire colon).

Lugol (iodine-based): brownish vital stain; incorporated in glycogen within non-keratinized squamous epithelium (reptile skin-like appearance), but not in tissue with low glycogen storages like neoplastic (e.g. squamous esophageal cancer = negative), intestinal (e.g. Barrett = negative) or inflammatory tissue (e.g. reflux esophagitis). Procedure: high-dose PPI during several days before endoscopy to reduce inflammatory changes. Lugol 1–2% sprayed from the Z line to the upper esophageal sphincter (20–30 ml). Cave: thyrotoxicosis, allergic reactions, retro-sternal discomfort (up to 30% of patients).

Acetic acid (vinegar): non-coloring vital stain; acid breaks up disulphide bridges ofglycoproteins resulting in a denaturation of protein with enhancement of the structural surface pattern (e.g. dysplasia in Barrett esophagus – sensitivity >95%, specificity 80%). Procedure: no pre-treatment required. 1.5–3.0% acetic acid in 20 ml aliquots sprayed on the mucosa.

Methylene blue: blue vital stain; active mucosal absorption by intestinal epithelium (e.g. Barrett = positive), poorly absorbed by high grade dysplasia and early cancer (e.g. HGD within Barrett or colonic neoplasia in IBD = negative), not absorbed by squamous or gastric epithelium. Procedure: requires prior mucus removal in the upper GI tract to ensure uptake. Upper GI tract: apply N-acetylcysteine 10% followed by methylene blue 0.5%. Colon: apply methylene blue 0.1%. Washing/suction off excessive dye after 1 minute. Cave: risk of oxidative damage to epithelial DNA with photosensitization by white light endoscopy (Davies J et al, Gut 2007), but no proven increased cancer risk.

Indigo carmine (E132): non-absorptive contrast stain; pools in mucosal grooves and crevices, allowing better topographic definition (e.g. dysplasia in IBD – sensitivity 93%, specificity 91% or Barrett) Procedure: gently apply small volume of indigo carmine 0.1% (5 ml ampule of 0.4% in 15 ml NaCl) diffusely during continuous extubation using a dye-spray catheter ("one-step low volume technique instead of multiple-step segmental staining).

[Trivedi PJ and Braden B. Indications, stains and techniques in chromoendoscopy. QJM 2013;106(2):117-31]

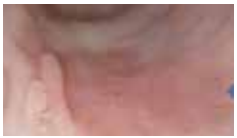
Chromoendoscopy for screening of dysplasia in the colon

	Indigo carmine 0.4 %	NaCl 0.9 %	Final dilution
Small amounts	1 Ampulla (each 5 ml = 20 mg)	15 ml	20 ml of 0.1%
Larger amounts	2 Ampullas (each 5 ml = 20 mg)	40 ml	50 ml of 0.1% for ALIANCE®-Pump

60 to 100 ml solution are needed for the whole colon

Chromoendoscopy procedure

- Adds about 11 minutes to the duration of the procedure
- After the cecum has been reached, to reduce spasm: i. v. butyl-scopolamine 20 mg
- Adequate air insufflation is necessary
- A dye-spray catheter is inserted down the instrumentation channel, and the tip protruded 2 to 3 cm
- Firmly squeezing the syringe, a fine mist of dye is then painted onto the mucosa by withdrawing the colonoscope in a spiral fashion
- Spraying should be done in a segmental fashion (every 20–30 cm)
- Excess dye is suctioned, and the colonoscope reinserted proximally
- Wait a few seconds for indigo carmine to settle into the mucosal contours
- Once that segment has been examined, the next segment is sprayed, and so on



[Kiesslich R, Neurath M.; Gastroenterol Clin North Am. 2012; 41(2):291-302]

Procedures without bleeding risk	Procedures with low-bleeding risk
Endoscopy without biopsy	Endoscopy with biopsy
EUS without FNA	ERCP with stent placement
ECP without Intervention	Enteroscopy with/without biopsy

Procedures with high-bleeding risk
Polypectomy
Sphincterotomy
Sphincterotomy with large ballon dilatation
Dilatation of digestive stenosis
Digestive stenting
PEG
EUS with FNA
Laserablation, APC
Therapy of varices
EMR, ESD, ampullary resection
Ligation of hemorroids
Transcutaneous liver biopsy and FNA

Management of antiplatelet agents during endoscopy

Table 1

Drugs / Risk for Bleeding	Aspirin	Clopidogrel or Prasugrel	Aspirin + Clopidogrel	VKA
No Risk	Continue	Continue	Continue	Continue
Low Risk	Continue	Continue	Continue	Ok if INR in therapeutic range

Table 2

High Risk	**→For polypectomy see Table 3**
	Aspirin
	Clopidogrel or Prasugel
	ASS + Clopidogrel
	VKA
	DOAC

DOAC	VKA + Aspirin or Clopidogrel	DOAC + Aspirin or Clopidogrel	VKA or DOAC + Aspirin + Clopidogrel
Continue	Continue	Continue	Continue
Only at through plasma level and delay next dose to the next morning	Discontinue	Discontinue	Discontinue

Continue* Consider discontinuation in patients with low thromboembolic risk, e. g. cardiovascular primary prophylaxis. Consider discontinuation for EMR, ESD, Papillectomy, EUS-FNP of cystic lesion, sphincterotomy with large ballon dilatation (consult hematology / cardiology). Liver biopsy: discontinue if appropriate, consider transjugular liver biopsy**
Switch to Aspirin*
Low thromboembolic risk *(see Table 4):* discontinue P2Y12 receptor antagonist* High thromboembolic risk *(see Table 4):* Consult hematology/ cardiology: e.g. discontinue P2Y12 receptor antagonist + bridging with GPIIbIIIa receptor antagonist Aspirin should be maintained in all cases
Low thromboembolic risk *(see Table 5):* discontinue (INR <1.5) High thromboembolic risk *(see Table 5):* discontinue with bridging
Low thromboembolic risk *(see Table 5):* discontinue High thromboembolic risk *(see Table 5):* consult hematology / cardiology for discontinuation +/- bridging

Management of antiplatelet agents during endoscopy	
	DOAC
	VKA + ASS or Clopidogrel
	DOAC + ASS or Clopidogrel
	VKA or DOAC + ASS + Clopidogrel

* *Caution: In patients with bleeding disorder, liver cirrhosis, severe renal insufficiency: consider discontinuation of antiplatelet agents if appropiate (consult hematology/cardiology).*

** *The Society of Interventional Radiology recommends: do not withhold Aspirin before liver biopsy (J Vasc Interv Radiol 2012;23:727)*

Polypectomy

Table 3

	Polypectomy safe in patients taking:
Polyps <5 mm	ASS
Polyps 5–10 mm	
Polyps 10–20 mm	

Low thromboembolic risk (see Table 5): discontinue High thromboembolic risk (see Table 5): consult hematology/ cardiology for discontinuation +/- bridging
Consult hematology / cardiology for discontinuation of anticoagulation (e.g. discontinuation of VKA and switching from Clopidogrel to Aspirin)
Consult hematology / cardiology for discontinuation of anticoagulation (e.g. discontinuation of DOAC and switching from Clopidogrel to Aspirin)
Consult hematology / cardiology for discontinuation of anticoagulation

[Endoscopy in patientson antiplatelet or anticoagulant ttherapy, including direct oral anticoagulants: British Society o fGastroenterology(BSG) and European Society of Gastrointestinal Endoscopy(ESGE) guidelines. Endoscopy2016;48:385-402
The management of antithrombotic agents for patients undergoing GI endoscopy. ASGE Guideline. Gastrointestinal Endoscopy2016;Volume83,No1:3-16 SFED –HAS Recommendation De Bonne Pratique:Antiagrégants plaquettaires: prise en compte des risques thrombotique et hémorragique en cas de geste endoscopique chez le coronarien; Juin2012 (www.has-sante.fr)]

	Polypectomy probably safe with reventive measures in patients taking:
	• Clopidogrel • ASS und Clopidogrel • VKA (INR in therapeutic range • DOAC if procedure is done in through plasma level
	• Clopidogrel

Anticoagulation

Anticoagulant	Risk of bleeding (no intervention)	Stop before procedure	Start after procedure	
UFH		4–6 h	12 h	
LMWH		Prophylactic dosing: 12 h Therapeutic dosing: 24 h	12 h	
Coumarin	1.3 % / year	Low thrombotic risk: - 3–5 days - when INR <1.8 5000 IE LMWH s.c. till 12 h	Start on the same evening with	Coumarin and 12 h 5000 IE LMWH till INR >1.8
		High thrombotic risk: - Bridging therapy with UFH/LMWH (see above)		12 h bridging therapy with UFH for 24–48 h
Rivaroxaban [anti-Xa]	2 % / year	Low risk intervention*: -1–2 days*	24 h–72 h**	
Dabigatran [anti IIa]	1.8 % / year	High risk intervention*: - 2–3 days		
Apixaban [anti-Xa]	0.8 % / year	CAVE creatinine clearance <50ml/min: 3–5 days		
Ticagrelor		5 days	24 h–72 h**	
Prasugrel		7—10 days		
Clopidogrel		7—10 days		
ASA / NSAR	0.4 % / year	7—10 days	48 h	

** assuming normal renal function*
*** depending on bleeding risk of the procedure*

NB: bridging therapy with high thrombotic risk can be considered but there should be no overlap between heparin and NOACs (major increase in hemorrhagic risk) [Source: Blood 2012; 120 (15): 2954-62, Gastrointestinal Endosc. 2013 ; 78 (2) :227-39, European Journal of Internal Medicine 2014; 25: 213–20 and www.sggssg.ch]

Thromboembolic risk – cardiovascular risk

Table 4

	High Risk
Bare metal stent	<6 weeks
Drug eluting stent	<12 months
Acute coronary syndrome	<6 weeks

Thromboembolic risk – venous thromboembolism, atrial fibrillation, mechanical heart valve

Table 5

	High Risk
Mechanical heart valve	All
Atrial fibrillation	History of CVI/TIA
Venous thromboembolism	<3 mnths, or history of recurrent idiopathic VTE

	Low Risk
	>6 weeks
	>12 months
	>6 weeks

[SFED-HAS Recommendation De Bonne Pratique: Antiagrégants plaquettaires: prise en compte des risques thrombotique et hémorragique en cas de geste endoscopique che le coronarien; Juin 2012: 7-8 (www.has-sante.fr)]

	Low Risk
	All other

[Kopp G. Rev Med Suisse 2013; 9: 1875; Pernod G. Thromb Res 2010; 126: e167]

Discontinuation of the anticoagulation

Table 6

Anticoagulant	Risk of bleeding (no intervention)	Stop before procedure
Aspirin NSAR	0.4% / year	5 d
Clopidogrel		5 d
Prasugrel		7 d
Ticagrelor		5 d
Phenprocoumon	1.3% / year	Low Thromboembolic risk: no bridging (procedure = day 0)
		Day –7 to –5
		Day –2
		Day 0
		High thromboembolic risk: bridging (procedure = day 0)
		Day –7 to –5
		Day –4 to –2
		Day –1
		Day 0

	Start after procedure
	Restart usually 24 h after procedure In patient with high thromboembolic risk receiving a P2Y12 receptor antagonist consider loading dose of 300 mg clopidogrel, and switch to prasugrel or ticagrelor later if appropriate
Stop Phenprocoumon; consider INR testing before INR testing; if INR >1.5 administer vitamin K 1–2.5 mg po Procedure	Resume in the evening after procedure (Coumarin and 12 h 5000 IE LMWH till INR >1,8
Stop Phenprocoumon INR testing; if INR <2.0 start LMWH (2 sc doses/day) INR testing; if INR >1.5 administer vit. K 1–2.5 mg po; last LMWH dose >24 h beforeprocedure, consider anti-factor Xa testing before procedure in renal insufficiency Procedure	If adequate hemostasis, LMWH at prophylactic or therapeutic (2 sc doses/day) level according to bleeding risk ≥6 h after procedure; resume phenprocoumon, stop LMWH when INR is within target range

Discontinuation of the anticoagulation

Table 6

Anticoagulant	Risk of bleeding (no intervention)	Low Thromboembolic risk: no bridging (procedure = day 0)
Acenocoumarol		Day –3
		Day –1
		Day 0
		High thromboembolic risk: bridging (procedure = day 0)
		Day –4 to –3
		Day –3 to –2
		Day –1
		Day 0
Rivaroxaban	2%/year	
Apixaban	0,8%/year	
Edoxaban		
Daigatran	1,8%/year	
UFH		
LWMH		

	Start after procedure
Stop Acenocoumarol; consider INR testing before INR testing; if INR >1.5 administer vitamin K 1–2.5 mg po Procedure	Resume in the evening after procedure (Coumarin and 12 h 5000 IE LMWH till INR >1.8
Stop Acenocoumarol INR testing; if INR <2.0 start LMWH (2 sc doses/day) INR testing; if INR >1.5 administer vit. K 1–2.5 mg po; last LMWH dose >24 h before procedure, consider anti-factor Xa testing before procedure in renal insufficiency Procedure	If adequate hemostasis, LMWH at prophylactic or therapeutic (2 sc doses/day) level according to bleeding risk ≥6 h after procedure; resume acenocoumarol, stop LMWH when INR is within target range
Low risk intervention: 1–2 days High risk intervention: 2–3 days CAVE creatinine clearance <50 ml/min: min 3–5 days!!	24 h–72 h (depending on bleeding risk of the procedure)
4–6 h	12 h
Prophylactic dosing: 12 h Therapeutic dosing: 24 h	12 h

[Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology(BSG) and European Society of Gastrointestinal Endoscopy(ESGE) guidelines. Endoscopy2016;48:385-402
The management of antithrombotic agents for patients undergoing GI endoscopy. ASGE Guideline. Gastrointestinal Endoscopy2016;Volume83,No1:3-16
SFED –HAS Recommendation De Bonne Pratique: Antiagrégants plaquettaires: prise en compte des risques thrombotique et hémorragique en cas de geste endoscopique chez le coronarien; Juin2012 (www.has-sante.fr)]

Indications
- perforation, fistula, anastomotic leak
- malignant stricture:
  - established: esophagus, gastric outlet
  - controversial: colon
- experimental: small intestine
- controversial: benign strictures
- pancreatic pseudocysts

Products / Methods
- uncovered
- fully covered
- partially covered
  - e.g. Ultraflex®: both ends uncovered
    Hanaro®: below the ends uncovered
- resorbable
- length, diameter, radiopaque markers, shortening
- tulips (e.g. manufactured to dimension)
- TTS (Through The Scope): 3,7 mm
- proximal release or distal release
- over guidewire (e.g. Amplatz superstiff)
- controlled release: side by side endoscopy, fluoroscopy

Duration
- uncovered: definitive
- fully covered: months
- partially covered: change every 2–3 weeks
- resorbable: ? (Cave: granulation tissue: PPI, steroids)

Pitfalls /Tips
- perforation esophagus: partially covered, proximal release, side by side endoscopy, large diameter if no stricture, duodenal feeding tube
- esophagus: stent too near to the upper sphincter → painful
- too large diameter: stent is not expanding properly
- shortening: stent is slipping over the lesion
- too long examination in the colon (also with CO_2): air trapping and risk of perforation
- Amplatz superstiff guidewire in the dilated colon: risk of perforation
- colon: angulation, chemotherapy → higher risk of perforation

Hemostatic agents (e.g. Hemospray™)

Indications
- Upper non-variceal GI bleeding (approved), for variceal bleeding not yet approved
- Lower GI bleeding (currently still "off-label use")
- Suitable for monotherapy or salvage therapy

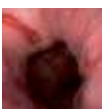
Product
- Hemostatic inorganic powder
- In contact with moisture, the hemostatic powder becomes cohesive and adhesive, creating a mechanical barrier and effecting hemostasis.
- Technique of application:
  - Apply in short bursts from the canister, with carbon dioxide propulsion, through a 10-Fr catheter to the active bleeding site until hemostasis is noted
  - One burst on average contains 1 to 5 g of powder (Apply max. 20 g)
  - Place the distal end of the catheter 2 to 3 cm away from the bleeding to prevent sticking of the catheter in moisture.

Pitfalls/Tips
- Conditions ideal to prefer a hemostatic powder as first-line therapy over standard hemostatic methods:
  - ozing bleeding from a malignant tumor
  - bleeding involving larger areas of mucosa that were not easily amenable to targeted standard therapies, such as portal hypertensive gastropathy or gastric antral vascular ectasia.
- CAVE: Do not place the catheter in moisture!

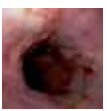
[Sulz MC, Frei R, Meyenberger C, et al. Routine use of Hemospray for gastrointestinal bleeding: prospective two-center experience in Switzerland. Endoscopy 2014; 46(7): 619-24] [Smith LA, Stanley AJ, Bergman JJ et al. Hemospray application in nonvariceal upper gastrointestinal bleeding: Results of the survey to evaluate the application of Hemospray in the luminal tract. J Clin Gastroenterol 2014; 48(10):89-92]

Reflux esophagitis: Los Angeles classification
Armstrong et al. Gastroenterology 1996;111:85-92

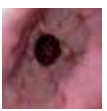
Grade A
Erosion(s)
≤5 mm
One mucosal fold



Grade B
Erosions
>5 mm
One mucosal fold



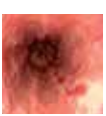
Grade C
Erosions
Multiple mucosal folds
≤75% circumference



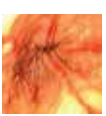
Grade D
Erosions
Multiple mucosal folds
>75% circumference

We recommend using this classification.

Reflux esophagitis: Savary-Miller classification
M. Savary, G. Miller 1978



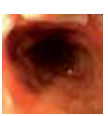
Grade I
one or more non-confluent lesions with erythema and edema



Grade II
confluent erosive and edematous lesions not covering the complete esophageal circumference

Grade III
lesion covers the complete esophageal circumference

Grade IV
esophageal ulcer, Barrett´s epithelium, strictures and other chronic mucosal lesions



Grade V
Barrett esophagus

Updated Guidelines for Diagnosis, Surveillance and Therapy of Barrett's Esophagus (BE)

Endoscopic biopsy should not be performed in the presence of a normal Z line or a Z line with <1 cm of variability.

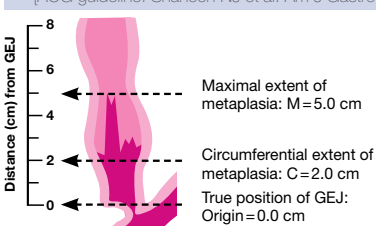
If evidence of inflammation, 4 weeks PPI, then quadrant biopsy.

Patients with BE should receive once-daily PPI therapy.

Endoscopic surveillance should employ four-quadrant biopsies at 2 cm intervals in patients without dysplasia and 1 cm intervals in patients with prior dysplasia.

Dysplasia	Documentation/Therapy	Follow-up
None	control EGD within 1 year not mandatory	after 3–5 years
Low Grade	• expert pathologist confirmation • ER or ablative therapy	if only surveillance: endoscopy after 6, then every 12 months
High Grade	• expert pathologist confirmation • ER (diagnostic & therapeutic) • followed by ablation therapy	after ER: first year every 3 months, every 6 months in the second year and annually thereafter

EGD - esophagogastroduodenoscopy
ER- endoscopic resection
[DGVS guideline: Koop H et al. Z Gastroenterol. 2014; 52(11):1299-346.]
[ACG guideline: Shaheen NJ et al. Am J Gastroenterol. 2016; 111(1):30-50.]



Diagrammatic representation of endoscopic Barrett's esophagus showing an area classified as *C2M5*. *C*: extent of circumferential metaplasia; *M*: maximal extent of the metaplasia (C plus a distal «tongue» of 3 cm); *GEJ*: gastroesophageal junction.

[Sharma P. Gastroenterology 2006;131:1392–1399]

Definitions	
Gastroesophageal Reflux Disease (GERD)	A presumptive diagnosis of GERD can be established in the setting of typical symptoms of heartburn and regurgitation.
Erosive reflux disease	Erosive esophagitis at endoscopy
Non-erosive reflux disease (NERD)	No mucosal break at endoscopy and abnormal esophageal acid exposure at 24-h esophageal pH monitoring.
Acid hypersensitive esophagus	No mucosal break at endoscopy, normal esophageal acid exposure and positive symptom-reflux association analysis (SI>50%, SAP>95%) at 24-h esophageal pH monitoring.
Functional heartburn	Heartburn refractory to PPIs without any mucosal break at endoscopy, normal esophageal acid exposure and negative symptom-reflux association analysis (SI<50%, SAP<95%) at 24-h esophageal pH monitoring.

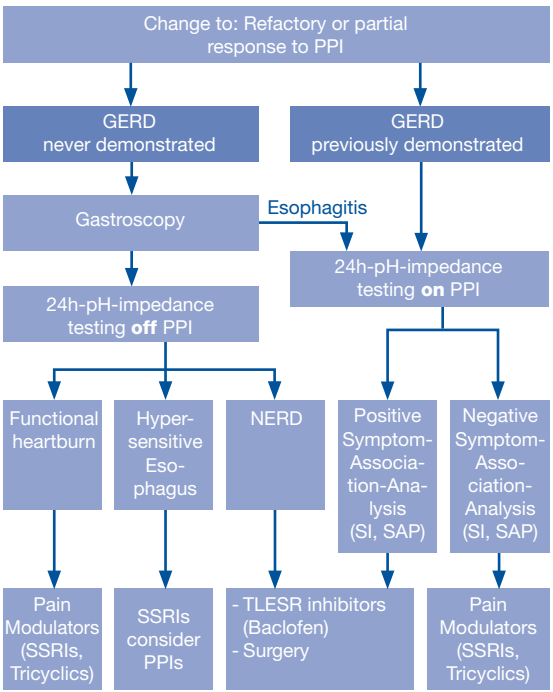
SI = Symptom Index
Number of reflux related symptom episodes/total number of symptom episodes ×100

SAP = Symptom Association Probability
Statistical parameter that expresses the likelihood that the patient's symptoms are related to reflux

Reflux symptoms refractory to PPI

- Definition of PPI-refractory reflux: no response of reflux symptoms (heartburn, regurgitation) to a stable double dose of a PPI during a treatment period of at least 12 weeks.
- Approximately 1/3 of patients with suspected GERD are resistant or partial responders to PPIs.
- Many of these patients do not have GERD, but suffer from functional heartburn or dyspepsia.

Algorithm for management of patients with refractory reflux symptoms



[Modified from:
Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors – Sifrim and Zerbib – Gut – 2012 61: 1340–54]

Eosinophilic Esophagitis (EoE)

Definition:
Chronic, local immune-mediated esophageal disease, characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation. Other systemic and local causes of esophageal eosinophilia should be excluded. Clinical manifestations or pathologic data should not be interpreted in isolation.
[Lucendo AJ, et al. United European Gastroenterol J 2017;5:335-358.]

Important facts to remember:
Cumulative prevalence about 35/100,000
(roughly one in 3,000 inhabitants in industrialized countries)
Male : female = 3 : 1
Allergies to food and/or aeroallergens in 70–90% of the population

Diagnosis:
EoE diagnosis is based on 3 pillars:
1. Symptoms of esophageal dysfunction (mostly dysphagia in adults)
2. ≥15 eosinophils per high power field (400x magnification)
3. Exclusion of other conditions that might be associated with esophageal eosinophilia (eg. GERD, esophageal infections, achalasia, celiac disease, Crohn's disease, tissue-invasive parasites, eosinophilic gastrointestinal diseases [EGID], hypereosinophilic syndrome, connective tissue diseases, vasculitis)

Remember:
- Take 4 biopsies from distal and 4 from proximal esophagus and in addition biopsies from esophageal lesions such as white exudates
- For diagnostic endoscopy take gastric and duodenal biopsies as well to rule out eosinophilic gastritis and/or enteritis
- The term «proton-pump responsive esophageal eosinophilia» does no longer exist as it has been shown to be eosinophilic esophagitis. The «diagnostic test» with double-dose PPI to discriminate EoE from GERD is no longer used.
- Performance of allergy testing using skin prick test, atopy patch test, and food-specific IgE to identify offending food allergens is poor (diagnostic accuracy about 45% in adults). Nevertheless,

EoE patients should be referred to an allergist for workup of conco mitant allergic diseases (asthma, rhinoconjunctivitis, atopic dermatitis)

[Lucendo AJ, et al. United European Gastroenterol J 2017;5:335-358.]

Natural history:
Untreated EoE leads to esophageal strictures with the risk of food bolus impactions and the inherent risk of esophageal perforation, either retching-induced (Boerhaave syndrome) or procedure-induced (especially if performed by rigid esophagoscopy).

[Schoepfer AM, Gastroenterology 2013;145:1230-6.]
[Dellon ES, Hirano I. Gastroenterology 2018;154:319-332]

Treatment options:

1. Drugs:
- Proton pump inhibitors: histologic and clinical improvement in about 30% of patients
- Orodispersible budesonide tablets (Jorveza®): Induction treatment with 1mg tablet 1–0–1 provides clinical and histologic remission in 58% of patients after 6 weeks and 85% after 12 weeks

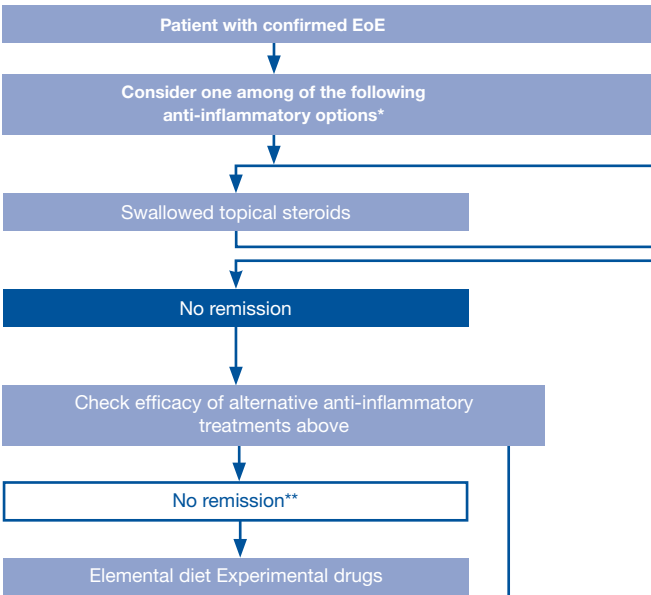
2. Diets:
- Elemental diet (powder, no proteins, just amino acids): histologic remission rate at 90%
- Empirical 6-food elimination diet: histologic remission rate of 72%
- Targeted elimination diet based on allergy testing: histologic remission rate of 45%.

3. Esophageal dilation:
- Target diameter 17–18mm
- Maximum increase of esophageal diameter per dilation session: 3–4 mm

Remember:
- EoE is a chronic disease. After therapy stop median time to clinical relapse is 3 months => patients need maintenance treatment (either budesonide tablets 1–2 mg/day or PPI or continued elimination diet)

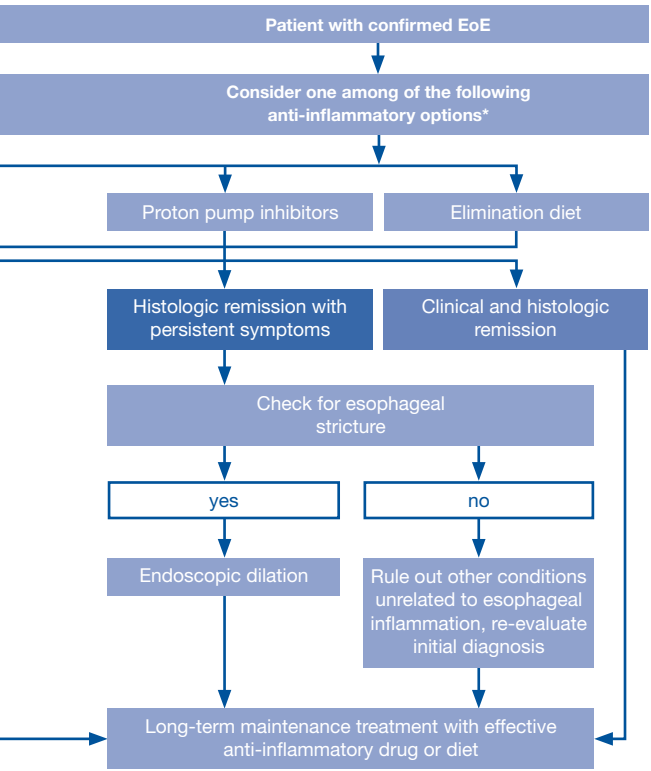
[Lucendo AJ, et al. United European Gastroenterol J 2017;5:335-358.]
[Lucendo AJ, et al. Gastroenterology 2019;157:74-86.]

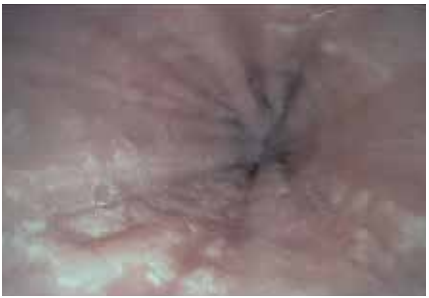
EoE Treatment Algorithm



* Consider dilation in patients with persistent symptoms under anti-inflammatory drugs
**Refer patient to an EoE center

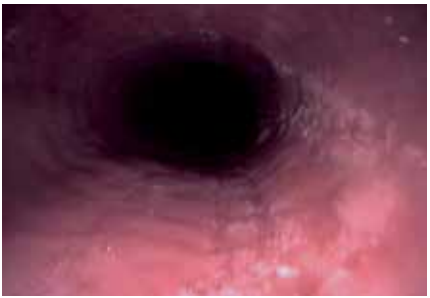
[Modified from Lucendo AJ, et al. United European Gastroenterol J 2017;5:335-358]


Patient with confirmed EoE
Consider one among of the following anti-inflammatory options*
Proton pump inhibitors
Elimination diet
Histologic remission with persistent symptoms
Clinical and histologic remission
Check for esophageal stricture
yes
no
Endoscopic dilation
Rule out other conditions unrelated to esophageal inflammation, re-evaluate initial diagnosis
Long-term maintenance treatment with effective anti-inflammatory drug or diet

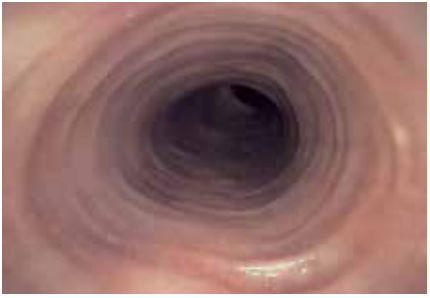


White exudates, edema
(loss of vascular pattern) and
longitudinal furrows

Pinpoint-shaped white exudates
(corresponding histologically
to eosinophilic microabscesses)



Linear furrows (railroad track), trachealization and some white exudates



Concentric rings (trachealization) in a non-inflamed esophagus

Eosinophilic gastro-entero-colitis (EGE)

Epidemiology and pathophysiology: rare (prevalence: 25/100,000), males >females, peak in the first 3 decades of life; probably allergy-related; involvement of mucosa and/or muscularis and/or serosa, often chronic-relapsing.

Clinical presentation: *depending on localization and depth of involvement*
- mucosal layer: nausea, pain, diarrhea, malabsorption, weight loss
- muscular layer: obstruction (mechanical ileus)- serosa: ascites

Diagnosis: *combination of clinical, laboratory and histologic findings*
- laboratory: peripheral eosinophilia (in 80%), IgE-elevation (particularly in children), iron deficiency anemia, protein losing enteropathy
- imaging: unspecific, normal in most cases, segmental wall thickening in muscular layer involvement (with/without signs of ileus), ascites in serosa involvement
- endoscopy: macroscopic findings often subtle/unspecific; at histology: eosinophilic infiltration (>50/HPF) (normal: no eosinophils in the oesophagus, raising number of eosinophils in stomach and small intestine with peak in terminal ileus and right colon,declining number of eosinophils in left colon and rectum *[Matsushita T et al, Am J SurgPathol 2015; 36(4):521-7]).* Cave: false negative biopsies possible with isolated muscularis/serosa involvement → «full thickness biopsy» (surgical)

Differential diagnosis: *secondary gut eosinophilia*
protozoal infections (anisakis, strongyloides, ...), drugs (NSAID, rifampicin, carbamazepine, tracrolimus), hypereosinophilic syndrome, vasculitis and connective tissue disease (e.g.Churg-Strauss), lymphoproliferative disorders, graft-versus-host disease, IBD, celiac disease, reflux esophagitis, Drug rash with eosinophilia and systemic symptoms (DRESS), etc.

Treatment: *(sparse evidence)*

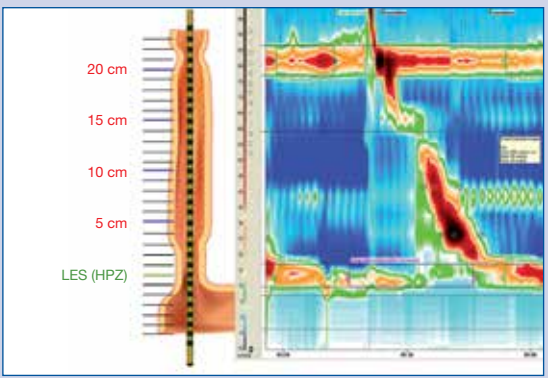
1. six-food-elimination diet (soy, wheat, eggs, milk, peanuts, shellfish)
2. steroids: systemic (prednisone 40 mg for 2 weeks, then 2 weeks tapering) or topic (budesonide)
3. experimental alternatives (PPI, mast cell stabilizers, antihistamines, leukotriene antagonists, anti-IL5-AB, ...)

[Spergel JM, Book WM, Mays E, et al.Variation in prevalence, diagnostic criteria, and initial managementoptions for eosinophilic gastrointestinal diseases in the United States. J. Pediatr. Gastroenterol Nutr2011;52:300-6.Uppal V, Kreiger P, Kutsch E. Eosinophilic Gastroenteritis and Colitis: a Comprehensive Review. Clin RevAllergy Immunol 2016;50:175-88. Ann Allergy Asthma Immunol. 2018 Aug;121(2):162-167. Eosinophilic gastrointestinal diseases beyond eosinophilic esophagitis. "Egan M1, Furuta GT2.]

Classification of Eosinophilic Gastrointestinal disorders (EGID)

Primary (EGID)	Secondary gut eosinophilia
Eosinophilic Esophagitis Eosinophilic Gastroenteritis • Eosinophilic Gastritis • Eosinophilic Enteritis • Eosinophilic Colitis Food Hypersensitivity/Allergy • IgE mediated • Non-IgE mediated Food protein induced proctocolitis of infancy	Reflux esophagitis Infections: protozoal and other pathogens Drugs: NSAIDs, clozapine, rifampicin, enalapril, carbamazepine, tacrolimus Systemic diseases: • Hypereosinophilic syndrome • Connective tissue disease/ vasculitis • Lymphoproliferative disorders • Graft-versus-host disease • Inflammatory bowel disease • Celiac disease

High resolution manometry – per swallow analysis



Lower esophageal sphincter (LES)

- **Integrated relaxation pressure over 4 seconds (IRP 4-sec):** Sum of lowest average LES pressures over a 4-second period (not continuous) in the LES during deglutition

Esophageal body

- **Distal contractile integral (DCI):** Integration of contraction amplitude, distance and time of the area below the transition zone and above the proximal border of the LES after deglutition
- **Contraction front velocity:** speed of propagation of the onset of esophageal contraction below the transition zone to the distal esophageal deceleration point
- **Distal latency period (DL):** time between beginning of UES relaxation and distal esophageal deceleration point
- **Proximal contractile integral (PCI):** Integration of contraction amplitude, distance and time of the area above the transition zone and below the distal border of the UES after deglutition

Normal values

Lower esophageal sphincter (LES)

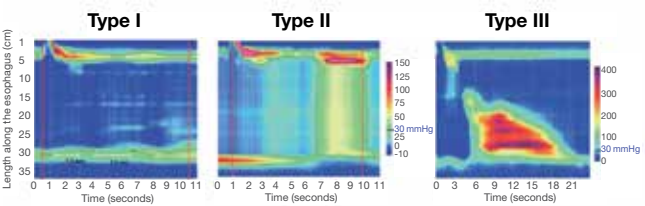
- **IRP 4-sec <15 mmHg**
  - EGJ outflow obstruction if IRP >15 mmHg

Esophageal body

- **Peristaltic integrity: no breaks larger than 3 cm in the 30 mmHg isobaric contour or no breaks larger than 2 cm in the 20 mmHg isobaric contour**
  - Breaks >3 cm in 30 mmHg isobaric or >2 cm in 20 mmHg isobaric contour: hypotensive contraction
  - No 30 mmHg isobaric contour in the distal esophagus: absent peristalsis
  - Simultaneous increase in esophageal pressure from the LES to UES >30 mmHg: pan-esophageal pressurization (PEP)
- **Distal contractile integral (DCI) <5,000 mmHg*s*cm**
  - hypercontractile peristalsis if DCI >5,000 mmHg*s*cm
  - jackhammer esophagus if DCI >8,000 mmHg*s*cm

Achalasia in HRM/EPT*

*** = High resolution manometry / esophageal pressure topography**



- Failure of LES-Relaxation
- Aperistalsis
- No pressurization in distal esophagus <30 mmHg in >8/10 swallows

- **Response to therapy:**
  →
  Surgical myotomy (4/6)

  Pneumatic dilation (3/8)

  Botulinum toxin (0/2)

- Failure of LES-Relaxation
- Aperistalsis
- Panesophageal pressurization >30 mmHg in ≥2/10 swallows

- **Response to therapy:**
  →
  Surgical myotomy (13/13)

  Botulinum toxin (6/7)

  Pneumatic dilation (19/26)

- Failure of LES-Relaxation
- «Vigrous Achalasia»
- Spastic contractions (DL <4.5 s) in in ≥2/10 swallows

- **Response to therapy:**
  →
  Botulinum toxin (2/9)

  Surgical myotomy (0/1)

  Pneumatic dilation (0/11)

[Pandolfino, Gastroenterology 2008;135:1526-33]

Grading system for evaluating clinical symptoms of achalasia (Eckhardt score)

Score	Weight loss	Dysphagia	Retrosternal pain	Regurgitation
0	None	None	None	None
1	<5 kg	Occasional	Occasional	Occasional
2	8–10 kg	Daily	Daily	Daily
3	>10 kg	Each meal	Each meal	Each meal

[Eckardt VF, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. Gastroenterology 1992;103(6):1732-1738]

Characterisation of esophageal contractility

Contraction vigor

Failed	DCI <100 mmHg*s*cm
Weak	DCI >100 mmHg*s*cm, but <450 mmHg*s*cm
Ineffective	Failed or weak
Normal	DCI >450 mmHg*s*cm <8000 mmHg*s*cm
Hypercontractile	DCI >8000 mmHg*s*cm

Contraction pattern

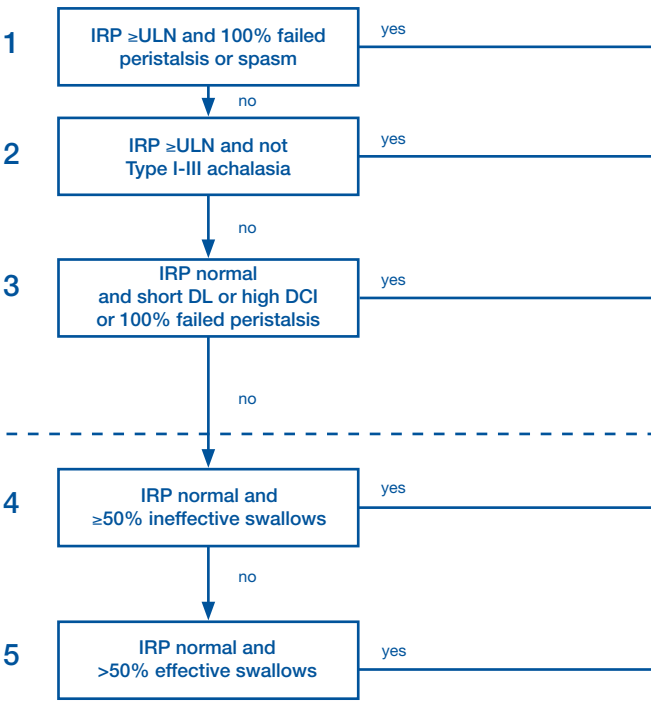
Premature	DL <4.5 s
Fragmented	Large break (>5 cm length) in the 20 mmHg isobaric contour with DCI >450 mmHg*s*cm
Intact	Not achieving the above criteria

Intrabolus pressure pattern
(30 mmHg isobaric contour referenced to athmospheric)

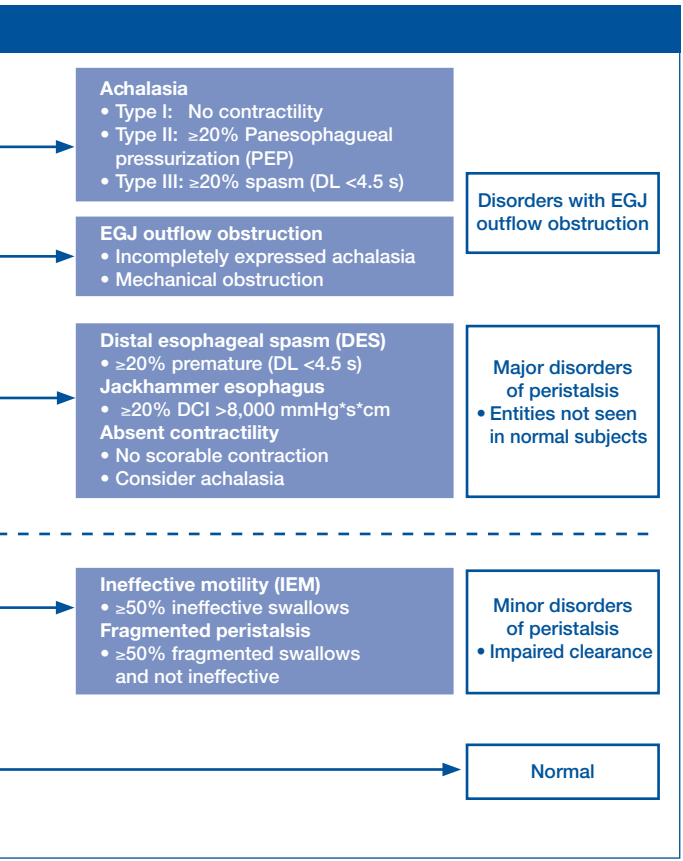
Panesophageal pressurization	Uniform pressurization of >30 mmHg from UES to EGJ
Compartmentalised oesophageal pressurization	Pressurization >30 mmHg from CF to EGJ Pressurization restricted to area LES to CD
EGJ pressurization Normal	No bolus pressurisation >30 mmHg

[Kahrilas et al. Neurogastro and Motility, Feb 2015]

The Chicago Classification v 3.0 *Hierarchical analysis*



[Kahrilas et al, Neurogastroenterol Motil. 2015 February ; 27(2): 160–174]


Achalasia
• Type I: No contractility
• Type II: ≥20% Panesophageal pressurization (PEP)
• Type III: ≥20% spasm (DL <4.5 s)
EGJ outflow obstruction
• Incompletely expressed achalasia
• Mechanical obstruction
Disorders with EGJ outflow obstruction
Distal esophageal spasm (DES)
• ≥20% premature (DL <4.5 s)
Jackhammer esophagus
• ≥20% DCI >8,000 mmHg*s*cm
Absent contractility
• No scorable contraction
• Consider achalasia
Major disorders of peristalsis
• Entities not seen in normal subjects
Ineffective motility (IEM)
• ≥50% ineffective swallows
Fragmented peristalsis
• ≥50% fragmented swallows and not ineffective
Minor disorders of peristalsis
• Impaired clearance
Normal

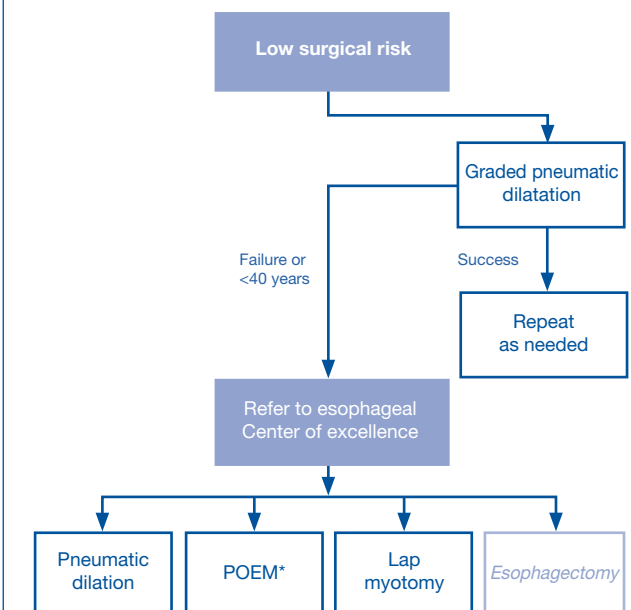
Achalasia – Diagnosis and treatment

Definition:

Radiographic and Manometric Features of Achalasia
Timed barium swallow

Essential features:
- «bird's beak» appearance of the LES with incomplete opening
- Loss of primary peristalsis
- Delayed esophageal emptying

Algorithm Achalasia



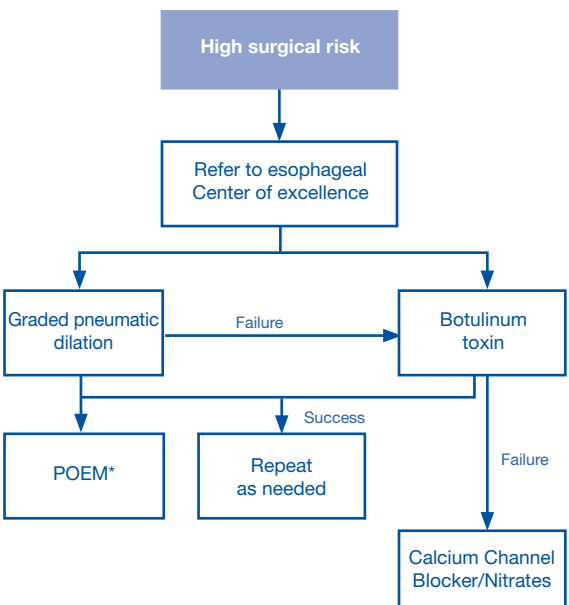
[Richter JE, Boeckxstaens GE. Gut 2011; 60(6):869-76.
Vaezi MF, Richter JE. Am J Gastroenterol. 1999; 94(12):3406-12]

Supportive features:
- Dilated or sigmoid-like esophagus
- Epiphrenic diverticula

Manometry

Essential features:
- Aperistalsis in distal 2/3 of the esophagus
- Abnormal LES relaxation

Supportive features:
- Hypertensive LES pressure
- Low amplitude esophageal contractions



* Peroral endoscopic myotomy

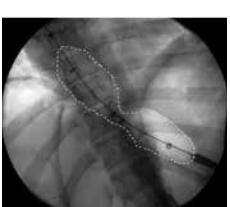
Pneumatic dilatation for achalasia

Preparation

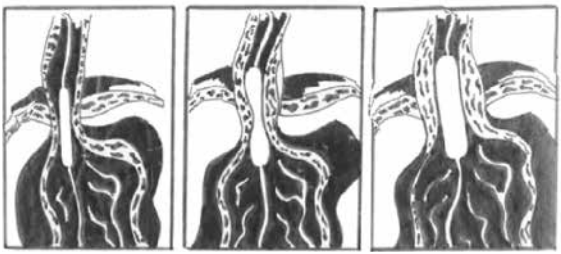
- Confirmed diagnosis of achalasia (endoscopy, barium esophagogram and esophageal manometry)
- Informed consent: efficacy 85–90%, may require 2–3 sessions, perforation risk 2–3%; alternative laparoscopic myotomy (not superior to dilatation, perioperative risks, risk of GERD symptoms in up to 20% of patients), Botox injection of LES (recurrence rate 50% after median of 6 months)
- Day before procedure only liquid diet; npo at least 6 hours prior to procedure

Procedure (balloon 30 – 35 – 40 mm, 10 PSI, at least 60 seconds)

- Sedation, preferably with propofol
- Intubate esophagus in right lateral decubitus to minimize risk of aspiration of esophageal content rapid sedation with patient in semi-upright position
- Clearing fluids and solids out of the esophagus; if esophagus cannot be cleared consider reschedule intervention
- Position guide wire in the stomach antrum
- Turn patient on his/her back
- Locate gastroesophageal transition (Z-line) endoscopically and radiographically
- Insert dilatation balloon (recommendation to start with 30 mm balloon)
- Position center of balloon at the level of the EG-junction
- Confirm waist in the middle of the balloon (caution: propulsive esophageal forces tend to drag the balloon into the stomach)



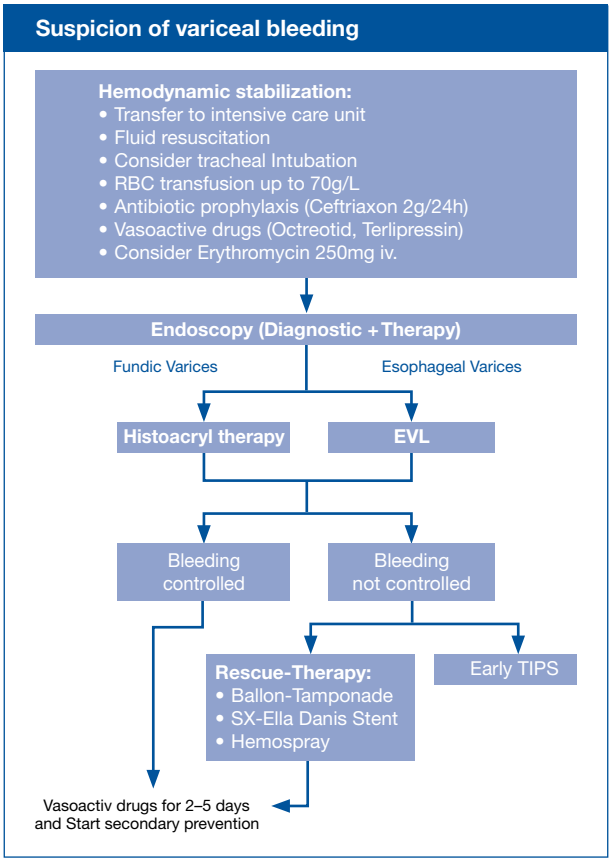
- Inflate the balloon until waist disappears but not more than 10 PSI
- Maintain balloon inflation for at least 60 seconds



- Deflate balloon and remove (in most cases there will be blood on the balloon)
- Endoscopic control so that there is no transmural perforation
- In case of esophageal / cardia perforation: place 1 naso-gastral and 1 naso-esophageal tube, prescribe sufficient analgesia, perform CT-thorax-abdomen, inform the surgeons of complication consider covered stent, apply broad-spectrum antibiotics and anti-fungals i.v.,. Baseline hemogram (Lc-count), CRP. Arrange for parenteral nutrition and in-hospital observation (hospitalization 10 – 14 days), the first 24 – 48 hours ideally intermediate care (IMC) level.

Post-dilatation procedure

- Clinical observation for 2-4 hours, trial with water swallow
- Treat chest pain (muscular tear with acetaminophen, mefenamic acid or pethidine/fentanyl); pain should subside over the next 2 – 3 hours
- In case of a perforation after pneumatic dilatation consider covered esophageal prothesis and antibiotics
- Patient stable without evidence of leak can be discharged the same day
- Only liquids for lunch and dinner. Normal diet starting next morning
- 2–4 weeks, repeat barium esophagogram.
- Clinical re-evaluation after 4 weeks. If symptoms persist, consider repeating pneumatic dilatation with 35 mm and if required, a third time with a 40 mm balloon.
- Patients with persistent symptoms after 2–3 dilatations (up to 40 mm) should be regarded as failures to pneumatic dilatation and referred for laparoscopic myotomy or POEM.

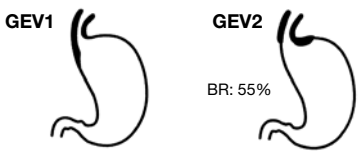


[Abb Algorithm for management of acute variceal bleeding.
TIPS: Transjugular intrahepatic portosystemic shunt;
EVL: Endoscopic Band Ligation;* Decision dependent on local availability.]

Gastric varices

Bleeding risk: 25% in 2 years

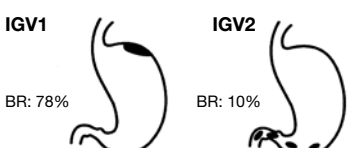
Gastro Esophageal Varices (GEV)



GEV1: extension of esophageal varices along the lesser curvature
(- management as for esophageal varices)

GEV2: extend along the fundus and are usually convoluted and longer

Isolated Gastric Varices (IGV)
(absence of esophageal varices)



BR = Bleeding risk in 2 years

IGV1: isolated in the fundus and are usually convoluted and complex
(- exclude splenic vein thrombosis)

IGV2: located in the body, antrum, or around the pylorus

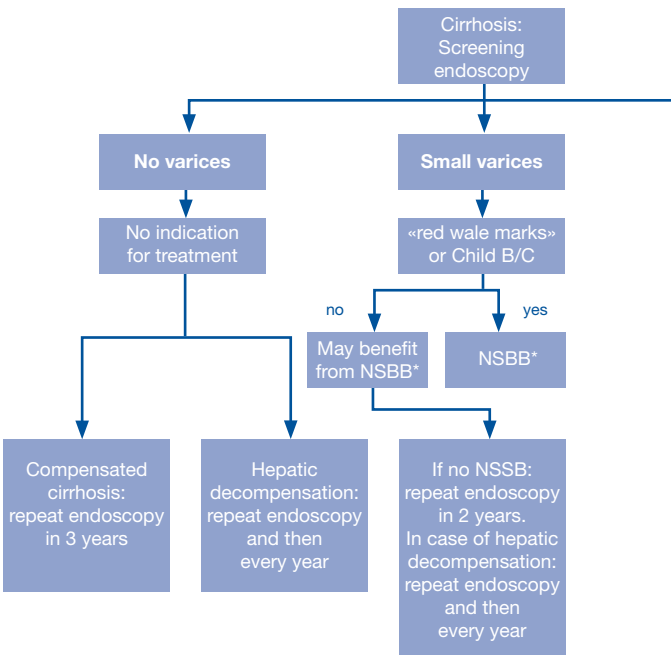
[According to Garcia et al. Hepatology 2007]

Esophageal varices – size classification and screening

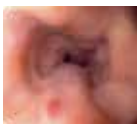
Size classification

Small varices <5 mm
Large varices >5 mm
+ presence or absence of red signs
(i.e. red wale marks, red spots)

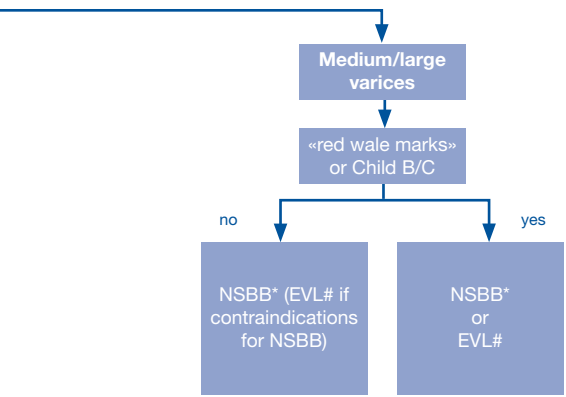
Screening and primary prevention



«Red spots».



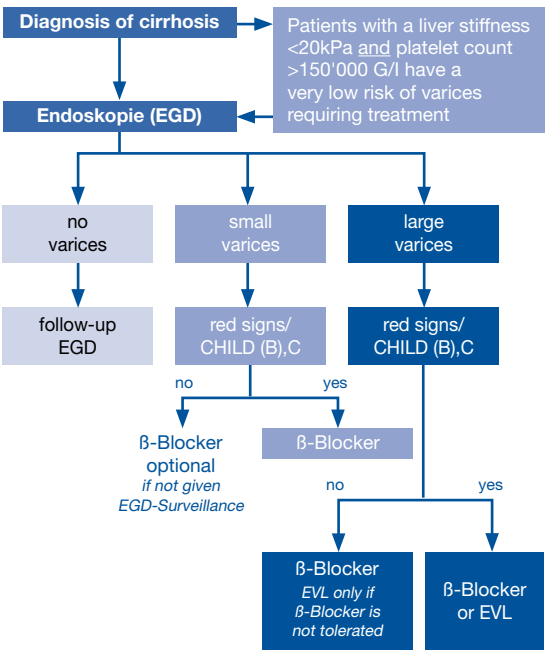
«Red wale marking».



* NSBB = nonselective betablocker; adjust to the maximal tolerated dose; no recommendation for surveillance

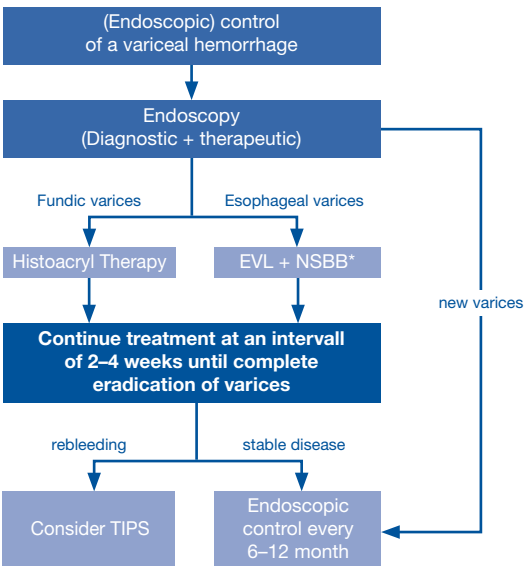
\# EVL = endoscopic variceal ligation; repeat every 1–2 weeks until obliteration, first surveillance after 1–3 months, then every 6–12 months

Esophageal varices – primary prophylaxis



[Abb Algorithm for management of primary prophylaxis of esophageal varices. Garcia-Tsao G, Hepatol 2007 de Franchis R, J Hepatol 2015.]

Esophageal varices – secondary prevention



[Algorithm for management of secondary prophylaxis for esophageal varices. TIPS: Transjugular intrahepatic portosystemic shunt; EVL: Endoscopic Band Ligation.
*If combination is not tolerated, consider monotherapy even with EVL or NSBB alone.]

Treatment Option with SX-ELLA Stent Danis

Reference: www.ellacs.eu
E-mail: info@ellacs.eu URL: www.ellacs.eu

Insertion with or without endoscope possible, use a guidewire when possible (guide wire included with stent)

Indications
SX-ELLA Stent Danis is intended for stopping the acute bleeding from esophageal varices. The stent implantation may be an option in refractory esophageal variceal bleeding as an alternative method to the early TIPS or the balloon tamponade.

Caution
Gastric/Fundic varices or not treated with this method
Always strictly adhere to manufacturer´s implantation Manual
www.nicolai-medizintechnik.de/anweisungen/danisstent.pdf

Contraindications
Esophageal strictures
Recent radiotherapy of the esophagus
Tumors of the upper respiratory tract, esophagus or stomach
Upper GIT bleeding from other causes (e.g. perforation,ulcers)

Follow up care

- Confirm proper stent placement by endoscopy as soon as possible (if inserted without endoscope)
- Check stent position after 24h (by X-ray or endoscopy) or in signs of bleeding
- After stent placement, stabilize pt. and evaluate TIPS
- Remove stent after a week, longer indwelling time often possible (individual decision)
- Remove stent urgently on suspicion of airway compression

For instruction see https://www.youtube.com/watch?v=1rbYext0cvg.

