Swiss Essentials in Gastroenterology
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Another gastroenterology handbook?
During the daily clinical routine as well as during the preparation for
specialist exams or student courses, it became evident that a suitable,
compact reference book comprising relevant decision-making
gastroenterological facts was lacking. Most of the ever-changing
data usually needs to be sourced from original publications,
current websites of the various gastroenterological associations
(e.g., SGGSSG, AASLD, AGA, DGVS), or diverse textbooks.
Our aim was to speed up and simplify this time-consuming process
with «Swiss Essentials in Gastroenterology».

During two meetings held in Berne (11.05.2012) and Zurich
(27.06.2012), the authors came together to develop a basic structure
of such a quick reference book. The outcome of our work is currently
only available in this print version, as we believe in the effectiveness
of the «white coat pocket guide book» even in the era of «apps» and
the Internet. This actual publication cannot and should not replace any
specialty text book. In addition, no responsibility can be taken for its
completeness. The original source data are referenced in the current
tables and figures.

Any additional and critical feedback is very welcome and should be
addressed to Stephan Vavricka (stephan.vavricka@triemli.stzh.ch).
We will try our best to incorporate your comments into a planned
updated version.

In the name of all authors

S. Vavricka
M. Wilhelmi
Zurich, July 2012

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Gastroenterology» assume no obligation to update the publication
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any damage or loss arising from the use of this information.
This also applies for indirect incidental or consequential damages
that have occurred as a result of the use of this publication.

This book has been critically reviewed by:
Dr. Melissa Wilhelmi, PhD.
We thank the reviewer for her invaluable feedback and input.
## Endoscopy in general

### Gastrointestinal Endoscopy

#### Checklist for home discharge after digestive endoscopy:

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGD</strong></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>0% in diagnostic EGD</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.1% after taking biopsies</td>
</tr>
<tr>
<td>Perforation</td>
<td>0.1–1% after dilatation of benign strictures</td>
</tr>
<tr>
<td></td>
<td>1–5% after dilatation of malignant strictures</td>
</tr>
<tr>
<td></td>
<td>1–3% after pneumatic dilatation of achalasia</td>
</tr>
<tr>
<td><strong>Colonscopy</strong></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.2% in total</td>
</tr>
<tr>
<td></td>
<td>0.3–10% after intervention</td>
</tr>
<tr>
<td>Perforation</td>
<td>0.1% in diagnostic colonoscopy</td>
</tr>
<tr>
<td></td>
<td>0.1–0.3% in therapeutic colonoscopy</td>
</tr>
<tr>
<td>Morbidity</td>
<td>0.2% in diagnostic colonoscopy</td>
</tr>
<tr>
<td></td>
<td>0.1–0.3% in therapeutic colonoscopy</td>
</tr>
<tr>
<td>Mortality</td>
<td>0–0.006% in total</td>
</tr>
<tr>
<td><strong>ERCP</strong></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1.3–6.7% post-ERCP</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.5% (mainly due to pancreatitis)</td>
</tr>
</tbody>
</table>

[Dumonceau JM et al.: Endoscopy 2010]
### Gastrointestinal Endoscopy

#### Management of antiplatelet agents during endoscopy:

<table>
<thead>
<tr>
<th>Bleeding Risk</th>
<th>Intervention</th>
<th>Continue aspirin</th>
<th>Continue clopidogrel or prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>EGD, colonoscopy and colonoscopy ± biopsies</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>EUS without FNA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Colonic polypectomy &lt; 1 cm</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Dilation of digestive stenoses</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Digestive stenting</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>ERCP without sphincterotomy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Argon plasma coagulation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>High</td>
<td>EMR, ESD, or ampullary resection</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>EUS FNA of cystic lesions</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Colonic polypectomy &gt; 1 cm</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>ERCP with sphincterotomy or large-balloon papillary dilation</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Percutaneous endoscopic gastrostomy</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Esophageal variceal band ligation</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Bleeding Risk Stratification for GI endoscopy under antiplatelet agents:**

**Low thrombotic risk:**
- Coronary DES > 12 months previously
- Bare metal coronary stents inserted > 6 weeks previously without associated risk factors
- Stroke without cardiac failure > 6 weeks previously

**Low bleeding risk:**
- Maintain antiplatelet agent therapy

**High thrombotic risk:**
- Coronary drug eluting stent ≤ 12 months previously
- Bare metal coronary stent ≤ 6 weeks previously or > 6 weeks with risk factors
- Stroke ≤ 6 weeks previously

**High bleeding risk:**
- Maintain dual antiplatelet agent therapy
- Delay endoscopy and/or consult cardiologist to discuss temporary cessation of thienopyridine: clopidogrel, 5 days prasugrel, 7 days
- Aspirin should be maintained in all cases

---

Esophagus
Reflux

Reflux esophagitis: Los Angeles

- **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

Reflux esophagitis: Savary-Miller
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**
  Eosinophilic ulcer, Barrett’s epithelium, strictures and other chronic mucosal lesions