Linton –Tube

Using a 100 mL syringe, slowly push air into the stomach balloon (300 mL) and seal the feeder with a clamp

Tube should be tested by inflating air before use

- Pull the tube back as far as possible until a flexible resistance is noticeable (cardia approx. at 40 cm). Thereafter, slowly push 200 –300 mL air into the stomach balloon again.
- Place a one-sided cut foam rubber piece in front of the nostril, and fix the tube under tension with a 500 g – 1 kg weight at the end of the bed.
- As a general rule, the stomach is washed clear every 30 minutes with water in order to control the bleeding and aspirate the blood.
- In order to avoid hepatic encephalopathy, lactulose syrup is sufficiently administered.
- The esophagus and stomach lumen are drained.
- Consider ulcer development if used for more than 24 hours.

Sengstaken – Blakemore tube

Indication: uncontrolled variceal bleeding after failed band ligation (+/- sclerotherapy)

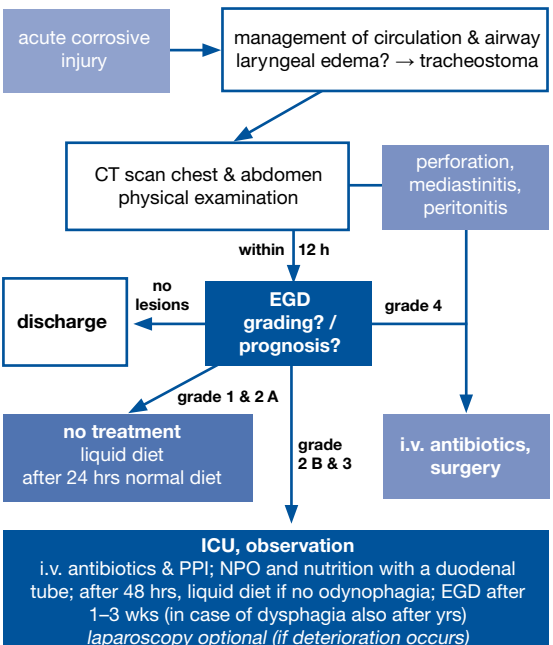
Procedure:

-1- Proof balloons with water (gastric : 250 ml; esophageal: about 80 ml)
-2- Patient should be intubated and the head of the bed up at 45 degrees.
-3- Insert through nose or mouth using anesthetic gel till 50–55 cm
-4- Inflate the gastric balloon [brown] with 50 ml of air and control position (x-ray or endoscopically) [complete with additional 200 ml of air and clamp the gastric port!]
-5- Traction: with 500 ml bag of saline solution, then reduce to 250 ml [mark the tube at the nose entry]
-6- Air pressure in the esophageal balloon [yellow] 35–45 mm/Hg*[clamp the esophageal port!]
-7- Test tube with water

** Air pressure: H0-H6 : 35-45 mmHg ; H6-H24: 30-35 mmHg; >H24 : 25-30 mmHg NB: Every 6 hours esophageal balloon pressure to 0 for 5 min (risk of mucosal necrosis).*

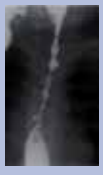
[Senstaken RW and Blakemore AH. Balloon tamponage for the control of hemorrhage from esophageal varices. Ann Surg 1950;131:781–89]

Algorithm for corrosive injuries in the esophagus and/or stomach



[Modified from Sleisenger 8th ed.]

Prognosis of corrosive injuries in the esophagus and/or stomach

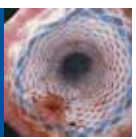
Grade 1	Grade 2 A/B	Grade 3 A/B	Grade 4
complete recovery	70–100% strictures or pyloric stenosis 	65% early mortality ~100% esophageal resection with jejunal or colonic interposition	

[Modified from Zargar SA et al. Gastrointestinal Endoscopy 1991 and from Cheng HT et al. BMC Gastroenterol 2008]

Complications of corrosive injuries in the esophagus and/or stomach

1. perforation *(acute)*
2. esophago-tracheal or -bronchial fistulas
3. esophageal motility disorder
4. pyloric stenosis *(mths – yrs)*
5. stenosis / strictures (from grades 2B to 3) *(2 wks – 5 yrs)*

therapeutic options:
frequent multiple dilations (bougie or balloon)
retrievable metal and plastic self-expanding stents
→ *possible problems: migration >40%,*
long-term success <50%



6. esophageal cancer *(after – 30 yrs)*

1000 x fold risk of developing esophageal cancer compared to general population → begin endoscopic surveillance 15 yrs after ingestion (generally not performed more than every 1–3 yrs)

Pseudodiverticulosis

Very rare syndrome characterised by multiple, flask-shaped outpouchings of pinhead size in the wall of the esophagus. Dilatation of excretory ducts of the esophageal submucosal glands. Unknown physiopathology. May be associated with gastroesophageal reflux, strictures, webs, herpes or candida, esophagitis and esophageal neoplasm.

Diagnosis: endoscopy or radiological evaluation.
Symptoms: dysphagia.
Treatment: dilatation of stricture and treatment of oesophagitis.

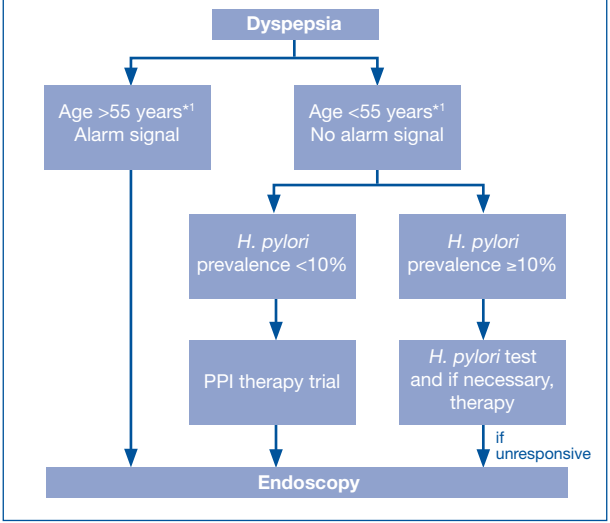
[Attila T, Marcon NE. Esophageal intramural pseudodiverticulosis with food impaction. Can J Gastroenterol. 2006; 20(1):37-8.]

Corrosive injury

Grading of corrosive injuries in the esophagus and/or stomach

Grade 1	Grade 2 A	Grade 3 A	Grade 4
edema & hyperemia of the mucosa	friability, bleeding, erosions, blisters, whitish membranes, exudates, and superficial ulcers **2 B** grade 2A plus deep discrete or circumferential ulceration	multiple ulcerations and small scattered areas of necrosis **3 B** multiple ulcerations and extensive necrosis	perforation

Endoscopy Algorithm Dyspepsia



Alarm signals:

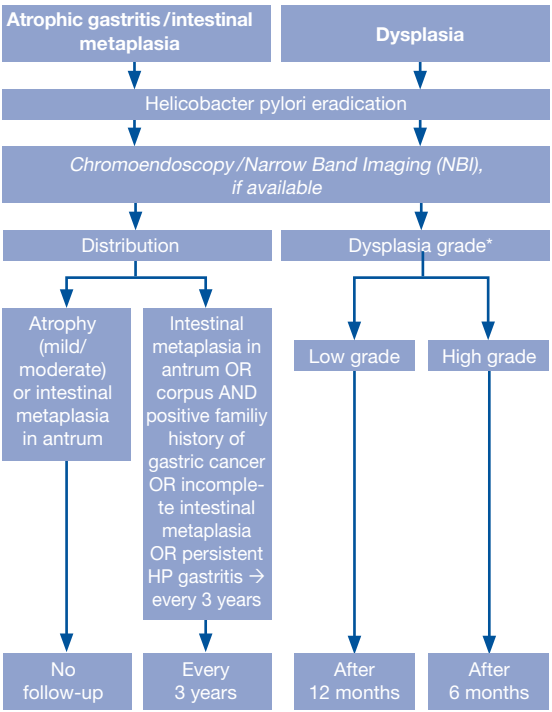
Age >55 years, newly occurring symptoms
Family anamnesis for malignancy of the upper gastrointestinal tract
Past history of peptic ulcer disease
Unintentional weight loss
Gastrointestinal bleeding or iron deficiency anemia
Increasing dysphagia or odynophagia
Persistent vomiting
Icterus
Tumor in abdomen, lymphadenopathy

[Talley NJ, et al: American gastroenterological association technical review on the evaluation of dyspepsia. Gastroenterology 2005; 129(5):1756-80]
[Talley NJ, et al: Guidelines for the management of dyspepsia. Am J Gastroenterol 2005; 100(10):2324-37]

*1 *Age might vary according to local guidelines*

Metaplasia

Algorithm Metaplasia



In the case of visible macroscopic lesions: consider staging and resection. Sampling: take ≥ 2 biopsies from the antrum, corpus, large and small curvature

[Dinis-Ribeiro M, et al. guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de En-doscopia Digestiva (SPED).Endoscopy 2019 Apr;51(4):365-388]

- High grade dysplasia might require longer follow-up but surgical or endoscopic resection as adenocarcinoma might be underlying and 25% of HGD patients will progress to adenocarcinoma.
- Surveillance can be stopped if 2 consecutive biopsies were negative.

Sydney Classification – Histology

Acute gastritis	Cause
• Acute hemorrhagic/erosive gastritis	→ Medication, intoxication
• Acute *H. pylori* gastritis	→ *H. pylori*
• Acute phlegmonous gastritis	→ Sepsis
Chronic gastritis	**Cause**
• Non-atrophic gastritis	→ *H. pylori* (Type B gastritis)
• Atrophic gastritis	→ Autoimmunity (Type A gastritis)
- Autoimmune gastritis	→ *H. pylori* environmental factors
- Multifocal atrophic gastritis	
• Special forms	→ chemical irritation, NSAID/ medication, bile (Type C gastritis)
- Chemical gastritis	
- Radiation gastritis	→ Irradiation
- Lymphocytic gastritis	→ Immune mechanisms, gluten, *H. pylori* idiopathic
- Granulomatous, not infectious	→ Crohn's disease, sarcoidosis, M. Wegener / other vasculitides, foreign bodies, idiopathic
- Eosinophilic gastritis	→ food allergies, other allergies
- Infectious gastritis	→ bacteria, viruses, fungi, parasites

[Dixon MF, et al. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 1996 Oct;20(10)]
[Tytgat GN. J Gastroenterol Hepatol. 1991]

Diagnostics of H. pylori

Method	Sensitivity (%)	Specificity (%)
Non-invasive methods		
Serology	70–90	70–90
13C breath test	85–95	85–95
Stool antigen	85–95	85–95
Invasive methods		
Fast urease test	90–95	90–95
Histology*	80–98	90–98
Culture	70–90	100
PCR-analysis	90–95	90–95

**Sydney recommendation: 6 biopsies (2x antrum, 2x corpus, large/small curvature)*

[Fischbach et al. S3-guideline "Helicobacter pylori and gastroduodenal ulcer disease". Z Gastroenterol. 2009; 47(12):1230-63.]

Test result

False positive: serology (previous infection, cross-reactive antibodies), atrophic gastritis / achlorhydria, bacterial overgrowth of the stomach

False negative: after partial gastrectomy, with acute gastrointestinal bleeding, with / after (<2 weeks) PPI therapy, with / after (4 weeks) antibiotic therapy

Management of *H. pylori* eradication therapy

Please consider risks and benefits of any eradication treatment before starting the medication. *H pylori* infection is the most consistent risk factor for gastric cancer and esophagastric junction cancer. Its elimination is therefore the most promising strategy to reduce the incidence of gastric cancer. Global prevalence of *H. pylori* is about 50% or higher. In CH, *H. pylori* prevalence is approximately 25% (1 of 4 persons), in south-eastern Europe *H. pylori* prevalence rises to 40–70%.

Confirmed indication

- Active peptic ulcer disease
- MALT-lymphoma of the stomach
- Atrophic gastritis
- Previous partial gastrectomy due to gastric carcinoma
- Positive family history (1° grade relative with gastric carcinoma)
- Dyspepsia
- Patient request

- Morbus Ménétrier
- Idiopathic thrombocytopenic purpura (ITP)
- Lymphocytic gastritis
- (Future) therapy with NSAID
- (Future) therapy with aspirin (ASA) in patients with history of peptic ulcer disease
- Otherwise unexplained iron-deficiency anemia

Helicobacter pylori

Controversial indication with tendency towards *H. pylori* eradication:

- Functional dyspepsia (number needed to treat = 12), «better than any other treatment», side effects 10–25%
- Long term low-dose aspirin (ASA) intake, especially in the elderly (>65 years)
- Other gastrotoxic drugs (e.g. Prednisone) in combination with low-dose aspirin (ASA) intake
- Lymphocytic gastritis
- Previous partial gastrectomy (after >10–15 years)
- H.p. Dyspepsia

Weak indication:

- Vitamin B12 deficiency
- Asthma and atopy
- Obesity and related illnesses

No evidence:

- There is no evidence that *H. pylori* eradication can lead to regression of intestinal metaplasia.
- On average, *H. pylori* status has no effect on symptom severity, symptom recurrence and treatment efficacy in **GERD.** *H. pylori* eradication does not exacerbate pre-existing GERD or affect treatment efficacy.

***H. pylori* therapy**

1) PPI (PPI standard dose)
Esomeprazole 20 mg ~ Pantozole 40 mg ~
Lansoprazole 30 mg ~ Rabeprazole 20 mg ~ Omeprazole 20 mg
PPI should be given as «1 – 0 – 1» regime during 7–10 (–14) days.
A higher PPI dose (e.g. doubled PPI dose with respect to the «standard» dose) may increase cure rates by 8–12%.

2) Antibiotics
Consider regional clarithromycin resistence levels («Clari-R» prevalence) before starting *H. pylori* treatment.
- low level (prevalence) if Clari-R < 20%
- high level (prevalence) if Clari-R > 20%

In Switzerland (CH) and Germany, Clari-R is considered to be **below 20 %.** In many parts of Italy, Clari-R is considered to be above 20 %. The following therapy schemes are used in CH.

In case of failure of first-line treatment, second-line treatment is selected without resistance testing, whereas with further failure, third-line treatment should be chosen based on *H. pylori* cultures and antibiotic susceptibility testing.

FIRST LINE THERAPY
Clarithromycin 2 x 500 mg/d AND Amoxicillin 2 x 1000 mg/d
10–14 days

In case of proven intolerance/allergy to penicillin:

Clarithromycin 2 x 500 mg/d AND Metronidazole 2 x 500 mg/d
10–14 days

plus PPI (various drugs, see above)

These two regimens are considered equivalent. Extending the duration of PPI-clarithromycin-containing triple therapies from 7 to 14 days improves the eradication success by about 5 % and may be considered.

OR

Bismuth Quadruple Therapy
- 4 x 3 capsules/d (postprandial intake) 10 days
  plus PPI 2 x /d for 10–14 days

SECOND LINE THERAPY
Bismuth Quadruple Therapy **plus** Omeprazole (see above)
10 days

OR

Levofloxacin 2 x 500 mg/d, Amoxicillin 2 x 1000 mg/d
7–14 days
Rising rates of levofloxacin resistance should be taken into account.

THIRD LINE THERAPY
based on susceptibility testing only (!)

[Malfertheiner et al., Gut 2012 ; 61:646–664.]

H. pylori in clinical practice

***H. pylori* testing under PPI therapy:**
PPI should be stopped for 2 weeks before testing by culture, histology, rapid urease test, urea breath test or stool Ag test. If it is not possible, **validated IgG serology can be performed.**

***H. pylori* and peptic ulcer disease:**
In uncomplicated duodenal ulcer, prolonging acid inhibition with PPI is not recommended after completion of *H. pylori* treatment. In gastric ulcer and complicated duodenal ulcer, prolonging PPI therapy is recommended.

H. pylori eradication treatment should be started at reintroduction of oral feeding in cases of bleeding ulcer.

***H. pylori* – tests to control eradication success:**
The urea breath test or a laboratory-based validated monoclonal (Ag) stool test are both recommended as non-invasive tests for determining the success of eradication treatment. There is no role for serology. The time for testing the success of *H. pylori* eradication after the end of treatment should be at least 4 weeks (>4 weeks after the last antibiotic dose, >2 weeks after the last PPI intake).

Possible causes for *H. pylori* treatment failure (relapse):
1. Low medication adherence (compliance)
2. Resistance of the specific *H. pylori* strain
3. Smoking, bacterial virulence, low absorption of antibiotics/PPI, etc.

Reinfection with *H. pylori* after eradication is rare in developed countries but more common in developing countries at around 13%.

[Federico A et al., World J Gastroenterol 2014 January 21; 20(3): 665-672. Malfertheiner P et al., Gut 2012;61:646-664 («Maastricht IV»). Fischbach W, et al., S3-guideline 'Helicobacter pylori and gastroduodenal ulcer disease']. Z Gastroenterol 2009; 47: 68–102]

Peptic Ulcer Disease

PPI therapy duration (standard dose):
Erosive gastritis/duodenitis: 4 weeks
Gastric/duodenal ulcer: 8 weeks

Differential diagnosis: *H. pylori*-negative, NSAID-negative peptic ulcer disease (approx. 10%)

- False negative *H. pylori*-test (under PPI-therapy, after antibiotic therapy)
- Undiscovered ASA/NSAID intake
- Ulcerogenic medication (bisphosphonate, iron preparations)
- Stomach carcinoma, lymphoma
- IBD (Crohn's disease)
- *H. heilmannii*
- Systemic mastocytosis
- Zollinger-Ellison syndrome
- History of partial stomach resection
- History of radiotherapy
- SSRI

Strategy for long-term NSAID therapy
Risk factors for NSAID-associated peptic ulcer disease
Gastrointestinal risk

- Age >65 years, high dose-NSAID therapy, history of peptic ulcer disease, co-medication with aspirin cardio, corticosteroids, or anticoagulation
- Low risk: no risk factors; moderate risk: 1–2 risk factors; high risk: >2 risk factors

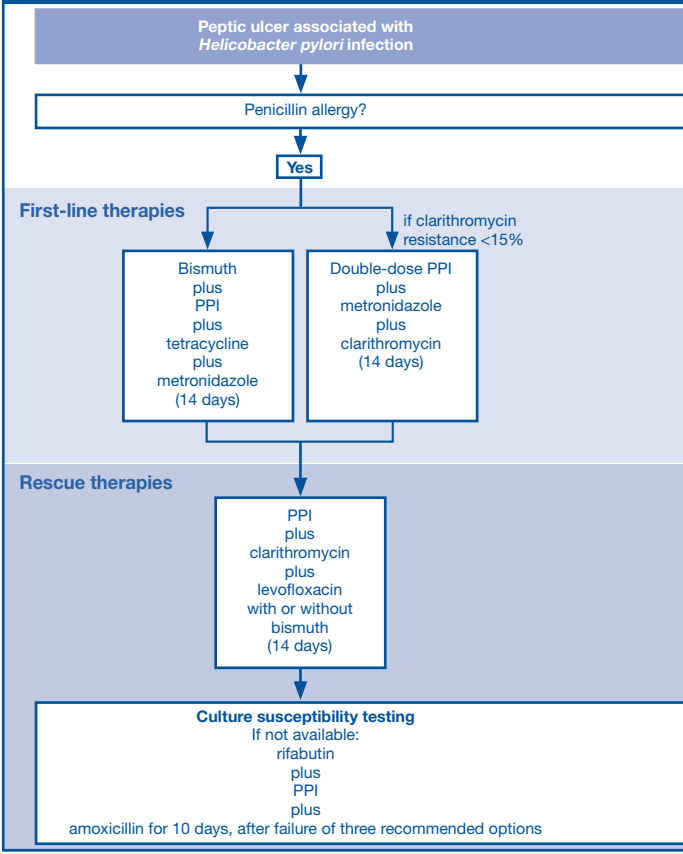
Cardiac risk

- Low: 10-year mortality <10%, High: 10-year mortality ≥10%

	Gastrointestinal risk		
	Low	Moderate	High
Low cardiac risk	NSAID	NSAID + PPI COX-2	NSAID + PPI COX-2 + PPI
High cardiac risk	Naproxen + PPI	Naproxen + PPI	No NSAID/COX-2

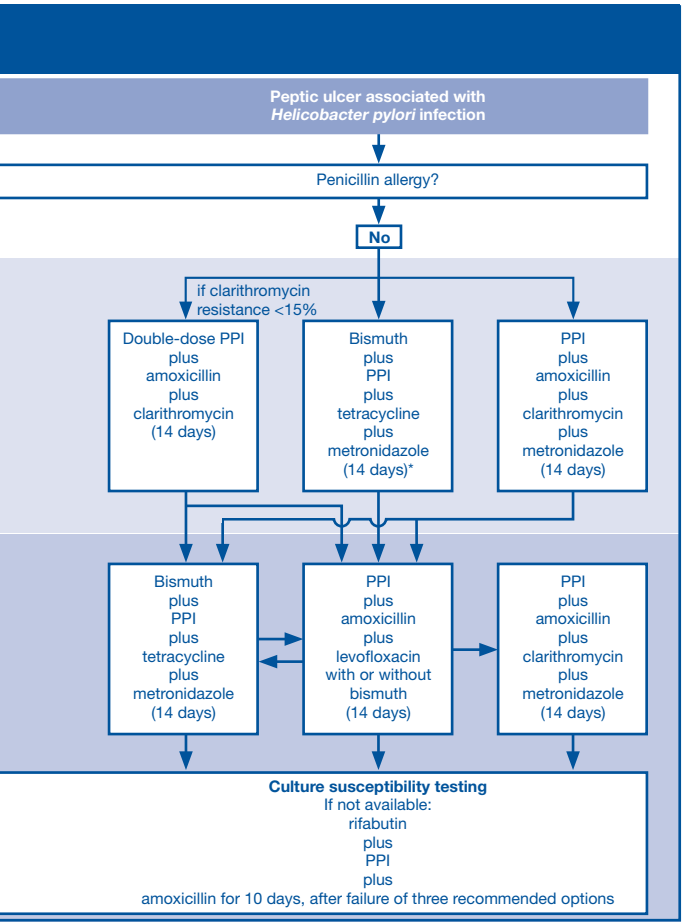
Cycloxygenase-2-inhibitors (COX-2); proton-pump inhibitor (PPI).

Algorithm for management of *Helicobacter pylori* in peptic ulcer disease



PPI = proton pump inhibitor

* Preferred option in areas with high resistance to clarithromycin and metronidazole



[Peptic ulcer disease. Lanas A, Chan FKL. Lancet. 2017 Aug 5;390(10094):613-624]

Peptic ulcers are described using the Forrest classification:

Forrest Classification:	Prevalence:	Relapse Bleeding Rate*	Fatality Rate*
Ia (Spurting hemorrhage) 	10%	90%	26%
Ib (Oozing hemorrhage)	10%	10–20%	10%
IIa (Visible vessel) 	25%	50%	11%
IIb (Adherent clot) 	10%	25–30%	7%
IIc (Hematin on ulcer base) 	10%	10%	3%
III (No signs of recent hemorrhage)	35%	< 5%	2%

**without endoscopic therapy*

[Adapted from: Forrest JA: Lancet 1974; Laine L: N Engl J Med 1994; Katschinski B: Dig Dis Sci 1994]

Risk stratification:
The use of risk stratification tools is recommended by the International Consensus Upper Gastrointestinal Bleeding Group.
[Barkun AN et al.: Ann Intern Med 2010]

Glasgow-Blatchford Score (GBS):
Need for intervention in suspected upper GI bleeding

Risk marker:		Score value:
Blood urea: (mmol/L)	6.5–7.9	2
	8–9.9	3
	10–24.9	4
	≥25	6
Hemoglobin: ♂ (g/L)	120–129	1
	100–119	3
	<100	6
Hemoglobin: ♀ (g/L)	100–119	1
	<100	6
Systolic blood pressure: (mm Hg)	100–109	1
	90–99	2
	<90	3
Pulse ≥ 100 /min		1
Melaena		1
Syncope		2
Hepatic disease		2
Cardiac failure		2

- The GBS is based only on clinical and laboratory variables and can be assessed in the ER without endoscopy

[Blatchford O, Murray WR, Blatchford M: Lancet 2000]

- A low-risk cohort (score value = 0) has a negative predictive value of 100% for rebleeding, endoscopic intervention, and death

[Stanley AJ et al: Lancet 2009]

- In the validation group, scores of 6 or more were associated with a greater than 50% risk of needing an intervention

Online Calculator:
http://www.mdcalc.com/glasgow-blatchford-bleeding-score-gbs

The **Rockall score** predicts mortality and re-bleeding risk from gastrointestinal ulcer bleeding:

Risk marker:		Score value:
Age (years):	<60 60–79 ≥80	0 1 2
Shock index:	No shock Pulse >100, SBP* >100 SBP* <100	0 1 2
Comorbidity:	No major comorbidity Major comorbidity Renal failure, Liver failure, metastatic cancer	0 2 3
Endoscopic diagnosis:	Mallory-Weiss lesion all other diagnoses GI malignancy	0 1 2
Evidence of bleeding:	None Blood, adherent clot, spurting vessel	0 2

[Rockall TA, Logan RFA et al.: Lancet 1996]
Online Calculator: http://www.bsg.org.uk/rockall-score-calculator.html
**SBP = Systolic blood pressure*

Score:	Relapse bleeding:	Mortality:
<3	5%	1%
3–5	15%	5%
≥6	>30%	>15%

CAVE: The Rockall score underscores the rate of recurrent bleeding.
[Church NI et al.: Gastrointest Endosc 2006]

Recommendations for the management of upper gastrointestinal bleeding:

- Immediately evaluate and initiate appropriate resuscitation
- Closely monitor vital signs and airway
- Give nothing orally
- Two large caliber (16 gauge or larger) peripheral catheters or a large central venous line
- Provide supplemental oxygen and crystalloid fluid
- Transfuse if hemoglobin <80–90 g/L in high-risk patients or <70 g/L in low-risk patients. (MEMO: Avoid over-transfusion in variceal bleeding, be restrictive)
- Prognostic scales are recommended for early stratification of patients into low-and high-risk categories for rebleeding and mortality
- Acid suppression with PPI: e.g. Pantoprazole 80 mg bolus followed by 8 mg/h infusion
- Prokinetics (erythromycine 250 mg i.v. in 0.9 % saline solution over 15 minutes, >30 minutes before endoscopy) can improve gastric visibility
- Early endoscopy (within 24 hours of presentation) is recommended for most patients with acute upper gastrointestinal bleeding
- Selected patients with acute ulcer bleeding who are at low risk for rebleeding on the basis of clinical and endoscopic criteria may be discharged promptly after endoscopy
- Routine second-look endoscopy is not recommended
- A second attempt at endoscopic therapy is generally recommended in cases of rebleeding
- In patients who receive low-dose ASA and develop acute ulcer bleeding, ASA therapy should be restarted as soon as the risk for cardiovascular complication is thought to outweigh the risk for bleeding
- In patients with previous ulcer bleeding who require cardiovascular prophylaxis, it should be recognized that clopidogrel alone has a higher risk for rebleeding than ASA combined with a PPI

[Barkun AN et al.: Ann Intern Med 2010]

	GAVE	PHG
Patient characteristics	No clear association with cirrhosis or portal hypertension; loose association with other autoimmune diseases	Predominantly seen in portal hypertension with/ without cirrhosis
Endoscopic findings	Erythema limited to the antrum	Tends to localize to fundus and corpus
Histological findings	Fibrin microthrombi; fibromuscular hyperplasia, increased neuroendocrine cells	Ectatic mucosal capillaries only
Management		
Pharmaco-therapy	Estrogen/progesterone; octreotide; tranexamic acid; thalidomide; serotonin antagonist; corticosteroids	Nonselective beta-blockers[a]; somatostatin/octreotide
Invasive therapy	Thermal ablation (argon plasma coagulation/ bipolar electrocoagulation); endoscopic band ligation	TIPS; liver transplantation

Comparison of GAVE (gastric antral vascular ectasia) and PHG (portal hypertensive gastropathy)

[a] Patient with PHG-associated bleeding: ß-blockers should be used for prevention of recurrent bleeding (Baveno V Workshop 2010).

[Bezawit D. et al.: Approach to the management of portal hypertensive gastropathy and gastric antral vascular ectasia. Clinical Liver Disease 2012, Vol. 1; 163-166]

Rome IV Criteria

B. Gastroduodenal Disorders

B1. Functional dyspepsia
- B1a. Postprandial distress syndrome (PDS)
- B1b. Epigastric pain syndrome (EPS)

B2. Belching disorders
- B2a. Excessive supragastric belching
- B2b. Excessive gastric belching

B3. Nausea and vomiting disorders
- B3a. Chronic nausea vomiting syndrome (CNVS)
- B3b. Cyclic vomiting syndrome (CVS)
- B3c. Cannabinoid hyperemesis syndrome (CHS)

B4. Rumination syndrome

B1. Functional Dyspepsia

Diagnostic criteria[a,b]

1. One or more of the following:

A. Bothersome postprandial fullness
B. Bothersome early satiation
C. Bothersome epigastric pain
D. Bothersome epigastric burning

AND

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

[a] Must fulfill criteria for B1a. PDS and/or B1b. EPS.
[b] Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

B1a. Postprandial Distress Syndrome

Diagnostic criteria[a]

Must include one or both of the following at least 3 days per week:
1. Bothersome postprandial fullness (ie, severe enough to impact on usual activities)
2. Bothersome early satiation (ie, severe enough to prevent finishing a regular-size meal)

No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy)
[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Supportive remarks
- Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present
- Vomiting warrants consideration of another disorder
- Heartburn is not a dyspeptic symptom but may often coexist
- Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia

Other individual digestive symptoms or groups of symptoms, eg, from gastroesophageal reflux disease and the irritable bowel syndrome may coexist with PDS

B1b. Epigastric Pain Syndrome

Diagnostic criteria[a]

Must include at least 1 of the following symptoms at least 1 day a week:
1. Bothersome epigastric pain (ie, severe enough to impact on usual activities)

AND/OR

2. Bothersome epigastric burning (ie, severe enough to impact on usual activities)

No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine in- vestigations (including at upper endoscopy).
[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

Supportive remarks
1. Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting
2. Postprandial epigastric bloating, belching, and nausea can also be present
3. Persistent vomiting likely suggests another disorder

[Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal Disorders. Gastroenterology 2016;150:1380-92.]

C1. Diagnostic Criteria[a] for Irritable Bowel Syndrome

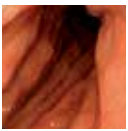
Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

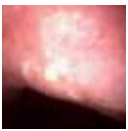
1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

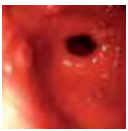
[Lacy BE, Mearin F, Chang L, et al. Bowel Disorders. Gastroenterology 2016;150:1393-07.]

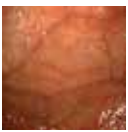
Gastritis – endoscopic classification


Erythematous / exudative

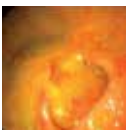

Erythematous / exudative

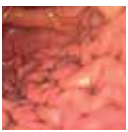

Flat erosive


Elevated erosive


Atrophic


Hemorrhagic


Reflux


Rugal / hyperplastic

Endoscopic follow-up

- NOT with duodenal ulcer
- Gastric ulcer after 8 weeks (5–11% of all stomach ulcers are malignant)
- For young patients with no suspicious stomach ulcer and risk status (H. pylori, ASS/NSAID), re-endoscopy can be waived.

[McColl Ke. Am J Gastroenterol. 2009] [Lanza FL, et al. Am J Gastroenterol 2009]

Gastritis

Sidney classification – Endoscopy

Morphology

- Erythematous/exudative gastritis
- Gastritis with flat erosions
- Gastritis with polypoid erosions
- Atrophic gastritis
- Hemorrhagic gastritis
- Reflux gastritis
- Ménétrier's disease («giant rugal folds» gastritis)

Localization

- Pangastritis, corpus gastritis, antrum gastritis

Alarm symptoms for further workup

- Abnormal blood studies
- Anemia
- Anorexia
- Blood in stools
- Family history of colon cancer or inflammatory bowel disease
- Fever
- Malnutrition
- Nocturnal symptoms
- Onset in patients >50 y
- Palpable abdominal or rectal mass
- Persistent diarrhea or severe constipation
- Recent antibiotic use
- Rectal bleeding
- Weight loss

Heterotopic gastric mucosa of the esophagus or inlet patch:

Definition:

Island of ectopic gastric mucosa in the proximal esophagus. Most accepted etiology is congenital. Can be colonized with H. pylori. Incidence 1–14% of endoscopy.

Localization: typically on the lateral walls a few cm distal to the upper esophageal sphincter

Size: mm to 3–5 cm. Unique or multiple.

Clinico-pathological Classification:

Typ I: Asymptomatic (most patients)

Typ II : Symptomatic without morphologic changes (regurgitation, dysphagia, hoarseness, globus, throat discomfort and chronic cough)

Typ III: Symptomatic with morphologic changes (benign complications: strictures, ulcers, webs, stenoses, fistula)

Typ IV: Intraepithelial neoplasia (dysplasia) (low-grade/high-grade)

Typ V: Invasive adenocarcinoma (extremely rare)

Treatment:

Typ I: No.

Typ II

And III: PPI-Therapy. Stenosis can be dilated. Biopsy is mandatory to rule out neoplasia.

Typ IV: Few cases no standard care. Endoscopic surveillance is recommended. Argon-plasma. Resection.

[Chong VH. World J Gastroenterol. 2013 Jan 21;19(3):331-8.Clinical significance of heterotopic gastric mucosal patch of the proximal esophagus.] [von Rahden BH1, Stein HJ, Becker K, Liebermann-Meffert D, Siewert JR.Am J Gastroenterol. 2004 Mar;99(3):543-51. Heterotopic gastric mucosa of the esophagus: literature-review and proposal of a clinicopathologic classification]

Stomach
OTSClip

Indications
- perforation
- fistula
- anastomotic leak
- bleeding
- narrowing the anastomosis after gastric-bypass surgery

Product
- 3 sizes: 11 – 12 – 14 mm
  maximal outer diameter of the endoscope-tip fitting the cap
- 2 depths of cap: 3 mm: better overview
  6 mm: grasping more tissue
- 3 shapes of teeth: type a: atraumatic
  type t: traumatic
  type gc: gastric closure (long and sharp)

Version of OTSC®: type a type t type gc

Endoscopie size		∅ 8.5–11 mm	∅ 10.5–12 mm	∅ 11.5–14 mm
Depth of cap	3 mm	● ●	● ●	● ●
	6 mm	● ●	● ● ●	● ●

- application aids: OTSC Anchor® (165 cm)
  OTSC Anchor® 220tt (220 cm) for thin tissue
  OTSC Twin Grasper® in 165 cm and 220 cm


OTSC Anchor

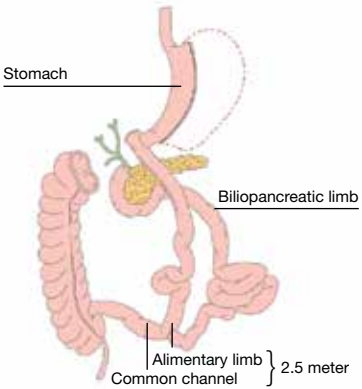
- working channel: Only OTSC System: minimal 2.8 mm
  OTSC System in combination with an application aid: minimal 3.2 mm
  optimal: >3.2 mm


OTSC Twin Grasper

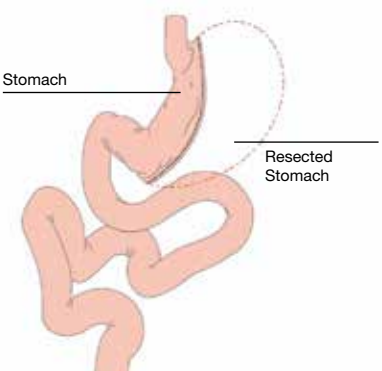
Pitfalls/Tips

- the size of the clip is dependent on the size of the endoscope, and not of the lesion
- OTSC System size14 is mostly too big to pass the upper esophageal sphincter
- retrieving the OTSC System with loaded clip back through the mouth: risk of accidental release on the tongue – therefore good sedation, cutting plier nearby
- if possible control the release of the clip with fluoroscopy
- OTSC Twin Grasper: do not open both sides simultaneously
- OTSC Twin Grasper: pull back into the cap, under fluoroscopic control, to be sure that it is not getting fixed in the clip. If it is not possible: only suction!
- Risk of perforation: therefore always use CO_2
- Risk of perforation in the esophagus: consider in combination with a covered stent

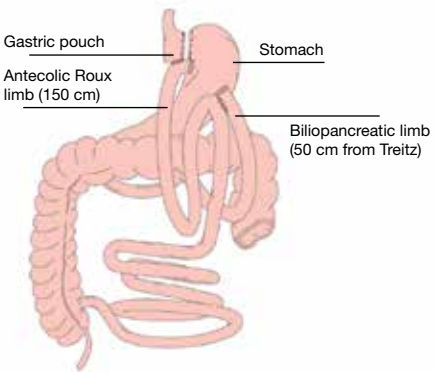
Biliopancreatic diversion with duodenal switch



Sleeve gastrectomy



Roux-en-Y Gastric Bypass



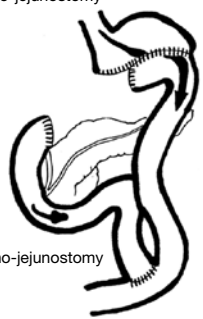
Gastric surgery 1

Billroth I

Billroth II

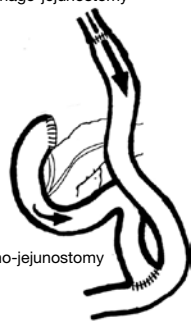
Gastric surgery 2

Roux-en-Y
gastro-jejunostomy



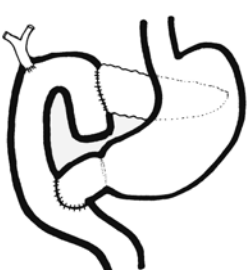
Jejuno-jejunostomy

Roux-en-Y
esophago-jejunostomy

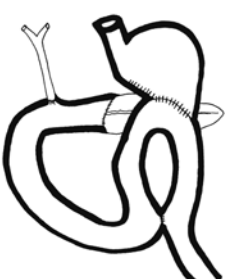


Jejuno-jejunostomy

Pylorus preserving
Pancreaticoduodenectomy



Pancreaticoduodenectomy
(Whipple Operation) with
Braun's anastomosis



Noninvasive pathogens (small intestine)	Invasive diarrhea (ileocolonic)
Viruses Rotavirus Calicivirus (norovirus, Norwalk agent) Adenovirus (enteric) Astrovirus	**Viruses** Cytomegalovirus Herpes simplex virus type II
Bacteria Vibrio cholera Salmonella Toxigenic E. coli (ETEC, EPEC, EAEC) Aeromonas hydrophila Listeria monocytogenes Tuberculosis	**Bacteria** Campylobacter species Salmonella species Shigella species E. coli 0157:H7 (EHEC) Yersinia Clostridium difficile Noncholera Vibrio Aeromonas hydrophila Plesiomonas shigelloides EIEC Listeria monocytogenes Tuberculosis
Parasites Giardia lamblia Cryptosporidia Isospora belli Cyclospora cayetanensis	**Parasites** Ameba Trichuris trichiura Balantidium coli Blastocystis hominis (facultative pathogen)

ETEC, enterotoxigenic E. coli; EPEC, enteropathogenic E. coli; EAEC, enteroaggregative E. coli; EHEC, enterohemorrhagic E. coli; EIEC, enteroinvasive E. coli.

[Adapted from DDSEP®7 Digestive Diseases Self-Education Program® (published by AGA 2013)]

Complications after bariatric surgery

- Late Anastomotic stricture (3%–12%)
- Marginal ulcer (0.5%–20%)
- «Candy Cane» syndrome
- Gastroesophageal reflux
- Bowel obstruction (2.5%)
- Incisional hernia (0.5%–8%)
- Internal hernia (1%–3%)
- Dumping syndrome (up to 30%)
- Cholecystitis (up to 30%)
- Anemia/Vitamin deficiencies

[Walsh et al. World J Gastrointest Endosc. 2015; 7(5): 518–523.]

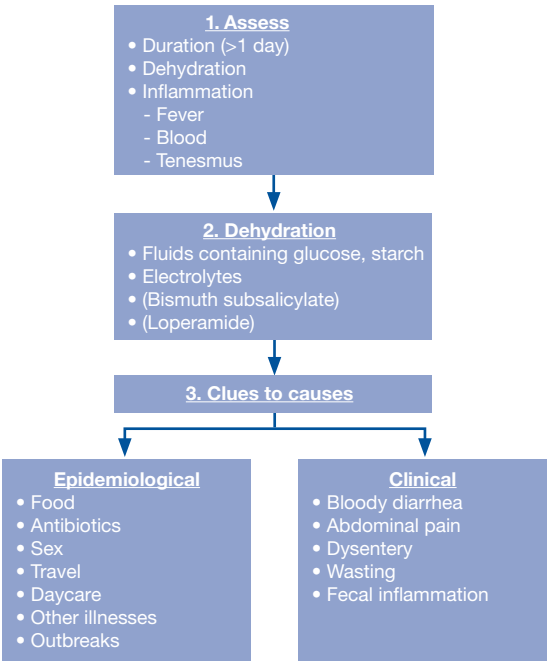
Assessment of patients with diarrheal disease

1: Adequately assess the patient and determine the level of dehydration. Important factors include duration of illness; alertness, skin turgor, mucous membrane dryness, sunken eyes or fontanelles, and postural hypotension all indicate moderate or severe hypovolemia and dehydration; signs of inflammation include fever, bloody stool, and tenesmus.

2: In cases of dehydration (panel 2), patients can be rehydrated by oral administration of fluids that contain glucose, sugar or starch, and electrolytes. If patients are unconscious or vomiting, fluids should be replaced intravenously. Consider loperamide.

3: Epidemiologic and clinical clues can be used to identify the infectious agent. Consider immunoglobulin A deficiency, which predisposes to giardiasis, and immunosuppression (particularly in patients with AIDS), which can lead to protozoal infections, Mycobacterium avium complex, and intestinal cytomegalovirus infections. Clinical features can also be used to identify the infectious agent. Bloody diarrhea is associated with Shiga toxin-producing E. coli, Shigella and E. histolytica infections; abdominal pain with Yersinia and some C. difficile infections; dysentery with Shigella or Campylobacter infection; wasting with Giardia or Cryptosporidium infection; and fecal inflammation with Shigella, Campylobacter, Salmonella, and some E. coli and C. difficile infections.

Diagnosis, treatment, and causes of diarrhea



[Pawlowski et al., Gastroenterology 2009;136:1874-86]

Algorithm for severe acute bloody, inflammatory, or outbreak-related infectious diarrhea

1. Obtain fecal specimen for one or more panels, if severe, bloody, inflammatory or outbreak suspected

A. Community-acquired or travelers's diarrhea

Culture and test for: *Salmonella, Shigella, Campylobacter* + (if blood or HUS) *E coli* O157:H7 + SLT + *C difficile* toxins A+B (esp if recent antibiotics, chemotherapy, or recent hospitalization)

- Consider empiric fluoroquinolone therapy for adults or sulfa-trimethoprim-sulfamethoxazole for children with inflammatory; modify therapy as needed following testing results.
- Consider erythromycin or azithromycin for suspected *Campylobacter* infection.
- Avoid antimotility, quinolone and sulfatrimethoprim if suspected EHEC infection (afebrile, bloody diarrhea).

B. Nosocomial diarrhea (onset >3 d of hospitalization)

Test for: *C difficile* toxins A+B +, if outbreak, >65 yo with comorbidity, immunocompromised, neutropenic or suspected systemic enteric infection add: *Salmonella, Shigella, Campylobacteer* and, if bloody, EHEC (as in Panel A)

- Discontinue antimicrobials if possible
- Consider empiric metronidazole or if illness is severe or patient is immunocompromised consider oral vancomycin

C. Persistent diarrhea (>7 d)

Consider protozoa: *Giardia, Cryptosporidium, Cyclospora, Isospora belli* + inflammatory screen

D. If immunocompromised (especially HIV+) add:

Microsporidia
Mycobacterium avium complex

- Treat per test results
- Consider empiric metronidazole or tinidazole if suspected *Giardia* infection

2. Consider antimicrobial therapy for specific pathogens

[Pawlowski et al., Gastroenterology 2009;136:1874-86]

Small and large bowel
Chronic Diarrhea

Definition: Decreased stool consistency up to >4 weeks

Differential diagnosis – chronic diarrhea

- **Osmotic diarrhea**
  - Laxative abuse (osmotic)
  - Nutritional (Mg^{2+}, PO_4^{3-}, SO_4^{2-})
  - Carbohydrate malabsorption
- **Steatorrhea**
  - Malabsorption syndrome
    - *Short bowel syndrome*
    - *Celiac disease*
    - *Bacterial overgrowth*
    - *Mesenterial ischemia*
  - Maldigestion syndrome
    - *Pancreas insufficiency*
    - *Excess bile acids*
- **Inflammatory diarrhea**
  - Inflammatory bowel disease
    - *Ulcerative C./Crohn's disease*
    - *Ulcerative jejunoileitis*
  - Infectious diarrhea
    - *Pseudomembranous colitis*
    - *Invasive bacteria (Yersinia, tuberculosis)*
    - *Ulcerative viruses (CMV, HSV)*
    - *Invasive parasites (amoebas)*
  - Ischemic colitis
  - Colitis
  - Neoplasms
    - *Colon carcinoma, lymphoma*
    - *Diverticulitis*

- **Secretory diarrhea**
  - Laxative abuse (not osmotic)
  - Chologenic diarrhea (terminal ileum, postcholecystectomy)
  - Bacterial toxins
  - Inflammatory bowel disease
    - *Ulcerative C./Crohn's disease*
    - *Microscopic colitis*
    - *Diverticulitis*
  - Vasculitis
  - Medications / toxins
  - Motility disorder
    - *Post-vagotomy diarrhea*
    - *Post-sympathectomy diarrhea*
    - *Diabetic autonomic neuropathy*
    - *Hyperthyroidism*
    - *Irritable bowel syndrome*
  - Neuroendocrine tumors
    - *gastrin, VIP, somatostatin*
    - *Mastocytosis, carcinoid*
    - *Medullary thyroid carcinoma*
  - Neoplasms
    - *Colon carcinoma, lymphoma*
    - *Villous adenoma*
  - M. Addison
  - Hereditary
  - Idiopathic

Differential diagnosis – medication

antibiotics, antidepressants, antihypertensives (beta blockers, ACE-inhibitors), diuretics, anticonvulsives, lipid lowering drugs, antidiabetics (biguanides), H2-blockers / PPIs, theophylline, chemotherapy, alcohol, especially Olmesartan (celiac-like)

Differential diagnosis – infections

Bacteria:	*Clostridium difficile, Campylobacter sp., Salmonella sp., Tropheryma whipplei, Aeromonas, Plesiomonas shigelloides*
Parasites:	*Giardia lamblia, Entamoeba histolytica, Cryptosporidium, Microsporidia, Isospora belli, Ascaris, Strongyloides stercoralis*

[Fine KD, et al. AGA technical review on the evaluation and management of chronic diarrhea. Gastroenterology. 1999]

Anamnesis	**Suspected diagnosis**
Nutrition	sweeteners, allergies, intolerances, milk products, caffeine, fibrous material, mint, fruits, seafood
Weight loss	malabsorption, pancreatic insufficiency, M. Whipple, neoplasia, abdominal angina
Pain	IBD, IBS, stenosis, abdominal angina
Extraintestinal symptoms	hyperthyroidism, diabetes mellitus, vasculitis, M. Whipple, IBD, mastocytosis, tuberculosis
Personal anamnesis	radiotherapy, operation, antibiotic therapy, chemotherapy

Small and large bowel
Chronic Diarrhea

Initial examinations

Blood	Hemogram with mechanical differentiation, INR/Quick, TSH, resorption parameters (i.e. potassium, calcium, phosphate, zinc (if applicable), albumin, cholesterol, ferritin, folic acid, vitamin B12, alkaline phosphatase, 1,25-OH vitamin D)
Stool	bacteriology, *C. difficile* toxin/culture, parasites (1 x native, 2 x SAF), calprotectin

Further diagnostics

Blood	Tissue transglutaminase antibodies, endomysium antibodies, total IgA (celiac disease) Chromogranin A, gastrin, calcitonin (neuroendocrine tumor) IgE tryptase (food intolerances)
Stool	Elastase, Chymoptrypsin (pancreas insufficiency) Bisacodyl and phenolphthalein, if applicable (laxative abuse)
Others	H2-lactose breath test (lactose intolerance) Gastroscopy with small intestinal biopsies and fluid (SIBO) ileocolonoscopy with biopsies from all segments (microscopic colitis) Secretin stimulation test (pancreatic insufficiency) Anthrachinone in urine (laxative abuse) Fecal collection for 72 hours as an important diagnostic tool for clarification of chronic diarrhea consider sorbitol or fructose intolerance

Stool Osmolar/ Osmotic Gap:

stool osmotic gap = stool osm – (2 * (Na + K))
>50 mosmo/kg suggests osmotic diarrhea
<50 mosmol/kg suggests secretory diarrhea
(The stool osmolality is usually not directly measured, and is often given a constant in the range of 290 to 300)

Osmotic diarrhea

Laxative abuse (osmotic)
- Nutritional (Mg,…)
- Carbohydrate malabsorption
- Bile salt deficiency
- Pancreatic insufficiency
- Celiac/ Tropical Sprue
- Whipple's disease
- Intestinal Lymphoma
- Medications
- Short bowel Syndrome

Inflammatory diarrhea

- Inflammatory bowel diseases
- Ulcerative Colitis/ Crohn's Disease
- Ulcerative jejunoileitis
- Diverticulitis
- NICHT: microscopic colitis
- Infectious diarrhea
- Pseudomembranous colitis
- Invasive bacteria (Yersinia, tuberculosis, others)
- Ulcerative viruses (CMV, HSV)
- Invasive parasites (amoebas, others)
- Ischaemic colitis
- Radiation colitis /NICHT: irradiation
- Neoplasms
- Colon carcinoma, lymphoma

Parasitic causes of chronic diarrhea

Parasite	Affected organ	Symptoms
Entamoeba histolytica	Colon, extraintestinal	Asymptomatic shedding of cysts Slight unspecific GI-symptoms, bloody dissentery, toxic megacolon, abscess
Cryptosporidiae	Small intestine, intracellular	Acute watery diarrhea, gastroenteritis Rarely fever, loss of weight, usually selflimiting, prlonged symptoms if immunosuppression
Giardia lamblia	Upper small intestine, Biliary tree, gallbladder	Asymptomatic shedding of cysts Acute diarrhoe Chronic diarrhoe with bloating , Malodorous stools Malabsorption
Microsporidia	Small intestine, intracellular	Chronic diarrhea, nausea, weightloss Rare: Cholangitis/ Cholecystitis
Blastocystis hominis	Small intestine, intracellular	Facultative pathogenic, asymptomatic shedding of cysts common; Rarely watery diarrhea, gastroenteritis, bloating
Dientamoeba fraglilis	Cecum, ascending colon	Facultative pathogenic, asymptomatic shedding of cysts common; Rarely watery diarrhea, gastroenteritis, international travelers diarrhea, eosinophilia

Occurence / affected population	Diagnostic tests	Treatment	Comments
Worldwide, mainly tropical / subtropical regions, developing countries	PCR or antigen from stool not older than 36 h Serology if suspicion of abscess	Paromycin 3x500 mg/d for 7–10 d or Diloxanide fuorate 3x500 mg/d for 10 d or Metronidazole 3x750 mg/d for 7–10 d	No differentiation from apathogenic E. dispar or E. moshokovskii by microscope only
Worldwide	SAF-Stool: Microscopic assessment with special staining	Paromomycin 3x500 mg for 7 d Alternatively Nitazoxanide 2x500 mg for 3 d	Treatment can be difficult if immunosuppressed; Oocytes are chloride-resistant
Worldwide Severer cases in children	Stool microscopy (SAF or native); Duodenal aspiration Antigen detection	Metronidazole 500 mg for 7 d	
Worldwide; usually in Immunosuppression, rare in Immunocompetent	PCR or microsopy with special staining from stool or biopsy; serology	Albedazole 2x500 mg/d for 21 d HIV: 2x400 mg until CD4>200	
Tropical/subtropical regions, developing countries; Immunocompentent; Prolonged in Immunosuppression	Stool microscopy	TMP/SMX 160/800 mg 2x1/d for 7 d Metronidazole 3x500 mg for 7 d, Nitazoxanide 2x 500 mg/d for 3 d	Aim of therapy is symptomatic response, since eradication often is difficult
Worldwide, mostly developing countries; International Travelers	Stool microscopy	Ornidazole 2 g single dose Paromomycin 3x500 mg for 7–10 d Metronidazol 3x500 mg for 7–10 d	

Parasitic causes of chronic diarrhea

Parasite	Affected organ	Symptoms
Nematodes		
Angylostoma duodenalis, necator americanus Hookworm	Small intestine, adherent	Slight abdominal discomfort; Anemia, growth retardation in children; Löffler Syndrome
Ascaris lumbricoides	Small intestine, luminal	Asymptomatic, Slight abdominal discomfort; malabsorption, rare mechanical obstruction, Löffler Syndrome
Enterobius vermicularis (Pinworm); oxyuria	Colon, appendix, perianal region	Perianal itching, rarely appendicitis, loss of appetite/ weightloss in children
Stronglyoides stercoralis	Small intestinal wall	Symptomatic, abdominal discomfort diarrhea, bloating, Löffler syndrome, eosinophilia, hypersensitivity syndrome in immunosuppression (severe)
Trichinella spiralis	Intestinal wall, cysts in smooth muscle cells	Acute infectious state with eosinophilia, muscle ache, periorbital edema
Trichuris trichuria	Terminal ileum, cecum	Bloody dysentery, anemia, rarely mechanical obstruction, rectal prolapse

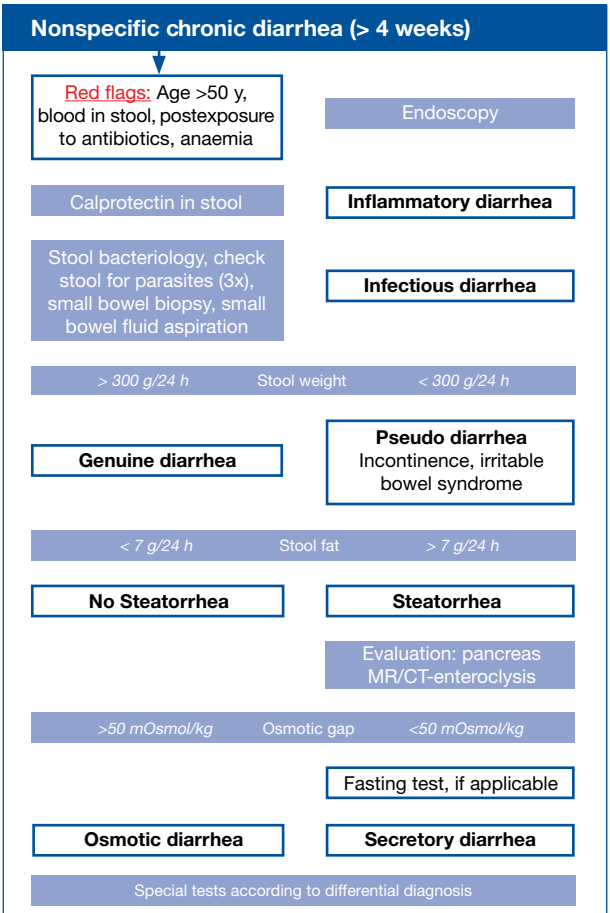
Occurence / affected population	Diagnostic tests	Treatment	Comments
Tropical / subtropical regions (migrants)	Eosinophilia (early stages), Stool microscopy	Albendazole 1x400 mg single dose	
Tropical / subtropical regions (migrants)	osinophilia (early stages), Stool microscopy	Albendazole 1x400 mg single dose Mebendazole 2x100 mg single dose, Ivermectin 1x200 µg / kg sinlge dose	
Worldwide, mostly children / retirement homes	Scotch tape technique; microscopy	Albendazole 400 mg or Mebendazole 100 mg single dose, repeat after 10–14 d	
Migrants from tropical regions, southeast Asia, sub-Saharan Africa	Stool microscopy, serology	Ivermectin 200 µg / kg / d for 3 d Albendazole 2x400 mg / d for 7–14 d	Hyperinfection in immunosuppression
Worldwide after consumption of venison (boar, bear)	Serology	Albendazole 400 mg / d for 10–14d plus Prednisone Mebendazole 3x500 mg / d for 10–14 d	
Tropical / subtropical regions (migrants)	Stool microscopy	Mebendazole 1x500 mg for 3 d Albendazole 1x400 mg / d for 3 d	

Parasitic causes of chronic diarrhea

Parasite	Affected organ	Symptoms
Trematodes		
Fasciola hepatica (Common liver fluke)	Biliary tree	Cholestasis, cholangitis, hepatomegaly, eosinophilia
Shistosoma japonicum (schistososomiasis)	Smalll intestine, venous system	Dermatitis (swimmer's itch) Katayama-fever with eosinophilia, chronic diarrhea, dystentery, hepatomegaly, cirrhosis,
Shistosoma mansoni (schistososomiasis)	Colon, venous system	HCC, pseudopolyps, rare: extraintestinal, cns affection
Cestodes		
Diphylobotrium latum (fish tapeworm)	Small intestine, luminal	Asymptomatic, slight abdominal discomfort, Vit-B12-deficiency, anemia
Taenia saginata (beef tapeworm)		Mostly asymptoma-tic, slight abdominal discomfort, proglottids in stool
Taenia solium (pork tapeworm)		
Cysticercosis	Tissue cysts, CNS	Mostly asymptomatic, epilepsia, elevated intracranial pressure

Occurence / affected population	Diagnostic tests	Treatment	Comments
Worldwide	Microscopy of Stool or biliary fluid, serology	Triclabendazole 10–12 mg/kg/d for 2 d Nitazoxanide 2x500 mg/d for 7 d	
Southeast Asia, China, Philippines (migrants and international travelers)	Stool microscopy, serology	Praziquantel 1x75 mg/kg in 2 or 3 doses, consider repeating in 2 months Prednisone if Katayama fever	Dermatitis 48 h and Katayama 4–8 weeks after exposure
Africa, middle east, south America, Caribbean (migrants and international travelers)		Praziquantel 1x60 mg/kg in 2 or 3 doses , consider repeating in 2 months Prednisone if Katayama fever	
Worldwide, mostly eastern Europe, Russia	Stool microsopy SAF-Stool (eggs and proglottids)	Praziquantel 1x10 mg/kg single dose Niclosamide 1x2 g single dose	
Worldwide			
	Serology from blood or Cereo-brospinal fluid, CT/MRI	Albendazole 15 mg/kg/d in 2 doses plus 50 mg/kg/d in 2 doses for 10 days plus dexamethasone 0.1 mg / kg/d (start steroids 1 week before antiparasitic medication)	

Small and large bowel
Chronic Diarrhea



[Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 10th Edition 2015]

Microscopic Colitis

Diagnostic Triad

- Chronic, watery diarrhea (+ potential weight loss, stomach pain)
- Macroscopically normal colonoscopy
- Pathologic histology

Abnormal immune response to luminal antigen in predisposed individuals. Common: medication (i.e. acarbose, aspirin, lansoprazole, NSAID, ranitidine, sertraline). Cumulative in autoimmune diseases (e.g. Hashimoto's thyroiditis, celiac disease!).