- **Grade V**
  Barrett esophagus

Reflux esophagitis: MUSE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Metaplasia</th>
<th>Ulcer</th>
<th>Stricture</th>
<th>Erosions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>absent</td>
<td>absent</td>
<td>absent</td>
<td>absent</td>
</tr>
<tr>
<td>1 (mild)</td>
<td>fingers ± islands circumferential</td>
<td>1 ulcer</td>
<td>≥ 9 mm</td>
<td>1 fold</td>
</tr>
<tr>
<td>2 (severe)</td>
<td>1 ulcer</td>
<td>&lt; 9 mm</td>
<td>&gt; 75% circumference</td>
<td></td>
</tr>
</tbody>
</table>

Hiatus hernia: □ yes □ no
Example: M2 U0 S2 E1

Barrett esophagus

Updated Guidelines 2008 for the Diagnosis, Surveillance and Therapy of Barrett’s Esophagus

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Documentation</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Two EGDs with biopsy within 1 year</td>
<td>Endoscopy every 3 years</td>
</tr>
<tr>
<td>Low Grade</td>
<td>• Highest grade on repeat EGD* with biopsies within 6 months</td>
<td>1 year interval until no dysplasia x 2</td>
</tr>
<tr>
<td></td>
<td>• Expert pathologist confirmation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mucosal irregularity</td>
<td></td>
</tr>
<tr>
<td>High Grade</td>
<td>• Repeat EGD with biopsies to rule out EAC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ER*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continued 3 month surveillance or intervention based on results and patient</td>
<td></td>
</tr>
</tbody>
</table>

*EGD – esophagogastroduodenoscopy; ER – endoscopic resection; EAC – esophageal adenocarcinoma.

[Wand KK. AM J Gastroenterol 2008]
Eosinophilic Esophagitis

**Definition:**
- Chronic inflammatory, immune mediated esophagitis with dysphagia and eosinophilic infiltrates of the esophageal mucosa
  
  [Furuta et al.: J Allergy Clin Immunl 2011]

**Important facts to remember:**
- Cumulative prevalence: 35/100,000
  - Male : female = 3:1
  - Additional atopy in 50 – 70%

**Diagnosis:**
- EGD: red furrows, white exudates (i.e. eosinophilic microabscesses), concentric rings (i.e. “trachealization”), “feline” esophagus
- Histology (≥ 8 biopsies): ≥ 15 eosinophils / high power field
- Rule out GERD!
  
  [Furuta: Gastroenterology 2007]

**Treatment:**
- PPI in patients with overlap to GERD
- Individual elimination diet in children with proven food allergy or 6-food elimination diet (excluding cow milk protein, soy, wheat, egg, peanut, and seafood)
  
  [Kagalwalla AF et al.: Clin Gastroenterol Hepatol 2006]

- Topic steroids as 1st line therapy:
  - Fluticasone (e.g. Axotide spray 250 µg) or
  - Budesonide (e.g. Pulmicort Spray 250 µg):
    swallow 4 spray doses b.i.d. for 12 weeks
- Systemic steroids (e.g. Prednisone 1 mg/kg) for a few weeks only in refractory patients

**Complications:**
- Bolus impaction with high risk of perforation
  - Esophageal fibrosis with stenosis in the long term
  - => endoscopic dilatation in symptomatic refractory patients
**Esophagus**

**Achalasia**

**Achalasia – Diagnosis and treatment**

**Definition:**

Table 1. Radiographic and Manometric Features of Achalasia

Barium esophagram

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

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

---

**Algorithm Achalasia**

<40 years

- Laparoscopic myotomy
- Graded pneumatic dilatation
- Repeat as needed

>40 years

- Repeat as needed
- Refer to esophageal Center of excellence

---

**Low surgical risk**

- Failure
- Success

**High surgical risk**

- Refer to esophageal Center of excellence
- Graded pneumatic dilatation
- Repeat as needed
- Success
- Failure

---

**Calcium Channel Blocker/ Nitrates**

[Richter JE, Boeckxstaens GE. Gut 2011]
Esophagus

Achalasia

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)
• Start PPI therapy at least 1 week prior to pneumatic dilatation
• Day before procedure only liquid diet; npo at least 6 hours prior to procedure

Procedure (balloon 30–35–40mm, 10 PSI, 15 seconds)
• Sedation, preferably with propofol
• Intubate esophagus in right lateral decubitus to minimize risk of aspiration of esophageal content
• 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 15 seconds

Post-dilatation procedure
• 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. 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.
• Clinical observation for 2-4 hours
• Treat chest pain (muscular tear with acetaminophen, mefenacid or pethidine/fentanyl); pain should subside over the next 2–3 hours
• Contrast esophagogram to confirm that there is no leakage (passage through EG-junction most likely delayed due to edema and muscle spasm)
• Patient stable without evidence of leak can be discharged the same day
• Only liquids for lunch and dinner. Normal diet starting next morning
• Continue PPI daily for 4 weeks
• 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.
**Esophagus**

**Varices**

### Algorithm gastroesophageal varices

1. **Acute variceal bleeding**
   - Volume restitution
   - i.v. ceftriaxone 2 g/d
   - Target hb level 7–8 g/dl
   - Vasoactive drugs (octreotide, somatostatin, terlipressin)
     (Octreotide 100 µg iv bolus followed by 50 µg/h i.v. 72h)
     - PPI
     - Discuss FFP, platelets
     - lactulose

2. **EGD** (within 12 hrs)

3. **Fundic varices?**
   - yes
     - Sclerotherapy
   - no
     - EVL

4. **Bleeding controlled**
   - Initiate secondary prophylaxis (non-selective beta-blockers)