Differential diagnosis – chronic diarrhea

- ALWAYS based on histology (≥5 biopsies, at least 1 biopsy per colon segment)
- No relevance for prognosis (clinical assessment) or severity

Lymphocytic colitis

- Intraepithelial lymphocytosis (>20 / epithelial cells)
- Mixed inflammatory infiltrate in the lamina propria
- Impairment of epithelial cells (flattening of epithelial cells, vacuolization and detachment)
- Minimal crypt architecture dysfunction possible

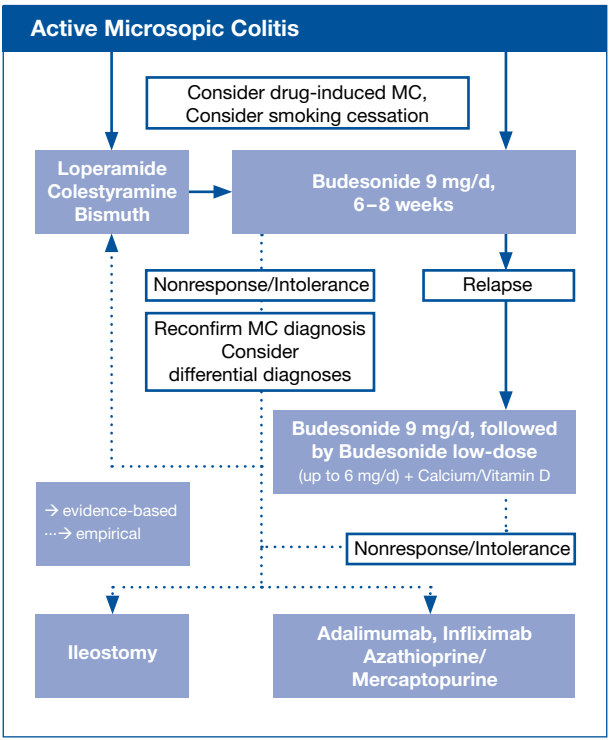
Collagenous colitis

- Broadened subepithelial collagen band 7–100 µm
- Intraepithelial lymphocytosis possible
- Impairment of epithelial cells (flattening of epithelial cells, vacuolization and detachment)
- Minimal crypt architecture dysfunction possible

Prognosis / Progression

- >80% spontaneous healing
- No increased mortality
- No increased risk of colon carcinoma
- 90% chronic intermittent progression
- No increased mortality
- No increased risk of colon carcinoma

Therapy of microscopic colitis



[Algorithm for the treatment of Microscopic Colitis proposed by the European Microscopic Colitis Group (EMCG) Münch A. et al., J Crohn Colitis 2012; 6: 932–45]

SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

SIBO syndrome: diarrhea, steatorrhea, vitamin B12 deficiency, hypoproteinemia
Most common bacteria: Streptococcus sp. (71%), E. coli (69%), Staphylococcus sp. (25%), Micrococcus (22%), Klebsiella (20%)

Promoting factors

Intestinal stasis – anatomical
Small intestinal diverticula, operations (Billroth II, gastric bypass), strictures (Crohn's disease, after operation)

Intestinal stasis – dysmotility
Diabetic autonomic neuropathy, sclerodermatitis, amyloidosis, idiopathic intestinal pseudo-obstruction, after radiotherapy, Crohn's disease

Achlorhydria
Chronic atrophic gastritis, proton pump inhibitor, older patients

Immunological factors
Hypo-/agammaglobulinemia, AIDS, immunosuppression

Multifactorial
Liver cirrhosis, kidney insufficiency, chronic pancreatitis, enterocolic fistula

Diagnosis

Invasive

- Small intestinal fluid aspirate
  Diagnosis: >10^5 CFU/mL *(cave: approximately 60% of the intestinal flora cannot be cultivated, low reproducibility (38%)*

Noninvasive

- Xylose breath test
  - 14C-Xylose: (standard in USA, radioactive isotope)
  - 13C-Xylose (expensive)
- H2 breath test
  - Glucose-H2 (most often used in Europe, but up to 15% false negatives due to non-hydrogen producers)
  - Lactulose-H2

Therapeutic approach

- Possible, but no standardized diagnostic criteria

Therapy

1. Treatment/correction of triggering factors
2. Treatment of bacterial overgrowth
3. Treatment of malabsorption syndrome

Antibiotic therapy over 7–10 days

- Ciprofloxacin (2x250 mg/d), norfloxacin (2x400 mg/d), metronidazole (3x250 mg/d), trimethoprim/sulfamethoxazole (2x160/800 mg/d), doxycycline (2x100 mg/d), amoxicillin/clavulanic acid (2x500 mg/d), rifaximin (1200 mg/d) or rifaximin 1650mg/day (high dose in SIBO therapy) Gentamycin 80mg/polymyxin 100mg 1-1-1-1 for 10 days. In case of relapse 1-1-1-1 for 14 days.

[Clinical Practice Inselspital Bern]

Return of bacterial growth: antibiotic therapy over 5–10 days every 4 weeks using various medications.

[Quigley, E. M. M. & Quera, R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics, and probiotics. Gastroenterology 130, 2006.]

[High dosage rifaximin for the treatment of small intestinal bacterial overgrowth E. SCARPELLINI, M. GABRIELLI, C. E. LAURITANO, A. LUPASCU, G. MERRA, G. CAMMAROTA, I. A. CAZZATO, G. GASBARRINI, A. GASBARRINI *Aliment Pharmacol Therapy 2007 Apr 1;25(7):781-6.*]

Treatment of Irritable Bowel Syndrome:

Cave:
Some of the agents have not been studied in randomised controlled trials in IBS and their efficacy may be limited.

Symptom	Treatment	Active pharmaceutical ingredient
Constipation	Fiber	Psyllium, Bran
	Osmotic laxatives	Polyethylene glycol/Macrogol
	Stimulant laxatives	Senna
		Bisacodyl
		Sodium picosulfate
	Prokinetic Agents	Prucalopride
		Lubiprostone
		Linaclotide
Diarrhea	Antidiarrheal agents	Loperamide
	Probiotics	Lactobacillus casei
		Bifidobacterium lactis
		Enterococcus faecalis
Abdominal Pain	Spasmolytics	Butylscopolamine
		Mebeverine
		Pinaverium bromide
	Tricyclic antidepressants	Amitriptyline
	Selective serotonin re-uptake inhibitors (SSRI)	Escitalopram
		Citalopram
		Sertraline
Bloating		Simethicone
		Dimethicone
Dyspepsia	Phytotherapeutics	STW 5
		Artichoke extract
		Peppermint oil

[Lacy BE, Mearin F, Chang L, et al. Bowel Disorders. Gastroenterology 2016;150:1393-07.]

	Dose per day	Comments
	individual	
	1–2 sachets	
	12–150 mg	
	5–10 mg	
	5–10 mg	
	1–2 mg	Not licensed for IBS with constipation
	2x24 µg	Not licensed for IBS with constipation
	1x290 µg, 30 min before meal	
	2–16 mg	
	individual	Dosing should be high and long enough
	10–100 mg	
	200–400 mg	
	50–200 mg	
	50–150 mg	Start with low doses
	10–50 mg	Start with low doses
	20–40 mg	
	50–200 mg	May cause diarrhea
	41–82 mg	
	1–3 tablets	
	3x20 drops	
	3x320 mg	
	3x187 mg	

Constipation

ROME IV Diagnostic Criteria[a] for Functional Constipation

1. Must include 2 or more of the following:[b]
   1. Straining during more than one-fourth (25%) of defecations
   2. Lumpy or hard stools (BSFS 1, 2) more than one-fourth (25%) of defecations
   3. Sensation of incomplete evacuation more than one-fourth (25%) of defecations
   4. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
   5. Manual maneuvers to facilitate more than one fourth (25%) of defecations (eg, digital evacuation, support of the pelvic floor)
   6. Fewer than 3 spontaneous bowel movements per week

2. Loose stools are rarely present without the use of laxatives

3. Insufficient criteria for irritable bowel syndrome

[a] Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

[b] For research studies, patients meeting criteria for OIC should not be given a diagnosis of FC because it is difficult to distinguish between opioid side effects and other causes of constipation. However, clinicians recognize that these 2 conditions might overlap.

[Lacy BE, Mearin F, Chang L, et al. Bowel Disorders. Gastroenterology 2016;150:1393-07.]

Causes of secondary constipation	
Organic	Colorectal cancer, extraintestinal mass, postinflammatory, ischemic or surgical stenosis
Neurological	Spinal cord injury, Parkinson's disease, paraplegia, multiple sclerosis, autonomic neuropathy, Hirschsprung's disease, chronic intestinal pseudo-obstruction
Myogenic	Myotonic dystrophy, dermatomyositis, scleroderma, amyloidosis, chronic intestinal pseudo-obstruction
Anorectal	Anal fissure and strictures, IBD, proctitis
Endocrine, metabolic	Diabetes mellitus, hypothyroidism, hypercalcemia, porphyria, chronic renal insufficiency, panhypopituitarism, pregnancy
Drugs	Opiates, antihypertensive agents, tricyclic antidepressants, iron preparations, anti-epileptic drugs, anti-Parkinsonian agents (anticholinergic or dopaminergic)
Diet, lifestyle	Low fiber diet, dehydration, inactive lifestyle

[Eoff JC. Optimal treatment of chronic constipation in managed care: review and roundtable discussion. J Manag Care Pharm. 2008;14:1–15]

Three Main Types of Primary (idiopathic) Constipation

Normal-transit constipation (NTC)	Most common subtype	Frequently overlaps with IBS-C
Slow-transit constipation (STC)	Mostly characterized by reduced phasic colonic motor activity	Common in woman
Pelvic floor dysfunction	Poor coordination of pelvic floor and anal sphincter	Considerable overlap with STC and NTC

[Tack J et al. Diagnosis and treatment of chronic constipation – a European perspective. Neurogastroenterol Motil. 2011; 23(8): 697–710.
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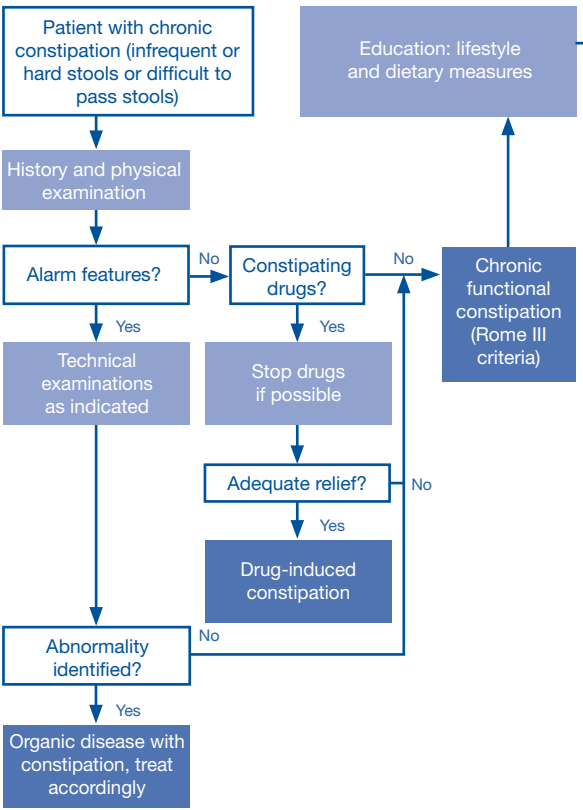
Guideline-supported General Treatment Pathways

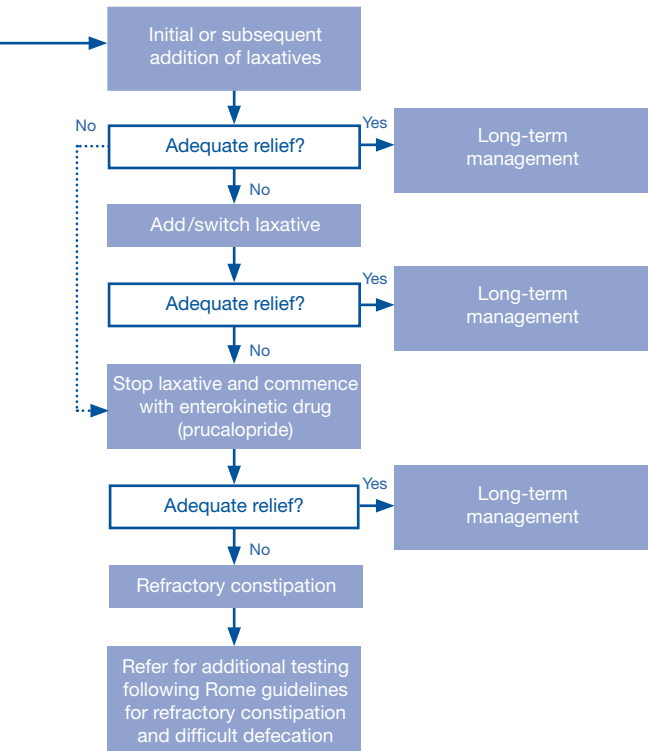
1. Exclude other pathologies and secondary causes
2. Begin treatment with dietary and lifestyle adjustments
3. Move to osmotic laxatives, stool softeners and bulk-forming agents (no consensus on the order in which these should be tried)
4. Move to stimulant laxatives, suppositories and/or enemas
5. Surgery should be used as a last resort or to treat identified disorders that require surgical correction

[Tack J et al. Diagnosis and treatment of chronic constipation – a European perspective. Neurogastroenterol Motil. 2011; 23(8): 697–710]

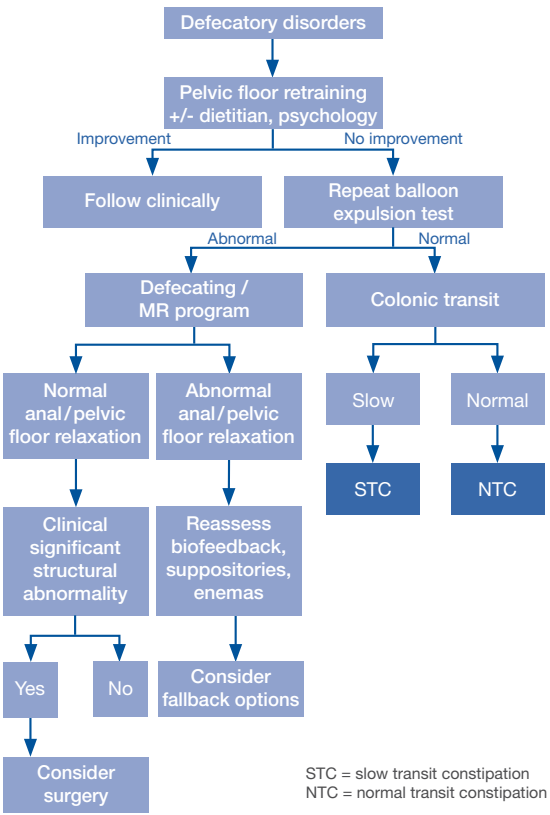
Enterokinetic treatment algorithm



[Tack J et al. Diagnosis and treatment of chronic constipation – a European perspective. Neurogastroenterol Motil. 2011 August; 23(8): 697–710].

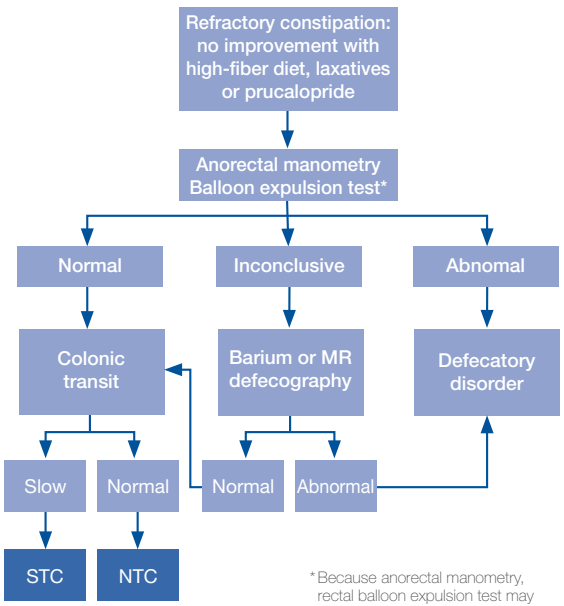


Algorithm: Defecatory disorders



[Adapted from: Adil E. Bharucha et al.; American Gastroenterological Association Medical Position Statement on Constipation. GASTROENTEROLOGY 2013;144:211–217]

Algorithm: Refractory constipation



*Because anorectal manometry, rectal balloon expulsion test may not be available in all practice settings, it is acceptable, to proceed to assessing colonic transit with the understanding that delayed colonic transit does not exclude a defecatory disorder

STC = slow transit constipation
NTC = normal transit constipation

[Adapted from: Adil E. Bharucha et al.; American Gastroenterological Association Medical Position Statement on Constipation. GASTROENTEROLOGY 2013;144:211–217]

Chronic constipation: New treatment approaches

Substance	Prucalopride
Mode of action	Potent, selective, high-affinity agonist at the 5-HT4 receptor
Indication	Constipation resistant to dietary and lifestyle adjustments, osmotic laxatives, stool softeners, bulk-forming agents and stimulant laxatives
Dosage	once-daily 1–2 mg
Administration	orally
Absorption/ Metabolism/ Elimination	yes/partially hepatic/renal
Contraindications	Bowel obstruction/hepatic and renal insufficienc/pregnancy
Side effects	headache, nausea, diarrhea, and abdominal pain
Effect (vs placebo)	over 3 bm/week in 24 % (vs 13 %)
CH/EU/USA	+/+/+

[Adapted from:
- Ford AC and Suares NC: Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut 2011;60:209e218.
- Brian E. Lacy et al. Chronic constipation: New diagnostic and treatment approaches. Therap Adv Gastroenterol. 2012 July; 5(4): 233–247]

Lubiprostone	Linaclotide	Methylnaltrexone
Direct (luminal) stimulation of chloride channels	Direct stimulation of intestinal guanylate cyclase type-C (GC-C) receptors	peripherally-acting μ-opioid antagonist
Laxative resistant chronic idiopathic (CIC) or opioid-induced constipation (OIC) in adults > 18y	moderate or severe IBS-C and CIC	Laxative-resistant opioid induced constipation (OIC)
2x24 μg IBS-C: 2x8 μg	1x290 μg/d	1x12 mg (>62 kg) 1x8 mg (<62 kg)
orally	orally	subcutaneous injection
Minimally/oxidation in stomach and duodenum	Minimally/no metabolization	/little hepatic metabolism /esp. renal
Bowel obstruction, pregnancy, breastfeeding	Bowel obstruction, Pregnancy, breastfeeding (relative ci)	Renal insufficiency (dose reduction)
Diarrhea, nausea, abdominal pain	Diarrhea	Headache, nausea, diarrhea
Spontaneous defecation within 24 h in 60 % (vs 35%)	Improvement of frequency of bm in 20 % (vs 5 %)	defecation within 4 h in 60 % (vs 14 %)
+/-/+	-/+/+	+/-/+

Treatment

Laxative	Active pharmaceutical ingredient	Indication
Bulk laxative	Psyllium Sterculiae gum	Stool softener in constipation, for long term use
Osmotic laxative / poorly absorbed sugars		Symptomatic treatment of constipation, for regular use
	Lactulose Lactitol	
	Polyethylene glycol / Macrogol	
Stimulant laxative		

Mechanism of action	Dose / maximum recommended dose	Commonest adverse events	Contraindication
Increases colonic residue, stimulating peristalsis; Natural fibers that undergoes bacterial degradation, increases colonic residue, stimulating persistalsis	Titrate up to ~20 g; should be taken with plenty of water to avoid intestinal obstruction	Bloating and flatus, especially at the onset of treatment	Ileus, acute constipation, stool impaction
Colonic retention of water, due to osmotic effect of poorly absorbed sugars, stimulating peristalsis			
Synthetic disaccharide consisting of galactose and fructose linked by bond resistant to disaccharidases; not absorbed by the small intestine; undergoes bacterial fermentation in the colon with formation of short-chain fatty acids	Lactulose: 15–45 ml once or twice (initial 3 days), then dose reduction to 10–25 ml Lactitol: 30 ml (=20 g) once a day (initial 4–5 days), then reduce to maintenance dose 15 ml (10 g) once daily	Gas and bloating, especially at the onset of treatment	Ileus, abdominal pain of unknown origin
Organic polymers that are poorly absorbed and not metabolized by colonic bacteria	6–36 g once or twice a day, can be mixed with noncarbonated beverages	Bloating and cramping (less than other poorly absorbed sugars)	Ileus, IBD, toxic megacolon, bowel perforation
Stimulates intestinal motility or secretion, effect within 6–12 hours			

Treatment		
Anthraquinones	Senna	Acute constipation, for occasional use
Diphenylmethane derivatives	Bisacodyl	Acute constipation, for short term use or prolonged use under medical supervision
	Sodium picosulfate	Acute constipation, for short term use or prolonged use under medical supervision in opioid induced constipation
Prokinetic agents (Benzofuran)	Prucalopride	Chronic constipation in woman after failure of dietary restrictions and 2 laxatives within 9 months, prescribed ***only*** by gastroenterologists
	Lubiprostone	Chronic idiopathic (CIC) and opioid-induced constipation (OIC) in adults >18y suffering from non-tumor pain after failure of at least 2 different laxatives within 9 months

Converted by colonic bacteria to their active form; colonic stimulation by active secretion of electrolytes into the lumen and inhibition of reabsorption	12–150 mg daily before bedtime	Abdominal cramping, diarrhea, nausea, may cause melanosis coli, a benign condition that is usually reversible within 12 months after the cessation of laxative use; no definitive association between anthraquinones and colon cancer or myenteric nerve damage has been established	Ileus,spastic constipation, abdominal pain of unknown origin, hypokalemia
Hydrolyzed by endogenous esterases; stimulates directly active secretion of water and electrolytes into the lumen and inhibition of water and electrolyte reabsorption, stimulates motility of small intestine and colon	5–10 mg every night	Abdominal cramping, pain, diarrhea	Ileus, colonic obstruction, acute appendicitis, dehydration, hypokalemia
Hydrolized to its active form by colonic bacterial enzymes; affects only the colon	5–10 mg every night	Diarrhea, abdominal cramping, pain, nausea	Ileus, colonic obstruction, acute appendicitis, dehydration, hypokalemia
Selective, high affinity 5-HT4 (serotonin) receptor agonist, altering colonic motility patterns	1–2 mg once daily, stop if no effect with 2 mg daily within 4 weeks	Headache, abdominal pain, nausea, diarrhea	End-stage renal disease and hemodialysis, End-stage liver disease (Child C cirrhosis), bowel perforation, IBD, toxic megacolon, colonic obstruction, Ileus, no contraception
Direct (luminal) stimulation of chloride channels (ClC-2), stimulating colonic motility by causing chloride and water secretion without altering electrolyte concentrations in the serum	24 µg twice daily, stop if no effect within 4 weeks	Nausea, diarrhea, headache, abdominal pain	Bowel obstruction, pregnancy, breastfeeding

Inflammatory bowel disease
- Crohn's disease (most common)
- Backwash ileitis due to ulcerative colitis

Infectious colitis
- Yersinia spp.
  - Yersinia enterocolitica
  - Yersinia pseduotuberculosis
- Salmonella spp.
- Clostridium difficile
- Typhlitis (neutropenic enterocolitis)
- Mycobacterial spp
  - Mycobacterium tuberculosis
  - Mycobacterium avium
- Actinomycosis
- Anisakiasis
- Cytomegalovirus
- Histoplasma capsulatum

Spondyloarthropathies
- Ankylosing spondylitis
- Reactive arthritis
- Psoriasis

Vascular
- Vasculitides
  - Systemic lupus erythematosus (SLE)
  - Polyarteritis nodosa (PAN)
  - Henoch-Schönlein purpura
  - Behçet's disease
  - Other vasculitides : Churg-Strauss syndrome, rheumatoid arthritis, Wegener granulomatosis, lymphomatoid granulomatosis, giant-cell arteritis, Takayasu arteritis, thromboangiitis obliterans
- Small bowel ischemia

Terminal ileitis differential diagnosis

Small-bowel neoplasms
- Adenocarcinoma of the small bowel / cecum
- Lymphoma - lymphoma of terminal ileum
- Carcinoid tumour
- Metastatic cancer

Drug-related
- NSAID enteropathy (isolated terminal ileal ulcerations (ITIU)
- Other drugs : KCl tablets, parenteral gold therapy, oral contraceptives, ergotamine, digoxin, diuretics, antihypertensives
- Eosinophilic enteritis
- Sarcoidosis
- Amyloidosis
- Systemic mastocystosis

Others: endometriosis, radiation enteritis, lymphoid nodular hyperplasia

[Dilauro S, Crum-cianflone NF. Ileitis: when it is not Crohn's disease. Curr Gastroenterol Rep. 2010;12 (4): 249-58]

Equivalent anti-inflammatory doses of different oral corticosteroids

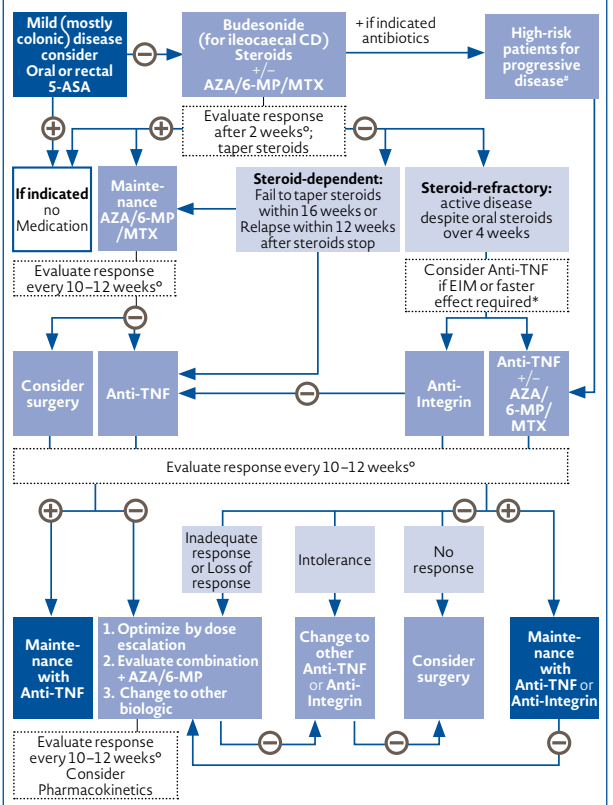
Prednisone	Other corticosteroids	
10 mg Prednisone are equivalent to	10 mg	Prednisolone
	40 mg	Hydrocortisone
	8 mg	Methylprednisolone
	1.6 mg	Dexamethasone
	1.6 mg	Betamethasone

Dosing of therapies[3]

	Substance	Dosage
5-ASA	Mesalazine	4.5 g/d
Corticosteroids	Budesonide	9 mg/d
	Prednisone	0.75 – 1 mg/kg bw/d
Immunosuppressives	Azathioprine (AZA)	2 – 2.5 (max. 3) mg/kg bw/d
	6-Mercaptopurine (6-MP)	1 – 1.5 mg/kg bw/d
	Methotrexate (MTX)	10 – 25 mg pro week + 5 mg folic accid
Antibiotics	Metronidazole	1000 –1500 mg/d
	Ciprofloxacin	1000 mg/d
Biologics	Adalimumab	Subcutaneous Week 0: 160 mg Week 2: 80 mg Week 4: 40 mg Then every 2 weeks: 40 mg
	Infliximab	Infusion over 30 – 90 min Week 0: 5 mg/kg Week 2: 5 mg/kg Week 6: 5 mg/kg Then every 8 weeks: 5 mg/kg
	Certolizumab Pegol	Subcutaneous Week 0: 400 mg Week 2: 400 mg Week 4: 400 mg Then every 4 weeks: 400 mg
	Vedolizumab	Infusion over 30 min Week 0: 300 mg Week 2: 300 mg Week 6: 300 mg Then every 8 weeks: 300 mg
	Ustekinumab	Infusion (weight adapted) Then use sc injections every 8–12 weeks (weight adapted)

bw = body weight; **d** = day

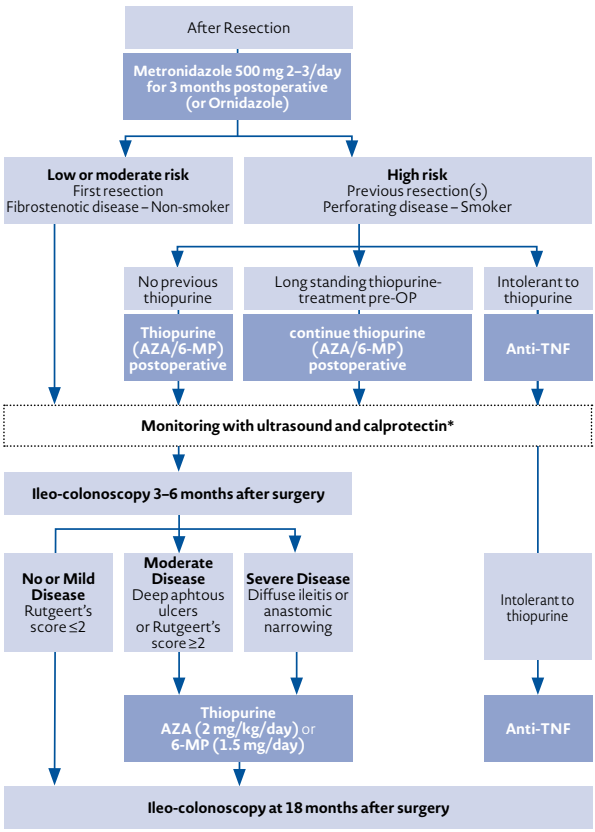
Luminal Crohn's Disease (without Fistula)[1, 2, 4–6]



* Swiss expert recommendation
# See page "Risk for severe disease progression", p.138
° See page "Target for CD treatment", p.138

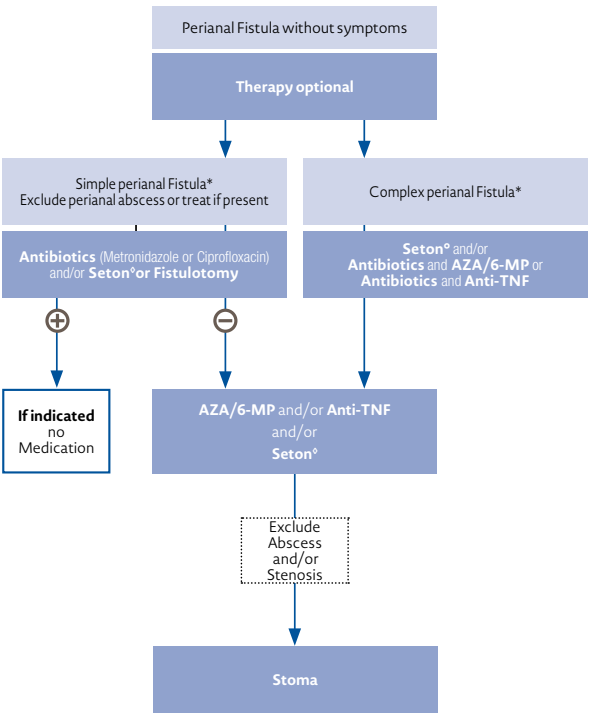
⊕ Response/remission
⊖ No response/no remission

Postoperative Crohn's disease[1, 2, 4, 7–9]



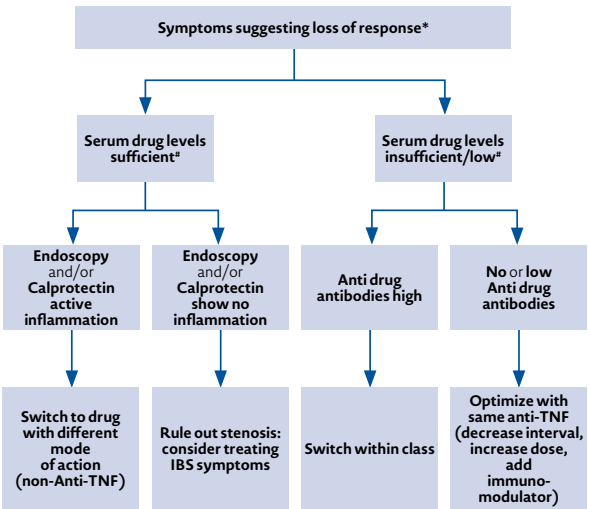
* Swiss expert recommendation

Fistulating disease[1, 2, 4]



* **Simple fistulas :** perianal fistula without branching; **complex fistulas :** Perianal branched fistula.
° Seton: Non-cutting Seton.

Pharmacokinetics under Biologic treatment [10, 11]



* Loss of response
- Low serum drug levels (just before next infusion/injection)
- Immunogenicity by neutralizing antibody formation
- Fibrostenotic structures

Range can vary according to used test

Risk for severe disease progression[12]

Prognostic factor	Impact
Young age at diagnosis	• Disabling CD[a] (<40 years) • Need for surgery • More frequent L4 disease (paediatric patients) • More frequent extensive disease (paediatric patients) • Intestinal failure
Requirement for steroids at diagnosis Complicated behaviour (B2 and /or B3)[c]	• Disabling CD[a] • Surgery • Hospitalization
Ileal disease (L1)[c] and ileocolonic disease (L3)[c]	• Surgery • Disabling CD[a] • Complicated behaviour • Disease behaviour progression[b] • Time to hospitalization
Colonic CD	• Inflammatory phenotype • Milder course (protective from hospitalization and surgery) • Permanent stoma (distal disease, severe rectal disease, rectal resection)
Upper GI extent (L4)[c]	• Complicated behaviour • Hospitalization • Multiple surgeries
Perianal disease	• Disabling CD[a] • Permanent stoma (refractory perianal disease, anal canal stricture, complex fistulizing disease)
Deep ulcerations at index colonoscopy	• Surgery • Penetrating complications
Smoking	• Complicated CD (disease progression) • Higher therapeutic requirements • Risk for first surgery (conflicting evidence)
Positive antimicrobial markers	• Risk of complicated phenotype and surgery (increasing with higher number of positive antibodies and higher titres)
NOD2 mutations	• Ileal disease • Risk for surgery

Target for CD treatment[13]

- Clinical/ PRO remission, defined as resolution of abdominal pain and diarrhea/altered bowel habit.
- Endoscopic remission, defined as resolution of ulceration at ileocolonoscopy
- Resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy.
- Biomarker remission (normal CRP and Calprotectin) – optional

a As defined by Beaugerie[14]; **b** B2 and/or B3; **c** According to Vienna and Montreal classifications: location, ileal (L1); colonic(L2); ileocolonic (L3); isolated upper gastrointestinal tract (L4) and behaviour, non-stricturing, non-penetrating (B1); stricturing (B2); penetrating (B3).
PRO = Patient reported outcomes

Screening before Anti-TNF-therapy [15]

Contraindications or warnings for Anti-TNF-therapy with respect to findings during screening before treatment.

Evaluation	If yes
1. Serious infection (incl. active TB) or sepsis[3]	Contraindicated[3]
2. In case of flare[6]: a. *Clostridium difficile* toxin positive in stools b. CMV infection proven by biopsies c. Parasites in stool d. stool culture to exclude infection	 Contraindicated Contraindicated Contraindicated Treat infection
3. Cardiac insufficiency NYHA III or IV	Contraindicated
4. Neurological disease	Consult neurologist
5. History of malignancy	Use with caution
6. Latent TB (i.e. positive IGRA test **or** abnormal x-ray suggestive of past TB not adequately treated **or** history of prior exposure to TB)[16]	Treatment with isoniazid 300 mg/d for 9 months or rifampicin 10 mg/kg daily for 4 months; TNF-therapy can be started after 1 month of preventive therapy[16]
7. HIV-positive, uncontrolled disease	Contraindicated
8. Positive HBV serology[17] a. HBsAg positive b. positive HBcAb and negative HBsAg	 Start anti-viral agents HBV DNA should be assessed every 2–3 months but antiviral therapy is not recommended unless HBV-DNA is detected
9. Chronic HCV infection	Use with caution[18]
10. Abnormal transaminase levels	Further evaluations
11. Women: last gynecological examination >1 year	Obtain exam

Vaccinations:
Check vaccination status prior to initiation of Anti-TNF-therapy,
follow ECCO recommendation [Rahier et al. J Crohns Colitis 2014]
No live vaccination during Anti-TNF-therapy

Monitoring efficacy and safety[19]

	Diagnosis	Monitoring: Symptomatic Disease
Symptoms	• Symptom assessment • HBI/CDAI/IBDQ (establish baseline)	**Each visit:** • Symptom assessment • HBI/CDAI/IBDQ
Laboratory	• Routine lab and inflammatory markers (blood count, liver profile, albumin, iron studies, renal function, Vitamins B12 + D, folic acid) • CRP • Faecal calprotectin	**Each visit:** • Frequency determined by severity and treatment: • Routine lab and inflammatory markers • CRP • Faecal calprotectin • Faecal cultures and rule out C. difficile toxins in stool If needed: Biologic drug serum levels
Endoscopy	• Ileocolonoscopy with segmental biopsies • Oesophagogastroduodenoscopy • If results inconclusive: Small-bowel capsule endoscopy	• Patients with unclear clinical presentation: • Ileocolonoscopy (confirm disease activity) • If results inconclusive: Small-bowel capsule endoscopy
Imaging	• Ultrasonography • MRI (evaluate involvement of small bowels, detect suspected extraintestinal complications)	• MRI (monitor disease activity) • CT for the detection of suspected complications (bowel obstruction, perforation, toxic colon distention)

	Monitoring: Asymptomatic Disease	Monitoring: Post-Surgery
Symptoms	**Each visit:** • Symptom assessment • HBI/CDAI/IBDQ (verify remission)	**Every 3 months in 1st year, then every 6–12 months:** • Symptom assessment • HBI/CDAI/IBDQ
Laboratory	**Each visit:** • CRP, Faecal calprotectin • Blood count **Every 3–12 months:** • Routine lab and inflammatory markers • Vitamins B12 + D If needed: Biologic drug serum levels (establish baseline)	**Every 3–6 months:** • Routine lab and inflammatory markers • CRP • Faecal calprotectin If needed: Biologic drug serum levels
Endoscopy	**In case of suspected disease progression or 6 months after start of biologics therapy:** • Ileocolonoscopy	**3–6 months after surgery:** • Ileocolonoscopy (detect recurrence) • Further endoscopy dependent on ileocolonoscopy findings
Imaging	**In case of suspected disease progression:** • Ultrasonography • MRI (evaluate involvement of small bowels)	• Ultrasonography (detect recurrence) • 3 months after small bowel resection • Regularly in patients with high risk of recurrence

CDAI = Crohn's Disease Activity Index; **CRP** = C-reactive protein; **CT** = Computer tomography;
HBI = Harvey-Bradshaw Index; **IBDQ** = Inflammatory Bowel Disease Questionnaire;
MRI = Magnetic Resonance Imaging

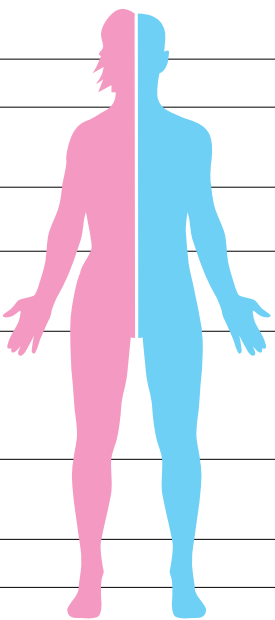
Treatments during pregnancy[20–24]

Class	Substance	FDA pregnancy category	Use during pregnancy	Use during breast feeding
Cortico-steroids	Budesonide	C	Low risk, likely compatible	Compatible; clinically insignificant concentration found in breast milk
	Systemic steroids	C	Moderate risk; possible orofacial cleft (1st trimester exposure), adrenal insufficiency, gestational diabetes, premature rupture of membranes, preterm birth, infant infections.	Compatible; clinically insignificant concentration found in breast milk Low risk, breastfeeding after 4 h
Antibiotics	Amoxicillin with clavulanic acid	B	Low risk, preferred antibiotic during pregnancy	Compatible, enters breast milk
	Ciprofloxacine	C	Low risk, affinity for cartilage	Compatible, enters breast milk
	Metronidazole	B	Low risk, avoid 1st trimester due to possible risk of orofacial clefts	Contraindicated; enters breat milk
5-ASA	Mesalazine	B	Low risk	Low risk
	Asacor	C	Low risk but contains DBP	Low risk
Immunosuppressives	Azathioprine 6-Mercapto-purine	D	1st trimester: no teratogenic risk in >1500 pregnant women treated orally. 2nd/3rd trimester: no evidence for fetotoxic risk.	In infants that are completely breastfed as a general rule no symptoms have been observed.
	Methotrexate	X	Contraindicated: teratogenic, abortifacient Supplement with folic acid. Discontinue 3 – 6 mo before conception	Contraindicated, enters breast milk
	Cyclosporine	C	Low risk. Limited data: possible risk of complications, preterm birth, low birthweight	Contraindicated, enters breast milk
Biologics	Adalimumab Infliximab	B	Low risk in monotherapy, most likely safe, recommended to stop in 3rd trimester. 1st trimester: no teratogenic effect has been shown. 2nd/3rd trimester: active diaplacental transfer in case of more mature placenta. Theoretical concerns regarding development of immune system and reduced immunity of the newborn.	High molecular weight and low oral availability; absorption by the newborn unlikely. No clinical abnormalities in case reports.
	Certolizumab	B	Low risk Does not actively cross placenta	Compatible; clinically insignificant concentration found in breast milk
	Vedolizumab	B	Limited human data, appears to be safe in animal studies	No human data, detected in milk of lactating monkeys
	Ustekinumab	B	Very limited data inhumans	No human data

Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). **Category B:** Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. **Category C:** Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Category D:** There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Category X:** Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. (http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf)

Extra-intestinal Manifestations [25–27]

20–40% of patients with inflammatory bowel disease will develop extra-intestinal manifestations[25-27]



Percentages represent prevalence in patients with at least one extra-intestinal manifestion.

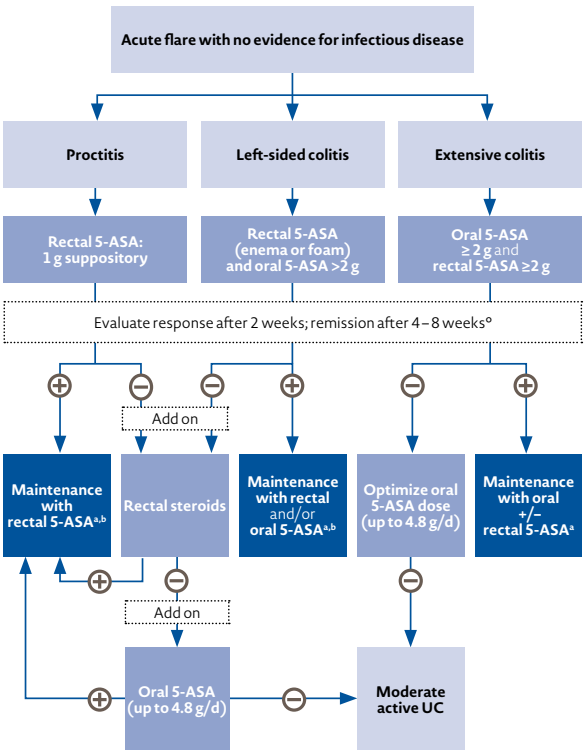
References:
1. Gomollon et al., Third EUROPEAN Evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management, Journal of Crohn's and Colitis (2016). **2.** Gionchetti et al. Third EUROPEAN Evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 2: Surgical management and special situations, Journal of Crohn's and Colitis (2016). **3.** www.swissmedicinfo.ch. **4.** Ferrante M et al., Physician perspectives on unresolved issues in the use of conventional therapy in Crohn's disease: Results from an international survey and discussion programme, Journal of Crohn's and Colitis (2012) 6, 116–131. **5.** Khanna R et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet. 2015 Nov 7;386(10006):1825-34. doi: 10.1016/S0140-6736(15)00068-9. Epub 2015 Sep 3. **6.** Singh S and Loftus EV, Crohn's disease: REACT to save the gut Lancet 2015; 386: 1800-1801. **7.** De Cruz et al, Lancet, 2015 Apr 11;385(9976):1406-17. **8.** Rutgeerts P et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. Gastroenterology 1995;108:1617–1621. **9.** Rutgeerts P et al. Ornidazole for Prophylaxis of Postoperative Crohn's Disease Recurrence: A Randomized, Double-Blind, Placebo-Controlled Trial. Gastroenterology. **10.** Adapted from Vermeire S et al. Value of drug level testing and antibody assays in optimizing biological therapy; Frontl Gastr 2013; 4: 41-43. doi:10.1136/flgastro-2012-100241. Published in accordance with the Creative Commons Attribution 3.0. https://creativecommons.org/licenses/by/3.0/de/. **11.** Burri E et al. Diagnostischer Nutzen von Calprotectin im klinischen Alltag; Swiss Medical Forum - Schweizerisches Medizin-Forum 2016; 16(3): 68-73. **12.** Torres J et al. Predicting Outcomes to Optimize Disease Management in Inflammatory Bowel Diseases; J Crohn's Colitis. 2016 Jun 9. pii: jjw116. **13.** Peyrin-Biroulet L. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target.Am J Gastroenterol. 2015 Sep;110(9):1324-38. doi: 10.1038/ajg.2015.233. **14.** Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. Gastroenterology 2006;130:650–6. **15**. Pache I et al., TNF-α blockers in inflammatory bowel diseases: Practical consensus recommendations and a user's guide. Swiss Med Wkly. 2009; 139 (19–20): 278–287. **16.** Beglinger C et al. Screening for tuberculosis infection before initiation of anti-TNF-α therapy. Swiss Med Wkly 20 07;137:621–622. **17.** Rahier JF et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohn's Colitis. 2014 Jun 1;8(6):443-68. **18.** Pompili M et al. Tumor necrosis factor-α inhibitors and chronic hepatitis C: a comprehensive literature review. World J Gastroenterol. 2013 Nov 28;19(44):7867-73. **19.** Adapted from Sauter B et al. Monitoring disease activity and progression in Crohn's disease. A Swiss perspective on the IBD ahead ›optimised monitoring‹ recommendations; Digestion. 2014;89(4):299-309. doi: 10.1159/000360283. **20.** www.embryotox.de. **21.** McConnell R A, Mahadevan U. Pregnancy and the Patient with Inflammatory Bowel Disease: Fertility, Treatment, Delivery, and Complications. Gastroenterol Clin North Am. 2016 Jun;45(2):285-301. doi: 10.1016/j.gtc.2016.02.006. **22.** Damas OM at al. Treating Inflammatory Bowel Disease in Pregnancy: The Issues We Face Today. J Crohns Colitis. 2015 Oct;9(10):928-36. doi: 10.1093/ecco-jcc/jjv118. Epub 2015 Jun 30. **23.** van der Woude et al. ECCO Reproduction and pregnancy consensus (Edition 2015) CJ. J Crohns Colitis. 2015; 107-124. **24.** Nguyen GC et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy. Gastroenterology. 2016 Mar;150(3):734-757.e1. doi: 10.1053/j.gastro.2015.12.003. Epub 2015 Dec 11. **25.** Vavricka SR et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011 Jan;106(1):110-9. **26.** Vavricka SR et al. Chronological Order of Appearance of Extraintestinal Manifestations Relative to the Time of IBD Diagnosis in the Swiss Inflammatory Bowel Disease Cohort. Inflamm Bowel Dis. 2015 Aug;21(8):1794-800. doi: 10.1097. **27.** Harbord et al. Extra-intestinal manifestations consensus Journal of Crohns and Colitis, 2016, 239–254.

Dosing of therapies[4]

	Substance	Dosage
5-ASA	Mesalazine	2–4.8 g/d (oral) 1–2 g/d (rectal)
Corticosteroids	Budesonide Budesonide MMX	2 mg/d (rectal) 9 mg/d (oral)
	Prednisone	0.75 –1 mg/kg bw/d
	Hydrocortisone	100 mg 4 times/d
Immunosuppressives	Azathioprine (AZA)	2–2.5 (max. 3) mg/kg bw/d
	6-Mercaptopurine (6-MP)	1–1.5 mg/kg bw/d
	Cyclosporine	2 mg/kg bw/24 hours i.v.
	Tacrolimus	0.1 mg/kg bw/d Serum concentration: 10–15 ng/ml
Biologics	Adalimumab	Subcutaneous Week 0: 160 mg Week 2: 80 mg Week 4: 40 mg Then every 2 weeks: 40 mg Dose escalation: every week 40 mg
	Golimumab	Subcutaneous Week 0: 200 mg Week 2: 100 mg Week 4: 50 mg Then every 4 weeks: 50 mg (100 mg for patients >80 kg)
	Infliximab	Infusion over 30–90 min Week 0: 5 mg/kg Week 2: 5 mg/kg Week 6: 5 mg/kg Then every 8 weeks: 5 mg/kg
	Vedolizumab	Infusion over 30 min Week 0: 300 mg Week 2: 300 mg Week 6: 300 mg Then every 8 weeks: 300 mg Dose escalation: every 4 weeks 300 mg

bw = body weight; **d** = day

Mild to moderate Ulcerative Colitis[2,5]

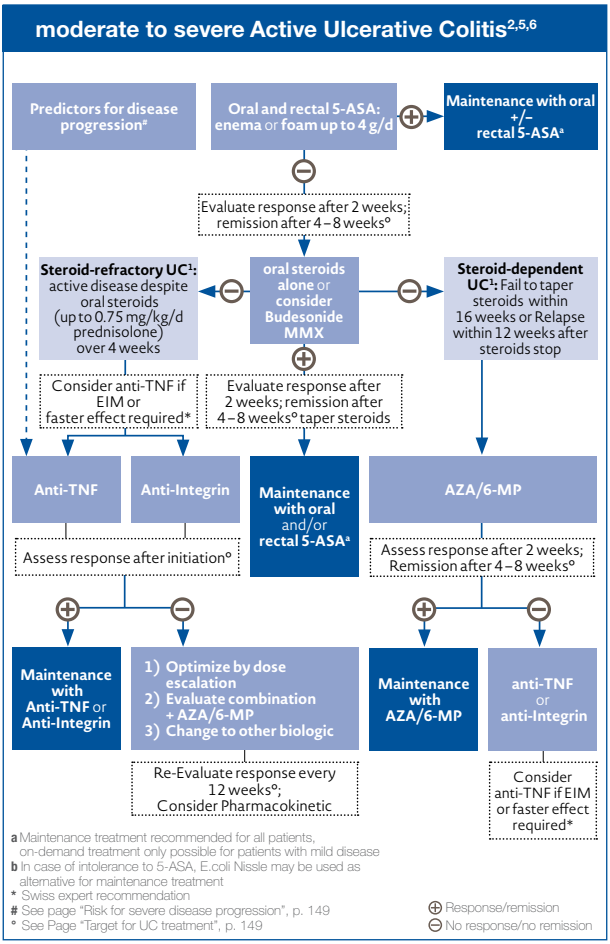


a Maintenance treatment recommended for all patients, on-demand treatment only possible for patients with mild disease

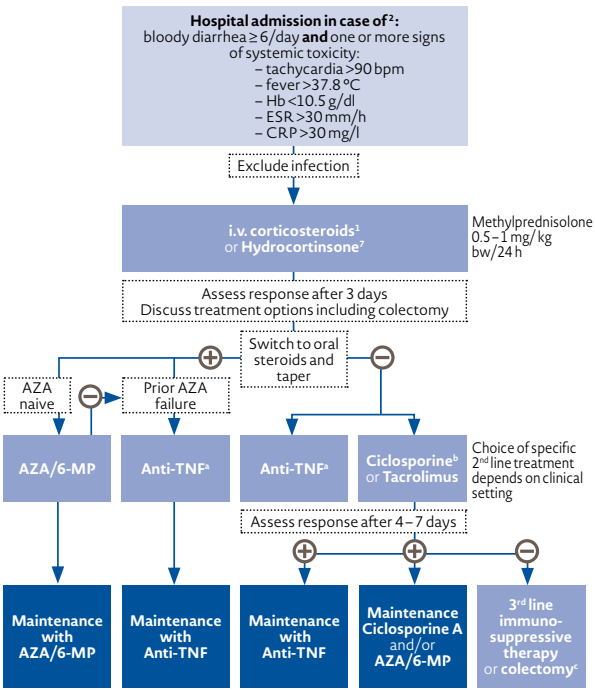
b In case of intolerance to 5-ASA, E.coli Nissle may be used as alternative for maintenance treatment

° See Page "Target for UC treatment", p.149

⊕ Response/remission
⊖ No response/no remission


moderate to severe Active Ulcerative Colitis[2,5,6]
Predictors for disease progression#
Oral and rectal 5-ASA: enema or foam up to 4 g/d
Maintenance with oral +/– rectal 5-ASA[a]
Evaluate response after 2 weeks; remission after 4 – 8 weeks°
Steroid-refractory UC[1]: active disease despite oral steroids (up to 0.75 mg/kg/d prednisolone) over 4 weeks
oral steroids alone or consider Budesonide MMX
Steroid-dependent UC[1]: Fail to taper steroids within 16 weeks or Relapse within 12 weeks after steroids stop
Consider anti-TNF if EIM or faster effect required*
Evaluate response after 2 weeks; remission after 4 – 8 weeks° taper steroids
Anti-TNF
Anti-Integrin
Maintenance with oral and/or rectal 5-ASA[a]
AZA/6-MP
Assess response after initiation°
Assess response after 2 weeks; Remission after 4 – 8 weeks°
Maintenance with Anti-TNF or Anti-Integrin
1) Optimize by dose escalation
2) Evaluate combination + AZA/6-MP
3) Change to other biologic
Maintenance with AZA/6-MP
anti-TNF or anti-Integrin
Re-Evaluate response every 12 weeks°; Consider Pharmacokinetic
Consider anti-TNF if EIM or faster effect required*
a Maintenance treatment recommended for all patients, on-demand treatment only possible for patients with mild disease
b In case of intolerance to 5-ASA, E.coli Nissle may be used as alternative for maintenance treatment
* Swiss expert recommendation
# See page "Risk for severe disease progression", p. 149
° See Page "Target for UC treatment", p. 149
⊕ Response/remission
⊖ No response/no remission

Severe Ulcerative Colitis[1,2,5]



Consider drug level testing to guide dose increases or modifications
a Data for hospitalized patients only available for Infliximab.
b Exclude low Mg/Cholesterol.
c 3rd line immunosuppressive therapy restricted to specialized centers
bw = body weight; **d** = day

⊕ Response/remission
⊖ No response/no remission

Pouchitis*[8,9]

Suspicious symptoms are increased stool frequency and consistency, cramping, tenesmus, incontinence and urgency
Bleeding, fever, and EIM are rarer presenting symptoms
Pouchitis more likely with:
- Extensive UC
- EIM especially PSC
- Non-smokers (smoking increases risk of Crohn's disease of the pouch)
- P-ANCA positivity
- NSAIDs
- Backwash ileitis
- Previous colonic dysplasia

Exclude infection

Ciprofloxacin 1 g/d for 2 weeks or **Metronidazole 20 mg/kg/d for 2 weeks 2nd line therapy**
or
Budesonide foam or enema (2 mg)
or
VSL#3(6 g/d)

Assess response after 4 weeks

⊕ → **If indicated** no Medication

⊖ → **Combination antibiotics or budesonide**[a]

⊕ → ⊖ → **Anti-TNF**

⊕ → **Alternative agents**[b,c] or **surgery**

* Pouchitis associated with a UC disease background
a Preferably combination antibiotic therapy, e.g. ciprofloxacin 1 g & tinidazole 1 g daily for 4 weeks. Remission in > 80% . Alternative treatment includes rifaximin 2 g daily or metronidazole 1 g daily for 4 weeks. Remission in > 80%.
b Ciclosporin enema; Azathioprine in those dependent on budesonide; Alicaforsen (anti-sense to ICAM-1) enema.
bw = body weight; **d** = day

⊕ Response/remission
⊖ No response/no remission

Risk for severe disease progression[10]

Prognostic factor	Impact
Young age at diagnosis	• More extensive disease (paediatric UC) • Colectomy • Proximal disease extension • Acute severe UC • Colorectal neoplasia
Family history	• Proximal disease extension (family history of IBD) • Colorectal neoplasia (family history of CRC)
Refractory proctitis (>3 relapses per year)	• Proximal disease extension
Male sex	• Colectomy
Extensive colitis	• Colectomy • Acute severe UC • Hospitalization • Colorectal neoplasia
High histological inflammation score	• Colorectal neoplasia
Disease duration >10 years	• Colorectal neoplasia • Colectomy
Steroid dependence/resistance	• Colectomy • Hospitalization
Smoking	• Less need for hospitalization • Proximal disease extension (protective) • Protective from colectomy
Concurrent infection (cytomegalovirus or Clostridium difficile)	• Flare and hospitalization
Primary sclerosing cholangitis	• Colectomy • Proximal disease extension • Colorectal cancer • Protective for hospitalization

Target for UC treatment[11]

- Clinical/ PRO remission, defined as resolution of rectal bleeding and diarrhea/altered bowel habit
- Endoscopic remission, defined as Mayo endoscopic subscore of 0–1
- Histological remission – optional

PRO = Patient reported outcomes

Monitoring efficacy and safety[14]

	Diagnosis	Monitoring: Symptomatic Disease
Symptoms	• Symptom assessment • Mayo score/IBDQ/CAI (establish baseline)	**Each visit:** • Symptom assessment • Mayo score/IBDQ/CAI
Laboratory	• Routine lab and inflammatory markers (blood count, liver profile, albumin, iron studies, renal function, Vitamins B12 + D, folic acid) • CRP • Faecal calprotectin	**Each visit:** • Frequency determined by severity and treatment • Routine lab and inflammatory markers • CRP • Faecal calprotectin • Faecal cultures and rule out C. difficile toxins in stool If needed: Biologic drug serum levels
Endoscopy	• Rectoscopy with segmental biopsies If inconclusive: Colonoscopy	• Patients with unclear clinical presentation: • Rectoscopy (confirm disease activity) if inconclusive: Colonoscopy
Imaging	• Ultrasonography	• CT for the detection of suspected complications (bowel obstruction, perforation, toxic colon distention)

	Monitoring: Asymptomatic Disease
Symptoms	**Each visit:** • Symptom assessment • Mayo score/IBDQ/CAI (verify remission)
Laboratory	**Each visit:** • CRP, Faecal calprotectin • Blood count **Every 3–12 months:** • Routine lab and inflammatory markers • Vitamins B12 + D If needed: Biologic drug serum levels (establish baseline)
Endoscopy	**In case of suspected disease progression or 6 months after start of biologics therapy:** • Rectoscopy if inconclusive: Colonoscopy
Imaging	**In case of suspected disease progression:** • Ultrasonography

CAI = Clinical Acitivity Index; **CRP** = C-reactive protein; **CT** = Computer tomography; **IBDQ** = Inflammatory Bowel Disease Questionnaire; **MRI** = Magnetic Resonance Imaging

Screening before Anti-TNF-therapy[15]

Contraindications or warnings for Anti-TNF-therapy with respect to findings during screening before treatment.