5. **Bleeding not controlled**
   - Consider TIPS, balloon tamponade, selfexpandable metal stent

6. **Bleeding controlled**
   - Repeat every 1–2 weeks until obliteration

**EGD** = esophagogastroduodenoscopy

**EVL** = endoscopic variceal ligation

**FFP** = fresh frozen plasma

**PPI** = proton pump inhibitor

---

**Gastric varices**

**Bleeding risk**: 25% in 2 years

**Gastro Esophageal Varices (GOV)**

**GOV1**: extension of esophageal varices along the lesser curvature

(- management as for esophageal varices)

**GOV2**: extend along the fundus and are usually convoluted and longer

**Isolated Gastric Varices (IGV)**

(absence of esophageal varices)

**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

**BR** = Bleeding risk in 2 years

---

[According to Garcia et al. Hepatology 2007]
Esophagus

Varices

Esophageal varices – size classification and screening

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

Algorithm Varices

Cirrhosis

EGD

Varices?

yes

no

Episode of bleeding?

Repeat EGD every 2 – 3 yrs

Non-selective beta-blocker and/
or EVL (large varices or con-traindication for beta-blocker)

no

yes

EVL

EGD yearly

EVL = endoscopic variceal ligation

[According to Garcia et al. Hepatology 2007]

Sengstaken – Tube

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

- 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, Duphalac is sufficiently administered.
- The esophagus and stomach lumen are drained.

Linton – Tube

EGD = esophagastroduodenoscopy
**Esophagus**

**Esophageal cancer**

<table>
<thead>
<tr>
<th><strong>Structure</strong></th>
<th><strong>Endosonographic view</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epithelium</strong></td>
<td>T1 into submucosa</td>
</tr>
<tr>
<td>Lamina propria</td>
<td>T2 into muscularis propria</td>
</tr>
<tr>
<td>Muscularis mucosae</td>
<td>T3 through muscularis propria into subserosa</td>
</tr>
<tr>
<td>Submucosa</td>
<td>T4 into other organs or tissues</td>
</tr>
<tr>
<td>Muscularis propria</td>
<td>1st layer</td>
</tr>
<tr>
<td>Adventitia</td>
<td>2nd layer</td>
</tr>
<tr>
<td></td>
<td>3rd layer</td>
</tr>
<tr>
<td></td>
<td>4th layer</td>
</tr>
<tr>
<td></td>
<td>5th layer</td>
</tr>
</tbody>
</table>

**Esophageal cancer uT1**

**Esophageal cancer uT2**

**Esophageal cancer uT2**
Esophagus
Esophageal cancer
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]
Esophageal cancer – Sievert III

Corrosive injury

Grading of corrosive injuries in the esophagus and/or stomach

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2 A</th>
<th>Grade 2 B</th>
<th>Grade 3 A</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>edema &amp; hyperemia of the mucosa</td>
<td>friability, bleeding, erosions, blisters, whitish membranes, exudates, and superficial ulcers</td>
<td>grade 2a plus deep discrete or circumferential ulceration</td>
<td>multiple ulcerations and small scattered areas of necrosis</td>
<td>perforation</td>
</tr>
</tbody>
</table>
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
5. stenosis / strictures (from grades 2B to 3) (mths – yrs) (2wks – 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)
Esophagus

Motility of the esophagus

Chicago classification motility abnormalities

Individual swallows

Integrity of contraction

Intact contraction 20 mmHg isobaric contour without large or small break

Weak contraction

a) Large break in the 20 mmHg isobaric contour (>5 cm in length)
b) Small break in the 20 mmHg isobaric contour (2–5 cm in length)

Failed peristalsis Minimal (<3 cm) integrity of the 20 mmHg isobaric contour distal to the proximal pressure through (P)

Contraction pattern (for intact or weak peristalsis with small breaks)

Premature contraction DL < 4.5 s

Hypercontractile DCI > 8000 mmHg-s-cm

Rapid contraction CFV > 9 cm s⁻¹

Normal contraction Not achieving any of the above diagnostic criteria

Intrabolus pressure pattern (30 mmHg isobaric contour)

Panesophageal pressurization Uniform pressurization extending from the UES to the EGI

Compartmentalized esophageal pressurization Pressurization extending from the contractile front to a sphincter

EGJ Pressurization Pressurization restricted to zone between the LES and CD in conjunction with hiatus hernia

Normal pressurization No bolus pressurization > 30 mmHg

Interpretation of studies

Diagnosis Diagnostic Criteria

Achalasia

Classic achalasia: mean IRP > upper limit of normal, 100% failed peristalsis

Type I achalasia Achalasia with esophageal compression: mean IRP > upper limit of normal, no normal peristalsis, panesophageal pressurization with ≥ 20% of swallows

Type II achalasia

Mean IRP > upper limit of normal, no normal peristalsis, preserved fragments of distal peristalsis or premature (spastic) contractions with ≥ 20% of swallows

EGJ outflow obstruction Mean IRP > upper limit of normal, some instances of intact peristalsis or weak peristalsis with small breaks such that the criteria for achalasia are not met

Motility Disorders

Distal esophageal spasm Normal mean IRP, ≥ 20% premature contractions

Hypercontractile esophagus At least one swallow DCI > 8000 mmHg-s-cm with single peaked or multipeaked (Jackhammer esophagus) contraction