Evaluation	If yes
1. Serious infection (incl. active TB) or sepsis[4]	Contraindicated[4]
2. In case of flare[10]: a. *Clostridium difficile* toxin positive in stools b. CMV infection proven by biopsies c. Parasites in stool d. Stool culture to exclude infection	 Contraindicated Contraindicated Contraindicated Treat infection
3. Cardiac insufficiency NYHA III or IV	Contraindicated
4. Neurological disease	Consult neurologist
5. History of malignancy	Use with caution
6. Latent TB (i.e. positive IGRA test **or** abnormal x-ray suggestive of past TB not adequately treated **or** history of prior exposure to TB)[16]	Treatment with isoniazid 300 mg/d for 9 months or rifampicin 10 mg/kg daily for 4 months; TNF-therapy can be started after 1 month of preventive therapy[16]
7. HIV-positive, uncontrolled disease	Contraindicated
8. Positive HBV serology[17] a. HBsAg positive b. positive HBcAb and negative HBsAg	 Start anti-viral agents HBV DNA should be assessed every 2–3 months but antiviral therapy is not recommended unless HBV-DNA is detected[17]
9. Chronic HCV infection	Use with caution[18]
10. Abnormal transaminase levels	Further evaluations
11. Women: last gynecological examination >1 year	Obtain exam

Vaccinations:
Check vaccination status prior to initiation of Anti-TNF-therapy,
follow ECCO recommendation [Rahier et al. J Crohns Colitis 2014]
No live vaccination during Anti-TNF-therapy

Colon cancer screening[3]

Proctitis

No evidence of previous or current endoscopic and/or microscopic **inflammation proximal to the rectum: surveillance according to nationally recommended colon cancer screening**

Left-sided/extensive colitis

Determine risk profile 6–8 years after first manifestation. Chromoendoscopy should be perforemd for surveillance if available (ECCO statement 13G)

High risk*: colonoscopy every 1–2 years from the 8th year after first manifestation

Low risk*: colonoscopy every 3–4 years from the 8th year after first manifestation

In case of concurrent PSC, surveillance colonoscopies should be carried out yearly from the point of PSC diagnosis irrespective of disease activity and extent.

Post-proctocolectomy: Endoscopic surveillance is recommended for patients with dysplasia or cancer before or at the time of proctocolectomy.[19,20]

* Risk stratification mainly depends on extent of disease, severity of endoscopic and/or histological inflammation, pseudopolyps, concurrence of PSC, and family history of CRC.

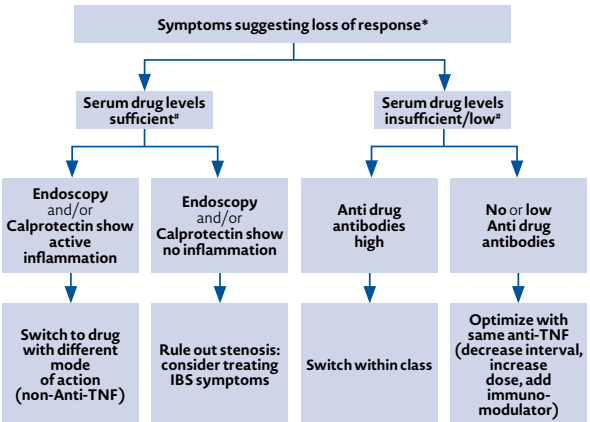
PSC = Primary sclerosing cholangitis

Treatments during pregnancy[21–25]

Class	Substance	FDA pregnancy category	Use during pregnancy	Use during breast feeding
Antibiotics	Amoxicillin with clavulanic acid	B	Low risk, preferred antibiotic during pregnancy	Compatible, enters breast milk
	Ciprofloxacin	C	Low risk, affinity for cartilage Avoid 1st trimester	Avoid if possible, breastfeeding after 12–24 h, Compatible, enters breast milk
	Metronidazole	B	Low risk, avoid 1st trimester due to possible risk of orofacial clefts	Contraindicated; enters breat milk Avoid if possible, breastfeeding after 12–24 h
5-ASA	Mesalazine	B	Low risk	Low risk
	Asacol®	C	Low risk but contains DBP	Low risk
Corticosteroids	Budesonide	C	Low risk, likely compatible	Low risk Compatible; clinically insignificant concentration enters breast milk
	Systemic Steroids	C	Moderate risk; possible orofacial cleft (1st trimester exposure), adrenal insufficiency, gestational diabetes, premature rupture of membranes, preterm birth, infant infections. Risk of Low Birthweight	Compatible; clinically insignificant concentration enters breast milk Low risk, breastfeeding after 4 h
Immunosuppressives	Azathioprine 6-Mercapto-purine	D	1st trimester: no teratogenic risk in >1500 pregnant women treated orally. 2nd/3rd trimester: no evidence for fetotoxic risk.	In infants that are completely breastfed as a general rule no symptoms have been observed.
	Cyclosporine	C	Low risk Limited data: possible risk of complications, preterm birth, low birthweight	Contraindicated, enters breast milk
Biologics	Adalimumab Infliximab	B	Low risk in monotherapy most likely safe, recommended to stop in 3rd trimester. 1st trimester: no teratogenic effect has been shown. 2nd/3rd trimester: active diaplacental transfer in case of more mature placenta. Theoretical concerns regarding development of immune system and reduced immunity of the newborn.	Low risk High molecular weight and low oral availability; absorption by the newborn unlikely. No clinical abnormalities in case reports.
	Golimumab	B	Low risk in monotherapy most likely safe, recommended to stop in 3rd trimester. Only case reports available[23]	Low risk No data published
	Vedolizumab	B	Limited human data, appears to be safe in animal studies	No human data, detected in milk of lactating monkeys

Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). **Category B:** Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. **Category C:** Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Category D:** There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Category X:** Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. (http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf)

Pharmacokinetics under Biologic treatment[12, 13]



* Loss of response:
a) Low serum Drug serum levels (just before next infusion /injection);
b) Immunogenicity by neutralizing antibody formation; c)Fibrostentic structures
Range can vary according to used test

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1. Dignass A et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. J Crohns Colitis. 2012 Dec;6(10):965-90. **2.** Dignass A et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management. J Crohn's Colitis. 2012 Dec;6(10):991-1030. **3.** Van Assche G et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 3: Special situations. Journal of Crohn's and Colitis (2013) 7, 1–33. **4.** www.swissmedicinfo.ch. **5.** Frei Pet al. Topical therapies in inflammatory bowel disease. Digestion. 2012;86 Suppl 1:36-44. **6.** Manz M et al. Treatment algorithm for moderate to severe ulcerative colitis. Swiss Med Wkly. 2011 Jun 27;141:w13235. **7.** Meyers S, Sachar DB, Goldberg JD, Janowitz HD et al. Corticotropin versus hydrocortisone in the intravenous treatment of ulcerative colitis. A prospective, randomized, double-blind clinical trial. Gstroenterology. 1983 Aug; 85(2):351-7. **8.** E-guide ECCO: http://www.e-guide.ecco-ibd.eu/algorithm/pouchitis. **9.** Greuter T et al. Alicaforsen, an antisense inhibitor of ICAM-1, as treatment for chronic refractory pouchitis after proctocolectomy: A case series. UnitedEuropean Gastroenterol J. 2016 Feb;4(1):97-104. doi: 10.1177/2050640615593681. Epub 2015 Jul 3. **10.** Torres J et al. Predicting Outcomes to Optimize Disease Management in Inflammatory Bowel Diseases;.J Crohns Colitis. 2016 Jun 9. pii: ijw116. **11.** Peyrin-Biroulet L. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol. 2015 Sep;110(9):1324-38. doi: 10.1038/ajg.2015.233. Epub 2015 Aug 25. **12.** Adapted from Vermeire S et al. Value of drug level testing and antibody assays in optimizing biological therapy; Fronti Gastr 2013; 4: 41-43. doi:10.1136/flgastro-2012-100241. Published in accordance with the Creative Commons Attribution 3.0. https://creativecommons.org/licenses/by/3.0/de/. **13.** Burri E et al. Diagnostischer Nutzen von Calprotectin im klinischen Alltag; Swiss Medical Forum - Schweizerisches Medizin-Forum 2016; 16(3): 68-73. **14.** Adapted from Sauter B et al. Monitoring disease activity and progression in Crohn,s disease. A Swiss perspective on the IBD ahead ‹optimised monitoring› recommendations; Digestion. 2014;89(4):299-309. doi: 10.1159/000360283. **15.** Pache I et al., TNF-α blockers in inflammatory bowel diseases: Practical consensus recommendations and a user's guide. Swiss Med Wkly. 2009; 139 (19–20): 278–287. **16.** Beglinger C et al. Screening for tuberculosis infection before initiation of anti-TNF-α therapy. Swiss Med Wkly 20 07;137:621–622. **17.** Rahier JF et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohn's Colitis. 2014 Jun 1;8(6):443-68. **18.** Pompili M et al. Tumor necrosis factor-α inhibitors and chronic hepatitis C: a comprehensive literature review. World J Gastroenterol. 2013 Nov 28;19(44):7867-73. **19**. Scarpa M et al. Systematic review of dysplasia after restorative proctocolectomy for ulcerative colitis. Br J Surg. 2007 May;94(5):534-45. **20.** Selvaggi F et al. Systematic review of cuff and pouch cancer in patients with ileal pelvic pouch for ulcerative colitis. Inflamm Bowel Dis. 2014 ul;20(7):1296-308. **21**. www.embryotox.de. **22.** McConnell R A, Mahadevan U. Pregnancy and the Patient with Inflammatory Bowel Disease: Fertility, Treatment, Delivery, and Complications. Gastroenterol Clin North Am. 2016 Jun;45(2):285-301. doi: 10.1016/j.gtc.2016.02.006. **23.** Damas OM at al. Treating Inflammatory Bowel Disease in Pregnancy: The Issues We Face Today. J Crohns Colitis. 2015 Oct;9(10):928-36. doi: 10.1093/ecco-jcc/jjv118. Epub 2015 Jun 30. **24.** Van der Woude et al. ECCO Reproduction and pregnancy consensus (Edition 2015) CJ. J Crohn's Colitis. 2015; 107-124. **25.** Nguyen GC et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy. Gastroenterology. 2016 Mar;150(3):734-757.e1. doi: 10.1053/j.gastro.2015.12.003. Epub 2015 Dec 11.

Treatment protocol / monitoring of Azathioprine

	Dose	Duration	Frequency of laboratory check by primary care physician: (blood count + liver enzymes*)
1.	50 mg/day	2 weeks	→ weekly for 2 weeks
			if ok then
2.	100 mg/day	2 weeks	→ weekly for 2 weeks
			if ok then
3.	Increase dose (50 mg every time)	2 weeks	→ weekly for 2 weeks
→	Up to target dose (2–2.5 mg/kg)	→ Cycle (3.) repeat until target dose is reached	
4.	Steady dose	Long-term therapy	→ monthly for 2 months
			→ every 2 months for 1 year
5.	Regular check-up		→ every 3 months

** an active Hepatitis B or an inactive carrier of the Hepatitis B virus should have been already excluded.*

Anti-drug antibodies (ADA) – Indications for ADA formation

Anti-drug antibodies, low serum albumin, high CRP (baseline), male sex (higher drug clearance), high BMI (may increase clearance), high baseline anti-TNF concentration (amount of drug cleared per time increases with the amount present in serum).

When is measurement of trough-level and ADA indicated?

- loss of response or insufficiently controlled disease activity (either derived by clinical parameters, endoscopy or radiology)
- ambiguous symptoms during or shortly after infusion of anti-TNF suggestive of an immediate or delayed infusion reaction
- potentially after prolonged anti-TNF mono- or combi-therapy when treatment de-escalation is considered
- potentially prior to initiate an anti-TNF in patients that previously have been exposed to the very same drug
- potentially always after completion of the induction phase
- potentially already sooner (prior to the third or even second infusion) in case of a highly active disease with substantial inflammatory burden, e.g. in the event of acute severe colitis

Guidelines for Chromoendoscopy in UC: SURFACE

Strict patient selection.
- Patients with histologically proven ulcerative colitis and at least eight years' duration in clinical remission.
- Avoid patients with active disease.

Unmask the mucosal surface.
- Excellent bowel preparation is needed. Remove mucus and remaining fluid in the colon when necessary.

Reduce peristaltic waves.
- When drawing back the endoscope, a spasmolytic agent should be used (if necessary).

Full length staining of the colon.
- Perform full length staining of the colon (panchromoendoscopy) in ulcerative colitis rather than local staining

Augmented detection with dyes.
- Intravital staining with 0.4% indigo carmine or 0.1% methylene blue should be used to unmask flat lesions more frequently than with conventional colonoscopy.

Crypt architecture analysis.
- All lesions should be analyzed according to the pit pattern classification.
- Whereas pit pattern types I–II suggest the presence of nonmalignant lesions, staining patterns III–V suggest the presence of intraepithelial neoplasia and carcinomas.

Endoscopic targeted biopsies.
- Perform targeted biopsies of all mucosal alterations, particularly of circumscript lesions with staining patterns indicative of intraepithelial neoplasia and carcinomas (pit patterns III–V).

[Kiesslich R, Neurath MF. Chromoendoscopy: an evolving standard in surveillance for ulcerative colitis. Inflamm Bowel Dis 2004;10:695–6]

Simplified dosage regimen for intravenous iron (iron sucrose, ferric carboxymaltose[1], iron isomaltose)

Total iron quantity ferric carboxymaltose

Hb (g/dl)	Body weight <70 kg	Body weight ≥70 kg
≥10	1000 mg	1500 mg
7–10	1500 mg	2000 mg

The total iron quantity was administered in individual weekly infusions of 500 mg or 1000 mg ferric carboxymaltose.
Patients with a body weight of less than 67 kg received individual doses of 500 mg.

[1 Evstatiev R et al. FERGIcor, a Randomized Controlled Trial on Ferric Carboxymaltose for Iron Deficiency Anemia in Inflammatory Bowel Disease. Gastroenterology. 141.3 (2011): 846–53]

Max. Dilution[2]

Iron quantity**	ferric carboxy-maltose	Maximum quantity of 0.9% NaCl solution for infusion dilution	Minimum infusion time	Means of filling	for the infusion
500 mg	10 ml	**100 ml***	6 minutes	10 ml syringe and pink needle (18G)	**Catheter blue (22G) or pink (20G), Venflon™**
1000 mg	20 ml	**250 ml***	15 minutes	20 ml syringe and pink needle (18G)	

*** Please observe the dilution:** ≥2 mg iron per ml
**** Refer to the Swiss product information for other iron dosages (www.swissmedicinfo.ch)**

[2 Swiss product information: www.swissmedicinfo.ch]

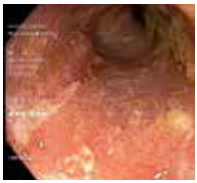
Disease activity in UC – Truelove and Witts

Patients characteristics	**Mild** Light clinical symptoms, but which can be worsened by the subjective perception of the patient. Especially urgencies contribute to a more severe perception of the disease. Localization of the disease is important as topical treatments will have to be adjusted accordingly.
Bloody stools per day	<4
Pulse	<90 bpm
Temperature	<37.5 C°
Hemoglobin	>11.5 g/dl
ESR	<20 mm/h
CRP	normal

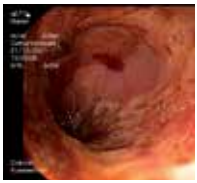
Mayo Classification for endoscopical disease activity

0 = remission	1 = mild	2 = moderate	3 = severe
erythema	+	++	+++
vascular pattern	↓	absent	
bleeding	contact, friability	spontaneous	
lesions	none	erosions	ulcerations

mild



moderate

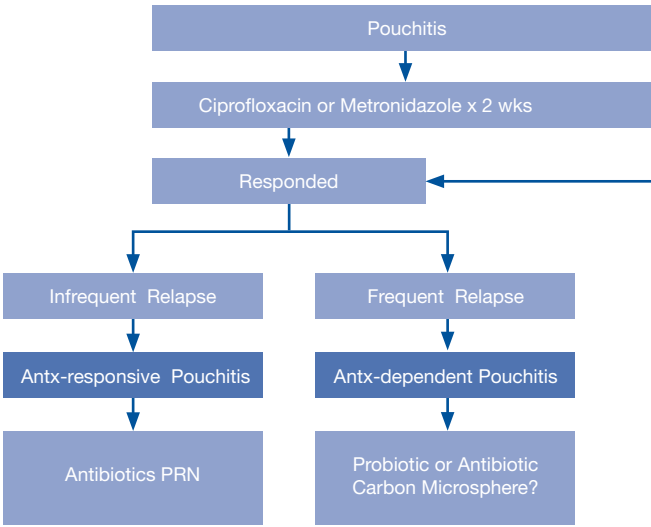


severe

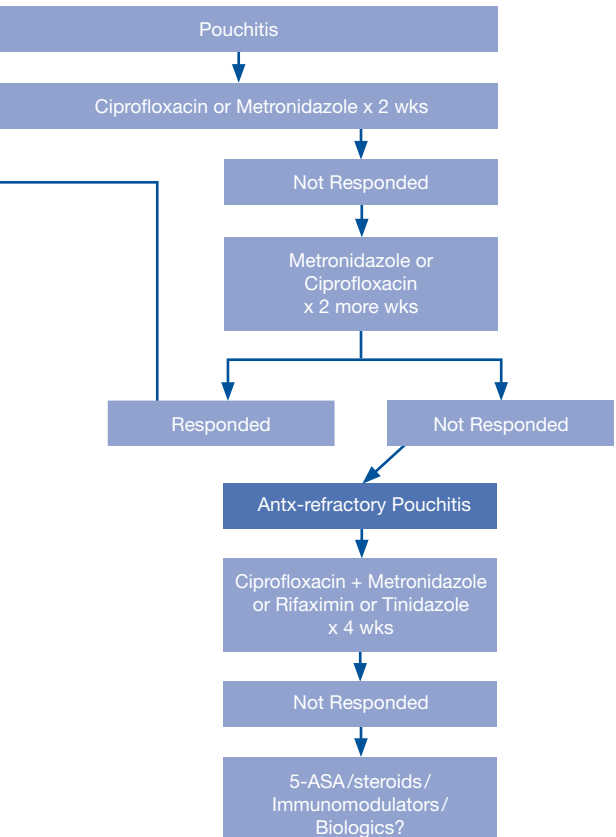
[Schroeder KW, *et al.* N Engl J Med. 1987.]

Moderate Increased clinical symptoms but only mild systemic symptoms. Steroid use is a good criterion to classify a patient as moderate or severe. Presence of mucosal friability (bleeding on light contact with the rectal mucosa on sigmoidoscopy.	**Severe** Severe active ulcerative colitis is best defined by Truelove and Witts Criteria. Patients should be admitted to hospital for intensive treatment.
>4	>6
=90 bpm	>90 bpm
<37.5 C°	>37.5 C°
>10.5 g/dl	<10.5 g/dl
<30 mm/h	>30 mm/h
<30 mg/L	>30 mg/L

Treatment algorithm for pouchitis



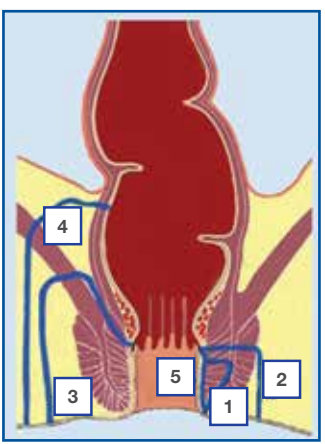
Antx = Antibiotics


Pouchitis
Ciprofloxacin or Metronidazole x 2 wks
Not Responded
Metronidazole or
Ciprofloxacin
x 2 more wks
Responded
Not Responded
Antx-refractory Pouchitis
Ciprofloxacin + Metronidazole
or Rifaximin or Tinidazole
x 4 wks
Not Responded
5-ASA/steroids/
Immunomodulators/
Biologics?

Anal Fistulas:
- Most sporadic fistula are a result of cryptoglandular infection
- The fistula represents the chronic process whereas the abscess is the acute inflammatory event
- 90% of anorectal abscesses are a result of cryptoglandular infection

Classification:
- Most helpful is in clinical routine a classification which describes the Fistula according to their relationship to the anal sphincter

1. Intersphincteric
2. Transsphincteric
3. Suprasphincteric
4. Extrasphincteric
5. Subanodermal



Diagnosis:
- Chronic inflammatory bowel disease should be ruled out (Different therapy)
- Assessment of sphincter function
- Examination under anesthesia and probing/dyeing preoperative/intraoperatively plus anal endosonography is helpful for showing the relation of the fistula tract to the anal sphincter (Correlation both is better than 90%)
- In case of recurrent or complex fistula MRI imaging should be considered

Treatment:
Diagnosis of anal fistula is usually an indication for surgery

Low fistula:	Subanodermal fistula Intersphincteric fistula Distal transsphincteric fistula	**Fistulotomy** (Healing rate up to 100%)
High fistula:	Proximal transsphincteric fistula Suprasphincteric fistula Extrasphincteric fistula	**Surgical reconstruction/ Biomaterial** (Lower healing rate and impaired sphincter function)

Surgical options for high fistula:

1. **Surgical reconstruction**
   a. Advancement flap: The aim is an excision of the fistula and the cryptoglandular focus and a following closure of the inner fistula cavity by different flap techniques
   b. Fistula excision with direct sphincter reconstruction: After excision of the fistula and reconstruction of the divided sphincter

2. **Biomaterial:**
   a. Fibrin glue: after curettage the tract is filled with fibrin glue as a biomatrix for the body`s own tissue to grow in.
   b. Anal fistula plug: The anal fistula plug is a biomedical product made of e.g. porcine small – intestinal submucosa which is brought into the tract as a biomatrix. It could be combined with a mucosal flap and a curettage.

[Ommer A et al: S3 Leitlinie: Kryptoglanduläre Analfisteln: Coloproctology 2011]

Initial therapy and therapy after initial *C. difficile* infection relapse

- early termination of current antibiotic therapy
- no motility inhibiting medication (e.g. loperamide)

Therapy	Duration (Days)	Comments
Metronidazole 3 x 500 mg/d p.o.	10–14	mild to moderate infection, few publications on i.v. therapy Inferior response rates compared to Vancomycin or Fidaxomycin. Not recommended in severe disease. Not recommendet in case of relapse. [Literatur: McDonald et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)]

(i.v. therapy possible)

Vancomycin
4 x 125–250 mg/d p.o. 10–14

Severe infection, pregnant women, children < 10 years, fulminant course, fewer relapse cases in comparison to metronidazole therapy. Vancomycin can be applied as an enterocapsule or oral solution (i.e. powder in infusion solution). In severe cases or when oral administration is not possible: intracolonic vancomycin 500 mg in 100 mL every 4–12 hours ± 4 x 500 mg via a nasogastric tube.

Teicoplanin
2 x 200–400 mg p.o. 10 Alternative to vancomycin therapy for severe infection

Fidaxomicin
2 x 200 mg p.o. 10

Alternative therapy; low relapse rate in comparison to other treatment options with a narrow antibiotic spectrum; first choice when the accompanying antimicrobial therapy for other indications is mandatory

Therapy after second and third *C. difficile* infection relapse

Therapy	Duration	Comments
Vancomycin 4 x 125–500 mg/d p.o.	10–14 days	
Vancomycin «taper» scheme		
• 4 x 125 mg/d	Week 1	
• 3 x 125 mg/d	Week 2	
• 1 x 125 mg/d	Week 3	
• 1 x 125 mg every 2 days	Week 4–5	
• 1 x 125 mg every 3 days	Week 6–7	
Ensure compliance		
Vancomycin «pulse & taper»		
• 4 x 500 mg/d	Day 1–10	
• 4 x 250 mg/every 2nd day	Day 11–18	
• 4 x 250 mg/every 3rd day	Day 19–27	
• 4 x 250 mg/every 4th day	Day 28–35	
• 4 x 250 mg/every 5th day	Day 36, 41	
• thereafter 4 x 250 mg (only 1 day)	On days 47, 54, 62, 71, 81	
Extensive treatment scheme, ensure compliance		
Vancomycin 4 x 250–500 mg/d p.o. followed by rifaximin 3 x 400 mg/d 10 d (vancomycin) followed by 14 d rifaximin		
Vancomycin 4 x 250–500 mg/d p.o. + Saccharomyces boulardii 2 x 500 mg/d 14 d		
Fidaxomicin 2 x 200 mg p.o. 10 d		
Fecal microbiota transplantation from a healthy donor (only at specialized centers)		

Preliminary examination prior to stool transplantation Preparation – Donor

Personal medical history – Donor

- healthy person (BMI between >17 and <35); no chronic morbidity
- no existing transmittable infectious disease(s)
- no antibiotic use within the last 3 months
- no recent travelling to a tropical country within the last 6 months
- no attenuated vaccine treatment within the last 4 weeks
- no infectious intestinal diseases within the last 3 months
- no medical history of intravenous drug use
- no treatment involving blood transfusion
- no tattoos within the last 3 months
- no promiscuous lifestyle
- no major gastrointestinal operation (e.g. Whipple OP; total colectomy)
- no immunosuppressive treatment
- no pathologies of the gastrointestinal tract; no polyps
- no systemic autoimmune diseases (e.g. multiple sclerosis); no atopia or allergies
- no chronic pain syndrome; no fibromyalgia

Laboratory examination – Donor
(italicized points are optional and recommended by certain centers)

- routine laboratory values (incl. blood, liver, and kidney values, bilirubin, CRP)
- hepatitis A (HAV IgM AB), B (HBsAg & HBcAb) and C (HCV IgG AB)
- HIV (HIV Ag/Ab)
- *syphilis (TPPA, TPHA or equivalent test)*
- stool culture or other pathogenic evidence of the following enteropathogenic bacteria: *C. difficile;* Salmonella; Campylobacter; EHEC/Shiga toxin; Yersinia; Shigella
- Cyclospora, Isospora, *Dientamoeba fragilis, Blastocystis hominis*
- microscopic worm eggs and parasites
- *G. lamblia* and *cryptosporidium AG test; microsporidia*
- noro- and rotavirus antigen test or PCR
- *Helicobacter pylori* stool antigen test
- normal levels of calprotectin
- exclusion of tuberculosis (e.g. using the QuantiFERON test)
- noro- and rotavirus antigen tests

Preparation – Recipient:
- potential transmission of infectious diseases
- potential transmission of risk factors for intestinal diseases (chronic inflammatory intestinal diseases)
- potential development of fever or systemic inflammatory reactions
- risk for colonoscopy
- informed consent is mandatory

Preparation on the day of stool transplantation

Preparation of stool suspension
- donor stool should be sampled and stored at 2–8° C in an airtight container for no longer than 6 hours; do not freeze
- dilute stool with sterile 0.9% NaCl or sterile water. The required volume is dependent on sample consistency, but is typically around 300 mL.
- homogenize with a domestic mixer
- filter mixture through a gauze, paper, coffee or metal (sieve) filter
- bacterial suspension to be applied as soon as possible (otherwise deep freeze storage is required)
- required amount of bacterial suspension ranges from 100 to 500 mL

Preparation – Recipient
- intestinal lavage similar to performing colonoscopy
- in the case of fecal microbiota transplantation (FMT) for *C. difficile,* pretreatment with, e.g., vancomycin is required for a minimum of 4 to 7 days. Antibiotic treatment must however, end at least >36 hours prior to FMT
- application of the suspension within 2 hours into the terminal Ileum (small volumes) and cecum
- loperamide (2 x 1 tablet) within 4 hours after transplantation
- application of the suspension with at least 12 hours of post-treatment observation
- stool transplantation appears to be also safe in immunosuppressed patients
- antibiotic therapy after FMT should only be undertaken where strictly indicated (possible high risk of relapse associated with antibiotic therapy)

Application of FMT for various diseases and the associated evidence

Medical condition	Evidence
Clostridium difficile colitis	monocenter RCT; large case series
Insulin resistence (Typ 2 DM)	monocenter RCT
Gastrointestinal graft-versus-host disease (GvHD)	case series
Chronic inflammatory bowel disease	case series
Irritable bowel syndrome	case series
Multiple sclerosis	case series
Chronic fatigue syndrome	case series
Idiopathic thrombocytopenic purpura (ITP)	case series
Obesity	animal model
Fatty liver	animal model
Atherosclerosis	animal model

(RCT= randomized controlled study) [Ridaura et al, Science 2013]

Definition:

Celiac disease is regarded as a life-long, immunologically modulated and chronic active disease affecting human beings bearing the genetically determined risk variants.
Celiac disease is a gluten-dependent auto-immune disease oft the small intestine from the duodenum to the terminal ileum. Apart from the known HLA-genes, genetic predisposition may also affect other unexplored or unknown gene loci and alleles.

Clinical course and new classification of celiac disease (CD)

Traditional Classification	Recommended Classification
Typical celiac disease	Classic celiac disease
Atypic celiac disease Overt celiac disease	Symptomatic celiac disease
Subclinical CD Asymptomatic CD Silent CD	Subclinical CD
Refractory CD	Refractory CD
Latent CD Potentially CD	Potentially CD

Presenting symptoms of adult celiac patients

Symptoms or signs	Frequency (%)
fatigue	82
abdominal pain or discomfort	77
gas or bloating	73
anemia	63
weight loss	55
diarrhea	52
depression, irritability or anger	46
nausea, cramping or vomiting	46
muscle, joint or bone pain	42
confusion or memory loss	37
hair loss	29

[Modified from Zipser RD et al. Dig Dis Sci 2003; 48(4):761-4]

Symptoms of celiac disease

Major intestinal symptoms
Chronic Diarrhea
Chronic abdominal pain
Motilitity disorders, ranging from diarrhea to constipation
Nausea/Vomiting
Flatulence
Bloating

Extraintestinal Symptoms
Weight loss/Malnutrition
Growth failure in children
Anemia, Iron deficiency
Recurring oral aphthous ulcers
Metabolic bone disorders e.g. premature osteomalacia/osteoporosis
Dental disorders e.g. discolorated teeth
Peripheral neuropathy/polyneuropathy
Muscle weakness or spasms
Night blindness
Hematomas and coagulation disorders
Amenorrhea
Edema
Abnormal liver function tests

Associated disorders
(Indications to rule out celiac disease)

Autoimmune disorders
Diabetes mellitus Type 1
Thyroid disease (e.g. Hashimoto-Thyroiditis)
Autoimmune Hepatitis
Primary Billiary Cholangitis (PBC)
Psoriasis
Collagenoses (e.g. Sjögren's Syndrome/systemic Lupus erythematodes)
M. Addison
Vitiligo
Alopecia areata
Dermatitis herpetiformis Duhring

Non-autoimmune mediated disorders
Migraine
Epilepsy or ataxia
Depression and/or anxiety disorders
Chronic fatigue
Neurologic disorders (e.g. peripheral neuropathies)
Down's Syndrome/Turner's Syndrome
Isolated IgA-Deficiency
Microscopic colitis
Irritable bowel syndrome
Amenorrhea, risk for miscarriage
Osteoporosis

Diagnosis in celiac disease

Clinical symptoms	Intention	Preferred procedure
asymptomatic people	screening	**serology** antiendomysial antibodies or tissue transglutaminase antibodies
unspecific symptoms	case finding	**serology** antiendomysial antibodies or tissue transglutaminase antibodies
strong suspicion of celiac disease	diagnostic	**>3 duodenal biopsies,** 1 biopsy from the bulbus, exclude *Heliobacter pylori*

Sensitivity and specificity of serological tests			
Antibody	**Sensitivity (%)**	**Specificity (%)**	**Comment**
Gliadin IgA	70–90	85–94	Should be abandoned completely, due to insufficient accuracy
Gliadin IgG	69–85	88–92	Similar as above, formerly the only reliable test in the event of IgA deficiency
Gliadin, deamidated	80–95	90–100	Considerably higher accuracy then former gliadin antibodies; also accurate in IgA deficiency
Trans-glutaminase (IgA)	90–98	94–97	Comparably high sensitivity to endomysial antibody, more expensive, worse specificity
Endomysial (IgA)	75–98	98–100	Excellent specificity, laborious, expensive

Important: Always exclude isolated IgA-Deficiency together with assessment of serologic celiac disease markers (measure Total-IgA in blood serum). Before starting treatment with a gluten-free diet, always obtain duodenal biopsies (including bulbus duodeni) if positive results or unexplained negative results for celiac disease-specific antibodies occur.
Biopsy: obtain at least 6 from the duodenum, of which 2 from the duodenal bulb, on a gluten-containing diet.

Genetic testing: HLA-DQ2/DQ8 are helpful only to rule out celiac disease

Clinical algorithm

- Suspicion for celiac disease:
  Assess Anti-Transglutaminase-IgA-Antibodies and Total-IgA levels in blood serum
- In case of low Total-IgA levels, assess IgG-Antibodies against Transglutaminase additionally
- Serology positive: Perform gastroscopy with at least 6 duodenal biopsies (which of 2 from the duodenal bulb)
- Diagnostic tests are to be performed on a gluten-containing diet (should be at least 15 g gluten/d for at least 2 months)
- In adult patients with autoimmune disorders (especially DM Type 1), other associated diseases and first-grade relatives of celiac disease patients a single serology assessment is recommended, in children serology should be repeated every 1–2 yrs.
- In celiac disease patients on gluten-free diet and no symptoms, serology should be controlled at least once a year.
- Subclinical celiac disease in childhood: gluten-free diet is highly recommended
- Subclinical celiac disease in adults: Advantages and disadvantages of a gluten-free diet should be discussed, still recommendation is on an individual basis

Monitoring

- Confirmed celiac disease, strict adherence to a gluten-free diet (GFD) and no symptoms: Assessment of the nutritional condition 1–2 x per year and assessment of antibody-levels once a year.
- In asymptomatic patients on GFD and normalized antibody levels repeat gastroscopy with biopsies is not required.
- In symptomatic patients on GFD, new-onset autoimmune disorders or continuously positive celiac-disease specific antibodies: control gastroscopy with biopsies is recommended.
- Continuous and strict gluten-free diet is the only life-long therapy known today

Complications

Refractory celiac disease (RCD)
Definition: Celiac disease is regarded as refractory or non-responsive, if, on gluten-free diet for at least 12 months, duodenal atrophy, intestinal or extraintestinal symptoms persist or reoccur.
Celiac disease refractory to gluten-free diet is rare (1.5% of celiac disease patients).
Most often, diet is not strictly kept.
Differential diagnoses that should be excluded: (e.g. by Ballon enteroscopy, MR-Enteroclysis, Laparoscopy with biopsies, capsule endoscopy or others)

- Ulcerative Jejunitis and EATL (Enteropathy-associated T-Cell-Lymphoma), microscopic colitis, food intolerances, etc.

RCD Type I (EATL not present): Therapy according to inflammatory bowel disease: Budesonide, Azathioprine, Calcineurin-Inhibitors, Anti-TNF-Antibodies.
Monitoring of nutritional status, check-up for malnutrition, nutritional support.
5-yr-survival is 93%

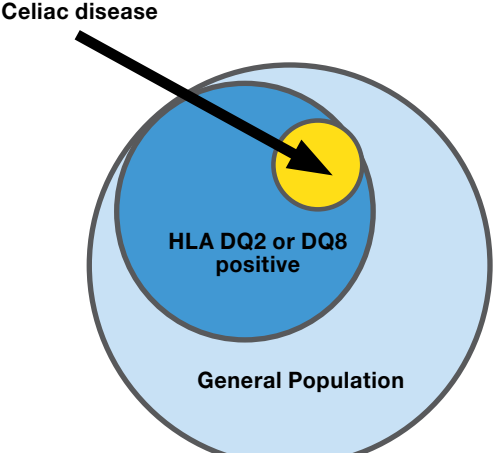
RCD Type II; EATL-associated (more than 20% intraepithelial lymphocytes on microscopy AND proof of clonal T-Cell-population): Budesonide, intensive dietary instruction; evaluation for chemotherapy up to stem cell mediated therapies e.g. transplantation.
5-yr-survival is 44%.

[1] DGVS: S2K Leitlinie Zöliakie, 04/2014; Erstautor: J. Felber et al, Korr. Autor: A. Stallmach
2) ACG Practice Guidelines: Diagnosis and Management of Celiac Disease; A. Rubio-Tapia et al Am. J. Gastro 2013; 108: 656 ff
3) Zöliakie-Eine Uebersicht zur Leitlinie der DGVS ; M Schumann et al ; Gastroenterologieup2date 10/2014; 235 ff]

HLA:
HLA-DQ2 is present in more than 90% of patients with celiac disease, (CD) while almost the complete rest of HLA-DQ2 negative CD patients is positive for DQ8 (combined negativity for both is extremely rare in true CD). Thus, excellent sensitivity renders this test an ideal tool to exclude CD. However, due to relatively high costs and also inaccurate specificity, HLA should only be performed in the following exceptional constellations:

Patient already on gluten-free diet; (strong) familial history of CD, in order to rule out potential to develop frank CD in the future; histology suspicious for CD with no clearcut serological constellation.

Due to high prevalence of DQ2 or DQ8 of roughly 30–40% in the general population, the specificity of this test is «lousy».



[Kagnoff, J Clin Invest. 2007; 117:41–9.]

Main causes of mid gastrointestinal bleeding:

Bleeding source:	Frequency:
Angiodysplasia	20–60%
Ulcerations (IBD, NSAIDs etc.)	10–40%
Neoplasia	1–10%

[Elta GH et al.: Gastrointest Endosc 2004]

Important facts to remember:

- Bleeding sources in the small bowel are rare (only 1 to 5% of all gastrointestinal bleedings)
  [Okazaki H et al.: J Gastroenterol 2009]

- «Push-and-pull» enteroscopy and small bowel capsule endoscopy have comparable sensitivity for the detection of a bleeding source in the small bowel
  [Pasha SF et al.: Clin Gastroenterol Hepatol 2008]

- Approximately 7 to 25% of the findings in capsule enteroscopy have been missed by EGD and colonoscopy
  [Kitiyakara T, et al.: Gastrointest Endosc 2005; Delvaux M, et al.: Endoscopy 2004]

[Kagnoff, J Clin Invest. 2007; 117:41–9.]

Causes of lower gastrointestinal bleeding:

Bleeding source:	Frequency:
Diverticula	30%
Colitis (ischemic, IBD)	15%
Carcinoma, Polyps	13%
Angiodysplasia	10%
Anorectal diseases	11%
Upper gastrointestinal bleeding	10%
Unknown (consider NSAIDs)	2–8%

[Elta GH et al.: Gastrointest Endosc 2004]

Important facts to remember:

- Overall mortality of lower GI bleeding is low (approx. 4%)
  [Strate LL et al.: Clin Gastroenterol Hepatol 2008]
- Up to 13% of patients with suspected lower GI bleeding have a bleeding source proximal to the ligament of Treitz
  [Strate LL et al.: Gastroenterol Clin North Am 2005]
- Urgent compared to elective colonoscopy improves detection rate of bleeding source, but has no effect on mortality and relapse bleeding rate
  [Green BT et al.: Am J Gastroenterol. 2005]

Recommendations for surveillance after colonoscopic polypectomy

[Adapted from recommendations of the Swiss Society of Gastroenterology]

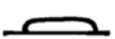
Preconditions:

- complete colonoscopy, optimally cleansed colon, complete resection of all polyps (so-called clearing colonoscopy), complete recovery of the resected specimens for histological examination ***please note:*** after piecemeal-resection of sessile polyps or in case of equivocal completeness of resection, a check colonoscopy is recommended within 3 months
- estimated life expectancy >10 years
- no evidence of hereditary cancer syndromes (FAP, HNPCC, Peutz-Jeghers) or other conditions with increased risk for colorectal cancer (chronic inflammatory bowel disease, acromegaly. etc.)

Risk category	Polyp histology & secondary criteria
I	**Tubular adenoma** • 1 – 2 polyps *and* • size ≤1 cm *and* • no high-grade dysplasia *and* • negative family history (1st degree relatives)
II	**Tubular adenoma** • > 2 polyps *or* • size >1 cm *or* • high-grade dysplasia *or* • positive family history (1st degree relatives)
	(Tubulo-) villous adenoma *or* serrated adenoma • any number and size • any grade of dysplasia
III	**pT1/carcinoma in situ within the polyp** • polypectomy endoscopically complete *and* • resection margins histologically free of carcinoma *and* • well or moderately differentiated (G1-G2) *and* • no invasion of lymphatic and/or venous vessels
IV	**pT1/carcinoma in situ within the polyp** • polypectomy endoscopically not complete *or* • resection margins histologically not free of carcinoma *or* • poorly differentiated or undifferentiated (G3-G4) *or* • invasion of lymphatic and/or venous vessels
Hyperplastic polyps proximal to the rectosigmoid *or* size >1 cm *or* >20 polyps	
in the rectosigmoid *and* size ≤1 cm	

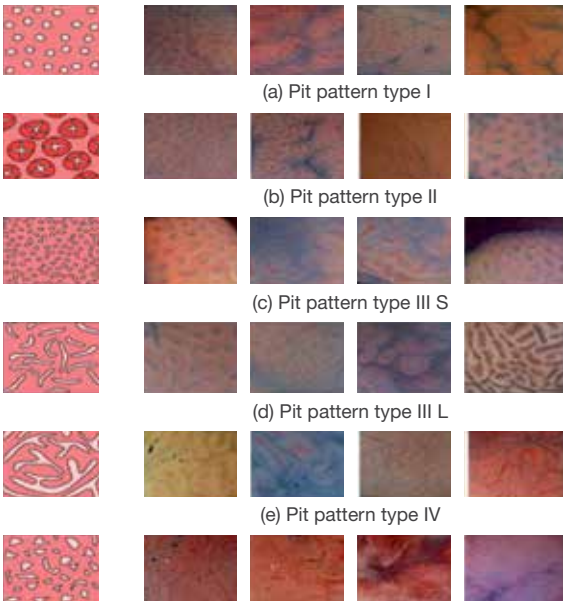
Colonoscopy interval	Colonoscopy interval when findings normal
5 y	stop surveillance
3 y	5 y
≤3 months for examination of the polypectomy site; then 3 y	5 y
→ ***surgical resection generally indicated***	
3 y	5 y
no surveillance	

Paris Classification of Colon-Polyps

Endoscopic appearance	Paris class		Description
Protruded lesions	Ip		Pedunculated polyps
	Ips		Subpedunculated polyps
	Is		Sessile polyps
Flat elevated lesions	0–IIa		Flat elevation of mucosa
	0–IIa/c		Flat elevation with central depression
Flat lesions	0–IIb		Flat mucosal change
	0–IIc		Mucosal depression
	0–IIc/IIa		Mucosal depression with raised edge

[The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon November 30 to December 1, 2002
VOLUME 58, NO. 6 (SUPPL), 2003 GASTROINTESTINAL ENDOSCOPY]

Kudo – Classification of Polyps



(a) Pit pattern type I

(b) Pit pattern type II

(c) Pit pattern type III S

(d) Pit pattern type III L

(e) Pit pattern type IV

(f) Pit pattern type V

I – Round pits
II – Stellar or papillary pits
IIIS – Small tubular or roundish pits
IIIL – Large tubular or roundish pits
IV – Branch-like or Gyrus-like pits
V – Unstructural pits
Types I and II are benign and show regular round or star-shaped pits, Types III to V are malignant and are more disordered and chaotic, with different sizes and more tubular and irregular pits.

[S. Kudo, S. Tamura et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy, Gastrointest. Endosc., 44 (1996), 8–14]

Recommendations for surveillance after curative surgery for colorectal cancer

[Adapted from recommendations of the Swiss Society of Gastroenterology]

Preconditions:

- postoperative stage II-III (T3/4 or N+, M0) in patients who would qualify for treatment of recurrence or metastases, judged on the basis of age and general condition
- surveillance is an interdisciplinary task, coordinated by one institution in permanent contact with the involved physicians (surgeon, general practitioner, gastroenterologist, radio-/oncologist etc.)
- a baseline complete colonoscopy is mandatory preoperatively (or postoperatively within 3 months) along with preoperative staging by imaging, usually by a CT scan of chest and abdomen (with additional pelvic CT in cases of rectal cancer)
- hereditary colorectal cancer syndromes (FAP, HNPCC, Peutz-Jeghers) or other high risk conditions for colorectal cancer (chronic inflammatory bowel disease, acromegaly etc.) are NOT included in these recommendations and require special surveillance

	Months postoperatively						
	6	12	18	24	36	48	60
Clinical examination[1] & CEA levels[2]	quarterly within 1st year		twice a year within 2nd and 3rd year			+	+
Colonoscopy		+				+[3]	
CT scan of chest & abdomen[4]		+		+	+	+	+
In case of rectal cancer: rectosigmoidoscopy & EUS	+	+	+	+			

1) in cases of low (extraperitoneal) rectal cancer, treated with total mesorectal excision (TME), quarterly rectal exam (by the responsible surgeon)
2) preoperative analysis of CEA levels routinely recommended; in case of postoperative elevation, imaging studies are recommended
3) once findings are normal, change to 5 years interval
4) triple contrast (oral-rectal-intravenous) CT scan of chest & abdomen (supplemented with a pelvic CT in case of rectal cancer) is standard; liver ultrasound plus chest X-ray is an alternative; chest CT scan is beneficial in rectal cancer

Amsterdam-II-Criteria (All must be fulfilled)

The Amsterdam Criteria have been highly successful, with estimated sensitivity and specificity of 60% and 70%, respectively. Certain deficiencies, however, have become increasingly recognized. For example, the original Amsterdam Criteria did not take into account extracolonic cancers, patients with new MMR mutations were not addressed, and some families with multiple polyps but without profuse polyposis were erroneously classified as having putative HNPCC. Therefore the **Amsterdam II Criteria** (see below) were introduced in 1999 with estimated sensitivity of 78% and specificity of 61%[1].

- At least 3 relatives with HNPCC-associated cancer (colorectum, endometrium, small bowel, ureter or renal pelvis) AND
- One should be a first-degree relative to the other two
- At least two successive generations should be affected
- At least one should be diagnosed before age 50
- Familial adenomatous polyposis should be excluded
- Tumors should be verified by pathological examination

Vasen, H., Watson, P., Mecklin, J.-P., & Lynch, H. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology, 116(6), 1453–1456.

[1Syngal S, Fox EA, Eng C, et al: Sensitivity and specificity of clinical criteria for hereditary non-polyposis colorectal cancer associated mutations in MSH2 and MLH1. J Med Genet 37:641-645. 2000]

Tumors from individuals should be tested for MSI (microsatellite instability) in the following situations (Bethesda guidelines)

1. colorectal cancer diagnosed in a patient who is less than 50 y
2. presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors*, regardless of age
3. colorectal cancer with the MSI-H† like histology‡ diagnosed in a patient who is less than 60 y§
4. colorectal cancer diagnosed in a patient with one or more 1st degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 y
5. colorectal cancer diagnosed in a patient with two or more 1st or 2nd degree relatives with HNPCC-related tumors, regardless of age

* *Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome), sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel.*

† *MSI-H: microsatellite instability–high in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.*

‡ *Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.*

§ *There was no consensus among the workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.*

[Adapted from Umar A et al. J Natl Cancer Inst 2004]

Small and large bowel
High risk colorectal cancer conditions

Characteristic features of High Risk Colorectal Cancer		
Condition/Inheritance	**Gene**	**Lifetime cancer risks**
Lynch-Syndrome *autosomal-dominant*	hMLH1 hMLH2 hMSH6 hPMS2 EpCAM	colon endometrium stomach ovary hepatobiliary tract upper urinary tract pancreatic small bowel CNS (glioblastoma)
Familial adenomatous polyposis (FAP) *autosomal-dominant*	APC	colon duodenum/periampullary stomach pancreas thyroid liver (hepatoblastoma) CNS (medulloblastoma)
Attenuated FAP *autosomal-dominant*	APC	colon duodenum/periampullary thyroid
MUTYH-associated polyposis *autosomal-recessive*	MUTYH	colon duodenum
Peutz-Jeghers syndrome *autosomal-dominant*	STK11	breast colon pancreas stomach ovary lung small bowel uterine/cervix testicle
Juvenile polyposis syndrome *autosomal-dominant*	SMAD4 BMPR1A	colon stomach, pancreas and small bowel
Hyperplastic polyposis **Serrated polyposis syndrome** *inheritance unknown*	?	colon

**Risks associated with EpCAM mutations are not yet known.*

Conditions	
%	Nonmalignant features
Non-polyposis	
50–80	physical or nonmalignant features – besides
40–60	keratoacanthomas and sebaceous adenomas/
11–19	carcinomas – are rare
9–12	
2–7	
4–5	
3–4	
1–4	
1–3	
Adenomatous polyposis	
100	100s to 1000s of colorectal adenomas gastric
4–12	fundic glands and duodenal adenomatous polyposis
<1	congenital hypertrophy of the retinal pigment
2	epithelium; epidermoid cysts; osteomas
1–2	dental abnormalities
1–2	desmoid tumors
<1	
70	<100 colonic adenomas
4–12	upper gastrointestinal polyposis similar to FAP
1–2	other non-malignant features are rare in attenuated FAP
80	colonic phenotype similar to attenuated FAP;
4	duodenal polyposis
Hamartomatous polyposis	
54	mucocutaneous pigmentation
39	gastrointestinal hamartomatous
11–36	(Peutz-Jeghers) polyps
29	
21	
15	
13	
9	
<1	
39	gastrointestinal hamartomatous (juvenile) polyps
21	features of hereditary hemorrhagic telangiectasia;
	congenital defects
Hyperplastic polyposis	
>50	hyperplastic polyps, sessile serrated polyps,
	traditional serrated adenomas and mixed adenomas

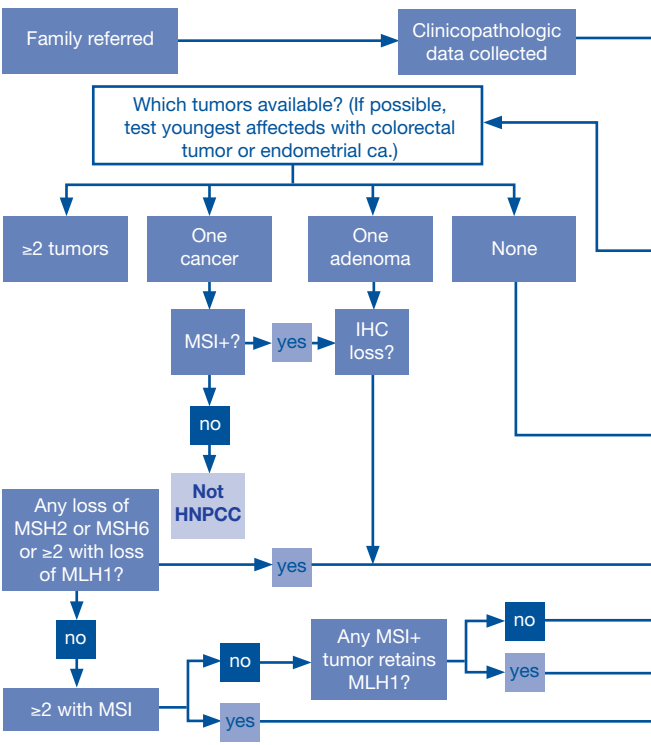
[Adapted from Jasperson KW et al. Gastroenterology 2010; 138(6):2044-58]

Management recommendations for High Risk Colorectal	
Condition	**Cancer**
Lynch-Syndrome	colon endometrium/ovary upper urinary tract upper GI tract other
Familial adenomatous polyposis (FAP)	colon upper GI tract other
MUTYH-associated polyposis	colon duodenum
Peutz-Jeghers syndrome	colon breast pancreas stomach/small bowel cervix/uterus/ovary testes
Juvenile polyposis syndrome	colon stomach
Hyperplastic polyposis	colon

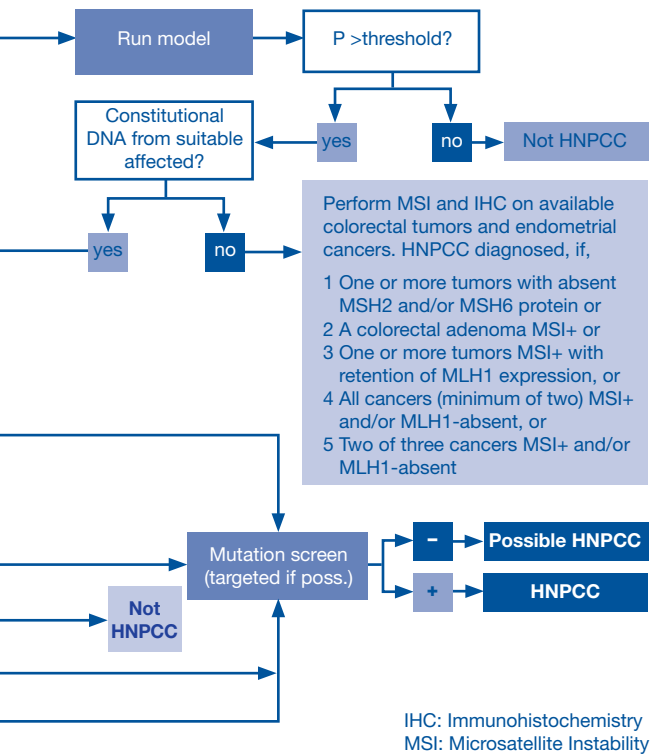
[Adapted from Jasperson KW et al. Gastroenterology 2010; 138(6):2044-58]

Cancer Conditions
Recommendations
colonoscopy every 1–2 y, start at 20–25 y consider prophylactic hysterectomy & bilateral salpingo-oophorectomy after childbearing complete; gynecological cancer screening consider annual urinalysis, beginning at 30–35 y consider EGD (incl. side view endoscope) every 1–2 y, start at age 30–35 y annual physical examination including skin (sebaceous carcinoma?)
colonoscopy every 1–2 y, start at 10–12 y (for attenuated FAP at 18–20 y) prophylactic colectomy when polyps become unmanageable (if remaining rectum or ileal pouch, screen every year) EGD every 1–3 y, start at 20–25 y annual physical examination, including thyroid
colonoscopy every 2–3 y, start at 25 y prophylactic colectomy when polyps become unmanageable EGD every 1–3 y, start at 20–25 y
colonoscopy every 2–3 y, start with symptoms or latest at 18–20 y annual mammogram & breast MRI, start at 25 y MRCP and/or EUS every 1–2 y, start at 30 y EGD and abdominal CT with oral contrast every 2–3 y, start at 10 y annual pelvic examination, pap smear and transvaginal US, start at 18 y annual testicular examination, start at 10 y
colonoscopy every 2–3 y, start with symptoms or latest at 18–20 y EGD every 1–3 y
colonoscopy every 1–2 y prophylactic colectomy when polyps become unmanageable

Suggested flow chart for investigation and diagnosis of possible hereditary nonpolyposis colon cancer (HNPCC) families.

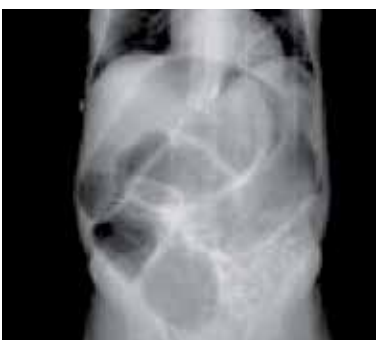


[Lipton L et al. JCO 2004;22:4934-4943]


Run model
P >threshold?
yes
no
Not HNPCC
Constitutional DNA from suitable affected?
yes
no
Perform MSI and IHC on available colorectal tumors and endometrial cancers. HNPCC diagnosed, if,
1 One or more tumors with absent MSH2 and/or MSH6 protein or
2 A colorectal adenoma MSI+ or
3 One or more tumors MSI+ with retention of MLH1 expression, or
4 All cancers (minimum of two) MSI+ and/or MLH1-absent, or
5 Two of three cancers MSI+ and/or MLH1-absent
Mutation screen (targeted if poss.)
–
Possible HNPCC
+
HNPCC
Not HNPCC
IHC: Immunohistochemistry
MSI: Microsatellite Instability

Acute colonic pseudo-obstruction (Ogilvie's syndrome)

definition	• Gross dilatation of the cecum and right hemicolon (occasionally extending to the rectum) in the absence of a stenosis
etiology	• Trauma; recent surgery; electrolyte abnormalities • Obstetric / gynecologic diseases • Medications (NSAIDs, opiates, antidepressants)
clinical symptoms	• Abdominal distention • Nausea & vomiting; abdominal pain • Constipation or paradoxically diarrhea
radiography	• Clearly dilated colon
diagnosis	• Diagnosis can be made only after excluding the presence of toxic megacolon or mechanical obstruction
treatment (algorithm next page)	• Conservative management • Neostigmine • Endoscopic decompression or surgery



Treatment algorithm in Ogilvie's syndrome

conservative management	• NPO, IVF, NG suction • *If no response…*
evaluation	• Evaluate and treat reversible causes (e.g. electrolyte abnormalities) • *If no response…*
neostigmine	• 1.5–2 mg IV (over 2–3 min) under cardiovascular monitoring (atropine bedside!) • CONTRAINDICATIONS: bronchial asthma, recent myocardial infarction, beta-blockers, bradyarrhythmias, hyperthyroidism, intestinal stenosis • *If no response…*
endoscopic decompression	• At the latest if cecum >12 cm • *If no response …*
surgery or PEC	• Endoscopic: percutaneous endoscopic colostomy (PEC) • Surgery: cecostomy or colectomy

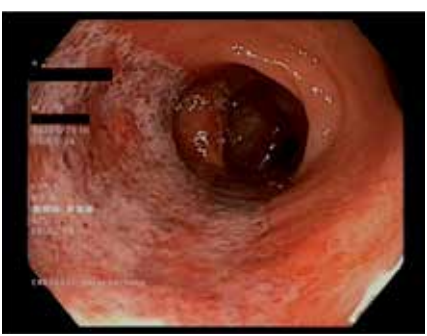
Colonic ischemia

- Colonic ischemia (CI) ensues when blood flow to the colon is reduced to a level insufficient to maintain cellular metabolic function and reperfusion injury may produce further damage
- Most frequently no cause for ischemia can be identified and nonocclusive ischemia resulting from small-vessel disease is postulated
- CI is associated with cardiovascular disease, diabetes mellitus, hypotension, aortic surgery, hypercoagulable states, drugs and IBS
- Signs and symptoms of CI include sudden cramping, mild, abdominal pain and passage within 24 h of blood or bloody diarrhea. In patients with CI isolated to the right colon (IRCI) pain is the cardinal symptom
- IRCI harbors a higher mortality and may be associated with acute mesenteric ischemia (AMI)
- CT with intravenous and oral contrast should be the first imaging modality
- Multiphasic computed tomography angiography should be considered if IRCI is suspected
- Early colonoscopy (within 48 h) should be performed to confirm the diagnosis. Use as little insufflation as possible
- In patients with severe CI limited colonoscopy is appropriate
- Endoscopy findings include longitudinally oriented erythema with erosions or ulcerations, hemorrhagic nodules, and, occasionally pseudomembranes and cyanotic mucosa may be seen; typically in segmental distribution

Colonic ischemia

- Most cases of CI resolve spontaneously
- Surgical intervention should be considered if CI is associated with hemodynamic instability, ongoing abdominal pain and in the presence of gangrene
- Antibiotics should be considered for patients with moderate or severe disease (low evidence).