Absent peristalsis Normal mean IRP, 100% of swallows with failed peristalsis

Peristaltic abnormalities (Defined by exceeding statistical limits of normal)

Weak peristalsis with large peristaltic Mean IRP < 15 mmHg and > 20% swallows with large breaks in the 20 mmHg defects isobaric contour (>5 cm in length)

Weak peristalsis with small peristaltic Mean IRP < 15 mmHg and > 30% swallows with small breaks in the 20 mmHg defects isobaric contour (2-5 cm in length)

Frequent failed peristalsis > 30%, but < 100% of swallows with failed peristalsis

Rapid contractions with normal latency Rapid contraction with ≥ 20% of swallows, DL > 4.5 s

Hypertensive peristalsis Mean DCI > 5000 mmHg-s-cm, but not meeting criteria for hypercontractile esophagus

(Nutcracker esophagus) Normal Not achieving any of the above diagnostic criteria

Esophagus
Motility of the esophagus

Conventional manometry – per swallow analysis

Lower esophageal sphincter (LES)
- LES resting pressure (LESP): average (mid-respiratory or end-expiratory) pressure in the lower esophageal sphincter over a period of 5-10 seconds
- LES residual pressure (LESRP): nadir pressure in the LES during deglutitive relaxation (i.e. after a swallow)

Esophageal body
- Contraction amplitude and duration in the distal and proximal esophagus
- Distal esophageal amplitude (DEA): average contraction amplitude in the distal esophagus measured 5 cm apart (i.e. 5 and 10 cm above the LES high-pressure zone or 3 and 8 cm above the proximal border of the LES)
- Distal esophageal duration (DED): average contraction duration in the distal esophagus measured 5 cm apart (i.e. 5 and 10 cm above the LES high-pressure zone or 3 and 8 cm above the proximal border of the LES)
- Contraction onset velocity: speed of propagation of the onset of esophageal contraction in the distal esophagus measured 5 cm apart (i.e. between 10 to 5 cm above the LES high-pressure zone or 8 to 3 cm above the proximal border of the LES)
- Contraction peak velocity: speed of propagation of the contraction peak in the distal esophagus measured 5 cm apart (i.e. between 10 to 5 cm above the LES high-pressure zone or 8 to 3 cm above the proximal border of the LES)

Upper esophageal sphincter (UES)
- UES resting pressure (UESP): average pressure in the upper esophageal sphincter over a period of 2-5 seconds
- UES residual pressure (UESRP): nadir pressure in the UES during deglutitive relaxation (i.e. during a swallow)
- Pharyngo-UES coordination: Time elapsed between beginning of UES relaxation and onset of pharyngeal contraction

Normal values
Lower esophageal sphincter (LES)
- LES resting pressure (LESP) 10-45 mmHg:
  - Hypertensive LES if LESP > 45 mmHg
  - Hypotensive LES if LESP < 10 mmHg
- LES residual pressure (LESRP) < 8 mmHg:
  - Poorly relaxing LES if LESRP > 8 mmHg

Esophageal body
- Contraction amplitude 30–180 mmHg:
  - Ineffective contraction if amplitude at 5 or 10 cm above LES < 30 mmHg
- Distal esophageal amplitude (DEA) 30–180 mmHg:
  - Hypercontractile esophageal body DEA > 180 mmHg; nutcracker esophagus if DEA > 180 mmHg
  - Clinically more robust diagnosis if average DEA > 220 mmHg
- Distal esophageal duration (DED) 3-6 sec:
  - Hypercontractile esophageal body DED > 6 sec; nutcracker esophagus if DED > 6 sec
- Contraction onset velocity <8 cm/sec:
  - Simultaneous contraction if onset velocity > 8 cm/sec or retrograde (i.e. contraction in distal esophagus before onset in the mid-esophagus – negative onset velocity)
Esophagus

Motility of the esophagus

Upper esophageal sphincter (UES)
- UES resting pressure (UESP) 30-180 mmHg:
  - Hypertensive UES if UESP > 180 mmHg
  - Hypotensive UES if UESP < 30 mmHg
- UES residual pressure (UESRP) < 8 mmHg:
  - Poorly relaxing UES if UESRP > 8 mmHg
- Pharyngo-UES coordination -300 to -500 msec:
  - Pharyngo-UES dyscoordination if delay shorter than -300 msec or onset of pharyngeal contraction before the begin of UES relaxation

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
- Distal contractile integral (DCI) < 5’000 mmHg*sec*cm
  - Hypercontractile peristalsis if DCI > 5,000 mmHg*sec*cm
  - Jackhammer esophagus if DCI > 8,000 mmHg*sec*cm
Esophagus
Motility of the esophagus

Esophageal pressure topography scoring of individual swallows

**Integrity of contraction**

<table>
<thead>
<tr>
<th>Intact contraction</th>
<th>Weak contraction</th>
<th>Failed peristalsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mmHg isobaric contour without large or small break</td>
<td>a) Large break in the 20 mmHg isobaric contour (&gt;5 cm in length) b) Small break in the 20 mmHg isobaric contour (2–5 cm in length)</td>
<td>Minimal (&lt;3 cm) integrity of the 20 mmHg isobaric contour distal to the proximal pressure trough (P)</td>
</tr>
</tbody>
</table>

**Contraction pattern (for intact or weak peristalsis with small breaks)**

<table>
<thead>
<tr>
<th>Premature contraction</th>
<th>Hypercontractile</th>
<th>Rapid contraction</th>
<th>Normal contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL &lt; 4.5 s</td>
<td>DCI &gt; 8000 mmHg-s-cm</td>
<td>CFV &gt; 9 cm s⁻¹</td>
<td>Not achieving any of the above diagnostic criteria</td>
</tr>
</tbody>
</table>

**Intrabolus pressure pattern (30 mmHg isobaric contour)**

<table>
<thead>
<tr>
<th>Panesophageal pressurization</th>
<th>Compartmentalized esophageal pressurization</th>
<th>EGJ Pressurization</th>
<th>Normal pressurization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniform pressurization extending from the UES to the EGJ</td>
<td>Pressurization extending from the contractile front to a sphincter</td>
<td>Pressurization restricted to zone between the LES and CD in conjunction with hiatus hernia</td>
<td>No bolus pressurization &gt;30 mmHg</td>
</tr>
</tbody>
</table>
**Stomach**

**Dyspepsia**

### Endoscopy Algorithm Dyspepsia

**Dyspepsia**

- Age > 55 years
  - Alarm signal

- Age < 55 years
  - No alarm signal

  - *H. pylori* prevalence < 10%
    - PPI therapy trial

  - *H. pylori* prevalence ≥ 10%
    - *H. pylori* test
    - and if necessary, therapy

### 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

*Prevalence of *H. pylori* infection in adults is approximately 12% in Switzerland [8].*


---

**Metaplasia**

### Algorithm Metaplasia

**Atrophic gastritis/intestinal metaplasia**

- Helicobacter pylori eradication

- *Chromoendoscopy/Narrow Band Imaging (NBI), if available*

**Expansion**

- **Dysplasia grade***

- **Low grade**

- **High grade**

- **Atrophy (mild/moderate) or intestinal metaplasia in antrum**

- **Atrophy or intestinal metaplasia in antrum and corpus**

- **No follow-up**

- **Every 3 years**

- **After 12 months**

- **After 6 months**

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

Stomach

Gastritis

Gastritis – endoscopic classification

<table>
<thead>
<tr>
<th>Erythematous/exudative</th>
<th>Erythematous/exudative</th>
<th>Flat erosive</th>
<th>Elevated erosive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic</td>
<td>Hemorrhagic</td>
<td>Reflux</td>
<td>Rugal/hyperplastic</td>
</tr>
</tbody>
</table>

Endoscopic follow-up
- NOT with duodenal ulcer
- Gastric ulcer after 8–12 weeks (5–11% of all stomach ulcers are malignant)
- For young patients with no suspicious stomach ulcer and risk status (H. pylori, ASS/NSAR), re-endoscopy can be waived.

Gastritis

Sydney classification – Endoscopy

Morphology
- Erythematous/exudative gastritis
- Gastritis with flat erosions
- Gastritis with polyloid erosions
- Atrophic gastritis
- Hemorrhagic gastritis
- Reflux gastritis
- Ménétrier’s disease (‘giant rugal folds’ gastritis)

Localization
- Pangastritis, corpus gastritis, antrum gastritis

Sydney Classification – Histology

Acute gastritis
- Acute hemorrhagic/erosive gastritis
- Acute H. pylori gastritis
- Acute phlegmonous gastritis

Caused by
- Medication, intoxication
- H. pylori
- Sepsis

Chronic gastritis
- Non-atrophic gastritis
- Atrophic gastritis
  - Autoimmune gastritis
  - Multifocal atrophic gastritis
- Special forms
  - Chemical gastritis
  - Radiation gastritis
  - Lymphocytic gastritis
- Granulomatous, not infectious
  - Eosinophilic gastritis
  - Infectious gastritis

Caused by
- H. pylori (Type B gastritis)
- Autoimmunity (Type A gastritis)
- H. pylori, environmental factors
- Chemical irritation, NSAR/medication, bile (Type C gastritis)
- Irradiation
- Immune mechanisms, gluten, H. pylori, idiopathic
- M. Crohn, sarcoidosis, M. Wegener / other vasculitides, foreign bodies, idiopathic
- Food allergies, other allergies
- Bacteria, viruses, fungi, parasites

Grading

- Lymphocellular infiltration
- Inflammation activity (neutrophilic leucocytes)
- Atrophy
- Intestinal metaplasia

- normal
- low-grade
- moderate
- high-grade

[Tytgat GN. J Gastroenterol Hepatol. 1991]
Stomach
Gastritis (Helicobacter pylori)

Diagnostics

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-invasive methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>70-90</td>
<td>70-90</td>
</tr>
<tr>
<td>13C breath test</td>
<td>85-95</td>
<td>85-95</td>
</tr>
<tr>
<td>Stool antigen</td>
<td>85-95</td>
<td>85-95</td>
</tr>
<tr>
<td><strong>Invasive methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast urease test</td>
<td>90-95</td>
<td>90-95</td>
</tr>
<tr>
<td>Histology*</td>
<td>80-98</td>
<td>90-98</td>
</tr>
<tr>
<td>Culture</td>
<td>70-90</td>
<td>100</td>
</tr>
<tr>
<td>PCR-analysis</td>
<td>90-95</td>
<td>90-95</td>
</tr>
</tbody>
</table>