[Brandt L. et al. ACG Clinical Guideline: Epidemiology, Risk Factors, Patterns of Presentation, Diagnosis, and Management of Colon Ischemia (CI), Am J Gastroenterol 2015; 110:18–44]



Longitudinally oriented erythema with erosions in IC

a) Diverticulosis

Definition: asymptomatic, acquired herniations of mucosa and submucosa through the colonic wall (pseudo-diverticula)
Epidemiology: more frequent in industrialized countries, higher age is the only risk factor (not low fibre diet, constipation, sedentary lifestyle), left colon predominantly affected
Clinical presentation: asymptomatic but risk of diverticulitis or hemorrhage. Diagnosis: accidentally by imaging or within work-up for complications. Treatment: no therapy, but high fibre diet recommended for diverticulitis prophylaxis (does not prevent diverticula formation)

b) Diverticulitis

Epidemiology: 10–20% life-time risk with diverticulosis, mostly at 60–70 years
Clinical presentation: abdominal pain (often left-sided) +/- signs of peritonitis, fiver, constipation > diarrhea, nausea +/- vomiting, dysuria
Laboratory: neutrophilic leukocytosis, CRP elevation
Imaging: emergency triple-contrast abdominal CT (diverticula? diverticulitis? complication? differential diagnosis?), or ultrasonography
Endoscopy: contra-indicated!
Diagnosis: abdominal pain + leukocytosis + typical CT scan findings
Differential diagnosis: gastroenterological (appendicitis, infectious colitis, IBD, …), gynecological (adnexitis, extrauterine pregnancy, …) urological (cystitis, pyelonephritis, urolithiasis, …)
Complications: perforation, abscess, fistula, stenosis
(Cave: the first episode of diverticulitis is the most dangerous one!)

Classification and management

Classification:	Hansen & Stock	Hinchey	Mortality	Management:
Asymptomatic	0	-	0%	Conservative: - Fasting for solids - Antibiotics - Regular reassessment within 48 h
Acute, uncomplicated	I	0		
Acute, complicated	II	I-IV		
- Confined pericolic inflammation, phlegmon	IIa	Ia		
- Confined pericolic abscess	IIb	Ib	<5%	Abscess drainage and possibly surgery
- Pelvic or distant abscess	IIb	II		Early elective surgery
- Purulent peritonitis	IIc	III	13%	Emergency surgery
- Fecal peritonitis		IV	43%	
Chronic recurrent diverticulitis	III	-		Elective surgery in stenosis

[Adapted from: Hinchey EJ: Adv Surgery 1978; Hansen O: Langenbecks Arch Chir 1999; Kaiser AM: Am J Gastroenterol 2005; Jacobs D: N Engl J Med 2007]

CT Findings according to Kaiser et al. Am J Gastroenterol 2005:		
Modified Hinchey Classification		**Comments**
0	Mild clinical diverticulitis	LLQ pain, elevated WBC, fever, no confirmation by imaging or surgery
Ia	Confined pericolic inflammation-phlegmon	
Ib	Confined pericolic abscess	
II	Pelvic, distant intraabdominal, or retroperitoneal abscess	
III	Generalized purulent peritonitis	No open communication with bowel lumen
IV	Fecal peritonitis	Free perforation, open communication with bowel lumen
Fistula	Colo-vesical/-vaginal/-enteric/-cutaneous	
Obstruction	Large and/or small bowel obstruction	

Treatment: depending on severity (Hinchey and clinical presentation +/- comorbidities), interdisciplinary decision making with surgeons and gastroenterologists.

1) Mild-moderate diverticulitis (Hinchey 0-Ia) without complication or comorbidities/immunosuppression: out-patient, rest and liquid diet until pain-free, NO antibiotics!, possibly 5-ASA
   [Chabok A et al. Br J Surg 2012]
2) Severe/complicated diverticulitis (Hinchey >Ia) or comorbidities/immunosuppression: hospitalization, nothing by mouth, antibiotics (covering gram-negative bacteria, enterobacteriaceae and anaerobic bacteria), i.v. fluids

2a) abscess <5 cm or concealed perforation: conservative treatment with antibotics

2b) abscess >5 cm: drainage if possible + antibiotics, discuss surgery

3) Free perforation (Hinchey III/IV) or failure of 72 h of conservative treatment: surgery (primary anastomosis with diverting ileostomy preferred)
[Oberkofler CE et al. Ann Surg 2012]
4) Postdiverticulitis stenosis/fistula: resection

Follow-up: colonoscopy within 4–8 weeks to rule out colorectal cancer; no proven measure to prevent recurrence of diverticulitis; elective (hemi-)colectomy to prevent relapse only after careful and individual risk/benefit assessment (Cave: fecal incontinence, incomplete evacuation, …)

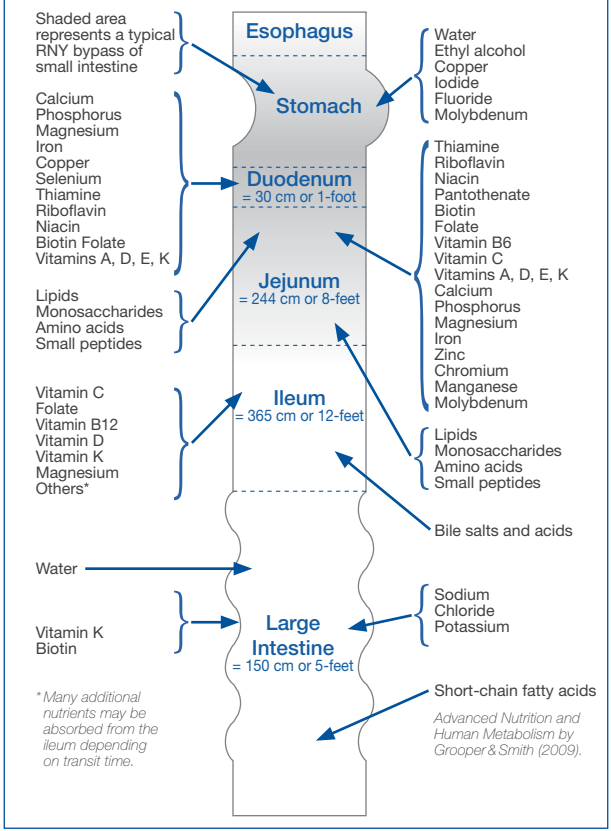
c) Diverticular bleeding

Epidemiology: 5% life-time risk with diverticulosis, risk of recurrence 20–30%
Clinical presentation: massive rectal hemorrhage of bright red blood, sometimes with anemia +/- hemodynamic instability, self-limited in 80%
Diagnosis: endoscopy including gastroscopy + ileo-colonoscopy (after PEG-preparation if possible); imaging with CT angiography (sensibility 0.5–1.0 ml/min) or scintigraphy (sensibility >0.1 ml/min)
Differential diagnosis: anal fissure, hemorrhoids, actinic rectitis, angiodysplasia, IBD, tumor/polyp, upper GI hemorrhage, Meckel's diverticulum, enterovascular fistula, urogenital/gynecological bleeding, …
Treatment: if not self-limited → endoscopy with injection of adrenaline and clipping; if failure or instable → embolisation; (hemi-)colectomy = ultima ratio.

[Kruis W, Germer CT, Leifeld L. Diverticular Disease: Guidelines of the German Society for Gastroenterology,Digestive and Metabolic Diseases and the German Society for General and Visceral Surgery. Digestion 2014;90:190-207.]

Differential Diagnosis

Phase and nature of malabsorptive defect	Example
Luminal phase	
A. Substrate hydrolysis	
1. Digestive enzyme deficiency	Chronic pancreatitis
2. Digestive enzyme inactivation	Zollinger-Ellison syndrome
3. Dyssynchrony of enzyme release, inadequate mixing	Post Billroth II procedure
B. Fat solubilization	
1. Diminished bile salt secretion	Cirrhosis
2. Impaired bile secretion	Chronic cholestasis
3. Bile salt deconjugation	Bacterial overgrowth
4. Increased bile salt loss	Ileal disease or resection
C. Luminal availability of specific nutrients	
1. Diminished gastric acid	Atrophic gastritis – vitamin B12
2. Diminished intrinsic factor	Pernicious anemia – vitamin B12
3. Bacterial consumption of nutrients	Bacterial overgrowth – vitamin B12
Mucosal (absorptive) phase	
A. Brush border hydrolysis	
1. Congenital disaccharidase defect	Sucrase-isomaltase deficiency
2. Acquired disaccharidase defect	Lactase deficiency
B. Epithelial transport	
1. Nutrient-specific defects in transport	Hartnup's disease
2. Global defects in transport	Celiac sprue
Postabsorptive, processing phase	
A. Enterocyte processing	Abetalipoproteinemia
B. Lymphatic	Intestinal lymphangiectasia


Shaded area represents a typical RNY bypass of small intestine
Calcium
Phosphorus
Magnesium
Iron
Copper
Selenium
Thiamine
Riboflavin
Niacin
Biotin Folate
Vitamins A, D, E, K
Lipids
Monosaccharides
Amino acids
Small peptides
Vitamin C
Folate
Vitamin B12
Vitamin D
Vitamin K
Magnesium
Others*
Water
Vitamin K
Biotin
Esophagus
Stomach
Duodenum
= 30 cm or 1-foot
Jejunum
= 244 cm or 8-feet
Ileum
= 365 cm or 12-feet
Large Intestine
= 150 cm or 5-feet
Water
Ethyl alcohol
Copper
Iodide
Fluoride
Molybdenum
Thiamine
Riboflavin
Niacin
Pantothenate
Biotin
Folate
Vitamin B6
Vitamin C
Vitamins A, D, E, K
Calcium
Phosphorus
Magnesium
Iron
Zinc
Chromium
Manganese
Molybdenum
Lipids
Monosaccharides
Amino acids
Small peptides
Bile salts and acids
Sodium
Chloride
Potassium
Short-chain fatty acids
* Many additional nutrients may be absorbed from the ileum depending on transit time.
Advanced Nutrition and Human Metabolism by Grooper & Smith (2009).

Diagnosis Evaluations

	Test	Impaired intraluminal Digestion
Stool	Stool fat (qualitative, quantitative)	Increased (concentration usually >9.5%)
	Stool elastase	Low in moderate and severe pancreatic exocrine insufficiency
	Stool ova and parasites and specific parasitic antigens	May be positive in parasitic biliary cholangiopathy
Laboratory (serum)	Serum carotene	Decreased
	Serum cholesterol	Decreased
	Serum albumin	Usually normal, except with bacterial overgrowth
	Prothrombin activity	Decreased if severe
	Serum calcium	Usually normal if pancreas is the cause
	Serum 25-OH vitamin D	Decreased
	Serum iron	Normal
	Serum folate	Normal
Absorption/ Stimulation tests	Xylose absorption	Normal, except with bacterial overgrowth
	Lactose absorption (lactose tolerance test or breath hydrogen after lactose load)	Normal, except in some instances of bacterial overgrowth
	Vitamin B_{12} absorption (Schilling test)	Decreased in bacterial overgrowth and exocrine pancreatic insufficiency
	Lactulose and glucose breath hydrogen test	Early appearance of H_2 in breath in bacterial overgrowth
	Secretin/cholecystokinin stimulation tests	Abnormal in chronic pancreatic exocrine insufficiency
	IgA anti-tissue transglutaminase IgA antiendomysial antibody IgA antibodies to deaminated gliadin	Absent
Endoscopy	Endoscopic intestinal biopsy	Normal except in severe bacterial overgrowth
	Wireless capsule endoscopy	Usually normal

[modified from CURRENT Medical Diagnosis and treatment; Lange, 2011]

Useful laboratory tests in evaluation of intestinal malabsorption.

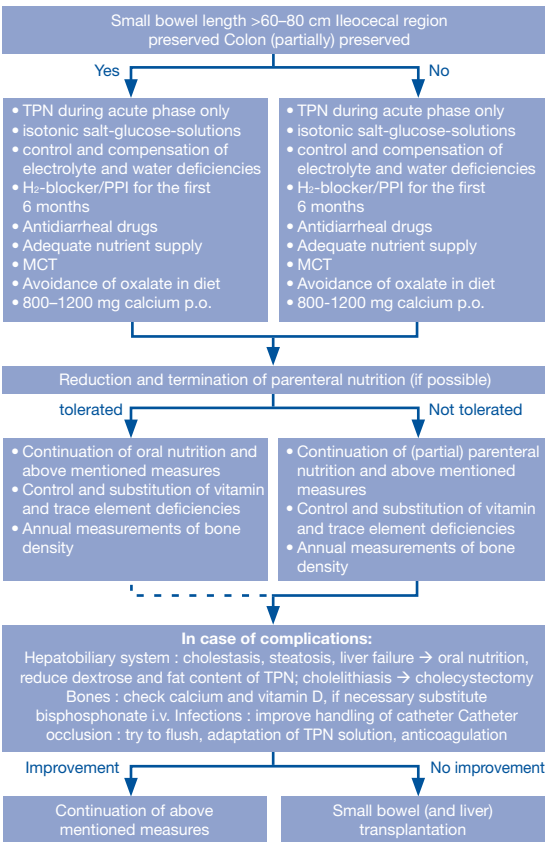
Mucosal Disease	Lymphatic Obstruction	Limitations
Increased (concentration usually <9.5%)	Increased	False-negative result if inadequate ingestion of dietary fat or recent barium ingestion; false-positive result with castor oil or mineral oil ingestion
May be low due to dilution	Usually normal	Low specificity for pancreatic disease if small intestinal disease is present
May diagnose *Giardia,* Isospora, cryptosporidia, microsporidia, tapeworms	Negative	
Decreased	Decreased	Low values may occur in normal subjects who ingest little dietary carotene
Decreased	Decreased	May be normal or increased in patients with untreated lipoprotein abnormality
Often decreased	Often decreased	
Decreased if severe	Decreased if severe	May also be decreased in liver disease but parenterally administered vitamin K should induce normalization if caused by malabsorption
Decreased	Decreased	May reflect hypoalbuminemia
Decreased	Decreased	
Often decreased	Normal	
Often decreased	Normal	
Abnormal, unless disease confined to distal small intestine	Normal	Requires normal gastric emptying and renal function
Increase in plasma glucose <20 mg/dL (1.11 mmol/L) increased breath H_2	Normal	May be abnormal in all categories if patient has primary intestinal lactase deficiency; requires normal gastric emptying
Decreased in extensive ileal disease	Normal	Requires good renal function
Normal	Normal	Requires normal gastric emptying; false-positive results may occur in patients with rapid small intestinal transit
Normal	Normal	Relatively low sensitivity, cumbersome and labor intensive
Present in celiac sprue	Absent	Lower sensitivity in infants and all ages in mild disease, false negative results in IgA deficiency
Often abnormal	Often abnormal	May miss patchy mucosal disease
Often abnormal	Often abnormal	Labor intensive, cannot biopsy lesions, may obstruct strictured intestine

Enteral tube feeding

Indication	e.g.
GI stenoses no tolerance to fibers	Fresubin® original fibre, Osmolite®
Longterm feeding, maintenance of GI function, diabetes, constipation	Fresubin original fibre®, Jevity®
Energy requirement ↑, fluid intake ↓	Fresubin® energy fibre, Jevitiy Hical®, Osmolite Hical®
Diarrhea (and constipation)	-
Maldigestion, -absorption, short bowel, deep position of feeding tube	Perative®, Survimed (OPD)®
Acute and chronic kidney failre	Nepro®, Fresumin Hepa®
Critical care patients	Oxepa®, Reconvan®, Intestamin®
Increased demands (e.g. fistulas, burn) or tube feeding <1500 ml/day	Zn, Se, Cu
Tube feeding <1500 ml/day	Supradyn®, Berocca®, Benerva®
Deficiencies	P, K, Ca, Mg

Tube feeding		
High caloric tube feeding	Isocaloric (1 kcal/ml)	without fibers
		with fibers
	High caloric (>1- max. 2 kcal/ml)	with/ without fibers
		soluble fibers
Low molecular tube feeding	Main nutrition as monomeric or easy resorbable components	
Metabolism-adapted tube fedding	High caloric, low electrolyte, ev. low protein	
Immun-modulated tube feeding	Pharmacologic effect (as amino acids, Omega 3-FS, nucleotides, Vitamin C and E, trace elements)	
Supplements	Trace elements	
	Vitamins	
	Electrolytes	

Therapeutic options and algorithm in short bowel syndrome



Intestine	Malabsorbed nutrient	Pathophysiology and Symptoms
Duodenum	Calcium, Magnesium, Phosphate, Iron, Folic acid	Anemia, Osteoporosis
Jejunum	Electrolytes (Na, K), Glucose, Amino acids, Water soluble Vitamins, Iron, Micronutrients	Secretion of intestinal hormones↓ → gastric acid secretion ↑ → peptic ulcers Cholecystokinin and secretin ↓ → gall bladder contraction ↓ → risk for bile stones ↑
Ileum	Vit. B12, bile acids, fat/essential fatty acids, fat soluble vitamins	Discontinuation of the entero-hepatic circulation of bile acids → steatorrhea, diarrhea, loss of electrolytes, colitis, formation of bile stones Resection >50 cm of Ileum: Vit.-B12-absorption ↓
Ileocoecal valve	Vitamin B12	Vit.-B12-malabsorption Bacterial synthesis of D–Lactate → Lactate acidosis Deconjugation of bile acids → Diarrhea, Steatorrhea
Colon	water, electrolytes (Na, Mg, Ca), Medium-chain triglycerides (MCT)	In case of steatorrhea “lime soap” formation → Oxalate ↑ → Hyperoxaluria → nephroli-thiasis Dehydratation, electrolyte disturbances

Small and large bowel
Short bowel syndrome

Incidence:
- 1–2 per 100,000 inhabitants

Etiology:
- repetitive bowel resections in Crohn's disease
- consequence of vascular disorders in adults (intestinal infarction)
- congenital vascular aberrations in children
- complications after abdominal surgery
- volvulus
- multiple intestinal fistulas
- intestinal irradiation
- abdominal trauma
- bariatric surgery

Assessment:
- degree of (small) bowel loss
- functional disturbances

Regular lab test:
(initially as often as appropriate, later on every 3–6 months, after 12 months yearly)

Na, K, Cl, Ca, Mg, phosphate, urea, creatinine, iron, ferritin, transferrin, glucose, pre-albumin,
Albumin, ALAT, ASAT, GGT, AP, Bilirubin, CRP
Bicarbonate (blood gas analyses), lactate
RBC (incl. thrombocytes)
Quick or INR
Vitamin: Folic acid, Vit. B12 and B1, Vitamins A, D, E
Micronutrients: Fe, Zn, Se

3 phases of postoperative adaptation process

	Acute Phase
Begin	Immediately after resection
Duration	Generally less than 4 weeks
Goal	to stabilise the patient
Main losses	Fluid, electrolytes
Main clinical problem	massive diarrhea
Treatment	parenteral nutritional support, gastric acid secretion inhibitors and, in severe cases, the somatostatin-analogue octreotide
Nutrition	**Energy:** 32–35 kcal/kg/d **Glucose:** max. 4–6 g/kg/d **Fat:** 1.2–1.8 g/kg/d (30–50% of energy supply) **Amino acids:** 1.0–1.5 g/kg/d (to be increased to max. 2 g/kg/d)

Adaptation Phase	Maintenance Phase
1–2 years	
to induce maximal adaptation by gradually increasing nutrient exposure	To individualise permanent dietetic maintenance nutrition, dependent on extent and quality of nutritive deficits. Effective therapy of acute exacerbations and optimal maintenance therapy of Crohn's disease
	average malabsorption of 30% of nutrients ingested
	for a target absorption rate of 30–40 kcal/kg/d (ideal body weight), about 45–60 kcal/kg/d must be ingested
	Adequate and regular supplementation of vitamins, minerals and trace elements. If no distal ileum is left, vitamin B12 must be supplemented parenterally. Calcium should be given generously by mouth (800–1200 mg/d)

3 phases of postoperative adaptation process

1) Acute Phase	
	1./2. postoperative day: Infusion therapy using Ringer, glucose and amino acid solutions, substitution of water soluble vitamins and trace elements
	2./3. postoperative day: Start of total parenteral nutrition
	4./5. postoperative day: Oral/enteral nutrition with gradually increasing nutrient loads: isoosmolar salt–glucose-solutions, tea, carbohydrate solutions, medium chain triglycerides, amino acids

2) Adaptation Phase	3) Maintenance Phase
	Drug Therapy
Oral/enteral nutrition with gradually increasing nutrient loads to 30–40 kcal/kg/d: isoosmolar salt–glucose-solutions, tea, carbohydrate solutions, medium chain triglycerides, amino acids. Frequent small solid meals are advisable. If this is not sufficient to ensure adequate energy supply or not tolerated continuous enteral nutrition can be used.	Oral nutrition in stable patients: many small meals, high fat diet, small amounts of medium chain triglycerides in patients with preserved colon, fluids can usually be taken with meals, substitution of vitamins and minerals as needed, in particular calcium. Avoidance of nutrients rich in oxalate if distal small intestinal resection.
Predominantly long chain triglycerides, free fatty acids, small amounts of medium chain triglycerides in patients with preserved colon, saccharose, maltose, glutamine, pectin, substitution of vitamins and minerals as needed, in particular calcium. Growth hormone (and GLP-2) may improve the adaptive process.	

Recommended dietetic treatment

	Colon present	No colon
Carbohydrates	50–60%	40–50%
Fat	20–30% MCT/LCT	30–40% LCT
Proteins	20–30%	20–30%
Fibre	soluble	No
Fluids	isotonic or hypotonic	isotonic
Oxalate	avoid	No limitation

It appears possible to treat even some patients with very short bowel, i.e. less than 50 cm of small intestine left, with oral nutrition, only.

Still, a considerable proportion of patients will need long-term parenteral nutrition.
These patients require 30-40 kcal/kg/d; 32 kcal/kg/d are recommended for total parenteral nutrition.
In addition, electrolytes, minerals, vitamins and trace elements must be supplemented.

Prevention of nephrolithiasis
Supplementation of Vitamin B6
(=Coenzyme for Oxalate degradation) 300 mg/d
Sufficient oral fluids
(and urine production at least 2000 ml urine/d)
Avoid Oxalate excess
Calcium enriched nutrition (800–1200 mg/d) or Calcium supplementation during main meals
In case of hyperoxaluria: **Calcium** 3 g/d to the main meals, increase to 4 g/d if necessary
In case of hypocitraturia: **Potassium citrate**
Substitution of **MCT** if necessary (reduces Oxalate absorption)
In case of increased uric acid in urine. Supplement alkalising sparkling water or Potassium citrate

Laboratory treatment goals **(in urine):**
Oxalate: <32 µmol/mmol Creatinine
Citrate: 107 mmol/mmol Creatinine,
(better >200 mmol/mmol Creatinine)

Calcium: <7,5 mmol/mmol Creatinine
Sodium: <287 mmol/mmol Creatinine
Uric acid: <2500 µmol/24 h

Prevention of nephrolithiasis

Substitution of vitamins and trace elements in short bowel syndrome	
Vitamin A	10,000–50,000 U/d if liver function is normal
Vitamin B12	300 mg s.c. per month following resection of terminal ileum
Vitamin C	200–500 mg/d
Vitamin D	1600 U/d
Vitamin E	30 IU/d
Vitamin K	10 mg/week
Selenium	60–100 mg/d
Zinc	220–440 mg/d

Doses given above are for orientation, only. The exact individual requirements must be evaluated and doses adjusted according to regularly performed appropriate laboratory measurements.

Drug therapy in short bowel syndrome

Drug	Recommended dose per day*
Loperamide (and codeine to slow transit)	4–16 mg
H2-antagonists (to reduce gastric (acid) secretion)	
- Ranitidine	300–600 mg
- Famotidine	40–80 mg
PPI (to reduce gastric (acid) secretion)	20–40 mg
Octreotide (to reduce gastric (acid) secretion)	2–3 x 50–100 µg subcutaneously
Cholestyramine (to reduce cholerheic diarrhea)	4–16 g (may deteriorate steatorrhea)
Pancreatin (to improve digestion)	25,000–40,000 U per meal
Metronidazole (in bacterial overgrowth)	800–1200 mg

**Oral application if not stated otherwise.*

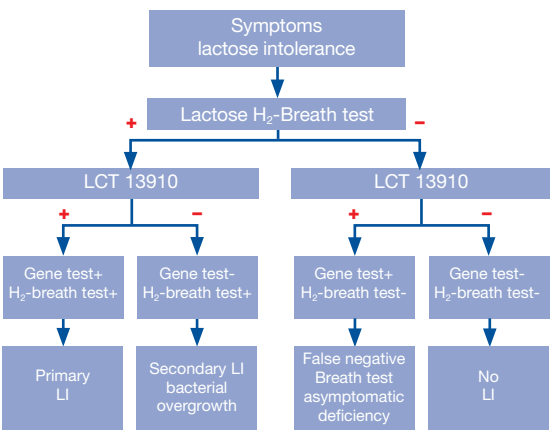
[Ref.: 1.Keller J et al. Management of the short bowel syndrome after extensive small bowel resection. Best Pract Res Clin Gastroenterol 2004; 18(5):977-92 2. Leuenberger M et al. Das Kurzdarmsyndrom: Eine interdisziplinäre Herausforderung. Aktuel Ernaehr Med 2006; 31:235-42]

Primary lactose intolerance is caused by a down-regulation in the expression of lactase along the villous membranes of the enterocyte.

Secondary lactose intolerance results from the reduction of enterocytes (e.g. post-infectious, celiac disease, Crohn's disease, etc.) or the early degradation of lactose in the small intestine by bacteria (e.g. bacterial overgrowth) or parasites (e.g. Giardia, Ascaris, Cestodes, etc.).

Reduced lactase expression (i.e. primary lactose intolerance) is associated with the „single-nucleotide polymorphisms“ C13910T or G22018A. The LCT13910 gene test can be performed within the daily clinical routine. Patients with the genotype CC have reduced lactase activity, and those with the genotypes CT and TT have normal enzyme activities. The LCT13910 gene test has a sensitivity ranging from 61–97% and a specificity of between 93–98% in the diagnosis of an abnormal H2-lactose breath test.

Algorithm for the evaluation of lactose intolerance



Rapid lactase test

Test:
- 2 postbulbar duodenal biopsies
- incubation of duodenal biopsy material with lactose in a plate in which a strong colour reaction develops within 20 min if lactase activity is present and if glucose appears in the test cup from hydrolysed lactose

Interpretation:
Severe Hypolactasia: Symptomatic hypolactasia very likely. Duodenal lactase activity <10 U/g protein. C/C genotype common. DD: Celiac disease.

Mild Hypolactasia: Symptomatic hypolactasia unlikely (20%). Duodenal lactase activity 10 U/g protein or more in 80% at least. C/T genotype common.

Normolactasia: Symptomatic hypolactasia impossible. Duodenal lactase always 10 U/g protein or more. TT genotype common. Untreated celiac disease impossible.

Sensitivity 93.8%, Specificity 94.1%

[Orlandi M, Netzer P, Inauen W. IDENTIFYING LACTOSE INTOLERANCE WITH A NOVEL BIOPSY-BASED RAPID LACTASE TEST, Gut 2006; Vol 55 (suppl V): A98]

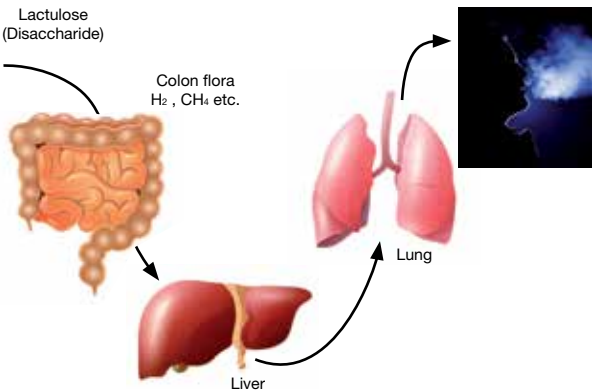
Lactose-Intolerance-Tests

	H_2-breath test	Lactose tolerance test	Genetic test of –13910 C/T polymorphism	Lactase activity at jejunal brush border
Test principle	Increase of H_2 in respiratory air after lactose challenge	Increase of blood sugar after lactose challenge	Genetic Polymorphism 13910 upstream of lactase gene	Enzymatic activity of Lactase activtiy in biopsy sample
Cut off	>20 ppm within 3 hours	<1.1 mmol/l within 3 hours	13910C/C indicates lactase non-persistence	<17–20 IU/g
Availability	Good	Excellent	Variable	Rare
False positives (malabsorption incorrectly diagnosed)	Rapid GI-transit, small intestinal bacterial overgrowth	Rapid GI-transit, impaired glucose tolerance	Rare (<5%) in Caucasians	Probably rare
False negatives (malabsorption wrongly excluded)	Non-H_2-producers. Full colonic adaptation	Fluctuations in blood sugar	All causes of secondary lactose malabsorption	Patchy enzyme expression
Secondary causes	Cannot be excluded, kinetic of H_2-increase can be suggestive	Cannot be excluded	Cannot be excluded	Can be excluded (histopathology obtained at same procedure)
Assessment of symptoms/ lactose tolerance	Possible	Possible	Not possible	Not possible
Comment	Method of choice for assessment of lactose malabsorption and intolerance	Rarely performed due to inferior sensitivity and specificity	Definitive test for lactase non-persistence in Caucasians. Less suitable in other populations. Not suitable in patients with intestinal disease at risk of secondary lactase deficiency	Reference standard for detection of lactase deficiency (primary or secondary)
Cost	Low	Lowest	High	Highest

[Misselwitz et al: Lactose malabsorption and intolerance: pathogenesis, diagnosis and treatment; United Eur Gastroenterol J 2013; 1(3):151-9]

Lactulose H_2-Breath Test (bacterial overgrowth)

Principle of the lactulose H_2-breath test

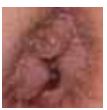


The human intestine cannot metabolize lactulose (disaccharide). Approximately 90–120 min after oral ingestion, undigested lactulose enters the colon (normal orocecal transit time), where it is metabolized by local intestinal flora. The resulting gases (H_2, CH_4) are transported via the portal venous system through the liver unmetabolized, and are expelled out via the lungs. An increase in the concentrations of H_2 and CH_4 of greater than 20 ppm and 8 ppm over the normal value respectively, after oral ingestion of 30 g lactulose, is normal. An early increase (i.e. 60 or even 30 min after oral ingestion of lactulose) is indicative of bacterial overgrowth in the small intestine.

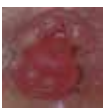
Definition

Hemorrhoids

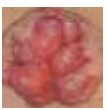
Grade I
Protrusion in proctoscope



Grade II
Emerging towards outside with pressing; spontaneous reposition



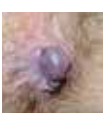
Grade III
Emerging towards outside with pressing; digital reposition



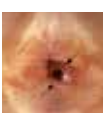
Grade IV
Spontaneous prolapse without reposition

- Plexus hemorrhoidalis internus
- Normal: hemorrhoidal cushion/padding

Thrombosed hemorrhoids



Thrombosed external hemorrhoids



Perianal hematoma caused by vein rupture

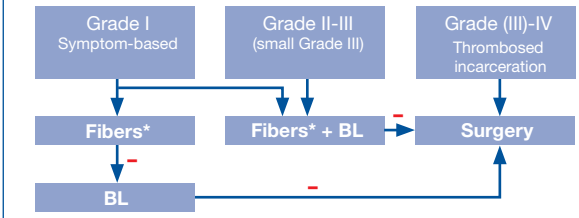
- Plexus hemorrhoidalis externus
- Normal: not visible

[Banov, J S C Med Assoc 1985]

Hemorrhoids:

Classification of Hemorrhoids (Goligher et al., 1983):	
First degree	Cushions bulge into the lumen of the anal canal but do not prolaps below the dentate line on straining
Second degree	Cushions prolapse while straining or defecation and can be seen at the exterior. They disappear spontaneously
Third degree	Cushions prolapse while straining or defecation and can be seen at the exterior. They can only be replaced digitally into the anal canal
Fourth degree	The prolapse of the cushions is permanent and irreducible

Treatment for internal hemorrhoids



BL = Band ligation
[*Diet, stool regulation (stabilizing agent)
AGA. Gastroenterology 2004]

Hemorrhoids treatment

First degree	Second degree	Third degree
Conservative Treatment: Dietary and lifestyle Modifications: • Adequate fluid intake and high fiber diet • Fibre supplement (e.g. psyllium) • Diosmin 2 x 500 mg/day	Dietary and lifestyle + Rubber band or Stapled hemorrhoidopexy	Dietary and lifestyle + Stapled hemorrhoidopexy or Excisional hemorrhoidectomy (Ferguson)
If conservative treatment fails:	or	or
Rubber band	Hemorrhoidal Artery Ligation (HAL)	Hemorrhoidal Artery Ligation (HAL)
or	or	or
Sclerotherapy	(Sclerotherapy)	(Rubber band)
	After intervention/ surgery: Diosmin 2 x 500 mg/d (14 d)	After intervention/ surgery: Diosmin 2 x 500 mg/d (14 d)

*when additional symptomatic skin tags

Fourth degree	Acute Prolaps with thrombosis
Dietary and lifestyle + Excisional hemorrhoidectomy* (Ferguson) or (Stapled hemorroidopexy) After intervention/ surgery: Diosmin 2 x 500 mg/d (14 d)	Dietary and lifestyle + Initial conservative inpatient treatment: • Analgetic Therapy with NSAID/Morphin • Lidocaine gel • Diosmin 3 x 1000 mg • Coldpack Early surgery: Excisional hemorrhoidectomy or (Stapled hemorrhoidopexy)

Rubber Band Ligation:

+ Low complication rate
  Easy office procedure
  Low Pain
  Repetitive application possible

- High recurrence rate

Sclerotherapy

+ Low complication rate
  Easy office procedure
  Little Pain

- High recurrence rate
  Low evidence

Hemorrhoidal Artery Ligation (HAL)

+ Low complication rate
  Little pain
  Low recurrence rate

- Low evidence

Stapled Hemorrhoidopexy

+ High evidence
  Low recurrence rate
  Little pain

- Higher recurrence rate
  in Grad IV Hemorrhoids

Excisional Hemorrhoidectomy

+ Low recurrence rate
  High evidence

- postoperative pain

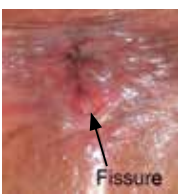
[M. Grandel, FH Hetzer: Evidence basierte Therapie des Hämorrhoidalleidens: Therapeutische Umschau 2013]

Thrombosed external hemorrhoids

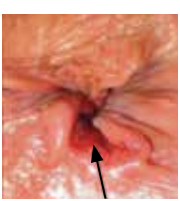
Symptoms <72 h Operative Treatment	Symptoms >72 h Conservative Treatment
Excision (No Incision!!!)	Diosmin 3 x 1000 mg (Day 1–3)
Diosmin 2 x 500 mg (14 days)	Diosmin 2 x 500 mg (Day 4–14)
NSAID (2–3 days)	NSAID (2–3 days)
	topical Lidocaine gel
Stool softeners – e.g. Macrogol, Psyllium	Stool softeners – e.g. Macrogol, Psyllium

Fissure-in-ano

- Primary fissure-in-ano (over 90% of all cases):
  - Location: 90% at posterior midline, 10% at anterior midline (most of those are female)
  - Etiology: unclear
  - Benign longitudinal ulcer of the lower third of the anal canal distal from the dentate line.
- acute fissure-in-ano: Symptoms lasting no longer than 6–8 weeks
  - simple tear of the anoderm with sharp margins



- chronic fissure-in-ano: Symptoms lasting longer than 6–8 weeks
  - Ulcer with edema and fibrosis. Edges are indurated and undermined. Visible internal sphincter. With or without a so called «sentinel pile» at its lower end.



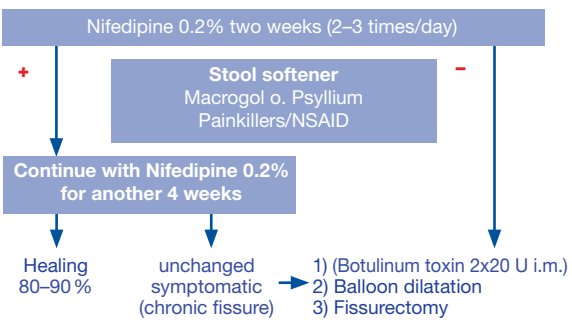
- Secondary fissure-in-ano:
  - Location: atypical at lateral position
  - Etiology: In association with other diseases: Crohn`s disease, anal tuberculosis, AIDS, STD, iatrogenic, anal carcinoma
  - Treatment: Therapy of the underlying pathology

Symptoms: Pain and bleeding during and particulary after defecation

Diagnosis: Patient history. Physical examination by simply spreading the buttocks. No anoscopy, no digital rectal examination because of the severe pain.

Therapy of primary acute fissure-in-ano:

Fissure Therapy



Therapy of secondary chronic fissure-in-ano:

Mostly operative treatment required. Conservative treatment fails in over 50% of all cases. No more sphincterotomy (High rate of incontinence).

Fissurectomy (with or without Botulinum toxin)

[Hetzer FH et al: Praxis 2000; Hetzer FH: procto workshop 2012]

Fissure – Drug treatment

	Nitro-glycerine	Ca-channel blocker	Botulinum toxin
Drug	Glyceryl trinitrate 0.2%	Nifedipine 0.2% Diltiazem 2%	Botulinum toxin Typ A
Method	Intrasphincter pressure ↓	Intrasphincter pressure ↓	Rev. sphincter paresis 2–3 months
Healing rate	27–85%	45–95%	25–96%
Recurrence	0–43%	4%	4%
Advantage(s)	Inexpensive	Inexpensive	Single injection 80% of patients pain-free after 7–10 day
Disadvantage(s)	Headache 20–70% Compliance	Compliance Less experience Headache 0–20%	Patient costs (Botox 100 E Painful injection Perianal thrombosis 5–10% Reversible inconti-nence 3–12%
Evidence Grade	Ia	Ib	Ic

[AGA technical review. Gastroenterology 2003]

Stool–Incontinence–Scores
Wexner Score–take reference below text

Type of incontinence	Never	Rarely	Sometimes	Usually	Always
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

Never 0; rarely <1/month; sometimes <1/week, >1/month;
Usually <1/day, >1/week,
Always >1/day.
0 = perfect, 20 = complete incontinence

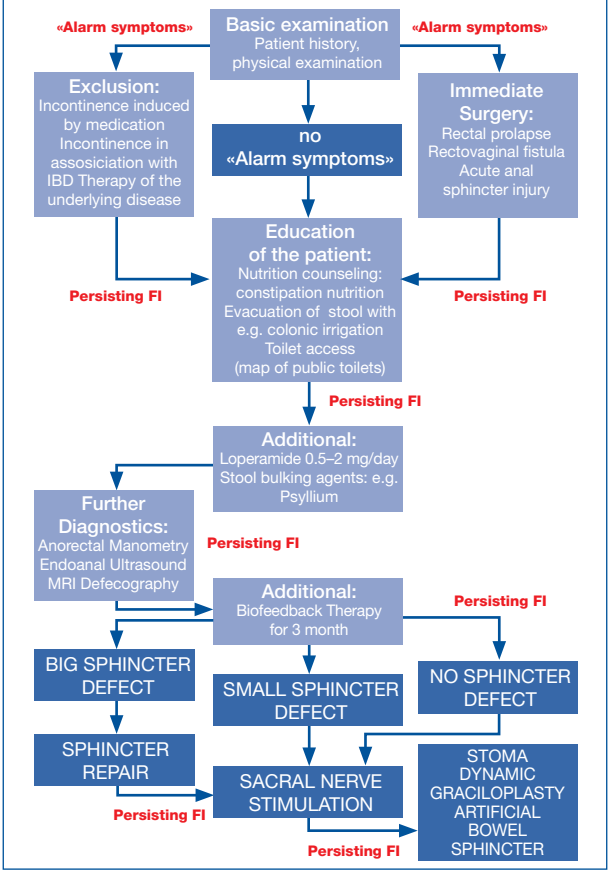
Stool–Incontinence–Score
Vaizey Score Gut 1999; 44: 77–80

Type of incontinence	Never	Rarely	Sometimes	Weekly	Daily
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

	No	Yes
Need to wear a pad or plug	0	2
Taking constipating medicines	0	2
Lack of ability to defer defecation for 15 min	0	4

Never: no episodes in the past 4 weeks;
Rarely: 1 episode in the past 4 weeks;
Sometimes: >1episode in the last 4 weeks but <1/week;
Weekly: 1 or more episodes a week but <1/day;
Daily: 1 or more episodes a day
Add one score from each row: minimum score = 0
= **perfect continence**
Maximum score = 24
= **total incontinence**

Fecal Incontinence (FI) of the adult



[Hetzer FH: Procto workshop 2012]

Condylomata acuminata

Location	Perianal		Endoanal
Size	<5 mm	≥5 mm	
1st line Therapy	Imiquimod cream 5% topical application*[1]	CO_2Laser#- / Scalpel incision	CO_2Laser#- / Scalpel incision
Adjuvant Therapy		Linola® Sept## b.i.d for 2 weeks followed by Imiquimod cream 5% topical application*[2]	Imiquimod anal tampon**[3]
Follow-up	3 months		

** 3x/week until inflammatory demarcation (usually at least for 12 weeks), follow-up after 12 weeks. Application before bedtime, skin exposure for 6–10 hours, rinse skin the following morning with mild soap and water [1,2]*

 # In high-risk patients (HIV.positive, carcinogenic HPV-positive, post-transplant patients) histology mandatory (for HPV-typing & to rule out dysplasia, malignancy)

not available in CH (= 0.5 g Clioquinol per 100 g Cream)

*** 3x/week before bedtime for 12 weeks, keep anal tampon until the following morning and rinse with water [3]*
HIV-patients: imiquimod 5% cream is indicated and effective in HIV-Patienten too. [4]

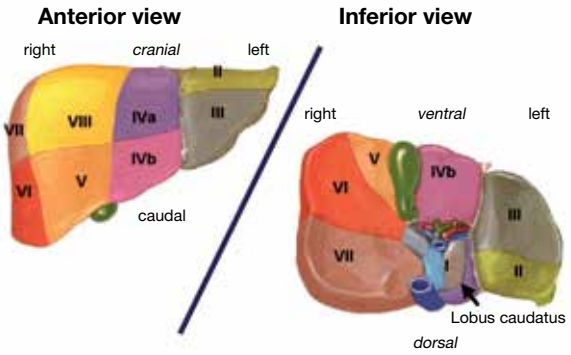
[[1] L. Edwards, A. Ferency, L. Eron et al., Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol 1998; 134:25–30]
[[2] Carrasco D, van der Straten M, Tyring SK. Treatment of anogenital warts with imiquimod 5% cream followed by surgical resection of residual lesions. J Am Acad Dermatol 2002; 47: S212-16]
[[3] Kaspari M, Gutzmer R, Kaspari T, Kapp A, Brodersen JP. Application of imiquimod by suppositories (anal tampons) efficiently prevents recurrences after ablation of anal canal condyloma. Br J Dermatol 2002; 147:757-9]
[[4] Cusini M, Salmaso F, Zerboni R, Carminati G, Vernaci C, Franchi C, Locatelli A, Alessi E. 5% Imiquimod cream for external anogenital warts in HIV infected patients under HAART therapy. Int J STD AIDS 2004; 15:17-20]

[D. Hahnloser, F. Hetzer (modified)]

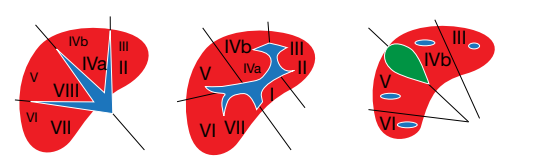
Sonographic Dimensions of Abdominal Organs and Vessel

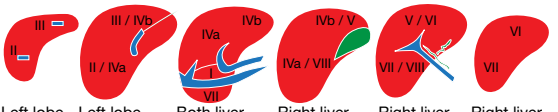
Liver:	Craniocaudal diameter **<140 mm,** anteroposterior diameter **<120 mm**
Liver:	Angle of inferior border left lobe **<30°** and right lobe **<45°**
Gallbladder:	Length **<120 mm,** width **<40 mm,** wall thickness **<4 mm**
Bile ducts:	Normal width of DHC **<6mm,** after cholecystectomy **<9 mm,** intrahepatic ducts **<4 mm**
Spleen:	Length **<110 mm,** thickness **<40 mm**
Appendix:	Diameter **<6 mm,** wall thickness **<2 mm**
Kidneys:	Length **100–120 mm,** width **50–70 mm,** width of parenchyma **13–25 mm**
Kidneys:	Parenchyma-Pyelon Index: >1.6:1 (<30 years), 1.2-1.6:1 (31–60 years), 1.1:1 (>60 years)
Adrenal gland:	**<10 mm**
Pancreas:	Head **<30 mm,** body **<25 mm,** tail **<25 mm,** pancreatic duct **<2 mm**
Prostate:	Width **<45 mm,** Depth **<35 mm,** Length **<35 mm,** Volume **25 mL**
Thyroid gland:	Width **40–70 mm,** Depth **10–30 mm,** Length **10–20 mm,** Volume **20–25 mL**
Urinary bladder:	Volume **<750 mL** (male)/ **<550 mL** (female), residual urine **<50 mL** wall thickness **<4 mm** (filled bladder), **<8 mm** (empty bladder)
Aorta:	Suprarenal part **<25 mm,** infrarenal part **<20 mm**
Vena cava:	**<20 mm**
Portal vein:	**<13 mm**
Hepatic veins:	**<7 mm**
Splenic vein:	**<10 mm**

Liver segments I



Liver segments II





1. Late venous phase	2. Arterial phase	3. Portal phase	suggestive for:
HypOechoic	Hyperechoic	**Iso-**/hypOechoic (chaotic vessels)	**HCC = Hepatocellular carcinoma**
		Iso- /hyperechoic	Hypervascular **metastasis**
	HypOechoic	HypOechoic	HypOvascular **metastasis**
	Rim enhancement	HypOechoic	**CCC = Cholangio-carcinoma**
	Non-enhancement	Non-enhancement	
Isoechoic	Hyperechoic	Hyperechoic (centrifugal filling, spoke wheel pattern, central scar, feeding artery)	**FNH**
		Hyper-/**Iso**echoic (centripetal filling, central non-enhancement, thrombosis)	**Haemangioma**
	Isoechoic	Hyper-/**Iso**echoic (in B-mode not detectable)	**Adenoma**
		Isoechoic (in B-mode not detectable)	**Regenerative Nodule**
Isoechoic (central non-enhancement)	Rim enhancement	Hypoenhancement/ rim enhancement/ central non-enhancement, septa	**Abscess**

CEUS – contrast-enhanced ultrasound

• Contrast harmonic imaging (CHI)

Analysis:

0–30 s: early arterial phase
30–90 s: portal venous phase,
followed by an investigational break to avoid early disintegration of bubbles
3–5 min: late (venous) phase

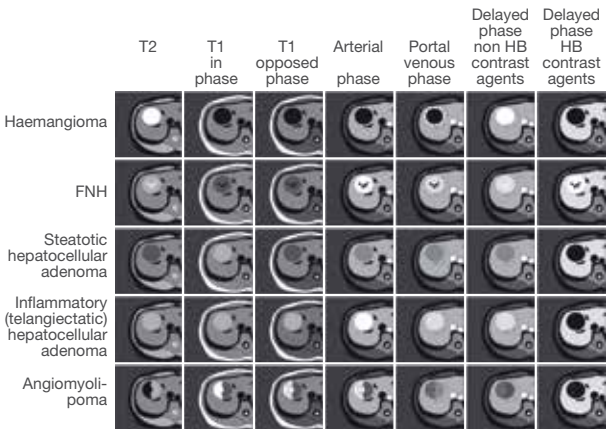
Interpretation: (after completing the CEUS-investigation)

1. Rate ultrasound contrast of focal lesion in late phase first
2. Rate ultrasound contrast of focal lesion in arterial phase next
3. Rate finally ultrasound contrast of focal lesion in portal phase

Liver lesions in CEUS

TYPE	Class Name	Arterial Phase (20–25 s)	Portal Phase (45–90 s)	Late Phase (>100 s)
BENIGN	Hemangioma			
	FNH			
MALIGNANT	HCC			
	Metastasis			

Benign liver lesions MRI



[Nature Reviews Gastroenterology & Hepatology 11, 737–749 (2014).]

Transient elastography

Criteria for LSM (liver stiffness measurement) interpretation:
1. Number of shots ≥10
2. Success rate ≥60%
3. Interquantile range (IQR) (Interval around median) ≤25%

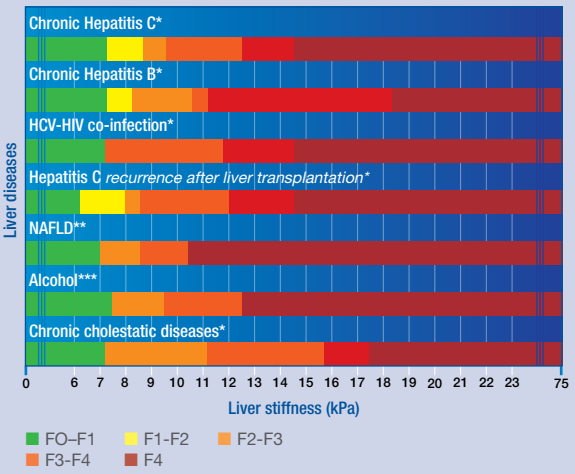
Failure: zero valid shot
Unreliable results: <10 valid shots, success rate ≤60%, IQR ≥25%

What the clinician needs to know:

- What is the underlying disease?
- Other evidence of advanced liver disease?
- What can affect the test?
  - Is the patient fasting?
  - What is the BMI?
  - What is the burden of inflammation (e.g. check ALT)
  - Is the patient actively drinking alcohol?
  - Is there evidence of cholestasis?

→ Do not use transient elastography in acute hepatitis, in acute exacerbation of chronic liver disease, ascites or extrahepatic cholestasis.

Interpretation Guide

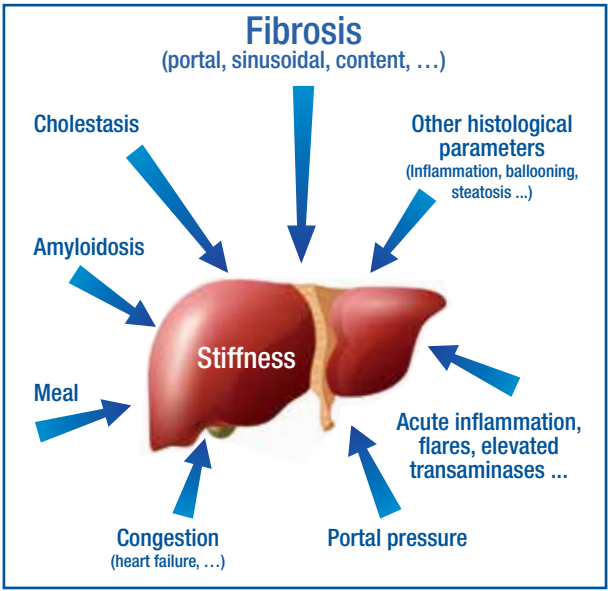


This guide is based on a selection of clinical studies from the existing literature reporting use of the FibroScan®. This guide is not intended to be used as a conversion table from liver stiffness readings in kilo-pascals (kPa) to fibrosis stage. This guide can in no way replace the judgment of the physician who is ultimately responsible for the final diagnosis. Echosens accepts no responsibility for the incorrect and/or inappropriate interpretation of liver stiffness values.

* *According to Metavir score: Transient elastography (FibroScan). V de Lédinghen, J Vergniol. Gastroenterol Clin Biol. 2008;32:58-67.*

** *According to Brunt score: Wong VW et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology. 2010;51(2):454-62.*

*** *According to Brunt score: CS Pavlov et al.Transient Elastography for Diagnosis of Stages of Hepatic Fibrosis and Cirrhosis in People With Alcoholic Liver Disease. Cochrane Database Syst Rev, 2015. 1: CD010542.*



[Mueller, S. and L. Sandrin, Liver stiffness: a novel parameter for the diagnosis of liver disease. Hepatic Medicine: Evidence ans Research, 2010: p. 49-67.]

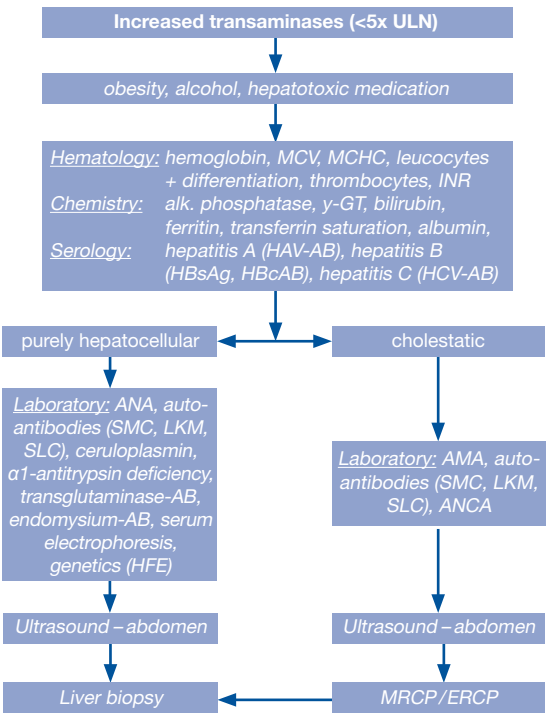
With kind permission from Echosens, France.

Castera L et al. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol. 2008;48(5):835-47.

Nahon P et al. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. J Hepatol. 2008;49(6):1062-8.

Nguyen-Khac E et al. Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: prospective comparison with seven non-invasive laboratory tests. Aliment Pharmacol Ther. 2008 15;28(10):1188-98

Hepatopathy



Hepatocellular Hepatopathy

Slightly increased transaminases (<5x ULN)

- Hepatic ALAT >ASAT
  - Non-alcoholic fatty liver disease (NAFLD)
  - Non-alcoholic steatohepatitis (NASH)
  - Medication/toxins (see separate list)
  - Chronic hepatitis B/C/D
  - Acute viral hepatitis (A-E, CMV, EBV)
  - Hemochromatosis
  - Autoimmune hepatitis
  - α1-Antitrypsin deficiency
  - Morbus Wilson
- Hepatic ASAT >ALAT
  - Alcohol
  - Non-alcoholic fatty liver disease (NAFLD)
  - Non-alcoholic steatohepatitis (NASH)
  - Liver cirrhosis
- Extrahepatic
  - Celiac disease
  - Hemolysis
  - Muscle disease
  - Thyroid disease
  - Endurance sport (Marathon)

Markedly increased transaminases (>15x ULN)

- Acute viral hepatitis (A-E, Herpes)
- Medication/toxins (see separate list)
- Ischemic hepatitis
- Autoimmune hepatitis
- Acute bile duct obstruction
- Acute Budd-Chiari syndrome

Medication / Toxins / Drugs: Drug-induced liver injuries

Medication
- Anabolic steroids
- Allopurinol
- Amoxicillin/clavulanic acid
- Captopril
- Carbamazepine
- Chlorpropamide
- Cyproheptadine
- Diltiazem
- Erythromycin
- Estrogens
- Floxuridine
- Flucloxacillin
- Fluphenazine
- Paracetamol/Acetaminophen
- Alpha-methyldopa
- Amoxicillin/ Clavulanic acid
- Amiodarone
- Azathioprine
- Carbamazepine
- Dantrolene sodium
- Disulfiram
- Etretinate
- Fluconazole
- Glibenclamide
- Halothane
- Heparin
- Isoniazide
- Ketoconazole
- Labetalol
- Methotrexate
- Nicotinic acid
- Nitrofurantoin
- Non-steroidal antirheumatics
- Phenylbutazone
- Phenytoin
- Protease inhibitors
- Sulfonamide
- Propylthiouracil
- Phenprocoumon
- Statins
- Trazadone
- Valproate
- Zafirlukast
- Gold salts
- Imipramine
- Indinavir
- Iprindole
- Nevapirin
- Methyltestosterone
- Oxaprozin
- Pizotyline
- Quinidine
- Tolbutamide
- Trimethoprim/sulfamethoxazole

Herbs/Alternative medicine
- Creosote bush (Larrea tridentata)
- Ephedra (Ephedra sinica)
- Bach flowers (Gentiana)
- Germander (Teucrium fruticans)
- Jin Bu Huan (Herba Lycopodii Serrati)
- Carob/locust bean (Senna alexandrina)
- Kava-Kava (Piper methysticum)
- Skullcaps (Scutellaria)
- Shark cartilage
- Vitamin A

Drugs
- Anabolic steroids
- Cocaine
- Ecstasy (3,4-methylenedioxy-N-methylamphetamine)
- PCP (Phencyclidine)

Toxins
- Tetrachloromethane (CCl_4)
- Trichlormethane/chloroform ($CHCl_3$)
- Dimethylformamide (C_3H_7NO)
- Dimethylnitropropane ($C_3H_7NO_2$)
- Hydrazine/diamide (N_2H_4)
- Chlorofluorocarbon (CFC)
- Trichloroethylene (C_2HCl_3)
- Toluene (C_7H_8, $C_6H_5CH_3$)

Cholestatic Hepatopathy

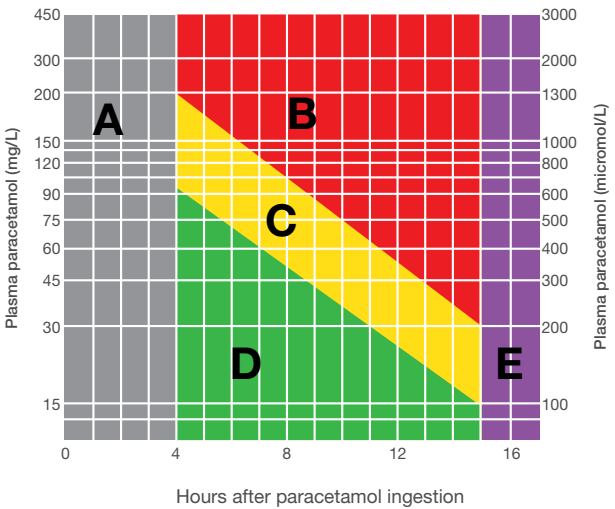
Unconjugated hyperbilirubinemia

- Gilbert-Meulengracht syndrome
- Neonatal jaundice (Icterus neonatorum)
- Hemolysis
- Hematoma
- Crigler-Najjar syndrome
- Ineffective erythropoiesis (thalassemia, megaloblastic anemia)

Conjugated hyperbilirubinemia

- Extrahepatic cholestasis
- Hepatitis (viral, autoimmune, alcoholic)
- Liver cirrhosis
- Sepsis
- Toxic hepatopathy (see separate list)
- Neoplasia (hepatic, metastases, lymphoma)
- Primary sclerosing cholangitis (PSC)
- Dubin-Johnson syndrome
- Rotor syndrome
- Vanishing bile duct syndrome
- Benign recurrent intrahepatic cholestasis (BRIC)
- Hyperemesis gravidarum
- HELLP syndrome
- Primary biliary cholangitis (PBC)

Paracetamol/Acetaminophen overdose treatment nomogram



Interpretation

(see **note** regarding slow relase preparations and drug effects)

- **A** Data uninterpretable if sample taken within 4 hours of ingestion. Repeat collection is recommended. Note the minimal single hepatotoxic dose of paracetamol is 7.5 g in an adult (150 mg/kg) and if there is suspicion of a large overdose then **treatment with N-acetyl cysteine** is recommended immediately.

- **B** Liver damage highly likely. **Treatment with N-acetyl cysteine** is recommended.

- **C** Liver damage possible, especially in **high risk patients.** These patients should be considered for **treatment with N-acetyl cysteine** and should be reviewed by a senior clinician.

- **D** Severe liver damage unlikely. If there is doubt about the timing of ingestion or the need for treatment, **treatment with N-acetyl cysteine** can be considered.

- **E** Severe liver damage is still possible if large doses of paracetamol have been ingested. These patients should be considered for treatment with N-acetyl cysteine and should be reviewed by a senior clinician.

*Note: Pharmacokinetic properties may vary if paracetamol is ingested in combination with codeine or dextropropoxyphene or other drugs that can slow gastrointestinal motility. Recent data suggest that this nomogram may not be applicable to overdoses of extended/slow release paracetamol[2,3]. Since drug levels tend to plateau rather than peak after the ingestion of sustained release preparations, any given drug level in this setting is indicative of greater drug absorption (area under the curve) than that occurring after the ingestion of immediate release preparations. Hence measurement of paracetamol levels after an overdose of extended/slow release paracetamol may lead to an underestimation of the need for antidote therapy if the current nomogram is used. Seek specialist advice, treatment with N-acetyl cysteine is recommended.

High Risk Patients & Factors increasing the hepatotoxicity of paracetamol[1,4]

Pregnancy – Paracetamol passes readily into the fetal circulation. There is no contraindication to the use of N-acetyl cysteine in pregnancy and a good prognosis in pregnancy depends on early treatment – however it does not appear to cross the placenta in sheep and the ability to prevent liver toxicity in the human fetus is uncertain. **Alcohol consumption** – Chronic alcohol abuse. **Patients on microsomal inducing drugs** – barbiturates, carbamazepine, rifampicin, isoniazid, omeprazole, oral contraceptives, HIV medications. **Patients likely to have glutathione depletion** – recent severe fasting, acute illness with prolonged vomiting or dehydration, anorexia nervosa, bulimia. **Underlying hepatic impairment** – viral hepatitis, alcoholic hepatitis, NASH. **Other factors** – HIV infection, Gilbert's syndrome.

Protocol for treatment with N-acetyl cysteine (NAC)[5]

Initial Dose: 150 mg/kg IV in 200 ml 5% dextrose over 15 minutes
Second Dose: 50 mg/kg IV in 500 ml 5% dextrose over 4 hours
Followed by: 100 mg/kg IV in 1000 ml 5% dextrose over 16 hours
Total dose: 300 mg/kg in 20 hours = 300 mg/kg

Actions: Protects the liver by restoring depleted hepatic reduced glutathione or by acting as an alternate substrate for the toxic paracetamol metabolite.
Hepatic necrosis is preventable if treatment can be instituted within <8 hours as the upper time limit has not yet been determined. Optimal therapy occurs when the patient is treated 10–12 hours post ingestions. Any presentation >15 hours must be considered carefully before treatment.
Indications: To be used as an antidote to paracetamol poisoning. Paracetamol levels should be assayed before commencing treatment.
Contraindications: Hypersensitivity or previous anaphylactic reaction to N-acetyl cysteine. N-acetyl cysteine is not compatible with rubber and metals.
Adverse Effects: Rash, bronchospasm and anaphylaxis.
NOTE: anaphylactoid reactions such as rash are not uncommon (10%) and may be treated with antihistamines, steroids and slowing the rate of infusion.
Monitoring: Continuous cardiac monitoring and regular potassium levels are recommended.

Potential complications of paracetamol toxicity[1]

Fulminant hepatic failure – assess with liver function tests
Haematological abnormalities – assess with coagulation studies, INR – note in moderate to severe paracetamol induced hepatic necrosis disseminated intravascular coagulation (DIC) may be present
Metabolic acidosis with impaired level of consiousness and hypotension – ABGs
Renal failure – acute renal failure requiring dialysis occurs in 1% of untreated cases of paracetamol overdose and may occur in patients with no clinical or biochemical evidence of hepatotocicity
Cardiomyopathy – ECG abnormalities may be noted
Pancreatitis – serum amylase
Muscle damage – rhabdomyolysis, serum CK

Reporting Units: Serum paracetamol is reported in different units from different laboratories. Some laboratories use the unit mg/L (use scale on left hand side of the nomogram). Other laboratories may use micromol/L (scale on right hand side of nomogram). Ensure the correct units are being used before interpreting results with the nomogram. To convert results in umol/L to mg/l multiply result by 0.151.

[1. Prescott LF. Paracetamol overdose. In Paracetamol (Acetaminophen) – A Critical Bibliographic Review. 2nd Edition 2001; pp. 527 – 624. London: Taylor & Francis Ltd. 2. Graudins A, Aaron CK, Linden CH. Overdose of extended-release acetaminophen. N Engl J Med. 1995 Jul 20; 333(3):196.Medline 3. Temple AR, Mrazik TJ. More on extended-release acetaminophen. N Engl J Med. 1995 Nov 30;333(22):1508-9. Medline 4. Reid A, Hazell W. Paracetamol poisoning: Which nomogram should we use? Emergency Medicine. 2003 15, 486-96. Medline 5. Prescott LF, Park J, Ballantyne A, Adriaenssens P, Proudfoot AT. Treatment of paracetamol (acetaminophen) poisoning with N-acetylcysteine. Lancet 1977; ii: 432-4. Medline]

Increased alkaline phosphatase

- Hepatobiliary
  - Bile duct obstruction
  - Primary biliary cholangitis (PBC)
  - Primary sclerosing cholangitis (PSC)
  - Medication (see separate list)
  - Hepatitis (viral, autoimmune, alcoholic)
  - Liver cirrhosis
  - Vanishing bile duct syndrome
  - Benign recurrent intrahepatic cholestasis (BRIC)
  - Venoocclusive disease
- Infiltration of the liver
  - Granulomatous diseases (sarcoidosis, tuberculosis)
  - Neoplasia (hepatic, metastases, lymphoma)
  - Fungal infection
  - Amyloidosis
- Extrahepatic
  - Bone metabolism (growth, bone diseases)
  - Pregnancy
  - Chronic kidney insufficiency
  - Heart insufficiency
  - Infection

[Green R, et al. Gastroenterology (2002)]

Hepatic encephalopathy (HE West Haven Criteria)

0	No abnormality detected
I	Trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction
II	Lethargy or apathy, disorientation for time, obvious personality change, inappropriate behavior
III	Somnolence to semistupor, responsive to stimuli, confused, gross disorientation, bizarre behavior
IV	Coma, unable to test mental state

Ascites

Degree of severity

Grade I (mild): sonographic; Grade II (moderate): moderate abdominal distension; Grade III (severe): severe abdominal distension

Diagnostic

Cell count with differentiation (leucocytes), albumin (as well as in serum), total protein, LDH (as well as in serum), glucose, culture (aerobic, anaerobic). In special cases: amylase, bilirubin, triglyceride, cholesterol, tuberculosis culture, cytology.

Serum Ascites Albumin Gradient (SAAG) = $\text{Albumin}_{\text{Serum}} - \text{Albumin}_{\text{Ascites}}$

SAAG > 11 g/L	SAAG < 11 g/L
Liver cirrhosis (80%)	**Malignant ascites (10%)** (often hemorrhagic; LDH, lactate, increased cholesterol/ triglyceride)
Alcoholic hepatitis, fulminant hepatic failure, right heart failure, metastatic liver, portal vein thrombosis, Budd-Chiari syndrome, acute fatty liver of pregnancy, nephrotic syndrome, exudative enteropathy	Ileus, pancreatitis, serositis with collagenosis, peritoneal tuberculosis, mesenteric infarct, chylous ascites, biliary ascites, nephrotic syndrome, exudative enteropathy

Therapy

General measures

Salt restriction (in addition, avoid using salt, no convenience foods), fluid restriction to 1 liter/d (only with Na^+ <125 mmol/L), no NSAID

First-time ascites

1. Spironolactone: initially 100 mg/d, then increase weekly up to 400 mg/d
   Side effects: hyperkalemia (stop at K^+ >6 mmol/L), gynecomastia
2. Torasemide: with therapy failure (<2 kg/week weight reduction) initially 10 mg/d, slowly increase up to a maximum of 40 mg/d
   Side effects: hypokalemia, kidney insufficiency

Recurring ascites
Direct combination spironolactone 100 mg/d + torasemide 10 mg/d. Increase to 400 mg/d + 40 mg/d depending on therapy response

Therapy-resistant ascites (5–10%)
Paracentesis: albumin substitution (20 g per 2 L ascites)
TIPS (Transjugular Intrahepatic Portosystemic Shunt)
- Indication:
  paracentesis >3x/month, contraindication for paracentesis (adhesions), hepatic hydrothorax
- Contraindication: severe heart insufficiency, sepsis, portal vein thrombosis, Child score >12 points, hepatic encephalopathy Grade 3–4, malignant liver tumors, retrograde portal venous flow
- Discontinue diuretics in the case of: encephalopathy, Na^+ <120 mmol/L despite fluid restriction, renal insufficiency (creatinine >133 µmol/L)

[Ginès et al. J Hepatol 53, (2010)]

Spontaneous Bacterial Peritonitis (SBP)

1–4% in the outpatient department, 10–30% for hospitalized cirrhosis patients with ascites (50% community-acquired, 50% nosocomial)

Diagnosis
Absolute neutrophil count >250/µL ± positive ascites culture (positive in 60%)

Bacteria
E. coli (37%), C. pneumoniae (17%), S. pneumoniae (12%), S. viridans (9%), other Gram +ve bacteria (15%), other Gram –ve bacteria (10%)

Risk factors
Medical history of SBP (70% recurrence rate), systemic infection (typical UTI), GI bleeding, high Child-Pugh score, low total protein in ascites (<10 g/L)

Therapy

SBP, empirical therapy

- Ceftriaxone 2 g/d IV for 5 days (alternative: amoxicillin/clavulanic acid)
- Albumin IV: 1.5 g/kg on Day 1 and 1 g/kg on Day 3
  Control paracentesis after 48 h: neutrophilic decrease >50%, otherwise adjust antibiotic therapy

Secondary prophylaxis after SBP

- Norfloxacin 400 mg/d p.o. (alternative: trimethoprim/sulfamethoxazole 800/160 mg) Risk of recurrence without prophylaxis = 70%, with prophylaxis = 20%

Primary prophylaxis

- Ascites protein <15 g/L + Child-Pugh score >9 points: norfloxacin 2x400 mg/d as longterm therapy
- Acute gastrointestinal bleeding: ceftriaxone 2 g/d IV for 5 days or norfloxacin 2x400 mg/d for 7 days

Hepatorenal Syndrome (HRS)

Type I: Doubling of creatinine in <2 weeks (typically after infection, GI bleeding)
Type II: Slower increase in creatinine (typically with therapy-resistant ascites)

Diagnosis

- Liver cirrhosis with ascites
- Creatinine >133 µmol/L (or 1.5 mg/dl)
- No shock (hypovolemic, septic, other)
- No improvement after discontinuation of diuretics + volume expansion (albumin 1 g/kg, maximal 100 g/d) over 2 days
- No nephrotoxic medication
- No nephropathy (urine: protein <0.5 g/d, erythrocytes <50/visual field, normal sonography)

Therapy

General measures

Cave: Hydration → hyponatremia, ascites/edema, stop diuretics, no NSAID, paracentesis (+ albumin IV 20 g / 2 L)

Hepatorenal syndrome (HRS) Type I

Primary	Terlipressin:	initial 1 mg IV 4–6x/d serum creatinine <133 µmol/L => stop therapy creatinine decrease <25% after 3 days => increase up to 2 mg IV 6x/d creatinine decrease <50% after 7 days => stop therapy creatinine decrease >50% after 7 days => continue until max. 14 days *Cave: tachyarrhythmia, ischemia (cardial, peripheral)*
	Albumin:	1 g/kg on Day 1 thereafter 20–40 g/d if serum albumin >45 g/L => stop therapy (lung edema)
Secondary	TIPS (Transjugular Intrahepatic Portosystemic Shunt)	

HRS Type II

Terlipressin + albumin or TIPS, although limited data

With HRS, always evaluate liver transplantation (poor longterm survival).

[Ginès et al. J Hepatol 53, (2010)]

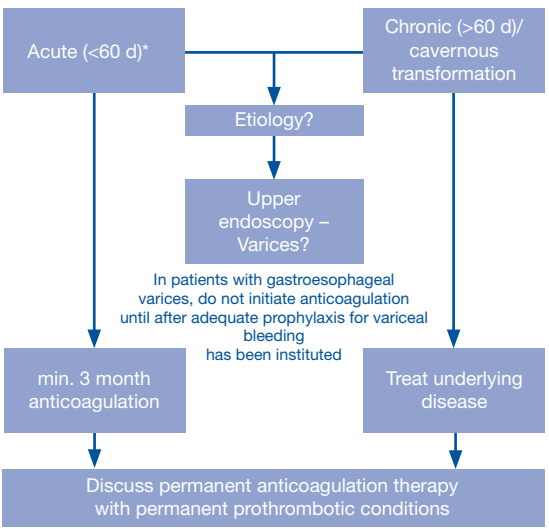
CHILD-PUGH-Score

Parameter / Points		1	2	3
PT	*s >contr.*	*<4*	*4–6*	*>6*
Quick	**%**	**>70**	**40–70**	**<40**
INR		**<1.7**	**1.7–2.3**	**>2.3**
Bilirubin	**µmol/l**	**<35**	**35–50**	**>50**
	mg/dl	*<2*	2–3	*>3*
in PBC	µmol/l	*<70*	**70–170**	*>170*
	mg/dl	*<4*	*4–10*	*>10*
Albumin	**g/l**	**>35**	**28–35**	**<28**
	g/dl	*>3.5*	*2.8–3.5*	*<2.8*
Ascites		**none**	**mild (response to diuretics)**	**moderate to severe (refractory to diuretics)**
Encephalopathy		**none**	**Grades 1– 2**	**Grades 3–4**

Point score	CHILD-Stage	1st year survival rate	2nd year survival rate
5–6	**A** – *compensated*	100%	85%
7–9	**B** – *impaired*	80%	60%
10–15	**C** – *decompensated*	45%	35%

[Pugh RN, Murray-Lya IM. Br J Surg 1973; 60: 646-9]

PVT Algorithm



***Possible criteria defining acute stage of portal vein thrombosis:**

- Recent abdominal pain
- No evidence of chronic portal hypertension (i.e. gastrointestinal bleeding, ascites, collateral porto-systemic circulation or hypersplenism)
- Contrast-enhanced CT or duplex Doppler ultrasound showing no porto-portal collaterals at the porta hepatis

Etiology of PVT

- Cirrhosis
- Transjugular intrahepatic portosystemic shunt
- Infection: abdominal sepsis, omphalitis, pylephlebitis
- Local Inflammation: appendicitis, diverticulitis, pancreatitis, cholecystitis, trauma, retroperitoneal fibrosis, endoscopic sclerotherapy, collagen vascular diseases (e.g. lupus), Behcet's disease, inflammatory bowel disease
- Malignancy: hepatocellular carcinoma, pancreas carcinoma, lymphoma, cholangiocarcinoma, compression or invasion of the portal vein by tumor (e.g. pancreatic cancer)
- Acquired: oral contraceptives, pregnancy, other malignancy, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, hyperhomocysteinemia, antiphospholipid syndrome
- Congenital: factor V Leiden, protein C or protein S deficiency, prothrombin gene mutation, antithrombin deficiency, MTFR gene mutation that raises homocysteine, myeloproliferative disorders, increased factor VIII levels

[Condat B, et al., Hepatology. 2000]

Portal hypertensive gastropathy

2-category classification system

1. Mild

- snake skin pattern of gastric mucosa
- risk of bleeding: 5–31%

2. Severe

- snake skin pattern and red marks, cherry red spots
- risk of bleeding: 38–62%

Patients with portal hypertensive gastropathy-associated bleeding: β-blockers should be used for prevention of recurrent bleeding. Baveno V workshop 2010

[McCormack TT. Gut 1985.26:1226 and Yoo HY. Gastrointest Endosc 2002]

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Indications for TIPS

Efficacy determined by controlled trials

- Secondary prevention and possible treatment of acute bleeding
- Refractory cirrhotic ascites

Efficacy assessed in uncontrolled series

- Refractory acute bleeding varices
- Portal hypertensive gastropathy
- Bleeding gastric varices
- Gastric antral vascular ectasia
- Refractory hepatic hydrothorax
- Hepatorenal syndrome Types 1 and 2
- Budd-Chiari syndrome
- Veno-occlusive disease
- Hepatopulmonary syndrome

Absolute contraindications to TIPS placement

- Primary prevention of variceal bleeding
- Congestive heart failure
- Multiple hepatic cysts
- Uncontrolled systemic infection or sepsis
- Unrelieved biliary obstruction
- Severe pulmonary hypertension

Relative contraindications to TIPS placement

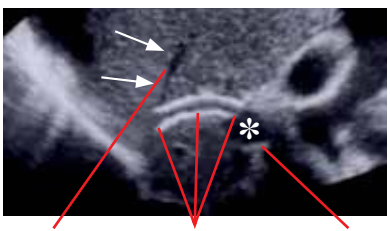
- Hepatoma, especially if central
- Obstruction of all hepatic veins
- Portal vein thrombosis
- Severe coagulopathy (INR >5)
- Thrombocytopenia of 20,000/cm^3
- Moderate pulmonary hypertension

Complications of TIPS

Complication frequency (%)

- TIPS dysfunction
- Thrombosis (10–15)
- Occlusion/stenosis (18–78)
- Transcapsular puncture (33)
- Intraperitoneal bleed (1–2)
- Hepatic infarction (1)
- Fistulae (rare)
- Hemobilia (5)
- Sepsis (2–10)

- Infection of TIPS (rare)
- Hemolysis (10–15)
- Encephalopathy new/worse (10–44)
- Encephalopathy chronic (5–20)
- Stent migration (10–20)



Hepatic vein **TIPS** **Portal vein**

* = measure point for Duplex sonography (halfway between the spleno-portal confluence and entry of the TIPS in the portal vein)

TIPS US-Doppler Control

Measurements:

- Main portal vein velocity (MPV) >30 cm/sec
- Distal stent velocity (DSV) 60–220 cm/sec
- Peak stent velocity (PSV) >60 cm/sec
- Indirect signs:
  - o Homogenous flow in TIPS
  - o Portal vein flow: Main portal vein should be hepatopetal. Flow direction in the entire portal system is towards the portal vein end of the stent with inversion of portal vein flow in intra-hepatic portal veins (inflow in TIPS and outflow from TIPS). If recanalized para-umbilical vein is present (with blood shunting away from the liver), flow in the left portal vein will be hepatopetal despite normal TIPS function.

Surveillance suggestion: Doppler sonograms between 3 and 6 months after TIPS; repeat at 6-month intervals for the first two years

Ultrasonographic findings suggesting TIPS dysfunction or recurrence of the complication of portal hypertension that led to the initial TIPS, should be followed by repeat shunt venography and intervention

[Abraldes et al. Am J Gastroenterol 2005
Boyer TD, Haskal Z. AASLD Practice Guidelines HEPATOLOGY, Vol. 51, No. 1, 2010]

Liver cirrhosis, MELD Score

MELD Score: *M*odel of *E*nd Stage *L*iver *D*isease

- **Serum creatinine, total serum bilirubin,** and **INR** within the MELD score formula reflect the severity of liver dysfunction in cirrhosis (Kamath PS et al, Hepatology 2001):

- MELD Score = 9.57× ln **(Creatinine)** + 3.78× ln **(Bilirubin)** + 11.20× ln **(INR)** + 6.43

- Best predictor of 3-month mortality in hospitalized patients with liver cirrhosis:
  - MELD ≥40 points: 100% mortality
  - MELD 30–39 points: 83% mortality
  - MELD 20–29 points: 76% mortality
  - MELD 10–19 points: 27% mortality
  - MELD <10 points: 4% mortality

- Online MELD score calculator: https://sasl.unibas.ch/11calculators-MELD.php

Indications for liver transplantation evaluation

- **After first major hepatic decompensation in patients with liver cirrhosis (i.e. ascites, variceal bleeding, hepatic encephalopathy)**

- or -

- CHILD Score ≥7

- or -

- MELD Score ≥10

- or -

- Hepatocellular carcinoma within Milan criteria (1 lesion up to 5 cm, 3 lesions not larger than 3 cm), no vascular invasion, no regional nodes or distal metastasis

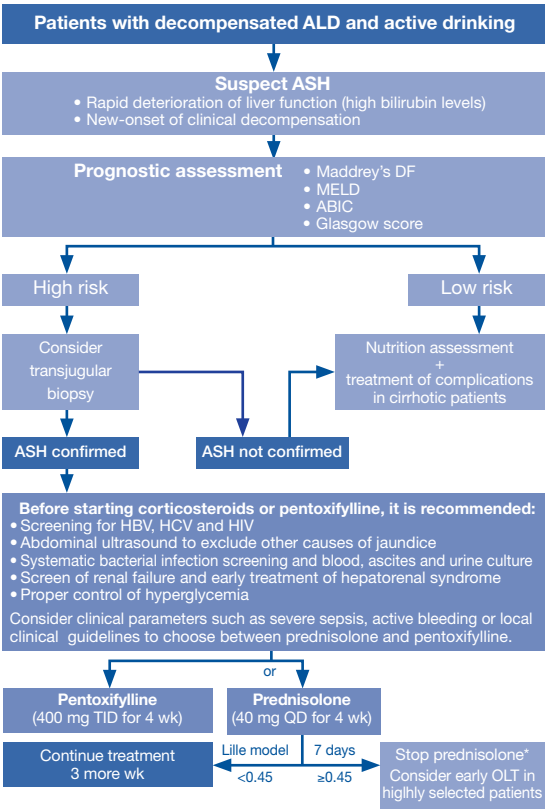
- or -

- Acute liver failure (see King's College criteria & Clichy criteria)

-or-

- **Other rare indications & under certain circumstances to consider: i.e. hepatopulmonary syndrome, portopulmonary hypertension, hemangioblastoma, hepatoblastoma, nodular regenerative hyperplasia, Budd-Chiari syndrome, familial amyloidosis, primary hyperoxaluria, polycystic liver disease, neuroendocrine tumors, glycogen storage disease**

Treatment algorithm in alcoholic steatohepatitis according to EASL guidelines (2012)



A Lille score ≥ 0.45 indicating non-response and increased risks of infection and death. In non responders, the interruption of corticosteroids is recommended particularly in those classified as null responders (Lille score >0.56)

Maddrey's Alcoholic Hepatitis Discriminant Function

Equation:
Discriminant = 4.6 x (Patient PT – 11.8 s)
+ Plasma Bilirubin (µmol/L)/17

PT = Prothrombin Time

A value more than 32 implies poor outcome with one month mortality ranging between 35% to 45%.

[Reference: Maddrey WC et al: Corticosteroid therapy of alcoholic hepatitis" Gastroenterology, 1978.]

Conversion Quick (%) to Prothrombin Time (s):

100%	≈10.1 s	50%	≈15.2 s
90%	≈10.7 s	45%	≈16.4 s
80%	≈11.3 s	40%	≈17.6 s
70%	≈12.3 s	35%	≈19.6 s
60%	≈13.5 s	30%	≈21.8 s
55%	≈14.2 s	25%	≈25.4 s

Glasgow Alcoholic Hepatitis Score (GAHS)

A GAHS score of ≥ 9 is associated with a poorer outcome.
The score is calculated as follows:

Score	1	2	3
Age (years)	<50	>50	-
WCC (x 10^9/L)	<15	>15	-
Urea (mmol/L)	<5	>5	-
PT ratio or INR	1.5	1.5–2.0	>2.0
Bilirubin (µmol/L)	<125	125–250	>250

[Reproduced from *Gut*, EH Forrest *et. al.*, 'Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score', 54, 8, pp. 1174–1179. Copyright 2005, with permission from BM) Publishing Group Ltd.]

Patients with GAHS score of ≥9 have a 28-day survival of 52% in untreated patients, compared with 78% in corticosteroid-treated patients. The 84-days survival is 38% in untreated patients, compared with 59% in corticosteroid-treated patients.

Lille Model

- **Goal:** Early identification of non-response to steroids after 7 days in patients with severe alcoholic hepatitis
- Lille model combines six reproducible variables **(age, creatinine, albumin, prothrombin time/INR, bilirubin, and evolution of bilirubin at day 7)** and is highly predictive of death at 6 months
- **Survival probability at 6 months is defined by the 0.45-cutoff:** 6-month survival probability of patients with a Lille model above 0.45 is about 25% contrary to patients with a Lille model **below this cutoff (85%)**
- **Calculation Link:** www.lillemodel.com

[Louvet, A et al.: The Lille Model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology, 2007]

Prognostic Model for Acute Liver Failure: King's College Hospital Criteria

Potentially helpful indicators of poor prognosis in patients with acute liver failure (sensitivity 68–69% and specificity 82–92%):

Acute liver failure secondary to paracetamol overdose:
- Grade 3 or 4 hepatic encephalopathy
- pH <7.30 or arterial lactate >3.0 mmol/L after fluid resuscitation
- INR >6.5 (PT >100 seconds) and serum creatinine > 300 µmol/L (>3.4 mg/dL)

Non-paracetamol associated acute liver failure:
- INR >6.5 (PT >100 seconds), or
- any 3 of the following:
  - age between 10 and 40 years
  - duration of jaundice before hepatic encephalopathy >7 days
  - INR ≥3.5 (PT >50 seconds)
  - serum bilirubin >300 µmol/L (>17.6 mg/dL)
  - unfavorable etiology: seronegative hepatitis, or idiosyncratic drug reaction or Wilson disease

[Modified from: AASLD Position Paper: The Management of Acute Liver Failure, Update 2011]

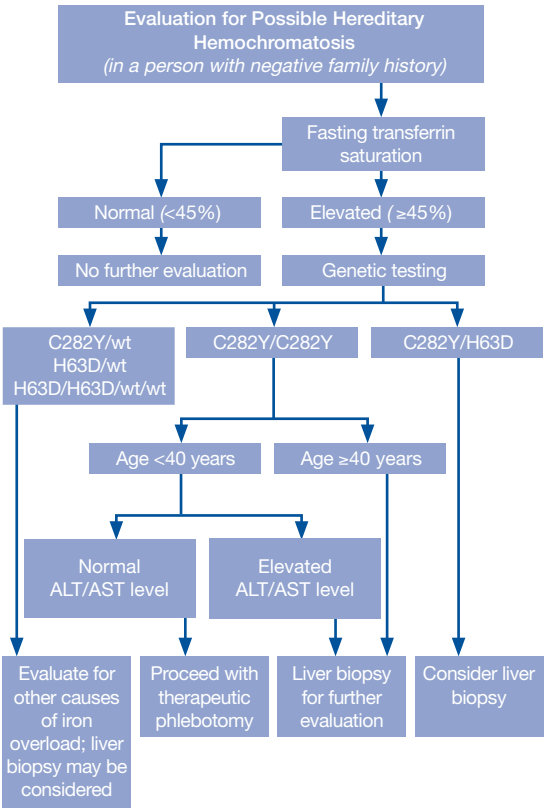
Prognostic Model for Acute Liver Failure: Clichy Criteria

Potentially helpful indicators of poor prognosis in patients with acute liver failure (positive predictive value 82%, negative predictive value 98%):

Presence of hepatic encephalopathy and factor V level:
- Factor V <20% of normal in patients <30 years of age, or
- Factor V <30% of normal in patients >30 years of age

[Modified from: AASLD Position Paper: The Management of Acute Liver Failure, Update 2011]

Diagnostic algorithm for hemochromatosis



[Bacon BR et al. HFE genotype in patients with hemochromatosis and other liver diseases. Ann Intern Med. 1999; 130:953-62.]

Diagnosis of hemochromatosis

Asymptomatic

Abnormal serum iron studies on routine screening chemistry panel
Evaluation of abnormal liver tests
Identified by family screening

Nonspecific, systemic symptoms

Weakness
Fatigue
Lethargy
Apathy
Weight loss
Specific, organ-related symptoms
Abdominal pain (hepatomegaly)
Arthralgias (arthritis)
Diabetes (pancreas)
Amenorrhea (cirrhosis)
Loss of libido, impotence (pituitary, cirrhosis)
Congestive heart failure (heart)
Arrhythmias (heart)

Treatment of hemochromatosis

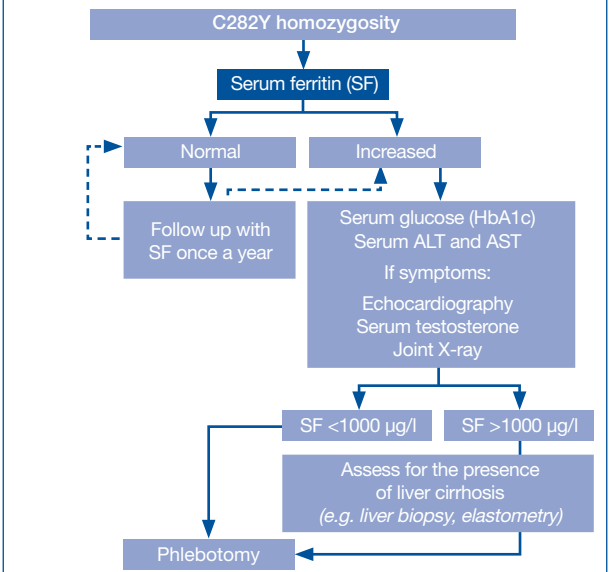
Hereditary hemochromatosis

- One phlebotomy (removal of 500 mL blood) weekly or biweekly
- Check hematocrit/hemoglobin prior to each phlebotomy.
- Allow hematocrit/hemoglobin to fall by no more than 20% of prior level
- Check serum ferritin level every 10–12 phlebotomies
- Stop frequent phlebotomy when serum ferritin reaches 50–100 mg/L
- Continue phlebotomy at intervals to keep serum ferritin between 50 and 100 mg/L
- Avoid vitamin C supplements

Secondary iron overload due to dyserythropoiesis

- Deferoxamine at a dose of 20–40 mg/kg body weight per day
- Deferasirox given orally
- Consider follow-up liver biopsy to ascertain adequacy of iron removal
- Avoid vitamin C supplements

Treatment of C282Y homozygous HFE hemochromatosis



[EASL clinical practice guidelines for HFE hemochromatosis. European Association For The Study Of The Liver. J Hepatol. 2010; 53(1):3-22]

Hepatic iron index

$$\frac{\text{amount of tissue iron µg/g}}{\text{age (years) x 56}}$$

or

$$\frac{\text{amount of tissue iron µmol/g}}{\text{age (years)}}$$

Index >2.0 → suggestive of hereditary hemochromatosis

[Kowdley KV et al. Utility of hepatic iron index in American patients with hereditary hemochromatosis: a multicenter study. Gastroenterology. 1997;113(4):1270.]

Diagnostic Methods for Wilson Disease

- Serum ceruloplasmin (<0.1 g/L)
- Serum „free“ (non-ceruloplasmin bound) copper (>200 µg/L)
- 24-hour urinary copper excretion (>1.6 µmol/24 h, >100 µg/24 h)
- Presence of Kayser-Fleischer rings by slit lamp examination
- Liver biopsy (histology, Rhodanine stain, Orcein stain)
- Hepatic parenchymal copper concentration (>4 µmol/g dry weight)
- Genetic testing for ATP7B mutations
- MRI of the brain with hyperintense basal ganglia in T2

[Modified after EASL Clinical Practice Guidelines, 2012]

Wilson Disease Scoring System (Leipzig Score)

• **Serum ceruloplasmin:**		
<0.1 g/L = **2**	0.1–0.2 g/L = **1**	>0.2 g/L = **0**
• **24-hour urinary copper excretion:**		
>2x ULN = **2**	1–2x ULN = **1**	Normal = **0**
• **Presence of Kayser-Fleischer rings:**		
Present = **2**	Absent = **0**	
• **Neurologic symptoms*:**		
Severe = **2**	Mild = **1**	Absent = **0**
• **Liver copper** (no cholestasis present):**		
>4 µmol/g = **2**	0.8–4 µmol/g = **1**	<0.8 µmol/g = **-1**
• **Genetic testing for ATP7B mutations:**		
2 chromosomes = **4**	1 chromosome = **1**	
• **Coombs-negative hemolytic anemia:**		
Present = **1**	Absent = **0**	

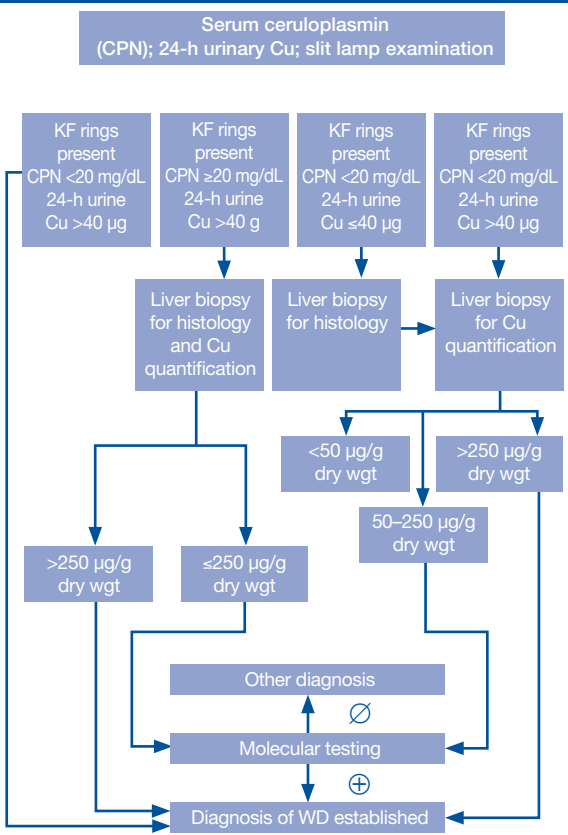
Score interpretation:

≥4 points: diagnosis established
3 points: diagnosis possible, but more tests needed
≤2 points: diagnosis very unlikely

** or typical abnormalities at brain MRI*
*** Rhodanine-positive granules if no quantitative liver copper available*

[Modified after EASL Clinical Practice Guidelines, 2012]

Diagnosis of Wilson Disease (WD)

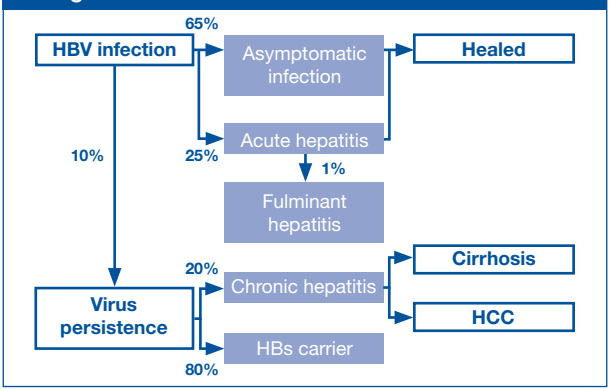


KF rings: Kayser-Fleischer rings

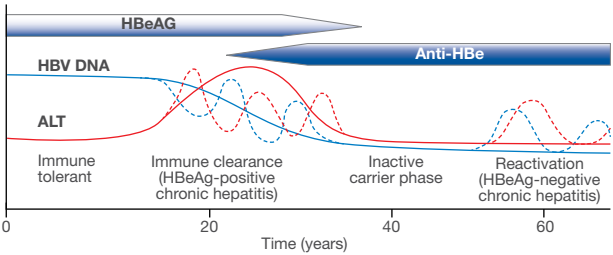
HBV diagnosis and progression

Inter-pretation	Old terminology	HBs Ag	HBS Ab	HBc IgM	HBc IgG	HBe Ag	HBe Ab	HBV DNA	AST/ ALT
Acute Hepatitis B	Acute Hepatitis B	+	-	+	-	+	-	high	high
Chronic HBe Ag pos. Infection	Immune tolerant HBV	+	-	-	+	+	-	$>10^7$ IU/ml	normal
Chronic HBe Ag pos. Hepatitis	Immune reactive HBe Ag pos. Hepatitis	+	-	-	+	+	-	10^4-10^7 IU/ml	high
Chronic HBe Ag neg. Infection	Inactive HBV Carrier	+	-	-	+	-	+	< 2000 IU/ml	normal
Chronic HBe Ag neg. Hepatitis	HBeAg neg. Chronic Hepatitis	+	-	-	+	-	+	> 2000 IU/ml	high
Resolved HBV		-	+	-	+	-	+	-	normal
Previously immunized		-	+	-	-	-	-	-	normal

Progression



Disease course



Indication for therapy

- **HBV-DNA >2000 IU/mL and increased ALAT**
- **Moderate inflammation/fibrosis in liver biopsy (Metavir ≥A2 or ≥F2)**

ALWAYS treat patients with liver cirrhosis

Pregnancy and Hepatitis B

Mother	• Risk of transmission varies; HBeAg positive (70%), HBeAg negative (2–10%, HBc only (1%))
	• With higher virus load (>10^7 IU/mL), antiviral therapy should be undertaken in the 3rd trimester (Lamivudine, Telbivudine, Tenofovir)
	• With antiviral therapy → no breastfeeding
Child	• Active (after 0, 1, and 6 months) and passive (200 IE HBsAb always after 0–12 h) immunization postpartum
	• Serological testing after 7–12 months (HBsAg, HBcAK and HBsAK with a titer goal of >100 IE)

[EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol 50, (2009). Cornberg, M. et al. Z Gastroenterol (2011)]

Management of antiviral-resistant HBV infection

Prevention

- Avoid unnecessary treatment
- Initiate treatment with potent antiviral that has low rate of drug resistance or with combination therapy
- Switch to alternative therapy in patients with primary non-response

Monitoring

- Test for serum HBV DNA (PCR assay) every 3–6 months during treatment
- Check for medication compliance in patients with virologic breakthrough
- Confirm antiviral resistance with genotypic testing

Treatment

Lamivudine-resistance →	Add adefovir or tenofovir Stop lamivudine, switch to Truvada*^
Adefovir-resistance →	Add lamivudine# Stop adefovir, switch to Truvada*^ Switch to or add entecavir#^
Entecavir-resistance→	Switch to tenofovir or Truvada^
Telbivudine –resistance+ →	Add adefovir or tenofovir Stop telbivudine, switch to Truvada

* *Truvada= combination pill with emtricitabine 200 mg and tenofovir 300 mg*

\# *Durability of viral suppression unknown, especially in patients with prior lamivudine resistance*

^ *In HIV coinfected persons: scanty in vivo data in non HIV infected persons*

\+ *Clinical data not available*

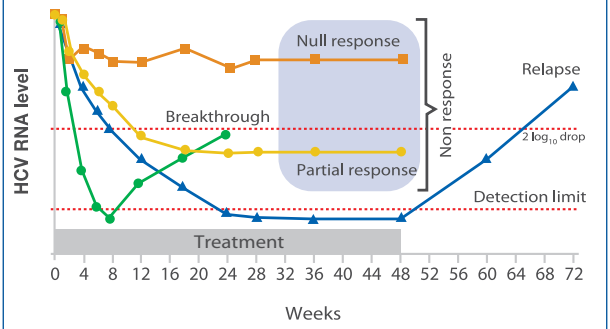
Definitions of virological response patterns

Rapid virological response (RVR)	Undetectable[1] HCV RNA at week 4
Extended RVR (eRVR)	Undetectable HCV RNA at weeks 4 and 12[2]
RVR8	Undetectable HCV RNA at week 8[3]
Early virological response (EVR)	>2 log drop of HCV RNA at week 12
Complete EVR (cEVR)[4]	Undetectable HCV RNA at week 12
Partial EVR (pEVR)	>2 log drop but still detectable HCV RNA at week 12
Delayed virological response (DVR)[5]	>2 log drop but still detectable HCV RNA at week 12, but undetectable at week 24
Partial response (PR)	>2 log drop of HCV RNA at week 12 but detectable at weeks 12 and 24
Null response (NR)	<2 log drop of HCV RNA at week 12
Breakthrough (BT)	Reappearance of HCV RNA at any time during treatment
Sustained virological response (SVR)	Undetectable HCV RNA 24 weeks after the end of treatment
Relapse	HCV RNA undetectable at end of treatment but detectable within 24 weeks of follow-up

1 The term «undetectable» refers to HCV RNA below the limited of detection (as opposed to the limit of quantitation) of a sensitive real-time PCR assay.
2 Relates to triple therapy comprising telaprevir.
3 Relates to triple therapy comprising boceprevir, including a 4-week lead-in phase of pegylated interferon-α and ribavirin.
4 Designated as early virological response in the recent EASL Clinical Practice Guidelines (ref. 2).
5 Formerly designated as slow virological response.

[Modified from: SASL, Treatment of chronic hepatitis C genotype 1 with triple therapy comprising telaprevir or boceprevir, Swiss Med Wkly 2012]

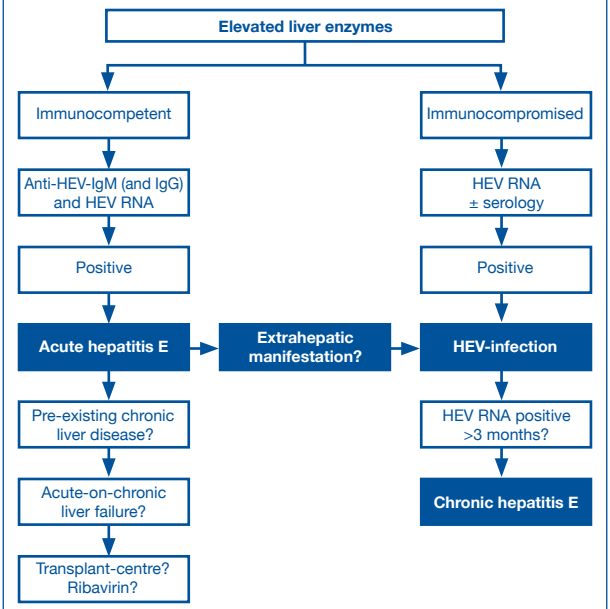
Hepatitis C Therapy – Definitions



[Adapted from Shiffman M. Curr Gastroenterol Rep 2006;8:46–52
Neumann A, et al. Science 1998; De Bruijne J, et al. Neth J Med 2008]

Please refer to HCV Advisor APP

Diagnostic algorithm for HEV infection



Serology and NAT testing are best used in combination, as a negative PCR does not exclude acute infection; serology is sometimes negative in immunosuppressed patients with chronic infection EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

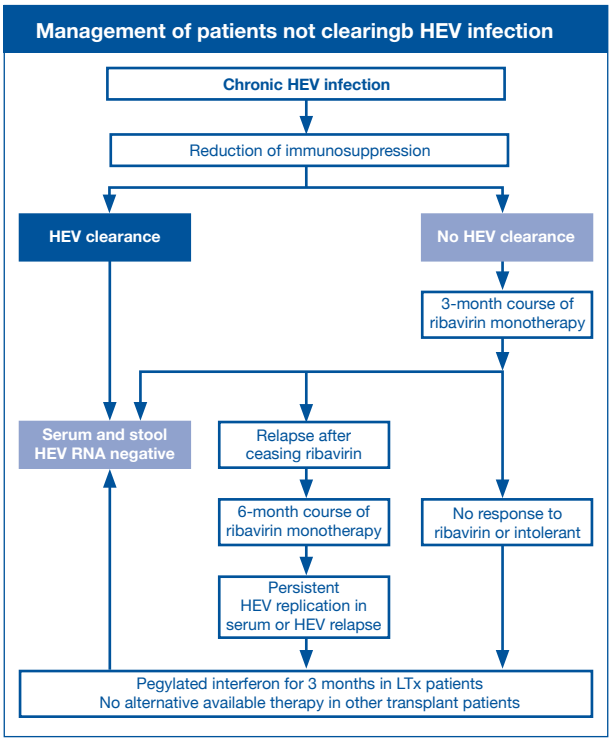
Laboratory diagnosis of HEV infection

- Acute HEV infection can be diagnosed by detection of anti-HEV antibodies
  - IgM, IgG or both by enzyme immunoassays in combination with HEV NAT

- Serological testing relies upon detection of anti-IgM and (rising) IgG

Infection status	Positive markers
Current infection – acute	• HEV RNA • HEV RNA + anti-HEV IgM • HEV RNA + anti-HEV IgG* • HEV RNA + anti-HEV IgM + anti-HEV IgG • Anti-HEV IgM + anti-HEV IgG (rising) • HEV antigen
Current infection – chronic	• HEV RNA (± anti-HEV) ≥3 months • HEV antigen
Past infection	• Anti-HEV IgG

*Patients with re-infection are typically anti-HEV IgM negative, but IgG and PCR positive EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]



EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005
[Epub ahead of print]

Extrahepatic manifestations

- Extrahepatic manifestations of HEV are increasingly recognized

Organ system	Clinical syndrome
Neurological	• Neuralgic amyotrophy* • Guillain–Barré syndrome* • Meningoencephalitis* • Mononeuritis multiplex • Myositis • Bell's palsy, vestibular neuritis, and peripheral neuropathy
Renal*	• Membranoproliferative and membranous glomerulonephritis • IgA nephropathy
Haematological	• Thrombocytopenia • Monoclonal immunoglobulin • Cryoglobulinaemia • Aplastic anaemia† • Haemolytic anaemia†
Other	• Acute pancreatitis • Arthritis† • Myocarditis† • Autoimmune thyroiditis†

*There is good evidence to support a causal role for HEV and these associated conditions. For the other extrahepatic manifestations, causality remains to be established; †Case reports only EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Notes
• ~150 cases of neurological injury (in HEV GT 3); mainly Europe • Most (>90%) cases in the immunocompetent
• Mainly immunosuppressed GT 3-infected patients • Renal function improves and proteinuria levels decrease following HEV clearance
• Mild thrombocytopenia is common; occasionally severe • Reported in 25% of cases of acute HEV in UK study • Occurs mainly in association with renal disease
• 55 cases worldwide. HEV GT 1 only; usually mild

Simplified diagnostic criteria for autoimmune hepatitis (AIH)

Variable	Cutoff	Points	Cutoff	Points
ANA or SMA	≥1:40	1*	≥1:80	2*
LKM			≥1:40	2*
SLA			positive	2*
IgG	>ULN	1	>1.1 x ULN	2
Histology	Compatible with AIH	1	Typical of AIH	2
Absence of viral hepatitis			Yes	2

Score interpretation: ≥6 points: Probable autoimmune hepatitis
≥7 points: Definite autoimmune hepatitis

**Maximal number of points for all autoantibodies is 2; AIH score maximum is 8.*
[Modified from: Choi et al., Hepatology 2008]

Indications for immunosuppressive treatment in autoimmune hepatitis

Absolute indications	Relative indications	No indication
Serum AST ≥10 fold ULN	Symptoms (fatigue, arthralgia, jaundice)	Asymptomatic with normal or near normal serum γ-globulin levels
Serum AST ≥5 fold ULN and γ-globulin ≥2 fold ULN	Serum AST and/or γ-globulin less than absolute criteria	Inactive cirrhosis or mild portal hypertension (portal hepatitis)
Bridging necrosis or multiacinar necrosis on histology	Interface hepatitis	Severe leucopenia (<2.5 x 10^9/L or thrombocytopenia <50 x 10^9/L or known complete deficiency of TPMT activity precludes treatment with azathioprine
Incapacitating symptoms	Leucopenia, (≤2.5 x 109/L) Thrombocytopenia (≤50 x 109/L) Osteopenia, emotional instability, hypertension, diabetes	Vertebral compression, psychosis, brittle diabetes, uncontrolled hypertension, known intolerances to prednisone or azathioprine

Abbreviations: AST = aspartate aminotransferase levels; ULN = upper limit of normal range; TPMT = thiopurine methyltransferase.

[Modified from: AASLD Practice Guidelines: Diagnosis and Management of Autoimmune Hepatitis, Manns et al., Hepatology 2010]

	Monotherapy	Combination therapy	
	Prednisone (mg/day)	Prednisone (mg/day)*	Azathioprine (mg/kg/day)
Week 1	60	30	1–2
Week 2	40	20	1–2
Week 3	30	15	1–2
Week 4	30	15	1–2
Maintainance until endpoint	20 and below	10	1–2
Reasons for preference	Cytopenia Thiopurine methyltransferase deficiency Pregnancy Malignancy Short course (<6 months)	Postmenopausal state Osteoporosis Brittle diabetes Obesity, acne Hypertension Emotional lability	

**Alternative: Oral budesonide (3mg, three or two times daily) in combination with azathioprine can induce and maintain remission in patients with noncirrhotic AIH, with a low rate of steroid-specific side effects (Manns et al. Gastroenterology 2010)*
[Modified from: AASLD Practice Guidelines: Diagnosis and Management of Autoimmune Hepatitis, Manns et al., Hepatology 2010]

Autoimmune hepatitis – Classification

	Type 1 (~80%)	Type 2 (~20%)
Age of onset	10–20 45–70	<15
Gender distribution	78% female	89% female
Characteristic antibodies	ANA SMA (F-actin) SLA pANCA	LKM-1 LC-1
IgG increase ↑	+++	+
Steroid response	+++	++

[Modified from: AASLD Practice Guidelines: Diagnosis and Management of Autoimmune Hepatitis. Manns et al.,Hepatology 2010]

Revised Original Scoring System of the International Autoimmune Hepatitis Group

		Score
HLA	DR3 or DR4	+1
Immune disease	thyroiditis, colitis, others	+2
Other markers	Anti SLA, anti-actin, anti-LC1, pANCA	+2
Histological features	Interface hepatitis	+3
	Plasmacytic	+1
	Rosettes	+1
	None of above	-5
	Biliary changes	-3
	Other features	-3
Treatment response	Complete	+2
	Relapse	+3
Sex	Female	+2
AP: AST (or ALT) ratio	>3	-2
	<1.5	+2
γ-globulin or IgG level above normal	>2.0	+3
	1.5–2	+2
	1.0–1.5	+1
	<1	0
ANA, SMA or anti-LKM1 titers	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
AMA	Positive	-4
Viral markers	Positive	-3
	Negative	+3
Drugs	Yes	-4
	No	+1
Alcohol	<25 g/day	+2
	>60 g/day	-2

Pretreament aggregate score	Definite diagnosis	>15
	Probable diagnosis	10–15
Posttreament aggregate score	Definite diagnosis	>17
	Probable diagnosis	12–17

[Modified from: AASLD Practice Guidelines: Diagnosis and Management of Autoimmune Hepatitis. Manns et al.,Hepatology 2010]

Autoimmune hepatitis – Recommendations for treatment

Remission induction – Aim: Transaminase and IgG levels

High-dose therapy with predniso(lo)ne	In patients who are particularly predniso(lo)ne, e.g. with diabetes, osteoporosis (e.g. post-menopause), tolerate a potential cosmetic Cushing syndrome, hirsutism)
Start with **predniso(lo)ne** (60 mg/day) with subsequent stepwise tapering of dosage following decline of transaminase levels From 30 mg/day additional **azathioprine** (1–2 mg/kg bw/day)	Remission induction with lower dosage of **predniso(lo)ne** (30 mg/day) **plus** **azathioprine** (1–2 mg/kg bw/day) stepwise tapering of dosage of **predniso(lo)ne** following decline of transaminases

Maintenance of remission

- **Duration of treatment: normally lifelong**
- **Consider treatment-free interval: (transaminase and IgG levels within normal range), repeatedly documented histological remission (liver biopsy).**

Continue the remission maintenance therapy with **azathioprine** (1–2 mg/kg bw/day) If required, combination of **azathioprine** (1–2 mg/kg bw/day) with **prednis(ol)one** (≤7.5 mg/day) **or** in patients without liver cirrhosis with **budesonide** (2 x 3 mg/day)	Continue the remission maintenance therapy with **azathioprine** (1–2 mg/kg bw/day) If required, combination of **azathioprine** (1–2 mg/kg bw/day) with **prednis(ol)one** (≤7.5 mg/day) **or** in patients without liver cirrhosis with **budesonide** (2 x 3 mg/day)

In the case of relapse during maintenance therapy

- **Increase dosage of/reintroduce therapy with predniso(lo)ne and, if required, increase of azathioprine dosage**

within normal range

sensitive to adverse effects of fatty liver disease/NASH, glaucoma or in patients who do not impairment (acne, weight gain)

In patients without liver cirrhosis remission induction with **budesonide** (3 x 3 mg/day) **plus** **azathioprine** (1–2 mg/kg bw/day)

In patients with azathioprine intolerance or contraindication (leukopenia/thrombocytopenia, cholestatic hepatitis, gastrointestinal adverse effects, pancreatitis)

Remission induction with **predniso(lo)ne** monotherapy (60 mg/day) **or** in patients without liver cirrhosis **budesonide** monotherapy (3 x 3 mg/day)

only in cases of complete biochemical/immunological remission verified over a minimum period of 2 years and simultaneously

Taper **budesonide** and continue the remission maintenance therapy with **azathioprine** (1–2 mg/kg bw/day) **or** continue combination therapy with **budesonide** (2 x 3 mg/day) **plus** **azathioprine** (1–2 mg/kg bw/day)

Continue the remission maintenance therapy with low dosage **predniso(lo)ne** (≤7.5 mg/day) **or** in patients without liver cirrhosis with **budesonide** (2 x 3 mg/day) **or** possibly off-label with **mycophenolate mofetil** (2 x 1 g/day)

or budesonide with subsequent stepwise tapering of dosage (up to 2 mg/kg bw/day)

If response to treatment is inadequate

- Check compliance, diagnosis and for presence of an overlap syndrome with PBC or PSC
- **If there is suspected inadequate compliance during prednis(lo)one therapy due to adverse effects (in patients without liver cirrhosis):**
  switch to budesonide (3 x 3 mg/day) and taper predniso(lo)ne
- After excluding the above factors, prediso(lo)ne 60 mg/day or 30 mg/day in combination with azathioprine (1–2 mg/kg bw/day) for a longer period (minimum of 4 weeks)
  Stepwise tapering of predniso(lo)ne dosage following decline of transaminase levels
- **Second line treatment options*:**
  Supplement or substitute the standard therapy with mycophenolate mofetil, cyclosporin A or tacrolimus (off-label) in consultation with a hepatological center
- **Third line treatment options*:**
  Supplement or substitute the standard therapy with rituximab or infliximab** (off-label) in consultation with a hepatological center

* *Consider patient-specific factors such as concomitant diseases, tolerance, drug interactions/toxicity and responce to treatment following initiation.*
** *Can induce AIH.*

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Biochemical changes during normal pregnancy	
hemoglobin	↓ (from 2nd trimester)
white cell count	↑
platelets	unchanged
prothrombin time	unchanged
transaminases (ALT, AST)	unchanged
alkaline phosphatase (ALP)	↑
γGT	unchanged
albumin	↓
bilirubin	unchanged
alpha-fetoprotein	↑
cholesterol	↑
uric acid	↓

Pregnancy-related liver diseases

Diagnosis	Onset (trimester)
Hyperemesis Gravidarum	1st
Pre-Eclampsia/ Eclampsia	2nd and/or 3rd
HELLP	2nd to 3rd or postpartum
Acute fatty liver of pregnancy	3rd
Intrahepatic cholestasis of pregnancy	3rd
Liver hematoma or rupture	3rd or postpartum

Diagnostic laboratory features in pregnancy-related liver diseases

Diagnosis	ALT	Bilirubin	Bile Acids	Prothrombin Time	Platelets
Hyperemesis Gravidarum	2–4 x ↑	up to 4 x ↑	=	=	=
Pre-Eclampsia/ Eclampsia	10–50 x ↑	2–5 x ↑	=	= / ↑	= / ↓
HELLP	10–20 x ↑	2–4 x ↑	=	= / ↑	↓
Acute fatty liver of pregnancy	5–10 x ↑	6–8 x ↑	=	↑	= / ↓
Intrahepatic cholestasis of pregnancy	1–10 x ↑	up to 6 x ↑	↑	= (↑)	=
Liver hematoma or rupture	10–50 x ↑	2–10 x ↑	=	= / ↑	↓

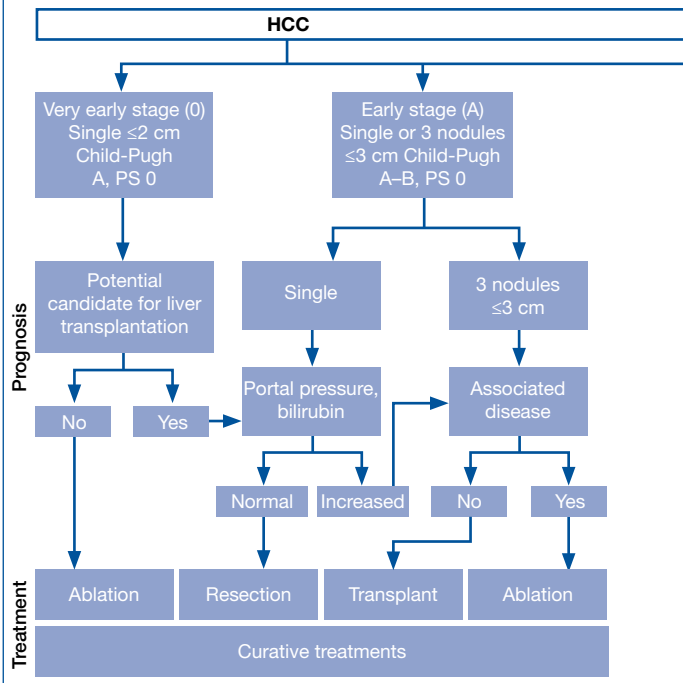
Symptoms	Therapy	Prevalence (%)
nausea, vomiting, weight loss >5%, dehydration, electrolyte abnormalities	supportive	0.3–1.0
headache, visual disturbances, RUQ pain, hypertension, edema, proteinuria, (with seizures: eclampsia)	supportive, prompt delivery	5–7
nausea, vomiting, headache, RUQ pain, edema, weight gain	supportive, prompt delivery	0.2–0.6
anorexia, nausea, vomiting, headache, RUQ pain, liver failure, encephalopathy	immediate delivery	0.005–0.010
pruritus, mild jaundice	ursodeoxycholic acid (10–15 mg/kg), delivery after fetal maturity	0.1–0.3
RUQ pain, pre-eclampsia, hypotension, shock	surgery	1 (in patients with HELLP)

Disorders severely affected by pregnancy

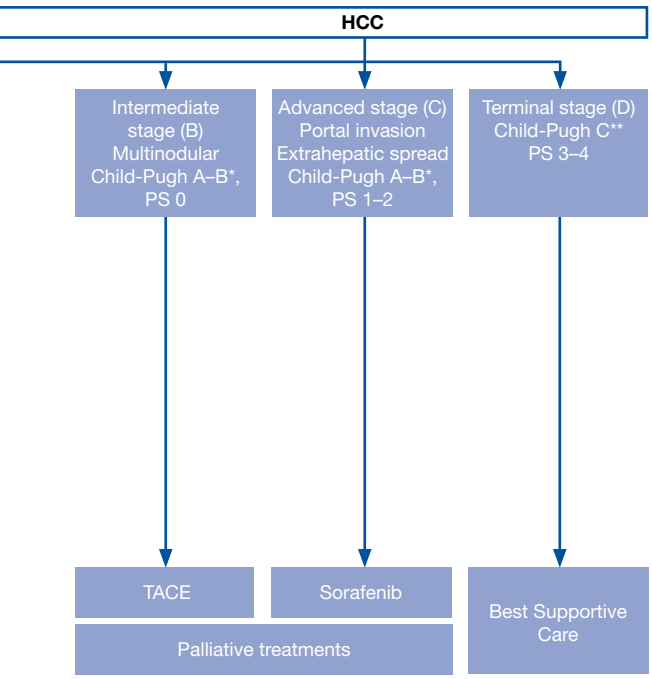
Disorder	Mechanisms of Effect of Pregnancy
Hepatitis E	particularly severe during pregnancy (especially 3rd trimester), possibly related to immunologic changes
Hepatic Adenoma	increased growth of adenoma because of hyperestrogenemia
Budd-Chiari syndrome	thrombosis promoted by increased gestational serum levels of estrogen and decrease in AT III levels
Splenic artery syndrome	artery can rupture during pregnancy because of compression by gravid uterus
Acute intermittent porphyria	symptoms worsened by hyperestrogenemia
Choledochal cysts	cyst compression by gravid uterus can lead to cyst rupture or cholangitis

Clinical Presentation	Diagnosis	Therapy
malaise, anorexia, nausea, vomiting, abdominal pain and jaundice	IgM antibody and PCR analysis of blood or feces for hepatitis E	supportive therapy for acute infection may require liver transplant
nausea, vomiting and RUQ pain	abdominal US	observe if size <5 cm surgery if size >5 cm or symptomatic or intralesional hemorrhage
RUQ pain, hepatomegaly and ascites	doppler abdominal US, hepatic venography or MR-angiography	selective thrombolytic therapy, surgical shunt or TIPS anticoagulation with heparin because warfarin is contraindicated in pregnancy
abdominal pain, pulsatile left upper quadrant mass and abdominal bruit in patient with portal hypertension	abdominal doppler US	surgical removal or angiographic occlusion
abdominal pain, vomiting, constipation, paresthesias in extremities, mental status changes, tachycardia, and ileus	increased urinary porphobilinogen, and Δ-aminolevulinic acid	discontinue precipitating drugs, avoid prolonged fasting, and administer hematin and glucose to prevent attacks
abdominal pain, jaundice, and abdominal mass	abdominal US, may require cholangiography	frequently requires surgery: cystectomy and cholecystectomy with either Roux-en-Y hepaticojejunostomy oder choledochojejunostomy

Therapeutic algorithm for hepatocellular cancer (HCC)



[Díaz-González et al, Dig Dis 2016;34:597–602]
[Reig M, Darnell A, Forner A, Semin Liver Dis 2014; 34: 444–455]


HCC
Intermediate stage (B) Multinodular Child-Pugh A–B*, PS 0
Advanced stage (C) Portal invasion Extrahepatic spread Child-Pugh A–B*, PS 1–2
Terminal stage (D) Child-Pugh C** PS 3–4
TACE
Sorafenib
Palliative treatments
Best Supportive Care

Non-Alcoholic Fatty Liver Disease Activity Score (NAS)		
Steatosis (%)	≤5	0
	5–33	1
	33–66	2
	≥66	3
Lobular inflammation (per 200x field)	none	0
	≤2 foci	1
	2–4 foci	2
	≥4 foci	3
Hepatocellular ballooning	none	0
	few, mild ballooning	1
	prominent ballooning	2
Fibrosis	no fibrosis	0
	zone 3 perisinusoidal fibrosis (special fibrosis staining required to identify)	1a
	zone 3 perisinusoidal fibrosis (easily seen on H&E)	1b
	periportal/portal fibrosis only	1c
	zone 3 with periportal/portal fibrosis	2
	as previous with bridging fibrosis	3
	cirrhosis	4

[modified from Kleiner, DE et al.: Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology, 2005]

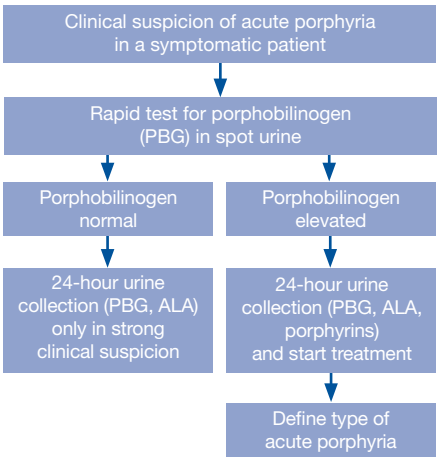
HOMA-IR: Homeostasis model assessment for insulin resistance

- **Goal:** Approximating equation for insulin resistance
- **Formula:** Fasting insulin (mIU/L) x Fasting glucose (mmol/L) / 22.5
- **Calculation Link:** https://sasl.unibas.ch/11calculators-HOMA.php

HOMA-IR Score (Unit: mIU/L x mmol/L)	
<3	Normal insulin resistance
3–5	Moderate insulin resistance
>5	Severe insulin resistance

[Matthews, DR et al.: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985.]