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

Test result
False positive: serology (status after 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

Indications for H. pylori eradication therapy
Confirmed indication
- Active peptic ulcer disease
- MALT-lymphoma of the stomach
- Atrophic gastritis
- Status after resection of stomach carcinoma
- Positive family anamnesis (1st grade relative with stomach carcinoma)
- Dyspepsia
- Patient request
- Morbus Ménétrier
- Idiopathic thrombocytopenic purpura (ITP)
- Lymphocytic gastritis

Gastritis (Helicobacter pylori)

Controversial indication
- Functional dyspepsia (number needed to treat = 15)
- Therapy with NSAR
- Unclear iron deficiency anemia

Therapy
For all treatment schemes: standard PPI dose is 1-0-1 (omeprazole 20 mg, esomeprazole 20 mg, Pantozol 40 mg, lansoprazole 30 mg, rabeprazole 20 mg)

Primary therapy
Triple therapy
- Clarithromycin 2 x 500 mg/d, Metronidazole 2 x 500 mg/d* 7–14 days
- Clarithromycin 2 x 500 mg/d, Amoxicillin 2 x 1000 mg/d ** 7–14 days
- Clarithromycin 2 x 500 mg/d, Levofloxacin 2 x 500 mg/d 7–14 days (penicillin allergy)

Sequential therapy
Amoxicillin 2 x 1000 mg/d
Clarithromycin 2 x 500 mg/d, Metronidazole 2 x 500 mg/d Day 1–5

Quadruple therapy
Amoxicillin 2 x 1000 mg/d, Clarithromycin 2 x 500/d, Metronidazole 2 x 500 mg/d 7–14 days

Bismuth quadruple therapy***
Metronidazole 2 x 500 mg/d, Tetracycline 4 x 500 mg/d, Bismuth 4 x 120 mg/d 7–14 days

Secondary therapy
Bismuth quadruple therapy
Metronidazole 2 x 500 mg/d, Tetracycline 4 x 500 mg/d, Bismuth 4 x 120 mg/d 10–14 days
Stomach
Gastritis (Helicobacter pylori)

Triple therapy
- Amoxicillin 2x1000 mg/d, Rifabutin 2x150 mg/d  10–14 days
- Amoxicillin 2x1000 mg/d, Levofloxacin 1x500 mg/d or Moxi-floxacin 2x400 mg/d  10–14 days
- Clarithromycin 2x500/d, Levofloxacin 1x500 mg/d or Moxiflox-acin 2x400 mg/d  10–14 days
- Amoxicillin 2x1000 mg/d, Furazolidone 2x100 mg/d  10–14 days
- Amoxicillin 3x1000 mg/d, Metronidazole 3x500 mg/d  10–14 days

Tertiary therapy / Rescue therapy
Bismuth quadruple therapy
Furazolidone 2x100 mg/d, Tetracycline 4x500 mg/d, Bismuth 4x120 mg/d  10–14 days

Triple therapy
- Amoxicillin 2x1000 mg/d, Levofloxacin 1x500 mg/d or Moxifloxacin 2x400mg/d  10–14 days
- Clarithromycin 2x500/d, Levofloxacin 1x500 mg/d or Moxifloxacin 2x400 mg/d  10–14 days
- Clarithromycin 2x500 mg/d, Rifabutin 2x 150 mg/d  10–14 days

* Clarithromycin resistance < 20% and metronidazole resistance < 40%,
** Clarithro-mycin resistance < 20% and metronidazole resistance > 40%,
*** Clarithromycin re-sistance > 20% and metronidazole resistance > 40%

Relapse rate < 1% per year in industrial countries (in developing countries, approx. 10%).

Gastric Ulcers

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

Differential diagnosis: H. pylori-negative, NSAR-negative peptic ulcer disease (approx. 10%)
- False negative H. pylori-testung (under PPI-therapy, after antibiotic therapy)
- Undiscovered ASS/NSAR intake
- Ulcerogenic medication (bisphosphonate, iron preparations)
- Stomach carcinoma, lymphoma
- IBD (M. Crohn)
- H. heilmannii
- Systemic mastocytosis
- Zollinger-Ellison syndrome
- Status after partial stomach resection
- Status after radiotherapy

Strategy for long-term NSAR therapy
Risk factors for NSAR-associated peptic ulcer disease
Gastrointestinal risk
- Age > 65 years, high dose-NSAR 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%

<table>
<thead>
<tr>
<th>Gastrointestinal risk</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low cardiac risk</td>
<td>NSAR</td>
<td>NSAR + PPI COX-2</td>
<td>NSAR + PPI COX-2 + PPI</td>
</tr>
<tr>
<td>High cardiac risk</td>
<td>Naproxen + PPI</td>
<td>Naproxen + PPI</td>
<td>No NSAR/COX-2</td>
</tr>
</tbody>
</table>

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

Upper GI bleeding

Peptic ulcers are described using the Forrest classification:

<table>
<thead>
<tr>
<th>Forrest Classification</th>
<th>Prevalence</th>
<th>Relapse bleeding rate*</th>
<th>Fatality Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia (Spurting hemorrhage)</td>
<td>10%</td>
<td>90%</td>
<td>26%</td>
</tr>
<tr>
<td>Ib (Oozing hemorrhage)</td>
<td>10%</td>
<td>10–20%</td>
<td>10%</td>
</tr>
<tr>
<td>Iia (Visible vessel)</td>
<td>25%</td>
<td>50%</td>
<td>11%</td>
</tr>
<tr>
<td>Iib (Adherent clot)</td>
<td>10%</td>
<td>25–30%</td>
<td>7%</td>
</tr>
<tr>
<td>Iic (Hematin on ulcer base)</td>
<td>10%</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>III (No signs of recent hemorrhage)</td>
<td>35%</td>
<td>&lt; 5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

*without endoscopic therapy


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]

The Rockall score predicts mortality from gastrointestinal ulcer bleeding:

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

The Rockall score underscores the rate of recurrent bleeding

Score: Relapse bleeding: Mortality:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>4</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>5</td>
<td>24%</td>
<td>11%</td>
</tr>
<tr>
<td>6</td>
<td>33%</td>
<td>17%</td>
</tr>
<tr>
<td>7</td>
<td>44%</td>
<td>27%</td>
</tr>
<tr>
<td>8–11</td>
<td>42%</td>
<td>41%</td>
</tr>
</tbody>
</table>

CAVE: The Rockall score underscores the rate of recurrent bleeding

*SBP = Systolic blood pressure

[Church NI et al.; Gastrointest Endosc 2006]
Stomach

Upper G1 bleeding

Glasgow-Blatchford Score (GBS):

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

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

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

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

Upper G1 bleeding

Recommendations for the management of upper gastrointestinal bleeding:

- Immediately evaluate and initiate appropriate resuscitation
- Closely monitor vital signs and airway
- Give nothing by mouth
- Two large caliber (16 gauge or larger) peripheral catheters or a central venous line
- Provide supplemental oxygen and crystalloid fluid
- Transfuse if hemoglobin < 100 g/L in high-risk patients or < 70 g/L in low-risk patients. MEMO: Avoid over-transfusion in variceal bleeding!
- 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 (erythromycin 200mg i.v. >30 minutes before endoscopy) can improve gastric visualization
- 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.
Stomach

Functional GI disorders

Rome III Criteria

<table>
<thead>
<tr>
<th>Rome III Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more of the following:</td>
</tr>
<tr>
<td>• Bothersome postprandial fullness</td>
</tr>
<tr>
<td>• Early satiation</td>
</tr>
<tr>
<td>• Epigastric pain</td>
</tr>
<tr>
<td>• Epigastric burning</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>No evidence of structural disease (including at the upper endoscopy) that is likely to explain the symptoms.</td>
</tr>
<tr>
<td>These criteria should be fulfilled for the last three months with symptom onset at least six months before diagnosis</td>
</tr>
</tbody>
</table>

[Tack J et al. Gastroenterology 2006]

Table 1. Functional Gastrointestinal Disorders

<table>
<thead>
<tr>
<th>B. Functional gastroduodenal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1. Functional dyspepsia</td>
</tr>
<tr>
<td>B1a. Postprandial distress syndrome</td>
</tr>
<tr>
<td>B1b. Epigastric pain syndrome</td>
</tr>
<tr>
<td>B2. Belching disorders</td>
</tr>
<tr>
<td>B2a. Aerophagia</td>
</tr>
<tr>
<td>B2b. Unspecified excessive belching</td>
</tr>
<tr>
<td>B3. Nausea and vomiting disorders</td>
</tr>
<tr>
<td>B3a. Chronic idiopathic nausea</td>
</tr>
<tr>
<td>B3b. Functional vomiting</td>
</tr>
<tr>
<td>B3c. Cyclic vomiting syndrome</td>
</tr>
<tr>
<td>B4. Rumination syndrome in adults</td>
</tr>
</tbody>
</table>

Functional GI disorders

Diagnostic criteria

B1. Diagnostic Criteria* for Functional Dyspepsia

Must include

1. One or more of:
   a. Bothersome postprandial fullness
   b. Early satiation
   c. Epigastric pain
   d. Epigastric burning

AND

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

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

B1a. Diagnostic Criteria* for Postprandial Distress Syndrome

Must include one or both of the following:

1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week
2. Early satiation that prevents finishing a regular meal, at least several times per week

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

Supportive criteria

1. Upper abdominal bloating or postprandial nausea or excessive belching can be present
2. EPS may coexist

B1b. Diagnostic Criteria* for Epigastric Pain Syndrome

Must include all of the following:

1. Pain or burning localized to the epigastrium of at least moderate severity at least once per week
2. The pain is intermittent
3. Not generalized or localized to other abdominal or chest regions
4. Not relieved by defecation or passage of flatus
5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders

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

Supportive criteria
1. The pain may be of a burning quality but without a retrosternal competent
2. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting
3. Postprandial distress syndrome may coexist

B2a. Diagnostic Criteria* for Aerophagia
Must include all of the following:
1. Troublesome repetitive belching at least several times a week
2. Air swallowing that is objectively observed or measured

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

B2b. Diagnostic Criteria* for Unspecified Excessive Belching
Must include all of the following:
1. Troublesome repetitive belching at least several times a week
2. No evidence that excessive air swallowing underlies the symptom

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

B4. Diagnostic Criteria* for Rumination Syndrome
Must include both of the following:
1. Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing
2. Regurgitation is not preceded by retching