Diagnosis of acute porphyria

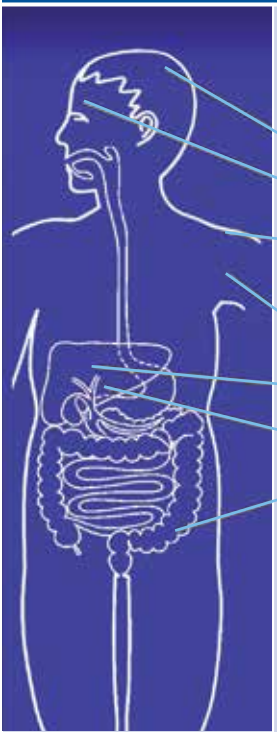


ALA: Aminolevulinic acid

Epidemiology		
	Primary biliary cholangitis (PBC)	**Primary sclerosing cholangitis (PSC)**
Sex	80–95% females	60–80% males
Age	35–50 years	30–60 years
Special characteristics	Independent of social class and/or race Children and adolescents only rarely affected	Inflammatory bowel diseases in 70–80% (85–90% ulcerative colitis, 10–15% Crohn's disease) Children and adolescents are often affected; often overlap with autoimmune hepatitis

Staging		
Stage	**Clinical features**	**Histology**
I	Pruritus; elevated γGT, AP (significant), AST, ALT (mild), antimitochondrial antibodies (AMA)	Portal inflammation, bile duct destruction and bile duct proliferation in the portal tracts
II	Same as stage I, increase in IgM and further elevation of above mentioned parameters	Same as stage I, inflammatory infiltration of hepatic parenchyma (piecemeal necrosis possible), beginning fibrosis
III	Same as stage I and II, mild increase in serum bilirubin possible	Rarefication of bile ducts, reduced inflammation, increasing fibrosis
IV	Jaundice, ascites, portal hypertension	Complete cirrhotic transformation

Symptoms and findings



- Fatigue
- Xanthelasmas and xanthomas
- Pruritus (especially at night, later also during the day; cause unkown. Pruritus is very common = main symptom)
- Jaundice (in late stages)
- Hepato-and splenomegaly (moderate to significant)
- Signs of liver cirrhosis (varices, ascites, etc.)
- Steatorrhea (due to cholestasis and pancreatic insufficiency: Sicca syndrome)

... and

- More rarely, vitamin deficiencies (due to cholestasis and steatorrhea); night blindness, coagulation disorders

Symptoms and findings in PBC and PSC

• Weight loss	25–80%	• AP, γGT, ALT and AST ↑	90–95%
• Jaundice	25–70%	• Bilirubin ↑	70%
• Recurrent fever	20–30%	• IgG ↑	40%
• Pruritus	10–70%	• IgM ↑	35%
• Upper abdominal complaints	40–75%	• Albumin ↓	25–30%
• Variceal hemorrhage	9%	• ANA positive	10–80%
• Ascites	6%	• AMA positive • AMA negative	>90% (PBC) (PSC)
• Diarrhea	unkown	• pANCA positive	65–80%
7–50 % of patients are believed to be asymptomatic			

Treatment options PBC

Basic drug therapy
Ursodeoxycholic acid 14 ± 2 mg/kg body weight/day

If non-responsive to ursodeoxycholic acid:
Ursodeoxycholic acid + obeticholic acid 5–10 mg/day

Combination therapy (in trials)
Ursodeoxycholic acid + budesonide 3 x 3 mg/day

Ursodeoxycholic acid + prednisone 10 mg/day
+ azathioprine 100 mg/day

End stage
Liver transplantation

Treatment options PSC

Basic drug therapy
Ursodeoxycholic acid* 15–20 mg/kg body weight/day

Inflammatory flares
Antibiotics, if necessary

Interventions on the bile duct
Endoscopic dilatation in dominant strictures

End stage
Liver transplantation

** Ursodeoxycholic acid is not approved for the treatment of PSC.*

[Bowlus CL & Gershwin ME Autoimmun Rev. 2014; 13: 441–4]
[Yimam KK & Bowlus CL Autoimmun Rev. 2014; 13: 445–50]

PBC response criteria

Criteria	Definition
Paris I	ALP <3 x ULN, AST <2 x ULN and bilirubin ≤1 mg/dl after 1 year of UDCA
Barcelona	ALP decline of more than 40% towards baseline value or a normal level after 1 year of UDCA
Rotterdam	Normalization of bilirubin and albumin after treatment with UDCA when one or both parameters were abnormal before treatment, or normal bilirubin or albumin after treatment when both were abnormal at entry
Paris II	ALP and AST ≤1.5 x ULN and normal total bilirubin after 1 year of UDCA
Toronto	ALP <1.67 x ULN after 2 years of UDCA

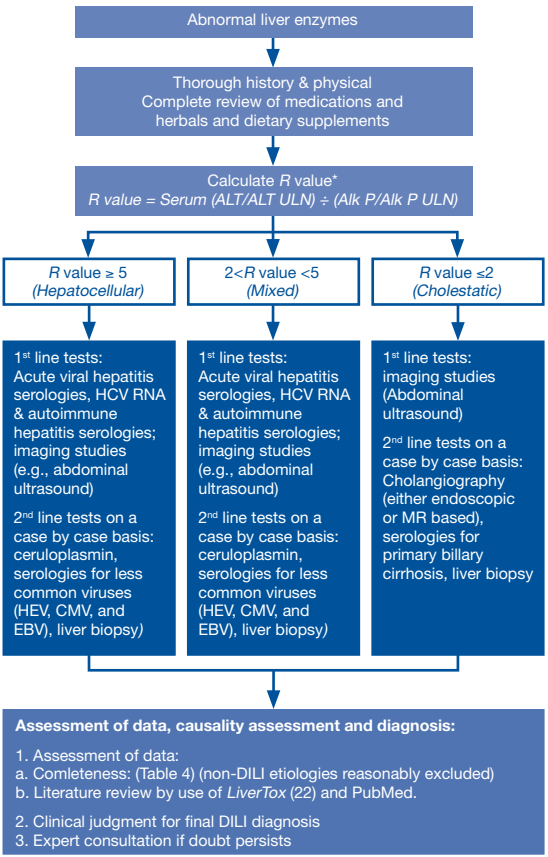
Classification of drug induced liver injury (DILI) (CIOMS criteria)

• Hepatocellular	ALT > 3 ULN	and R > 5
• Cholestatic	AP > 2 ULN	and R < 2
• Mixed	ALT > 3 ULN, AP > 2 ULN	and 2 < R < 5
R = (ALT/ULN) / (AP/ULN)		

Hepatology

Classification of drug induced liver injury (DILI) (CIOMS criteria)

How to diagnose DILI



[ACG Clinical Guideline, Chalasani et al., Am J Gastroenterology 2014]

Classification of drug induced liver injury (DILI) (CIOMS criteria)

Causative drugs

Drug No.	Ingredient	No. of Cases	Fatalities
1	Allopurinol	>100	1
2	Amiodarone	>100	1
3	Androgenic steroidsa	>100	1
4	Atorvastatin	65	1
5	Auranofin/Gold productsa	>100	1
6	Azathioprine/Mercaptopurine	>100	1
7	Busulfan	>100	1
8	Carbamazepine	>100	1
9	Chlorpromazine	>100	1
10	Clavulanate with Amoxicillin	>100	1
11	Dantrolene	51	1
12	Diclofenac	>100	1
13	Didanosine	>100	1
14	Disulfiram	>100	1
15	Efavirenz	>100	1
16	Erythromycin	>100	1
17	Estrogens/Progestinsa	>100	0
18	Floxuridine	>100	1
19	Flucloxacillin	>100	1
20	Flutamide	>100	1
21	Halothane	>100	1
22	Hydralazine	>100	1
23	Ibuprofen	52	1
24	Infliximab	>100	1
25	Interferon-α/Peginterferon	56	1
26	Interferon-β	>100	1
27	Isoniazid	>100	1
28	Ketoconazole	>100	1
29	Methotrexate	>100	1
30	Methyldopa	>100	1
31	Minocycline	>100	1
32	Nevirapine	>100	1
33	Nimesulide	>100	1
34	Nitrofurantoin	>100	1
35	Phenytoin/Fosphenytoin	>100	1
36	Propylthiouracil	>100	1
37	Pyrazinamide	>100	1
38	Quinidine	53	1
39	Rifampin	>100	1
40	Simvastatin	68	1
41	Sulfamethoxazole with TMP	>100	1
42	Sulfasalazine	>100	1
43	Sulfonamidesa	>100	1
44	Sulindac	>100	1
45	Telithromycin	79	1
46	Thioguanine	56	1
47	Ticlopidine	>100	1
48	Valproate	>100	1

A Groups of agents (see text for details). Abbreviations: CNS, central nervous system; N, never approved in the United States; TMP, trimethoprim.

Table 2. Category A (≥50 Published Cases)

Rechallenge	Year	Classification
1	1965	Rheumatologic
1	1985	Cardiovascular
1	1981	Endocrine
1	1996	Cardiovascular
1	1985	Rheumatologic
1	1968	Immunomodulatory
0	1954	Antineoplastic
1	1968	CNS
1	1957	CNS
1	1984	Antimicrobial
1	1974	CNS
1	1988	Analgesic
1	1991	Antimicrobial
1	1951	Substance abuse agent
0	1998	Antimicrobial
1	1967	Antimicrobial
1	Pre-1980	Endocrine
0	1970	Antineoplastic
1	N	Antimicrobial
1	1989	Antineoplastic
1	1956	CNS
1	1984	Cardiovascular
1	1974	Analgesic
1	1998	Immunomodulatory
1	1986	Antimicrobial
1	1993	Immunomodulatory
1	1974	Antimicrobial
1	1981	Antimicrobial
0	1971	Antineoplastic
1	1962	Cardiovascular
1	1971	Antimicrobial
1	1996	Antimicrobial
1	N	Analgesic
1	1953	Antimicrobial
1	1946	CNS
1	1948	Endocrine
1	1971	Antimicrobial
1	1950	Cardiovascular
1	1971	Antimicrobial
1	1991	Cardiovascular
1	1980	Antimicrobial
1	1950	Rheumatologic
1	1973	Antimicrobial
1	1978	Analgesic
0	2004	Antimicrobial
0	1966	Antineoplastic
1	1985	Hematologic
1	1978	CNS

[Björnsson & Hoofnagle, Hepatology 2016] [https://livertox.nih.gov/]

Serum – biomarkers for staging liver fibrosis

NAFLD Fibrosis Score:
http://nafldscore.com

Parameter
Age
AST
ALT
Thrombocytes
BMI
Albumin, g/L
(Pre-)Diabetes

FIB-4 Score:
http://gihep.com/calculators/hepatology/fibrosis-4-score

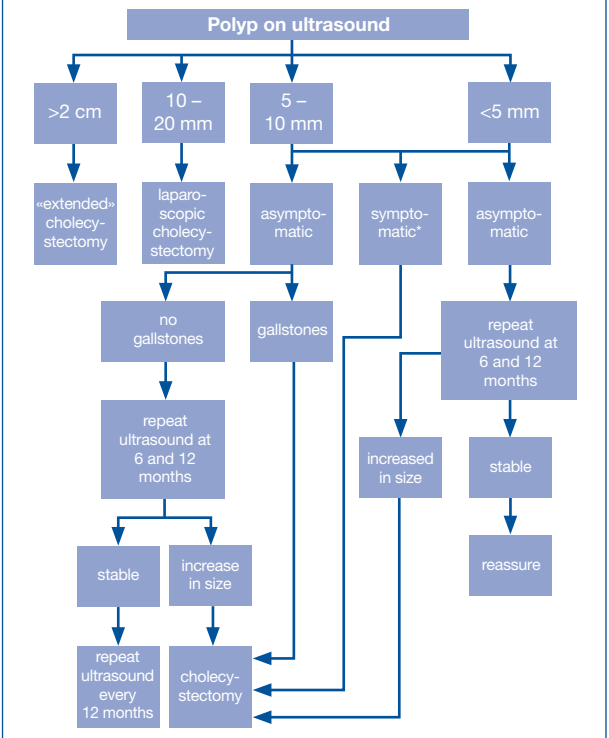
NAFLD Cutoff Value[1]	Stage
< -1.455	F0-F2
-1.455 to 0.676	Indeterminate
> 0.676	F3-F4

FIB-4 Cutoff Value[2]	Stage
< 1.45	F0-F2
1.45 to 3.25	Indeterminate
> 3.25	F3-F4

[1. Angulo P, Hui JM, Marchesini G et al. The NAFLD fibrosis score A noninvasive system that identifies liver fibrosis in patients with NAFLD Hepatology 2007;45(4):846-854
2. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al., Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317–1325.]

Biliary Diseases
Gallbladder polyps

Gallbladder Polyps



*Symptoms: Biliary type pain, common duct obstruction, cholangitis, or recurrent pancreatitis. Dyspepsia is not an indication for surgery.

Gallbladder polyps

Benign polyps

Cholesterol polyps	60%
Adenomyomas	25%
Inflammatory polyps	10%
Adenomas	4%
Miscellaneous	1%
Leiomyomas	
Fibromas	
Lipomas etc.	

Malignant polyps

Adenocarcinoma	80%
Miscellaneous	20%
Mucinous cystadenomas	
Squamous cell carcinoma	
Adenocanthomas	

Predictors for choledocholithiasis:

	Clinical predictor:
Very strong	Common bile duct (CBD) stone in transabdominal ultrasound. Clinical: Ascending cholangitis Bilirubin >4 mg/dL or >68 µmol/L
Strong	Dilated CBD on ultrasound (>6 mm with gallbladder in situ) Bilirubin 1.8–4.0 mg/dL (= 31–68 µmol/L)
Moderate	Abnormal liver biochemical test other than bilirubin Age older than 55 years Clinical: Gallstone pancreatitis

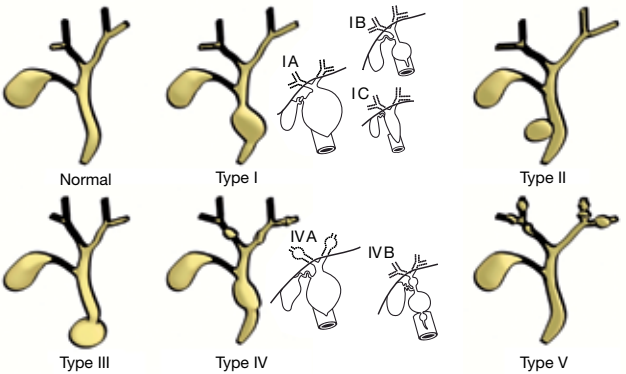
[Maple JT et al.: Gastrointest Endosc 2010]

Likelihood of choledocholithiasis:

Likelihood:		Management:
High:	Presence of any very strong predictor or both strong predictors	Preoperative ERCP
Intermediate:	All other patients	Preoperative EUS or MRCP or laparoscopic ultrasound
Low:	No predictors present	Laparoscopic cholecystectomy without cholangiography

[Maple JT et al.: Gastrointest Endosc 2010]

Todani classification of bile duct cysts



Choledochal cysts

[www.radiopaedia.org, Dr. Frank Gaillard]

Diagnostic work-up for cystic lesions of the pancreas

1. Clinical history, sex
2. Lab. BC, CRP, BS, HbA_{1c}
3. Abdominal ultrasound
4. In patients with an asymptomatic pancreatic cyst, particularly one of <10 mm in size
   → No further work-up, but
   → follow-up recommended
4. For cysts >1 cm or MPD size >5 mm or all symptomatic cysts:
   - **gadolinium-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP)** *(=procedure of choice)* or
   - pancreatic protocol multidetector CT (MDCT) (frequency of pancreatic cyst detection by MRI (20%) is higher than by CT (1–3%), based on its superior contrast resolution that facilitates recognition of septae, nodules, and duct communications)

5. Endoscopic UltraSound (EUS) for
- detecting mural nodules and invasion, and (most effective for)
- delineating malignant characteristics
- **EUS-FNA with cyst fluid (suptyp differentialich)** often useful, but no safe distriction of specific subtypes of cyst.

1) of cystic fluid: chemical analysis for subtype differentiation
2) of solid nodules: to exclude dysplasia

Combination of the clinical and imaging characteristics provides the best initial preoperative diagnosis of the cyst type:
→ mucinous vs. non-mucinous,
→ accurately identification of the specific subtypes

[International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas; Tanaka M et al., Pancreatology 2012; 12(3):183-97]

Management of pancreatic cysts according to their risk for malignancy

Cyst with invasive carcinoma uncommon	**Cyst without «worrisome» features"** on imaging
• Asymptomatic patient • **Cyst <1 cm**	*Largest* ***cyst <1 cm:*** → follow-up (CT)/MRI in 2–3 years
→ No further work-up → follow-up (CT)/MRI in 2–3 years	*Largest* ***cyst 1–2 cm:*** → follow-up (CT)/MRI yearly x2 years, then lengthen interval if no change
	Largest ***cyst 2–3 cm:*** → EUS in 3–6 months, then lengthen interval alternating MRI with EUS → Consider surgery in young, fit patients with need for prolonged surveillance
	Largest ***cyst >3 cm:*** → Close surveillance every 3–6 months alternating MRI with EUS → Strongly consider surgery in young, fit patients

«Worrisome features» on imaging	«high-risk stigmata» on imaging
• **Main pancreatic duct size 5–9 mm** • **Cyst ≥3 cm** • Thickened / enhancing cyst walls • non-enhancing mural nodule • abrupt change in the MPD caliber with distal pancreatic atrophy • lymphadenopathy • Clinical: pancreatitis	• **Main pancreatic duct size ≥10 mm** • obstructive jaundice in a patient with a cystic lesion of the pancreatic head • enhancing solid component within cyst
if any feature present: → EUS-FNA to further risk stratify	*if any feature present:* → resection without further testing, if clinically appropriate
if any feature present: → resection without further testing, if clinically appropriate	
Inconclusive: → Close surveillance every 3–6 months alternating MRI with EUS → Strongly consider surgery in young, fit patients	
• Definite mural nodule(s): - lack of mobility - presence of Doppler flow and - FNA of nodule showing tumor tissue DD mucin: - can move with change in patient position - may be dislodged on cyst lavage - does not have Doppler flow • Main pancreatic duct features suspicious for involvement (any one): - thickened walls - intraductal mucin - mural nodules *(in their absence: inconclusive)* • Cytology: suspicious or positive for malignancy	

Pancreatic cystic neoplasia and pancreatic pseudocysts (for more details on IPMN please go to chapter oncology)

	Intraductal papillary mucinous neoplasia (IPMN) - main duct (MD)-IPMN - branch duct (BD)-IPMN - mixed type IPMN	Mucinous cystic neoplasia (MCN)
Gender predominance	~55% female	>95% female
Age (decade)	6.–7.	4.–5.
Symptoms	Common when large (pancreatitis)	~50%
Location (%body/tail)	30% **(70% head!)**	**95%**
Common capsule	No	Yes
Calcification	No	Rare, curvilinear in the cyst wall
Gross appearance	Grape-like	Orange-like
Multifocality	Yes	No
Internal structure	Cyst by cyst	Cysts in cyst
Main pancreatic duct	Normal, or dilated to >5 mm, suggesting MD-IPMN or combined type	Normal or deviated
Communication to main pancreatic duct	**Always** (though not always demonstrable)	Infrequent
Malignant / invasive Carcinoma	**>40(-50)%** / 31% MD-IPMN: **>62%** / 44% BD-IPMN: **>24%** / 17% Mixed type: **>58%** / 45%	**30–50%** / <15% no malignancy in MCNs of <4 cm without mural nodules
«String sign»	Pos.	Pos.
CEA (in cystic fluid) [ng/ml]	>192-200 → mucinous*	>192-200 → mucinous*
Amylase (in cystic fluid)	High (i.e. 300)	Low (i.e. <100)***

N/A not applicable

* *distinguishes with an accuracy of ~80% mucinous from nonmucinous cysts, but not benign from malignant cysts*

** *does not exclude a mucinous cyst*

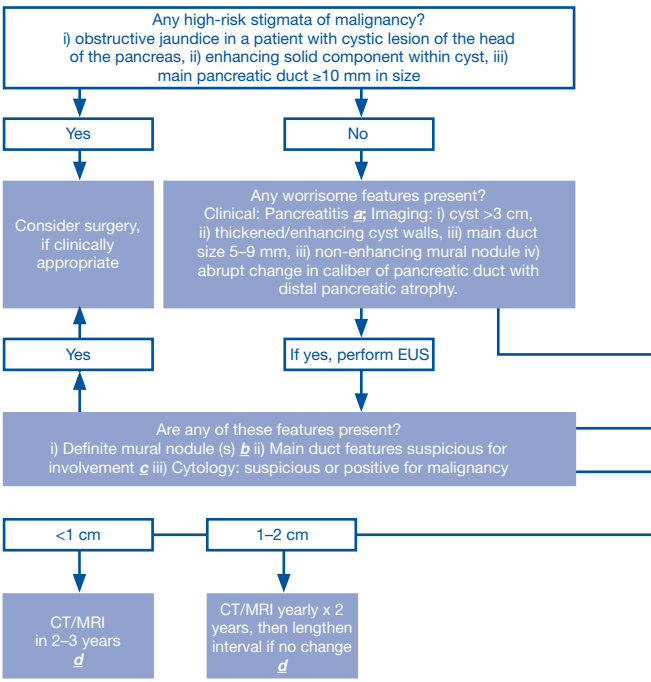
*** *may also exhibit elevated amylase levels*

[Ref.: International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas; Tanaka M et al., Pancreatology 2012; 12(3):183-97]

Solid papillary neoplasia («young women»)	Serous cystic neoplasia (SCN) - polycystic SCN - honeycomb SCN - oligocystic SCN - microcystic SCN - macrocystic SCN	Pseudocyst
87% female	~70% female	<25% female **(>75% male)**
3.	6.–7.	4.–5.
Rarely	~50%	Nearly always (pancreatitis)
	50%	65%
	Yes	N/A
	30–40%, central	No
round, well-demarcated, with solid and cystic areas with hemorrhage	Spongy or honeycomb-like	Variable
	No	Rare
	Microcystic and/or macrocystic	Unilocular
No	Normal or deviated	Normal or irregularly dilated, may contain stones
No	No	Common
Rarely (10%)	Rarely (< 5%)	N/A
	Neg.	Neg.
	<192 → non-mucinous** DD BD-IPMN	<192 → non-mucinous**
	Low (i.e. <100)	High (i.e. 300)

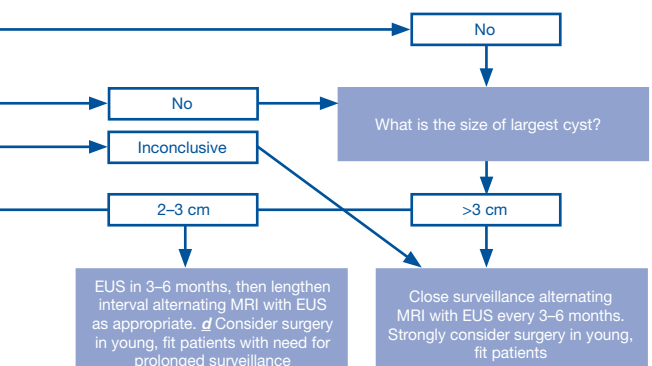
Branch duct (BD)- intraductal papillary mucinous neoplasia (IPMN)

Management of suspected BD-IPMN



a. Pancreatitis may be an indication for surgery for relief of symptoms. **b.** Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage and does not have Doppler flow. Features of true tumor nodule include lack of mobility, presence of Doppler flow and FNA of nodule showing tumor tissue. **c.** Presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement. In their absence main duct invol-

[Pancreatology 2012:12:183–97]



vement is incolclusive. ***d.*** Studies from Japan suggest that on follow-up of subjects with suspected BD-IPMN there is increased incidence of pancreatic ductal adenocarcinoma unrelated to malignant transformation of the BD-IPMN(s) being followed. However, it is unclear if imaging surveillance can detect early ductal adenocarcinoma, and, if so, at what interval surveillance imaging should be performed.

Main duct (MD), Branch duct (BD) and mixed type intraductal papillary mucinous neoplasia (IPMN):

Definitions

MD-IPMN

- segmental or diffuse dilation of the main pancreatic duct (MPD) of **>5 mm** without other causes of obstruction.
- MPD dilation of **5–9 mm:** «worrisome feature»
- MPD diameter of **≥10 mm:** «high-risk stigmata»

BD-IPMN

- **Pancreatic cysts of >5 mm** in diameter that communicate with the MPD DD pseudocyst (PC) for patients with a prior history of pancreatitis.

Reliable distinguishing features of BD-IPMN:
- multiplicity and
- visualization of a connection to the MPD, although such a connection is not always observed.

Mixed type

- criteria met for both MD-IPMN and BD-IPMN

[International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas; Tanaka M et al., Pancreatology 2012; 12(3):183-97]

Ranson's Criteria *(not useful)*

At admission or diagnosis

Age >55 years
WBC >16,000/mm^3
Blood glucose >200 mg/dL
Lactate dehydrogenase >350 IU/L
AST >250 IU/L

Within 48 hours after presentation

Hematocrit decrease >10%
Blood urea nitrogen increase >5 mg/dL
Serum calcium <8 mg/dL
Base deficit >4 mEq/L
Fluid sequestration >6 L
PaO_2 <60 mmHg
Scoring 1 point for each criterion

- 0–2: Mild
- 3–5: Moderate, mortality 10–20%
- 6–11: Severe, mortality >50%

[Ranson JH. Etiological and prognostic factors in human acute pancreatitis: a review. Am J Gastroenterol. 1982]

APACHE II Scale **Diagnosis:**

Equation includes these factors: age, rectal temperature, mean arterial pressure, heart rate, PaO_2, arterial pH, serum potassium, sodium, creatinine, hematocrit, WBC count, Glasgow coma scale score, chronic health status
Scoring calculation available at
http://www.mdcalc.com/apache-ii-score (accessed August 2016)
[Larvin M. et al. APACHE-II score for assessment and monitoring of acute pancreatitis. Lancet 1989]

CT Severity Index (Balthazar Score) *(not useful)*

Grade of pancreatitis on CT
A Normal pancreas (0 points)
B Pancreatic enlargement (1 point)
C Pancreatic enlargement with peripancreatic inflammation (2 points)
D Extrapancreatic changes plus 1 fluid collection (3 points)
E More than 1 fluid collection (4 points)
[Balthazar E, Robinson D, Megibow A, Ranson J. Acute pancreatitis: value of CT in establishing prognosis. Radiology. 1990]

Factors causing acute pancreatitis

Toxic
Alcohol
Scorpion toxin

Metabolic
Hypertriglyceridemia
Hypercalcemia
Hyperuricemia
Celiac disease

Drugs (with best proof)
Azathioprine
Sulfonamides
Thiazides
Furosemide
Pentamidine
Didanosine
Methyldopa
Tetracycline
Estrogens
Valproic acid
Sulindac
Mercaptopurine
5-aminosalicylic acid
L-asparaginase

Mechanical
Gallstones
Neoplastic process
Periampullary diverticulum
Sphincter of Oddi dysfunction
Blunt abdominal trauma
After abdominal operation
Post endoscopic retrograde cholangiopancreatography

Infectious
Viral
Mycoplasms
Worms

Vascular
Circulatory shock
Ischemia-reperfusion
Embolic
Hypothermia
Malignant hyperthermia
Autoimmune vasculitis

Hereditary
SPINK1
PRSS1
CFTR
CTRL gene

[Adapted from Waldthaler A et al., Dig Dis. 2010]

Increase of Amylase and Lipase

Causes of Increased Amylase and Lipase Levels	
Amylase	**Lipase**
Acute pancreatitis	Acute pancreatitis
Diseases that might mimic acute pancreatitis	
Pancreatic pseudocyst	Pancreatic pseudocyst
Chronic pancreatitis	Chronic pancreatitis
Pancreatic carcinoma	Pancreatic carcinoma
Biliary tract disease (cholecystitis, cholangitis, choledocholithiasis)	Biliary tract disease (cholecystitis, cholangitis, choledocholithiasis)
Intestinal obstruction, pseudo-obstruction, ischemia, or perforation	Intestinal obstruction, pseudo-obstruction, ischemia, or perforation
Acute appendicitis	Acute appendicitis
Ectopic pregnancy	
Other disorders	
Renal failure	Renal failure
Parotitis	Treatment with heparin
Macroamylasemia	
Ovarian cyst or cystic neoplasm	
Carcinoma of the lung	
Diabetic ketoacidosis	
Human immunodeficiency virus infection	
Head trauma with intracranial bleeding	

[Adapted from AGA Institute Technical Review on Acute Pancreatitis. Gastro 2007]

Chronic pancreatitis (CP)

Definition
Chronic pancreatitis (CP) is a progressive inflammatory disorder of the pancreas, characterized by irreversible morphologic changes and gradual fibrotic replacement of the gland. Loss of exocrine and endocrine function results from parenchymal fibrosis. The primary symptoms of CP are abdominal pain and maldigestion. Because of diagnostic and therapeutic challenges, an interdisciplinary management strategy is required.

Causes
TIGAR-O classification
- **T**oxic-Metabolic: alcohol, smoking, hypercalcemia, hyperparathyroidism, hyperlipidemia, chronic renal failure
- **I**diopathic: early onset, late onset, tropical pancreatitis
- **G**enetic: CFTR/PRSS1/SPINK1 mutations, Alpha-1-Antitrypsin deficiency
- **A**utoimmune: IgG4 associated, associated with PSC, Sjögren, PBC, Type 1 Diabetes
- **R**ecurrent acute pancreatitis
- **O**bstructive: cancer, duct obstruction, pancreas divisum, stones

90–95% of patients have alcoholic or idiopathic disease

Smoking as most important factor for complicated course

Clinical Features and complications
- Abdominal pain: acute or chronic
- Exocrine pancreatic insufficiency: Diarrhea, steatorrhea (>7 g of fat/24 h), weight loss, malabsorption (vitamin deficiency, osteoporosis)
- Endocrine pancreatic insufficiency: diabetes mellitus
- Biliary obstruction, jaundice
- Gastric outlet obstruction
- Pancreatic ascites
- Pleural effusion
- Splenic vein thrombosis, bleeding from gastric varices
- Pancreatic adenocarcinoma
- SIBO in 14.7% of patients with CP

[Kumar et al: Pancreatology 2014]

Diagnosis
- Pancreatic function test and imaging tests (histology rarely available)

Chronic pancreatitis (CP)

- **Functional tests for exocrine pancreatic insufficiency:**
  - Fecal elastase in the stool: 100–200 µg/g mild, <100 µg/g severe
  - C13 breath test, secretin test.
- **Imaging**
  1. Ultrasound
  2. CT
  3. Secretin-enhanced MRCP
  4. EUS-based criteria fort he diagnosis of chronic pancreatitis are sumnmorized in the Rosemont classification (see Gastrointest Endosc 2009;69:1251-61)

Further testing:
IgG4, genetic testing when patient <25y, (CA 19–9)
EUS-FNA when suspicious for carcinoma.

Management
- **Pain: multidisciplinary approach necessary**
  alcohol/smoking abstinence
  Step 1: non opoid analgesic plus A
  Step 2: weak opioid in combination with Step1 and A
  Step 3: strong opioid in combination with Step 1 and A
  Step 4: invasive techniques
    - Small duct disease: celiac plexus blockade
    - Large duct disease: endoscopic/surgical therapy
  A: Adjuvants: pain modulators (tricyclic antidepressants, SSRI, gabapentoids)

- **Exocrine Insufficiency**
  2000 IU lipase per gram of fat →
  20'000–40'000 IU for a main meal and
  10'000–20'000 IU for a snack
  max. dose of lipase per day 10'000–20'000 IU per kg of body weight
  Adjust the enzyme dose based on its effects (steatorrhea, body weight, levels of fat-soluble vitamins)
  Consider adding a PPI if inefficient (although most lipase preparations are acid resistant)
  Supplementation of fat-soluble vitamins

[Chronische Pankreatitis und Enzymersatztherapie für die Praxis. Schweiz Med Forum 2014.]

Chronic pancreatitis (CP)

- **Endocrine Insufficiency**
  Glucose measure every 6–12 months
  Cave: patients are prone to treatment-induced hypoglycemia
  Use simple insulin regimens

- **Metabolic bone disease**
  High prevalance of fractures in patients with CP (OR 4.4)
  DEXA Scan, therapy following guidelines

- **Endoscopic therapy**
  Symptomatic pseudocysts:
  transgastric/transduodenal or transpapillary drainage
  Symptomatic MPD stones <5 mm in the head/body low in number: direct ERCP
  Symptomatic MPD stones >5 mm:
  ESWL immediately followed by ERCP
  Dominant MPD stricture:
  use 10F single plastic stent, exchange after 1 year
  Pancreatitis related distal biliary stricture:
  Fully covered self expandable metal stents (SEMS), change every 3 months, maximum 12 months
  EUS guided celiac plexus block in refractory pain (small duct disease)

  [Endoscopic treatment of chronic pancreatitis, ESGE Guidelines 2012]

- **Surgical therapy**
  Pain with chronic need of analgesics
  Persistant symptomatic gastric/duodenal stenosis
  Recurrent pseudocysts after endoscopic treatment
  Distal biliary stricture after unsuccessful endoscopic treatment

  Surgical procedures:
  duodenum-preserving pancreatic head resection (Berger, Frey)
  Whipple procedure

  [S3 Leitlinie Chronische Pankreatitis 2012]

- **Pancreatic cancer**
  Incidence 1% every 5 years, 4–5% at 20 years
  No screening guidelines.
  Modify risk factors: smoking, alcohol cessation

Autoimmune Pancreatitis

- **Clinical features**
  2–4% of cases of chronic pancreatitis
  Type 1: systemic IgG4 related disease (biliary tree, salivary glands, lymph nodes, retroperitoneum, kidney)
  Type 2: pancreas alone (main pattern in Western countries) IBD in 20–30%.

- **Symptoms**
  obstructive jaundice, diabetes, pain

- **Diagnosis**
  IgG 4 (only elevated in Type 1), ANA
  CT/MRCP/EUS: diffusely enlarged pancreas («sausage-shaped pancreas»)
  MRCP: long or multiple strictures in the distal bile duct or sclerosing cholangitis improvement on a trial of steroids over 2 weeks
  Goldstandard: Histology

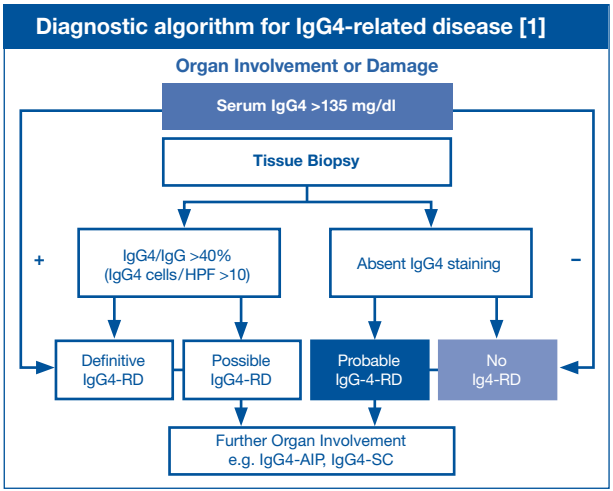
- **Management**
  Prednisolone 40–60 mg/d 4 weeks, taper 5 mg/week
  1° relapse Prednisolone, maintenance 5–10 mg
  Recurrent relapses: Azathioprine, MTX, Rituximab
  [Sah et al: Gastroenterology 2010]

If suspicious for malignancy steroid trial over 2 weeks (0.5 mg/kg Prednisolone) followed by imaging.
[Moon et al, Gut 2008]

Autoimmune pancreatitis and IgG4 related disorders

Summary:
Immunoglobulin G4-related disease (IgG4-RD) syndrome is a recently recognized entity that includes a number of already established conditions as well as novel entities which are now understood to be part of a systemic syndrome [1]. IgG4-RD is a condition characterized by an immune-mediated fibro-inflammatory process with a tendency to form tumefactive lesions in various organs, occurring in a synchronous or metachronous fashion [2,3]. The most frequent localizations include the pancreas and salivary glands. Other common manifestations are tubulointerstitial nephritis, dacryoadenitis, and periaortitis [4].

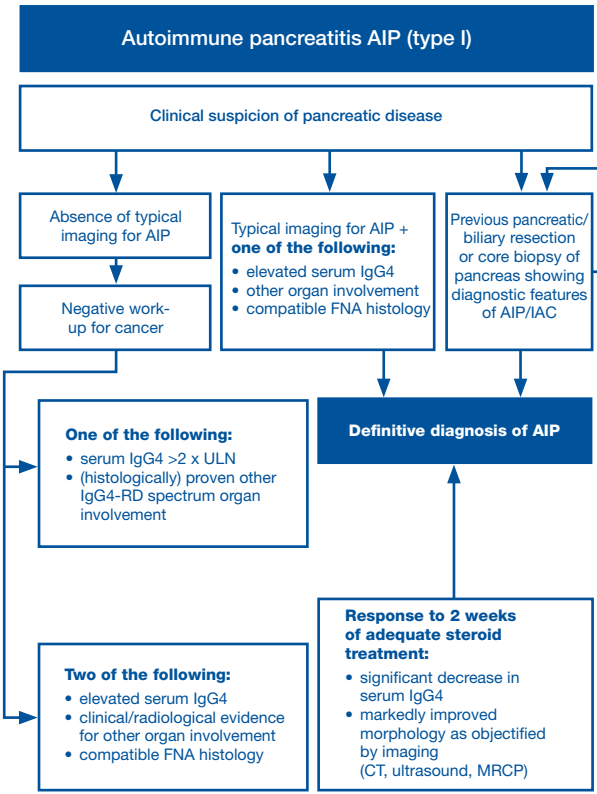
Comprehensive diagnostic criteria for IgG4-RD [5,6]	
1. Clinical examination (clinical history, physical examination, imaging)	1 + 2 = possible IgG4-RD
2. Immunological examination: IgG4 in serum >135 mg/dL or elevated IgG4/IgG ratio; optionally accompanied by other laboratory alterations like in immunoglobulin E, γ-globulin, or complement	1 + 3 = probable IgG4-RD
3. Histopathologic examination: lymphoplasmocytic infiltration with storiform fibrosis and obliterative phlebitis, infiltration by IgG4+ plasma cells (IgG4+/IgG+ >40%)	1 + 2 + 3 = definite IgG4-RD



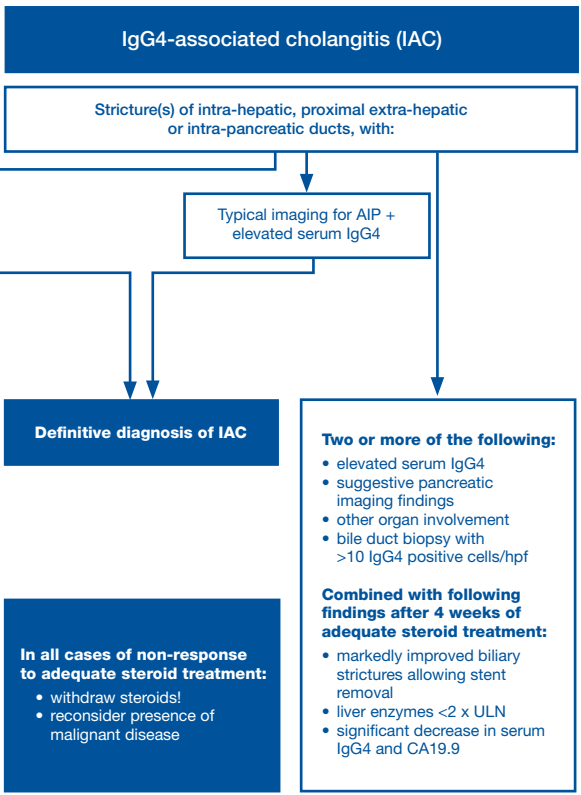
The proposed guidelines include three criteria: characteristic diffuse swelling or organ mass, increased serum IgG4 levels >135 mg/dl, and a positive histology. With all three criteria being positive, the definitive diagnosis can be made, with negative histology or histology not performed, the diagnosis is 'possible IgG4-related disease', and with histology but no serum markers, the diagnosis is 'probable IgG4-related disease'.
Treatment is carried out as at type I autoimmune pancreatitis.

[1. Beyer G, Schwaiger T, Lerch MM, Mayerle J. IgG4-related disease: a new kid on the block or an old aquaintance? United European Gastroenterol J. 2014;2(3):165-72. 2. Umehara H, Okazaki K, Masaki Y, et al. Research Program for Intractable Disease by Ministry of Health, Labor and Welfare (MHLW) Japan G4 team A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol. 2012;22(1):1–14. 3. Pieringer H, Parzer I, Wöhrer A, Reis P, Oppl B, Zwerina J. IgG4-related disease: an orphan disease with many faces. Orphanet J Rare Dis. 2014;9:110. 4. Inoue D, Yoshida K, Yoneda N, et al. IgG4-related disease: dataset of 235 consecutive patients. Medicine (Baltimore) 2015;94(15):e680. 5. Okazaki K, Umehara H. Are classification criteria for IgG4-RD now possible? The concept of IgG4-related disease and proposal of comprehensive diagnostic criteria in Japan. Int J Rheumatol.2012;2012:357071. 6. Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012;22(1):21–30.]

Autoimmune pancreatitis vs. IgG4-cholangitis



[Hubers LM, ...; Beuers U, Viszeralmedizin 2015; 31:185-8]


IgG4-associated cholangitis (IAC)
Stricture(s) of intra-hepatic, proximal extra-hepatic or intra-pancreatic ducts, with:
Typical imaging for AIP + elevated serum IgG4
Definitive diagnosis of IAC
Two or more of the following:
• elevated serum IgG4
• suggestive pancreatic imaging findings
• other organ involvement
• bile duct biopsy with >10 IgG4 positive cells/hpf
Combined with following findings after 4 weeks of adequate steroid treatment:
• markedly improved biliary strictures allowing stent removal
• liver enzymes <2 x ULN
• significant decrease in serum IgG4 and CA19.9
In all cases of non-response to adequate steroid treatment:
• withdraw steroids!
• reconsider presence of malignant disease

Esophageal Cancer (Squamous cell carcinoma = SCC)

Staging

- Endoscopy with biopsy
- Endoscopic ultrasound
- Triple contrast 3-phase CT scan neck/thorax/abdomen
- Bronchoscopy
- ENT-evaluation for exclusion for secondary cancers
- Tumor marker: SCC
- PET-CT scan
- Preoperative presentation in multidisciplinary tumor board

TNM and UICC

Primary tumour (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- T1a Tumor invades lamina propria or muscularis mucosae
- T1b Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades adventitia
- T4 Tumor invades adjacent structures
- T4a Tumor invades pleura, pericardium or diaphragm
- T4b Tumor invades other adjacent structures such as aorta, vertebral body or trachea (unresectable)

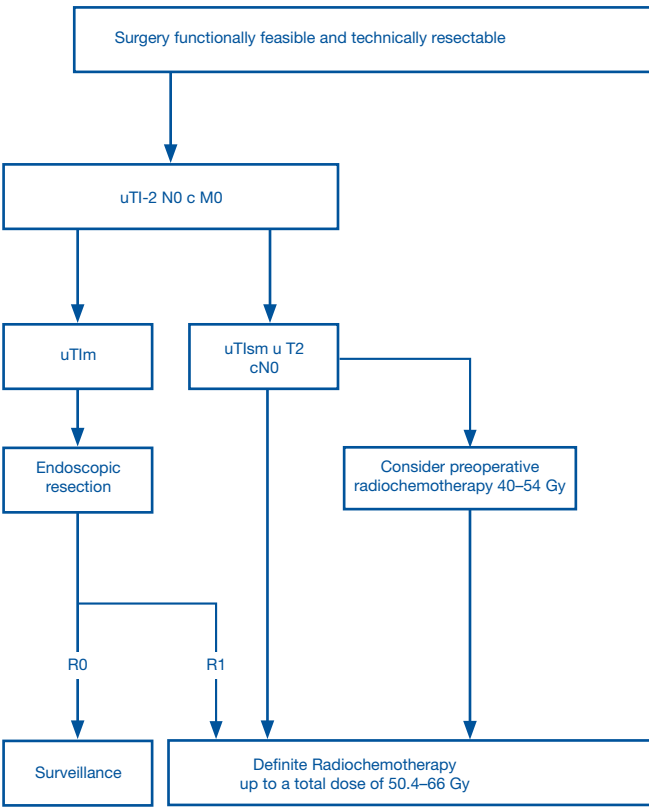
Regional lymph nodes (N)

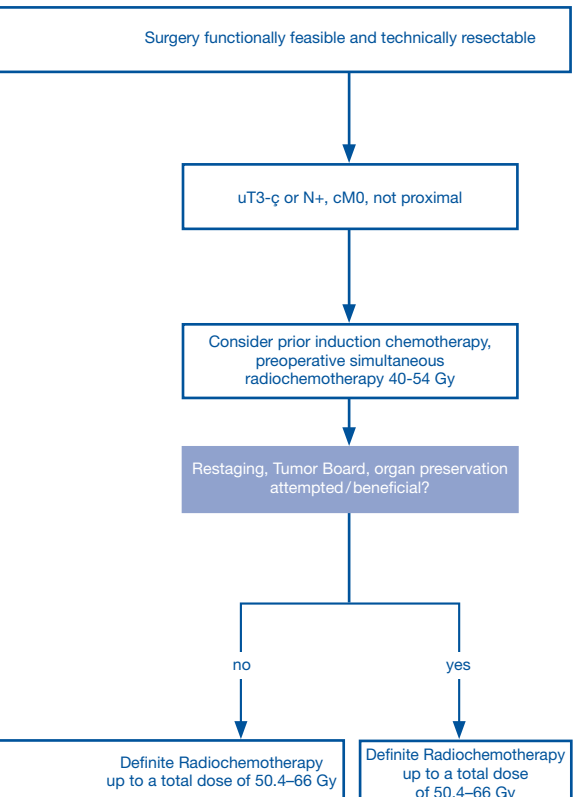
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis in 1–2 regional lymph nodes
- N2 Regional lymph node metastasis in 3–6 regional lymph nodes
- N3 Regional lymph node metastasis in 7 or more regional lymph nodes

UICC stage	TNM		
Stage 0	Tis	N0	M0
Stage I	T1	N0, N1	M0
Stage II	T2	N0, N1	M0
Stage II	T3	N0	M0
Stage III	T1, T2	N2	M0
Stage III	T3	N1, N2	M0
Stage IVA	T4a, T4b	every N	M0
Stage IVA	Any T	N3	M0
Stage IVB	Any T	Any N	M1
	T	**N**	**M**

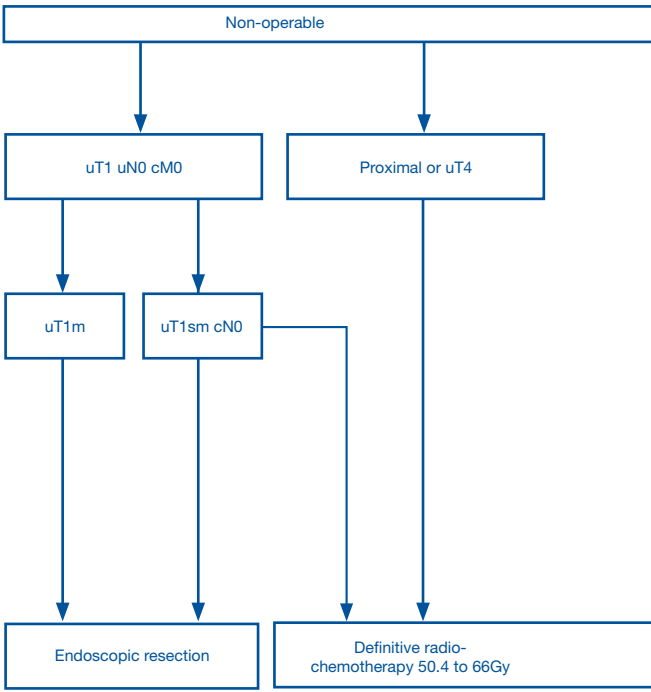
[Based on : C. Wittekind, TNM Klassifikation maligner Tumoren, 8. Auflage, 2017]

Treatment algorithm of squamous cell carcinoma (SCC)

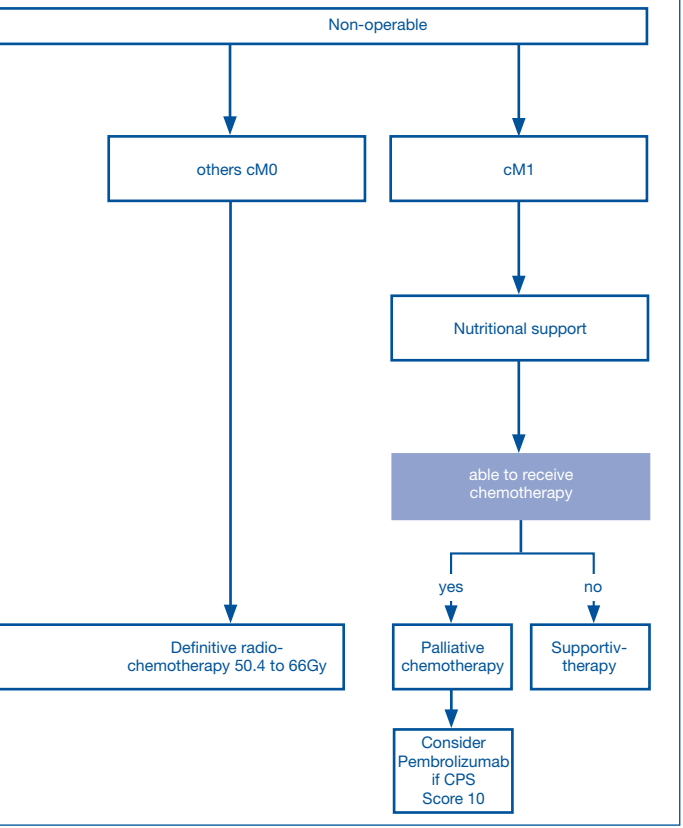



Surgery functionally feasible and technically resectable
uT3-ç or N+, cM0, not proximal
Consider prior induction chemotherapy, preoperative simultaneous radiochemotherapy 40-54 Gy
Restaging, Tumor Board, organ preservation attempted / beneficial?
no
yes
Definite Radiochemotherapy up to a total dose of 50.4–66 Gy
Definite Radiochemotherapy up to a total dose of 50.4–66 Gy

Treatment algorithm of inoperable or metastatic squamous cell carcinoma (SCC)



[Stahl M, Annals of Oncology 2013 (Suppl 6):vi51–vi56]
Therapiealgorithmen Onkologie 21.2. (last updated 04/2019)

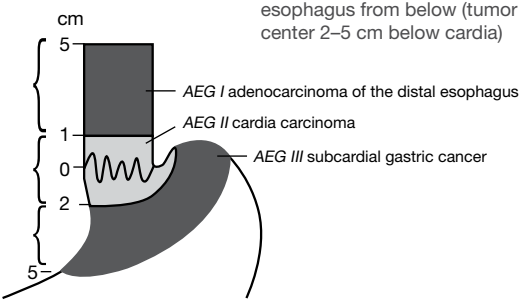

Non-operable
others cM0
cM1
Nutritional support
able to receive chemotherapy
yes
no
Definitive radio-chemotherapy 50.4 to 66Gy
Palliative chemotherapy
Supportiv-therapy
Consider Pembrolizumab if CPS Score 10

Siewert classification of adenocarcinoma of the Esophagogastric junction (AEG)

Type I:
Adenocarcinoma of the distal esophagus with tumor center more than 1 cm above the endoscopic cardia (Z-line). Generally originates from Barrett's metaplasia.

Type II:
True carcinoma of the cardia. Tumor center between 1 cm above to 2 cm below cardia. Arising from cardiac epithelium or a short segment with intestinal metaplasia.

Type III:
Subcardial gastric carcinoma infiltrating the cardia ± distal esophagus from below (tumor center 2–5 cm below cardia)



[Adapted from HJ Stein, M Feith, JR Siewert. Cancer of the esophagogastric junction. Surgical Oncology 9 2000]

AEG Cancer (Adenocarcinoma of the Esophagogastric Junction)

Anatomy and classification

The adenocarcinomas of the esophagogastric junction are classified according to the location of the main tumor in relation to the anatomical cardia according to Siewert et al. [Siewert JR et al. Chirurg 1987; 58: 25-32]

Adenocarcinoma of the distal esophagus (AEG type I) are distinguished from carcinomas arising at the level of the anatomical cardia (AEG type II) and subcardial gastric cancers (AEG type III).

Staging

- Triple contrast 3-phase CT scan neck/thorax/abdomen
- Endoscopy with biopsy
- EUS
- Abdominal ultrasound
- Tumor marker: CEA, CA 19–9
- PET-CT scan in selected cases to evaluate metastasis
- Diagnostic laparoscopy with peritoneal lavage in selected cases to exclude peritoneal carcinomatosis and before neoadjuvant treatment
- Preoperative presentation in multidisciplinary tumor board

AEG Cancer (Adenocarcinoma of the Esophagogastric Junction)

TNM and UICC

No specific TNM classification exists for AEG tumors. AEG I and II tumors are classified according to the TNM classification of esophageal cancer and AEG III tumors according to the TNM classification of gastric cancer

Esophageal cancer:

Primary tumour (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- T1a Tumor invades lamina propria or muscularis mucosae
- T1b Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades adventitia
- T4 Tumor invades adjacent structures
- T4a Tumor invades pleura, pericardium or diaphragm
- T4b Tumor invades other adjacent structures such as aorta, vertebral body or trachea (unresectable)

Regional lymph nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis in 1–2 regional lymph nodes
- N2 Regional lymph node metastasis in 3–6 regional lymph nodes
- N3 Regional lymph node metastasis in 7 or more regional lymph nodes

Distant metastases (M)

- M0 No distant metastases
- M1 Distant metastases

Stages: adenocarcinoma of the gastroesophageal junction			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N0	M0
Stage III	T1	N2	M0
Stage III	T2	N1, N2	M0
Stage III	T3, T4a	N0, N1, N2	M0
Stage IVA	T4b	N0, N1, N2	M0
Stage IVA	Any T	N3	M0
Stage IIIB	Any T	Any N	M1
	T	**N**	**M**

[TNM classification and stages modified after C. Wittelkind, TNM-classification of malign tumours, 8.edition, 2017]

AEG Cancer (Adenocarcinoma of the Esophagogastric Junction)

- N2 Regional lymph node metastasis in 3–6 regional lymph nodes
- N3 Regional lymph node metastasis in 7 or more regional lymph nodes
- N3a Metastasis in 7–15 regional lymph nodes
- N3b Metastasis in 16 or more regional lymph nodes

Distant metastases (M)

- M0 No distant metastases
- M1 Distant metastases

Gastric cancer:

Primary tumour (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- T1a Tumor invades lamina propria or muscularis mucosae
- T1b Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades subserosa
- T4 Tumor perforates serosa or invades adjacent structures
- T4a Tumor perforates serosa
- T4b Tumor invades adjacent structures

Regional lymph nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis in 1–2 regional lymph nodes

Gastric Cancer

Anatomy and classification

- Histological classification (Laurèn): Intestinal-type and diffuse-type gastric cancer.

Staging

- Triple contrast 3-phase CT scan neck/thorax/abdomen
- Endoscopy with biopsy (incl. Her-2)
- Endoscopic ultrasound
- Tumor marker: CEA, CA 19–9, CA 72–4
- PET-CT scan in selected cases to evaluate metastasis
- Diagnostic laparoscopy with peritoneal lavage in selected cases to exclude peritoneal carcinomatosis and before neoadjuvant treatment
- Preoperative presentation in multidisciplinary tumor board

TNM and UICC

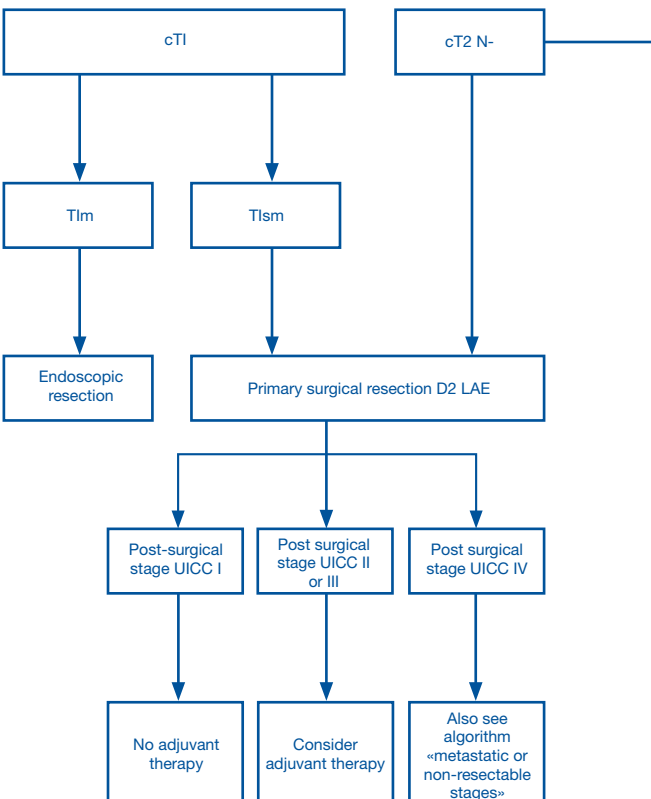
Primary tumour (T)

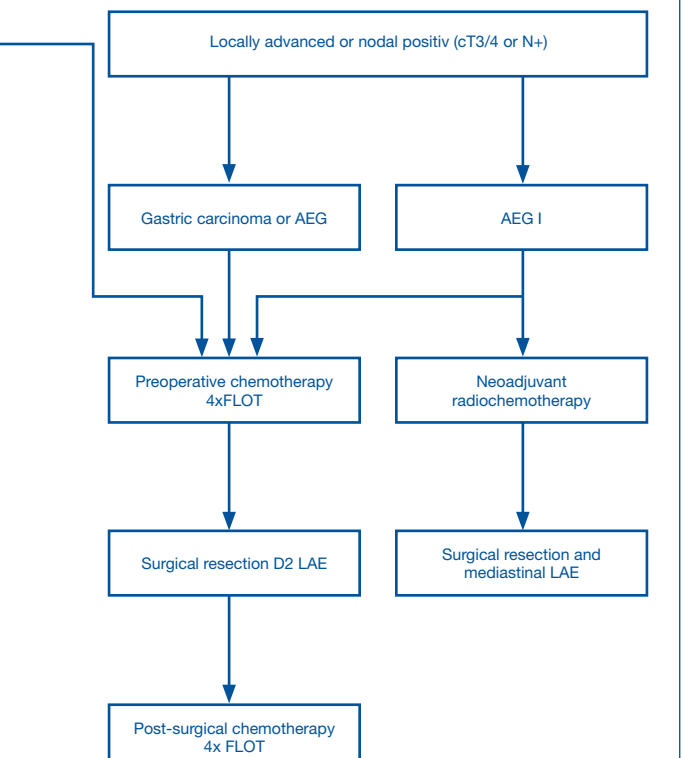
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- T1a Tumor invades lamina propria or muscularis mucosae
- T1b Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades subserosa
- T4 Tumor perforates serosa or invades adjacent structures
- T4a Tumor perforates serosa
- T4b Tumor invades adjacent structures

Regional lymph nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis in 1–2 regional lymph nodes
- N2 Regional lymph node metastasis in 3–6 regional lymph nodes

Treatment algorithm of gastric cancer and esophagogastric junction cancer




Locally advanced or nodal positiv (cT3/4 or N+)
Gastric carcinoma or AEG
AEG I
Preoperative chemotherapy 4xFLOT
Neoadjuvant radiochemotherapy
Surgical resection D2 LAE
Surgical resection and mediastinal LAE
Post-surgical chemotherapy 4x FLOT

Gastric Cancer

- N3 Regional lymph node metastasis in 7 or more regional lymph nodes
- N3a Metastasis in 7–15 regional lymph nodes
- N3b Metastasis in 16 or more regional lymph nodes

Distant metastases (M)

- M0 No distant metastases
- M1 Distant metastases

UICC stage	TNM		
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4a	N3	M0
	T4b	N2,N3	M0
Stage IV	Any T	Any N	M1
	T	**N**	**M**

Criteria for curative endoscopic resection in early gastric cancer

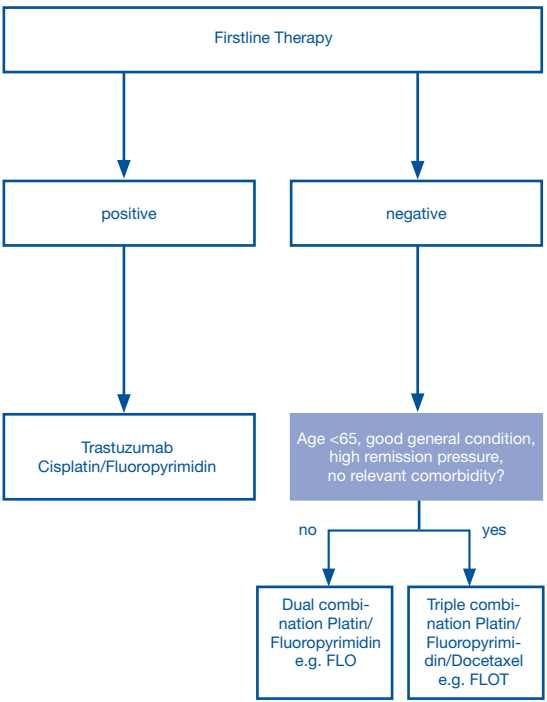
	Mucosal cancer				Submucosal cancer	
	No ulcer		Ulcer present		sm1 (<500 µm)	sm2 (>500 µm)
Size (mm)	<20	>20	<30	>30	<30	Any size
Differentiated cancer	EMR	ESD	ESD	Surgery	ESD	Surgery
Undifferentiated cancer	Surgery considered	Surgery	Surgery	Surgery	Surgery	Surgery

[EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; sm1: submucosal layer 1; sm2: submucosal layer 2]

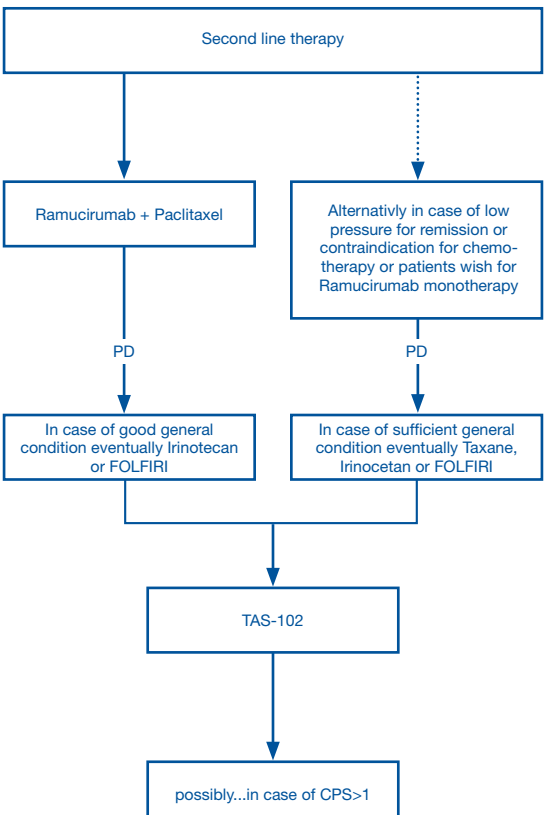
Early gastric cancers (T1a) may be amenable to endoscopic resection if they are well-differentiated, ≤2 cm, confined to the mucosa and not ulcerated.
Guidelines from the National Cancer Centre in Tokyo have expanded these criteria in patients with intestinal-type histology and no evidence of lymphovascular invasion to include: intramucosal cancers without ulceration regardless of tumor size; intra-mucosal cancers <3 cm with ulceration or cancers with early invasion into the sub-mucosa (sm1) measuring <3 cm.

Surgical therapy
In patients, which receive a preoperative chemotherapy, a baseline laparoscopy along with peritoneal washings should be considered. Surgical resection is the only curative modality for curative tumor resection and represents the gold standard for all resectable gastric cancer patients. The only exception is a gastric cancer limited to the mucosa (T1aN0M0), which was resected curatively R0 by endoscopy. Aim of tumor resection is the complete removal of the cancer (oral, aboral and circumferentially) together with the regional lymph nodes. The oral resection margin should be in intestinal type gastric cancer 5 cm and in diffuse type 8 cm. The resection of reginal lymph nodes in the compartments I and II (D2-lymphadenectomy) represents the standard in gastric cancer surgery. A minimum of 16 regional lymph nodes should be removed and examined histopathologically. Routine or prophylactic splenectomy is not required.

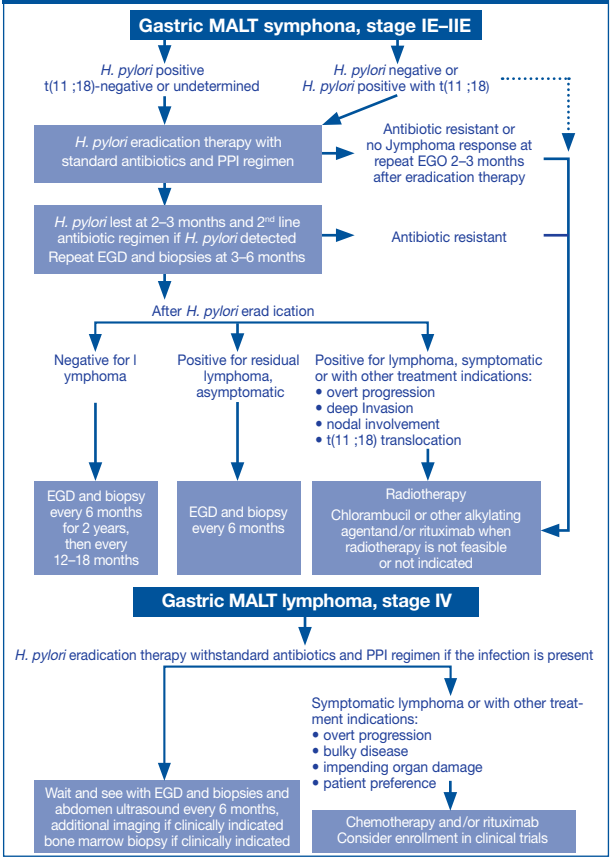
Treatment algorithm for metastatic or irresectable gastric cancer and esophagogastric junction cancer



[Al-Batran S., Lordick F., Bechstein W., Götze T. 03/2019]


Second line therapy
Ramucirumab + Paclitaxel
Alternativly in case of low pressure for remission or contraindication for chemo-therapy or patients wish for Ramucirumab monotherapy
PD
PD
In case of good general condition eventually Irinotecan or FOLFIRI
In case of sufficient general condition eventually Taxane, Irinocetan or FOLFIRI
TAS-102
possibly...in case of CPS>1

Algorithms for either localised or advanced Stages (Lugano Staging)



Colon Cancer

Staging

- Complete colonoscopy (<3 months after surgery if not possible prior)
- Tumor marker: CEA
- Triple contrast 3-phase abdominal and chest CT scan
- Abdominal sonography
- not standard, really selected cases

TNM and UICC

Primary tumor (T)

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma in situ: intraepithelial or invasion of lamina propria
- T1 Tumour invades submucosa
- T2 Tumour invades muscularis propria
- T3 Tumour invades through the muscularis propria into the pericolorectal tissues
- T4a Tumour penetrates into the surface of the visceral peritoneum
- T4b Tumour directly invades or is adherent to other organs or structures

Regional lymph nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in one to three regional lymph nodes
- N1a Metastasis in one regional lymph node
- N1b Metastasis in two to three regional lymph nodes
- N1c Tumour satellite deposits in subserous or in non peritonealised tissues
- N2 Metastases in ≥4 regional lymph nodes (a: 4–6, b: ≥7)

Distant metastases (M)

- M0 No distant metastases
- M1 Distant metastases

- M1a Metastases confined to one organ or site (for example liver, lung, ovary, non-regional node)
- M1b Metastases in more than one organ/site or the peritoneum

UICC stage	TNM			Dukes
Stage 0	Tis	N0	M0	-
Stage I T2 N0	T1 M0	N0 A	M0	A
Stage IIA	T3	N0	M0	B
Stage IIB	T4a	N0	M0	B
Stage IIC	T4b	N0	M0	B
Stage IIIA T1 N2a	T1-2 M0	N1-1c C	M0	C
Stage IIIB T2-3 T1-2	T3-4a N2a N2b	N1-1c M0 M0	M0 C C	C
Stage IIIC T3-4a T4b N1-2	T4a N2b M0	N2a M0 C	M0 C	C
Stage IVA	Any T	Any N	M1a	-
Stage IVB	Any T	Any N	M1b	-
	T	N	M	

Surgical therapy
The goal of surgical resection of primary colon cancer is complete removal of the tumor, the major vascular pedicles, and the lymphatic drainage basin of the affected colonic segment. En bloc resection of contiguous structures is indicated if there is attachment or infiltration of the tumor into a potentially resectable organ or structure. Laparoscopic-assisted colectomy may be considered if the surgeon has experience and there is no locally advanced disease. A minimum of 12 lymph nodes need to be examined for adequate lymph node staging.

Colon Cancer

Medical therapy

Stage I: No adjuvant chemotherapy

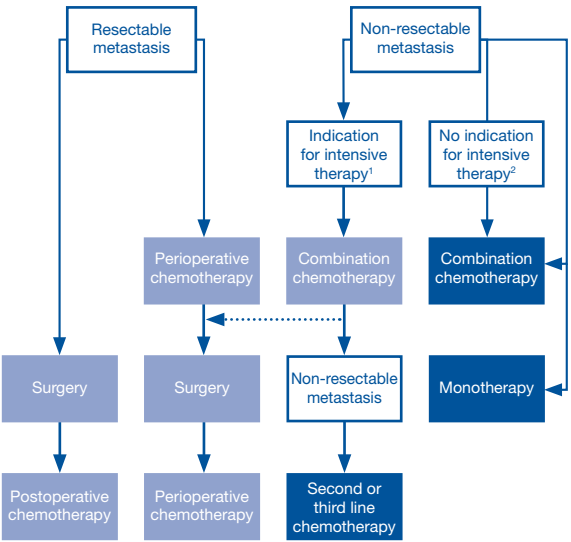
Stage II: Adjuvant chemotherapy with 5-FU possible in selected high-risk groups
- TNM stage T4, tumor perforation (also during surgery), less than 12 lymph nodes for evaluation of N-classification, undifferentiated tumor (G3), infiltration of vessels (V+) or lymphatic tissue (L+).

Stage III: Adjuvant chemotherapy reduces 5-year mortality
- FOLFOX (5-FU, Leukovorin, Oxaliplatin) or XELOX (Capecitabine = oral 5-FU, Oxaliplatin over 3–6 months). If Oxaliplatin is contraindicated, monotherapy with 5-FU/Capecitabine or if age >70 years.

Stage IV: Curative therapeutic concepts are possible in 20% of patients with synchronous liver metastasis.
- Combination therapy: FOLFOX (5-FU, Leukovorin, Oxaliplatin), XELOX (Capecitabine, Oxaliplatin) or FOLFIRI (5-FU, Leukovorin, Irinotecan) or FOLFOXIRI (5-FU, Leukovorin, Irinotecan, Oxaliplatin) +/- Bevacizumab or +/- Cetuximab (in kras/nras wild type) or +/- Panitumumab (in kras/nras wild type)
- Monotherapy: 5-FU/Leukovorin or Capecitabine +/- Bevacizumab or Cetuximab (in kras/nras wild type) or Panitumumab (in kras/nras wild type)

Capecitabine, Irinotecan, Oxaloplatin, Bevacuzumab, Cetuximab, Panitumumab

Stage IV



[1] potentially resectable liver-/lung metastasis after neoadjuvant therapy, tumor-related symptoms/complications, rapid progressive disease.

[2] multiple metastases without curative treatment options after neoadjuvant therapy, no tumor-related, comorbid patient

Consensus recommendations for surveillance after curative resection of early colorectal carcinoma
Version 02.10.2014

Requirements
- A complete colonoscopy is required preoperatively or as soon as possible after surgery (preferably within 3 months).
- Conditions with increased risk for carcinoma, such as hereditary syndroms (HNPCC, FAP, attenuated FAP, MUTYH-associated polyposis, Peutz-Jeghers, juvenile polyposis syndrome, serrated polyposis syndrome, etc.) or other situations associated with an elevated risk for colorectal carcinoma (chronic inflammatory bowel disease, acromegaly) are not covered in this schedule and need specific surveillance procedures.

Colon carcinoma	Months after surgery						
T3 / 4 or N+, M0	6	12	18	24	36	48	60
Clinical examination CEA[1]	Every 3 months during 1st year		Every 6 months during 2nd and 3rd year			+	+
Colonoscopy		+				+[7]	
CT - thorax and abdomen[2]		+		+	+	+	+

Colon carcinoma	Months after surgery						
T1 / T2 N0	6	12	18	24	36	48	60
CEA[3]		+		+		+	+
Colonoscopy		+				+[7]	

Rectal carcinoma	Months after surgery						
T1 – 4, N+/-, M0[4]	6	12	18	24	36	48	60
Clinical examination[5] CEA[3]	Every 3 months during 1st year		Every 6 months during 2nd and 3rd year			+	+
Colonoscopy		+				+[7]	
Lower flexible endoscopy	+		+	+			
Endosonography[3,6] or pelvic MRI[3,6]	+	+	+	+			
CT - thorax, abdomen and pelvis[2,3,6]		+		+	+	+	+

1 Preoperative CEA testing is routinely recommended. In case of CEA rise during postoperative monitoring, imaging investigations should be performed liberally.
2 At least dual-contrast-multidetector-computertomography (oral-intravenous contrast media) is standard. After multimodal treatment of colorectal carcinoma, follow-up may be performed for more than 5 years. However, longer duration of follow-up should be determined individually.
3 Not indicated for T1N0 carcinoma after radical resection (TME).
4 Exception: pT1 invasive carcinoma in a polyp risk category III (compare SGGSSG consensus recommendations 2014 for follow-up of colorectal polyps after endoscopic resection).
5 Rectal palpation is recommended at regular intervals in case of low colorectal anastomosis.
6 Fine needle biopsy in case of suspicious finding.
7 Subsequently perform colonoscopy every 5 years.

The Revised Bethesda Guidelines

MSI should be tested

A. in an individual diagnosed with colorectal cancer under age 50 years
B. in case that synchronous, metachronous colorectal, or other HNPCC-associated tumors* are present in the patient. This is regardless of the age of the affected individual
C. in an individual that suffers from colorectal cancer with MSI-H† like histology‡. This refers to individuals who are diagnosed under age 60 years
D. in an individual with colorectal cancer who has one or more 1st degree relatives suffering from colorectal cancer and an HNPCC-related tumor. One of those 1st degree relatives needs to be diagnosed with any one of those cancers under age 50 years
E. in an individual diagnosed with colorectal cancer who has two or more 1st or 2nd degree relatives with colorectal cancer and HNPCC-related tumors*. Under those circumstances the age of cancer diagnosis in the relatives does not matter

* *Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome), sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel (according to Lin et al. J Gastrointest Surg 1998;2:67–71).*

† *MSI-H: microsatellite instability–high in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.*

‡ *Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.*

[Umar et al. J Natl Cancer Inst (2004) 96 (4): 261-268, Page 189.]

[Since IHC for MSI became standard at many institutions testing is done the longer the more for all patients regardless of the Bethesda criterias.]

Rectal Cancer

Staging

- Digital-rectal examination
- Rigid rectoscopy and biopsy
- Complete colonoscopy
  (<3 months after surgery if not possible prior)
- EUS
- Triple contrast 3-phase chest, abdominal and pelvis CT scan
- Diffusion MRI
- MRI pelvis
- Abdominal sonography
- Tumor marker: CEA, CA 19–9
- PET-CT scan only in selected cases to evaluate metastasis
- Anal manometry, cystoscopy or gynecological evaluation in selected cases

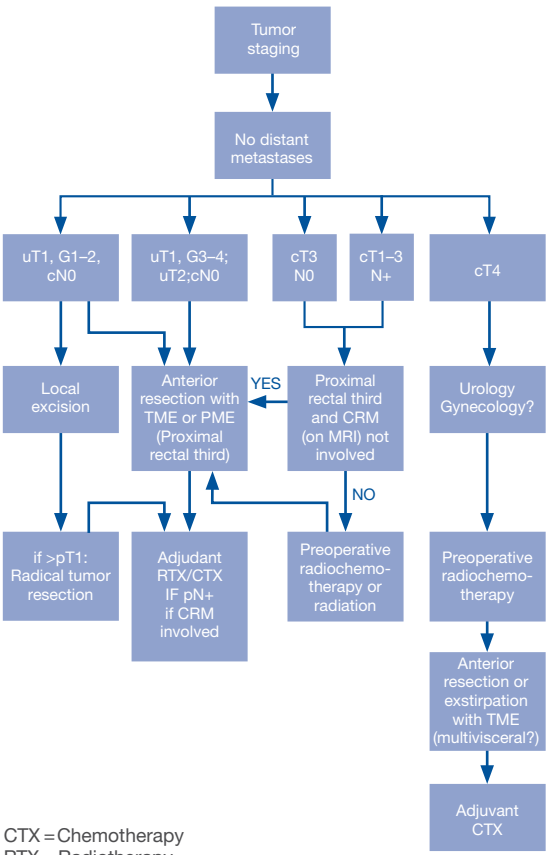
TNM and UICC

TNM-classification of the UICC (8th edition from 2017).
See chapter colon cancer.

Therapy

The goal of surgical resection of primary rectal cancer follows the principles described in the colon cancer chapter. Additional aims are the preservation of the anal sphincter if possible and the preservation of the autonomous nerves for urinary, sexual and anal function. The risk of local recurrence is significantly increased compared to colon cancer surgery. Therefore, the completeness of total or partial mesorectal excision (TME or PME) technique is essential in rectal cancer surgery.

Therapeutic algorithm of rectal cancer



CTX = Chemotherapy
RTX = Radiotherapy

In patients with liver metastases:

Rectal cancer with resectable liver or lung metastases:
Anterior resection with TME or abdomino-perineal exstirpation with TME, combined with one-stage or two-stage liver resection, in dependence to the rectal cancer shortterm radiation (5 x 5 Gy) or long-term radio-chemotherapy, e.g. intensified with oxaliplatin. Indisziplinary tumorboard discussion is very important for these cases. In principle: Systemic chemotherapy followed by resection of primary (with or without RT) and all metastases followed by systemic chemotherapy

Rectal cancer with unresectable liver or lung metastases:
Anterior resection with TME or abdominoperineal exstirpation followed by systemic chemotherapy or systemic chemotherapy alone

Neuroendocrine Tumor in Rectum

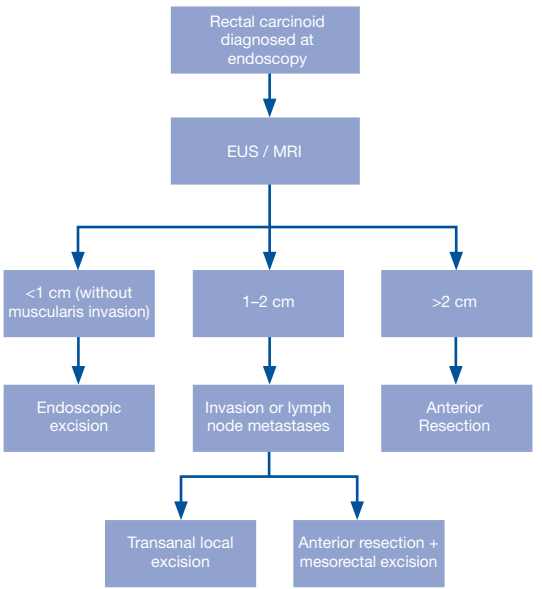
- Incidence Colon 0.2/100'000/year
- Incidence Rectum 0.86/100'000/year;
  - 27% of all neuroendocrine Tumor in GI-Tract
- Mainly incidental finding
- Following procedure can be recommended

Correlation Between Maximum Size of the Tumor and the Depth of Invasion, Frequencies of Vascular Invasion and Metastasis

Size (mm)	Depth		Vascular invasion		Metastasis	
	sm	mp			Lymph Node	Liver
~10 [57]	57	0	10	(18)	0[a]	0
11~ [9]	4	5	6	(67)	4[a]	1

sm = submucosa; mp = muscularis propria.
Data are numbers with percentages in parentheses and number of lesions in brackets unless otherwise indicated.
[a]Lymph node metastasis was examined for the lesions that were treated by colectomy with lymphadenectomy.

Treatment of rectal carcinoids



[Anthony, Pancreas. 2010 Aug;39(6):767-74
Kobayashi, Dis Colon Rectum. 2005 Feb;48(2):285-91
Mani, J Am Coll Surg. 1994;179(2):231Y248
Naunheim, Surgery. 1983;94(4):670Y676]

Primary tumor (T)

T1	Tumor diameter ≤2 cm
T2	Tumor diameter ≥2 cm-≤5 cm
T3	Tumor diameter ≥5 cm
T4	Tumor invades adjacent structures

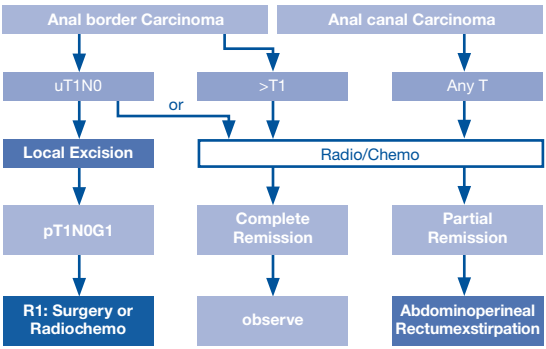
Lymph node (N)

N0	No Lymph Nodes
N1	Perirectal Lymph Nodes
N2	Parailiac and/or inguinal unilateral
N3	Parailiac and inguinal and/or parailiac/inguinal bilateral

Anal cancer – Follow-up

Intervall (months)	Local examination (anal, inguinal)	Endoscopy (flexible RS)	EUS
3	+		
6	+	+	+
9	+		
12	+	+	+
18	+	+	+
24	+	+	+
30	+	+	+
36	+	+	+
48	+	+	+
60	+	+	+

Treatment of anal cancer



Hepatocellular cancer (HCC)

Diagnosis

- Non-invasive criteria can only be applied to cirrhotic patients. One imaging technique is required for nodules beyond 1 cm in diameter, a more conservative approach with 2 techniques is recommended in suboptimal settings.
- 4-phase multidetector CT scan or dynamic contrast-enhanced MRI (hallmark = hypervascular in the arterial phase with washout in the portal venous or delayed phases).
- Constrast-enhanced ultrasound (CEUS) and angiography in selected cases.
- PET-scan is not accurate for early diagnosis.
- Liver biopsy in selected cases.

TNM and UICC

The BCLC staging system is recommended for prognostic prediction and treatment allocation.

TNM classification:

Primary tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Solitary tumor without vascular invasion
- T2 Solitary tumor with vascular invasion or multiple tumors <5 cm
- T3a Multiple tumors any more than 5 cm
- T3b Tumor involving a major branch of the portal or hepatic veins
- T4 Tumor invades adjacent organs other than gallbladder or with perforation of visceral peritoneum

Regional lymph nodes (N)

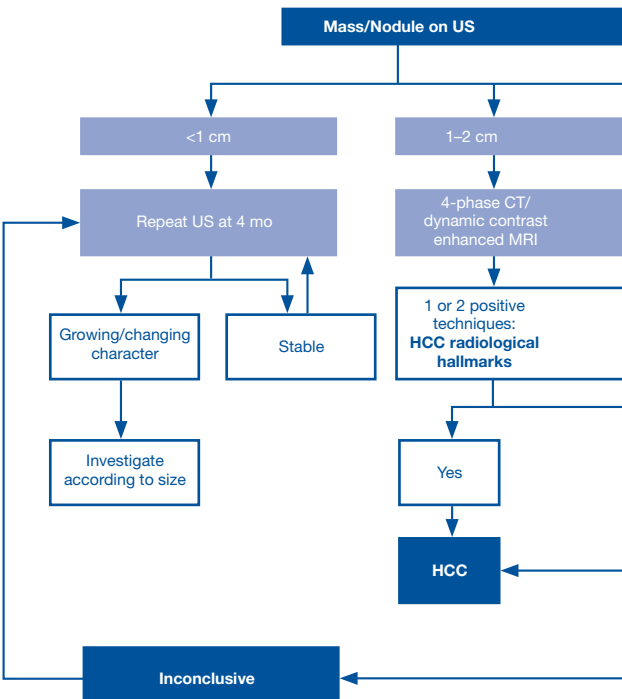
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

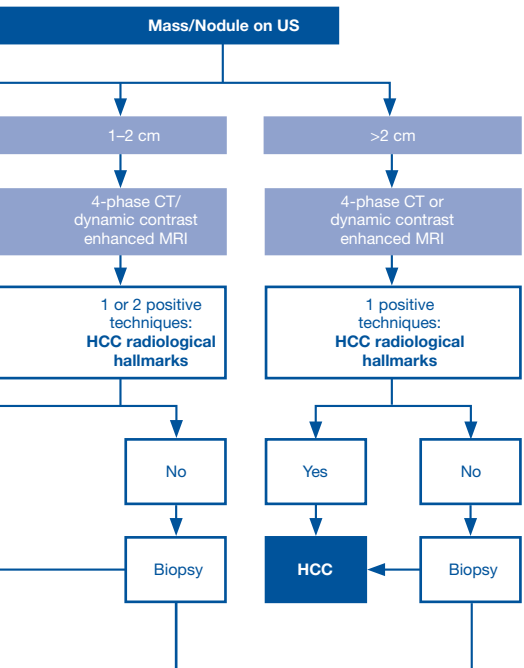
Distant metastases (M)

- M0 No distant metastases
- M1 Distant metastases

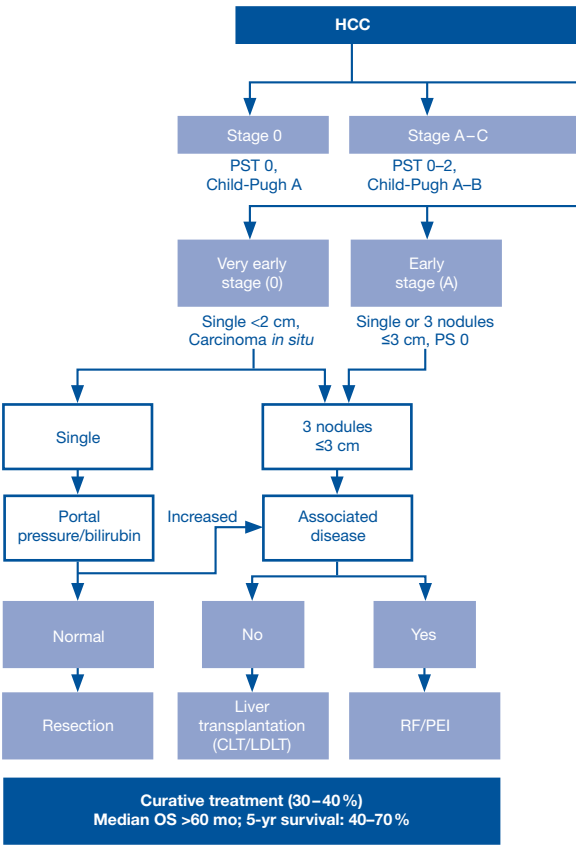
UICC stage	TNM		
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1
	T	**N**	**M**

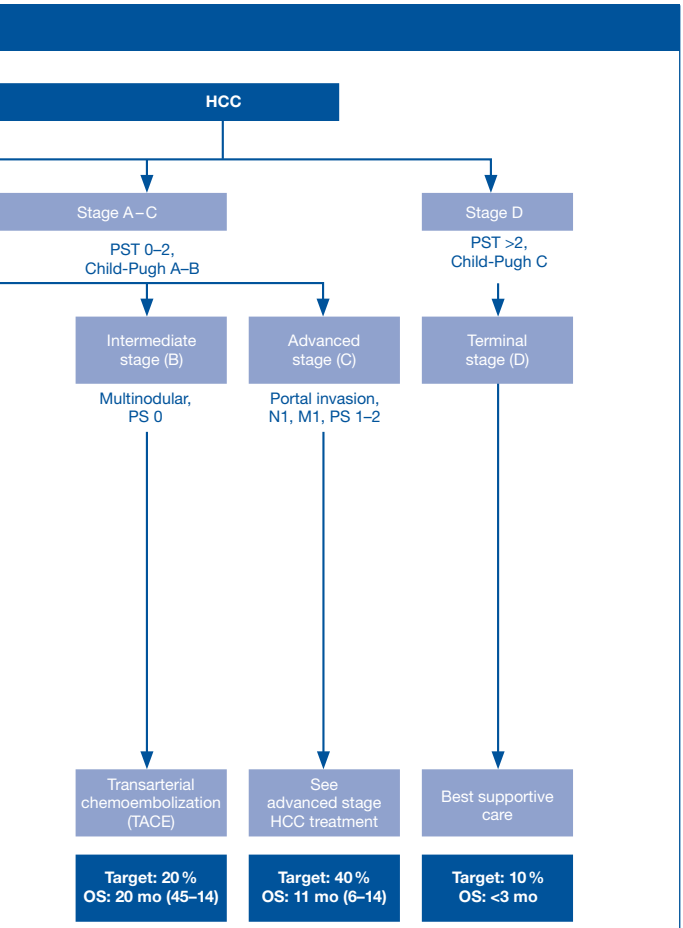
Diagnostic algorithm of liver mass / nodule on US



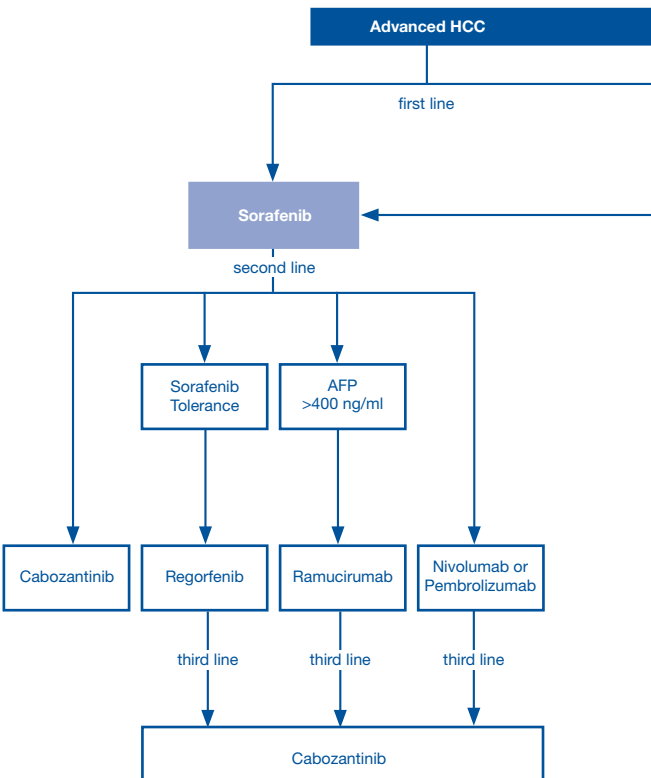

Mass/Nodule on US
1–2 cm
>2 cm
4-phase CT/ dynamic contrast enhanced MRI
4-phase CT or dynamic contrast enhanced MRI
1 or 2 positive techniques: HCC radiological hallmarks
1 positive techniques: HCC radiological hallmarks
No
Yes
No
Biopsy
HCC
Biopsy

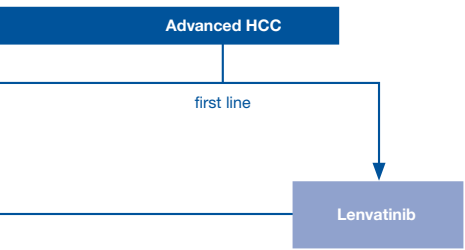
Treatment algorithm of hepatocellular cancer (HCC)




HCC
Stage A–C
PST 0–2,
Child-Pugh A–B
Stage D
PST >2,
Child-Pugh C
Intermediate stage (B)
Advanced stage (C)
Terminal stage (D)
Multinodular, PS 0
Portal invasion, N1, M1, PS 1–2
Transarterial chemoembolization (TACE)
See advanced stage HCC treatment
Best supportive care
Target: 20 %
OS: 20 mo (45–14)
Target: 40 %
OS: 11 mo (6–14)
Target: 10 %
OS: <3 mo

Treatment algorithm for advanced stage hepatocellular cancer (HCC)




Advanced HCC
first line
Lenvatinib

Pancreatic Cancer

Staging

- Tumor staging includes the evaluation of the local tumor (resectability status: resectable, borderline resectable, unresectable) and the presence of distant metastases
- Abdomen sonography
- Triple contrast 3-phase CT scan thorax/abdomen
- Tumor marker: CEA, CA 19–9
- EUS in selected cases to evaluate local tumor progression
- Fine needle aspiration in selected cases (not required before surgical resection)
- MRI liver and/or pancreas in selected cases to evaluate liver metastasis / local tumor progression
- Laparoscopy in selected cases to evaluate for peritoneal carcinomatosis
- PET-CT scan in selected cases to evaluate metastasis
- Preoperative presentation in multidisciplinary tumor board

TNM and UICC

Primary tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- T1 Tumor includes invasion of the peripancreatic soft tissue, ≤2 cm
- T2 Tumor includes invasion of the peripancreatic soft tissue, >2 cm but <4 cm
- T3 Tumor includes invasion of the peripancreatic soft tissue >4 cm
- T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional lymph nodes (N)

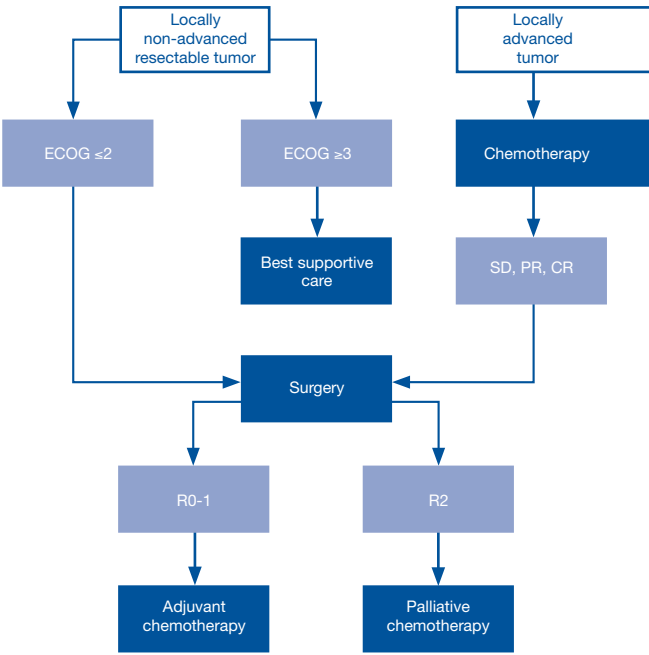
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in one to three regional lymph nodes
- N1a Metastasis in one regional lymph node
- N1b Metastasis in two to three regional lymph nodes

- N1c Tumor satellite deposits in subserous or in non peritonealised tissues
- N2 Metastases in ≥4 regional lymph nodes (a: 4–6, b: ≥7)

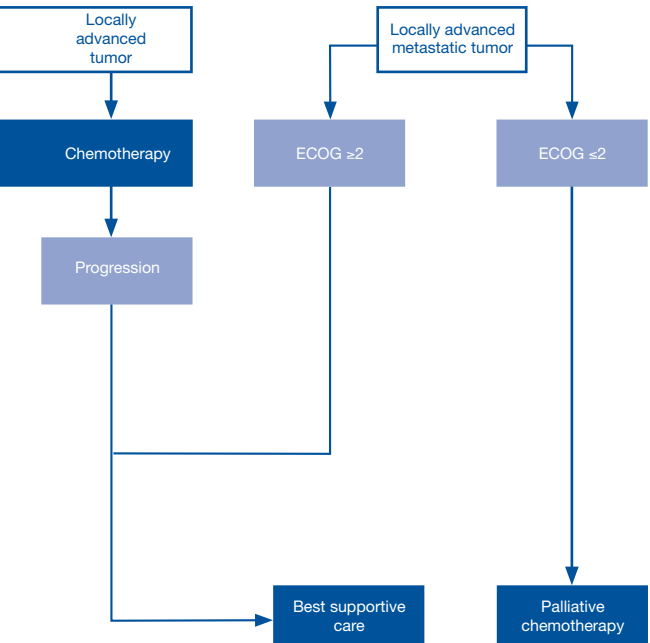
Distant metastases (M)
- M0 No distant metastases
- M1 Distant metastases

UICC stage	TNM		
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4 Any	N	M0
Stage IV	Any T	Any N	M1
	T	**N**	**M**

Treatment algorithm of pancreatic cancer

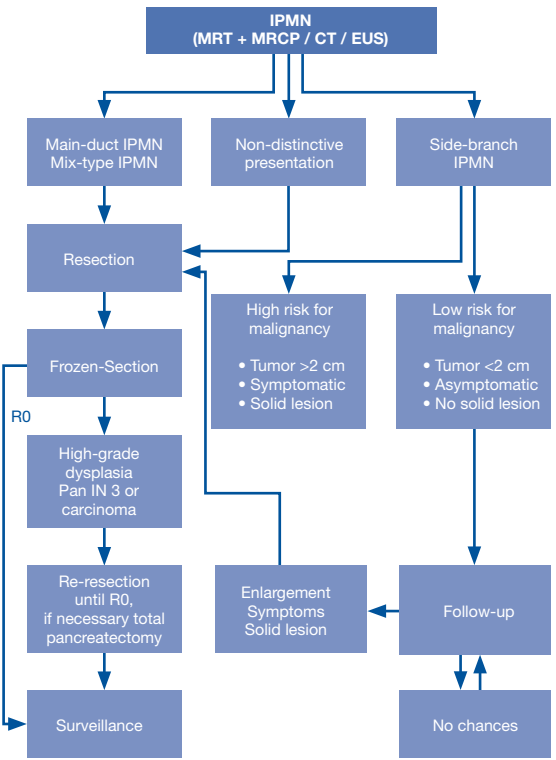


Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work



2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Intraductal papillary mucinous neoplasm (IPMN)



Surgical therapy of pancreatic cancer

Definition of borderline resectable tumors according to the NCCN guidelines:

- No distant metastases
- Solid tumor contact with the SMV or portal vein >180°, contact with the SMV or portal vein with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction
- Solid tumor contact with the inferior vena cava
- Pancreatic head / uncinated process: Solid tumor contact with the SMA <180° or solid tumor contact with common hepatic artery without extension to celiac axis or hepatic artery bifurcation
- Pancreatic body / tail: solid tumor contact with the celiac axis of <180°

Principles of surgical technique:

A preoperative stenting of the bile duct should be only performed if cholangitis is present.

The goal of surgical exstirpation of pancreatic carcinoma is to achieve an R0-resection. The biology of the cancer might not allow for an R0 resection even with the most meticulous surgery. The resection of the pancreatic head can be performed with or without preservation of the pylorus.
A total pancreatectomy should be avoided. A left pancreatomy with splenectomy is the procedure of choice in pancreatic tail or body cancer. The extent of lymphadenectomy should include a minimum number of 10 lymph nodes.

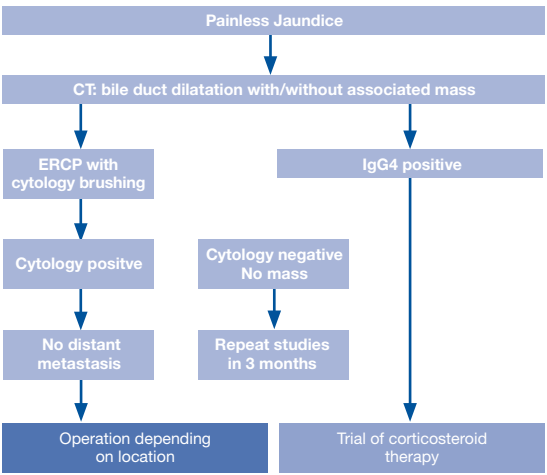
Medical therapy of pancreatic cancer

Adjuvant therapy:
- Incusion in clinical trials preferred.
- Capecitabine/Gemcitabine or mFOLFIRINOX +/- radiotherapy

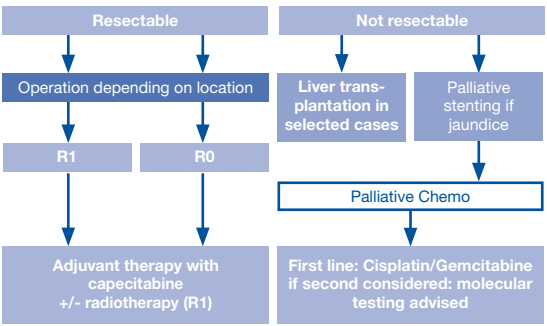
Palliative therapy (first line)
- Inclusion in clinical trials preferred
- Gemcitabine/Nab-Paclitaxel or mFOLFIRINOX or Gemcitabine

Palliative therapy (second line)
- Inclusion in clincial trials preferred
- Nal-Irinotecan/5-Fu
- Regarding further therapy molecular testing advised

Diagnosis of cholangiocarcinoma



Treatment of cholangiocarcinoma

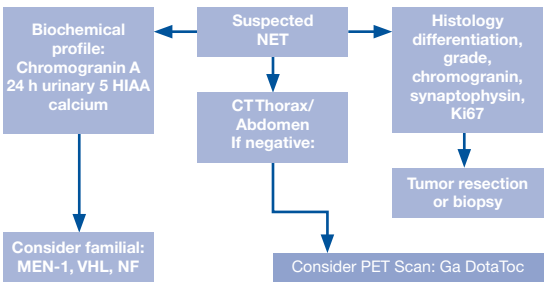


Treatment of gallbladder carcinoma

- T1a: Cholecystectomy (five-year survival rate >99%)
- T1b: Cholecystectomy (five-year survival rate 40–70%)
  ± segmental resection
  IVb and V, N1 LK- resection
  Laparoscopy is in high risk situation (G3, T3/4, R1) advised
- T2: Cholecystectomy+ segmental resection IVb und V, N1 LK- resection (five-year survival rate 50–100%)
- T3+: Surgery only if R0 possible
  Hepatectomy + pancreaticoduodenectomy
  (five-year survival rate 0–30%)

Overall five-year survival rate approx. 60%.
TNM-Stage >T1bN0: adjuvant combined radiation and chemotherapy has a survival benefit.

Diagnosis of neuroendocrine tumors (NET)



Histological classification of NET

nomenclature	mitosis (10 HPF)	Ki-67/MIB-1 index (%)
NET Grade 1 (G1-NET) = carcinoid	<2	≤2
NET Grade 2 (G2-NET)	2–20	3–20
NEC (G3-NET), large-/small cell	>20	>20

Risk factors for recurrence of GIST

Tumor parameter		Risk for progressive disease % based on site of origin			
Mitotic rate Per 50 HPF	Size	Stomach	Jejunum/ Ileum	Duodenum	Rectum
≤5	≤2	None (0%)	None (0%)	None (0%)	None (0%)
	>2–<5	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
	>5–≤10	Low	Moderate	Not known	Not known
	>10	Moderate	High (52%)	High (34%)	High (54%)
>5	≤2	None	High	Not known	High
	>2–<5	Moderate	High	High	High
	>5–≤10	High	High	Not known	Not known
	>10	High	High	High	High

[Miettinen, Semin Diagn Pathol 2006]

WHO classification of gastroenteropancreatic endocrine tumors

Site	Well differentiated endocrine tumor (benign behavior)	Well differentiated endocrine tumor (Uncertain behavior)
Pancreas	Confined to pancreas <2 cm <2 mitoses per 10 HPF <2% Ki-67 positive cells, no vascular invasion	Confined to pancreas <2 cm >2 mitoses per 10 HPF >2% Ki-67 positive cells or vascular invasion
Stomach	Confined to mucosa-submucosa <1 cm, no vascular invasion	Confined to mucosa-submucosa >1 cm or vascular invasion
Duodenum, upper jejunum	Confined to mucosa-submucosa <1 cm, no vascular invasion	Confined to mucosa-submucosa >1 cm or vascular invasion
Ileum, Colon, Rectum	Confined to mucosa-submucosa <1 cm (small intestine)	Confined to mucosa-submucosa >1 cm (small intestine)
Appendix	Non-functioning Confined to appendiceal wall <2 cm, no vascular invasion	Enteroglucagon-producing Confined to subserosa >2 cm or vascular invasion

Well differentiated endocrine carcinoma (Low grade malignant)	Poorly differentiated endocrine carcinoma (High grade malignant)
Well to moderately differentiated Gross local invasion and/or metastases Mitotic rate often higher (2-10 per 10 HPF) Ki-67 index >5%	Small cell carcinoma Necrosis common >10 mitoses per 10 HPF >15% Ki-67 positive cells Prominent vascular and/or perineural invasion
Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
Well to moderately differentiated Invasion to mesoappendix or beyond or metastases	Small cell carcinoma

Stadium systems of primary intestinal Lymphoma			
Ann-Arbor-System	**Lugano-System**	**TNM-Classification**	**Lymphoma Location**
E* I 1	I 1	T1N0M0	Mucosa, Submucosa
E I 2	I 2	T2N0M0	Muscularis propria, Subserosa
E I 2	I 2	T3N0M0	Serosa penetration
E I 2	II E**	T4N0M0	Continuous infiltration of adjectant organs or tissue
E II 1	II 1 E	T1-4N1M0	Infiltration regional Lymph nodes
E II 2	II 2 E	T1-4N2M0	Infiltration other than regional Lymph nodes including mesenteric, paraortal or retroperitoneal
III	-	T1-4N3M0	Infiltration of Lymph nodes on both sides of the diaphragma
IV	IV	T1-4N0-3M1	Generalisation of the Lymphoma

** E= primary extranodal localisation*
*** E= continuous, through the stomach infiltration in other tissue*

Malnutrition

- Standardized Screening Tools to recognize a risk for energy- and protein malnutrition: NRS, MNA, SGA, MUST

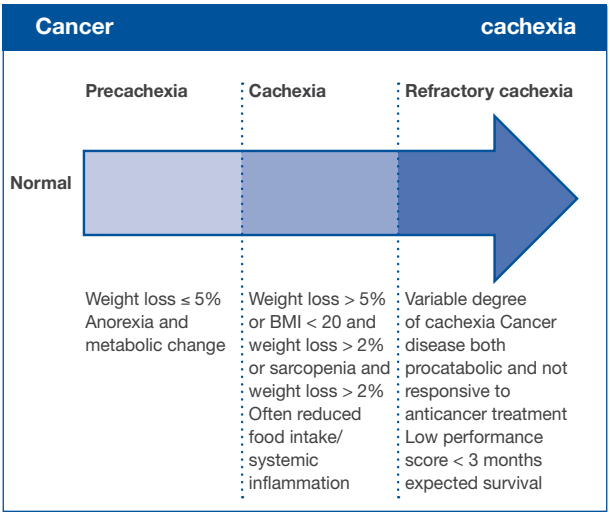
Nutritional Risk Screening (NRS)	
Score	**Impaired nutritional status**
Absent Score 0	Normal nutritional status
Mild Score 1	Weight loss >5% in 3 months or food intake below 50–75% of normal requirement in preceding week
Moderate Score 2	Weight loss >5% in 2 months or BMI 18.5–20.5 kg/m2 and impaired general condition or food intake 25–60% of normal requirement in preceding week
Severe Score 3	Weight loss >5% in 1 month (>15% in 3 months) or BMI <18.5 and impaired general condition or food intake 0–25% or normal requirement in preceding week.
Score	**+**
Age:	If ≥70 years add 1 to total score above
Score ≥3:	the patient is nutritionally at-risk and a nutritional care plan is initiated
Score <3:	weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status

[4]

- CAVE: parameters are not always reliable (p.e. weight, BMI), influencing determinants are: hydration and edema

- The encoding of a malnutrition has a cost relevance for hospitals in the Swiss DRG System[10]

Score	Severity of disease (increase in requirements)
Absent Score 0	Normal nutritional requirements
Mild Score 1	Hip fracture, chronic patients with acute complications: cirrhosis, COPD, chronic hemodialysis, diabetes, oncology
Moderate Score 2	Major abdominal surgery, Stroke, severe pneumonia, hematologic malignancy
Severe Score 3	Head injury, bone marrow transplantation, intensive care patients (APACHE>10)
Score	**=Total score**
	= age-adjusted total score



Macronutrients

Energy

- Gold standard to measure the REE (Resting Energy Expenditure): indirect calorimetry
- Equation to calculate the REE, p.e.
  Harris-Benedict-Formula
  (w=weight in kg, s=stature in cm, a=age in years):
  Women: REE kcal/ d = 447.6 + 3.1*s + 9.2*w – 4.3*a
  Men: REE kcal/ d = 88.4 + 4.8*s + 13.4*w – 5.7*a[9]
- The REE must be multiplied with a physical activity factor (PAL), p.e.: Lying or sitting patient: 1.2, mobilized patient (hospital): 1.4
- Additional requirement: operations, trauma, burns, sepsis, infection[6]
- CAVE: when BMI is < 18.5 kg/m^2 or > 24.9 kg/m^2, energy requirement must be adapted

Protein
- Requirement: 0.8–1 g per kg bodyweight[1]
- Individual adaption based on different factors, p.e. age, disease, metabolism, nutritional state or therapy goal is needed

Carbohydrates and Fats
- Adaption based on disease and metabolism is needed
- Requirement for fibre intake: 30 g per day[1], adaption based on individual needs

Fluid
- Requirement for daily liquid intake (fluid in drinks and foods): 30–40 ml per kg bodyweight in 24 hours[1]
- State of hydration need to be taken into account for interpretation of blood analysis
- CAVE: Increased loss of fluid because of diarrhea, emesis, transpiration[1], ileostoma[8] need to be compensated

Micronutrients

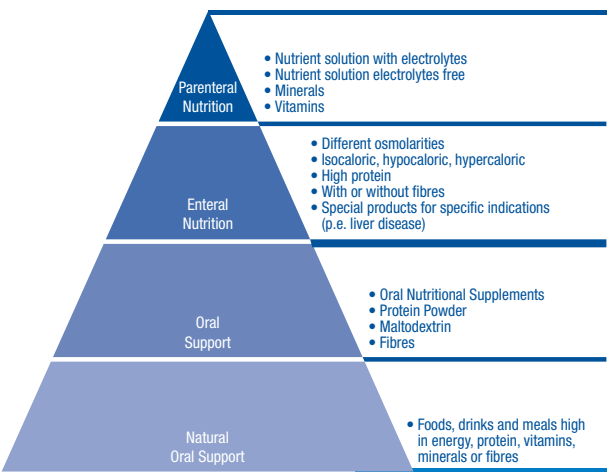
Vitamins and Minerals
- If energy intake is less than 1200 kcal substitution has to be considered
- Disease specific losses need to be compensated, p.e. with substitution
- CAVE: Increased loss of electrolytes because of: diarrhea, emesis, transpiration[1], ileostoma[8] need to be compensated

Individual nutrition support

Change of paradigm:

- No standard organ diets, p.e. for liver cirrhosis, pancreatitis, IBD etc.[7]
- Nutritional therapy based on individual requirements to prevent malnutrition: medical prescription for support by registered dietitians
- Individual blood analysis to adapt nutrition therapy
- Fast-track surgery for better postoperative recovery and reduced morbidity[3], p.e. ERAS (Enhanced Recovery after Surgery) concept for visceral surgeries

Steps of a nutrition therapy



- Guidelines: ESPEN guidelines in enteral nutrition[5], ESPEN guidelines in parenteral nutrition[12]

Refeeding-Syndrome

- May occur when refeeding malnourished individuals Groups of malnourished patients at particular risk of developing the refeeding syndrome:
- Unintentional weight loss
  - Loss of 5 % of body weight in 1 month
  - Loss of >7.5 % of body weight in 3 months
  - Loss of >10 % of body weight in 6 months
- Low nutrient intake, p.e.:
  - Prolonged hypocaloric feeding or fasting
  - Chronic swallowing problems and other neurological disorders
  - Chronic alcoholism
  - Patients with cancer
  - During convalescence from catabolic illness
  - Postoperative patients
  - Etc.
- Increased nutrient losses/decreased nutrient absorption, p.e.:
  - Significant vomiting and/or diarrhea
  - Dysfunction or inflammation of the gastrointestinal tract
  - After bariatric surgery
  - Etc.

Diagnostic parameters:
- Thiamine deficiency
- Hypophosphataemia
- Hypomagnesaemia
- Hypokalaemia
- Salt and water retention – edema

Treatment:

- Energy intake (oral, enteral or parenteral): carefully and gradually increasing over 4–10 days
- Electrolytes: measurement of serum concentrations basally and daily during feeding. Supplementation depending on patient size and plasma concentrations, p.e. 0.5–0.8 mmol phosphate per kg body weight per day when serum phosphate < 0.6 mmol/l
- Fluid: restrict to maintain renal function, replace deficits or losses, avoid weight gain, achieve a zero balance
- Vitamins: 200 % of Daily Recommended Intake (DRI) and 200–300 mg thiamine i.v. at least 30 min before feeding, 200–300 mg daily i.v. or orally until day 3
- Minerals and trace elements: 100% of DRI, iron should not be supplemented in the first week
- Daily monitoring (day 1–3 or until stable): body weight (fluid balance), edema, blood pressure, pulse rate, cardiovascular and respiratory system, phosphate, magnesium, potassium, sodium, calcium, glucose, urea, creatinine[11]

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