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

Supportive criteria
1. Regurgitation events are usually not preceded by nausea
2. Cessation of the process when the regurgitated material becomes acidic
3. Regurgitant contains recognizable food with a pleasant taste

B3a. Diagnostic Criteria* for Chronic Idiopathic Nausea
Must include all of the following:
1. Bothersome nausea, occurring at least several times per week
2. Not usually associated with vomiting
3. Absence of abnormalities at upper endoscopy or metabolic disease that explains the nausea

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

**Operation Techniques**

**Biliopancreatic diversion with duodenal switch**
- Stomach
- Biliopancreatic limb
- Alimentary limb
- Common channel
- 2.5 meter

**Sleeve gastrectomy**
- Stomach
- Resected Stomach

**Roux-en-Y Gastric Bypass**
- Gastric pouch
- Antecolic Roux limb (150 cm)
- Biliopancreatic limb (50 cm from Treitz)

**Gastric surgery 1**
- Billroth I
- Billroth II
**Intestine**

**Operation Techniques**

**Gastric surgery 2**

- Roux-en-Y gastro-jejunostomy
- Roux-en-Y esophago-jejunostomy
- Jejuno-jejunostomy
- Jejuno-jejunostomy

---

**Chronic Diarrhoea**

**Definition:** Decreased stool consistency up to > 4 weeks

**Differential diagnosis – chronic diarrhoea**

<table>
<thead>
<tr>
<th>Osmotic diarrhoea</th>
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**Steatorrhoea**

- Malabsorption syndrome
- Shortbowel syndrome
- Celiac disease
- Bacterial overgrowth
- Mesenterial ischemia
- Maldigestion syndrome
- Pancreas insufficiency
- Excess bile acids

**Inflammatory diarrhoea**

- Inflammatory bowel disease
- C. ulcerosa / M. Crohn
- Diverticulitis
- Malabsorption syndrome
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**Maldigestion diarrhoea**

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**Neoplasms**

- Colon carcinoma, lymphoma
- villous adenoma

- Colon carcinoma, lymphoma
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- M. Addison

- Hereditary
- Idiopathic

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**Intestine**

**Operation Techniques**

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Differential diagnosis – medication
antibiotics, antidepressives, antihypertensives (beta blockers, ACE-inhibitors), diuretics, anticonvulsives, lipid lowering drugs, antidiabetics (biguanides), H2-blockers / PPIs, theophylline, chemotherapy, alcohol

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, pancreas 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

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, Chymotrypsin (pancreas insufficiency) Bisacodyl and phenolphthalein, if applicable (laxative abuse)

Others
H2-lactose breath test (lactose intolerance) Gastroscopy with small intestinal biopsies and fluid (SIBO) Ileo-coloscopy with biopsies from all segments (microscopic colitis) Secretin stimulation test (pancreas insufficiency) Anthracinone in urine (laxative abuse) Fecal collection for 72 hours as an important diagnostic tool for clarification of chronic diarrhea
Intestine

Chronic Diarrhoea

Stool Osmolar/Osmotic Gap:
- Stool osmolal 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)

Causes of osmotic diarrhea include:
- Bile salt deficiency
- Pancreatic insufficiency
- Celiac/Tropical Sprue
- Whipple’s Dz
- Intestinal Lymphoma
- Medications
- Lactose Intolerance
- Laxative abuse (depending on the type of laxative)

Causes of secretory diarrhea include:
- Laxative abuse (depending on the type of laxative)
- Hormonal, Endocrine Tumors

Nonspecific chronic diarrhoea (> 4 weeks)

Red flags:
- Age > 50 y, blood in stool, postexposure to antibiotics, anaemia

Endoscopy

Calprotectin in stool

Inflamatory diarrhoea

Stool bacteriology, check stool for parasites (3x), small bowel biopsy, small bowel fluid aspiration

Infectious diarrhoea

> 300 g/24 h Stool weight < 300 g/24

Genuine diarrhoea

Pseudodiarhoea
Incontinence, irritable bowel syndrome

< 7 g/24 h Stool fat > 7 g/24

Steatorrhoea

Steatorrhoea

Evaluation: pancreas MR/CT-enteroclysis

> 50 mOsmol/kg Osmotic gap < 50 mOsmol/kg

Fasting test, if applicable

Osmotic diarrhoea

Special tests according to differential diagnosis

Secretory diarrhoea
Intestine
Chronic Diarrhoea

**Microscopic Colitis**

**Diagnostic Triad**
- Chronic, watery diarrhoea (+ potential weight loss, stomach pain)
- Macroscopically normal coloscopy
- Pathologic histology

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

**Differential diagnosis – chronic diarrhoea**

- **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

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  - 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**
  - 90% chronic intermittent progression
  - No increased mortality
  - No increased risk of colon carcinoma

**Therapy of microscopic colitis**

- **Eliminate all factors promoting chronic diarrhoea**
  - medication (NSAR, others), eating habits
  - **Mild/moderate symptoms**
    - Loperamide 2–16 mg/d
    - Cholestyramine 4x4 g/d, if applicable
  - **Severe symptoms**
    - Induction therapy
    - Budesonide 9 mg/d for 6–8 weeks

- **No response**

- **Response**
  - Evaluation: pancreas MR/CT-enteroclysis
  - **Genuine diarrhoea**
  - Strategy for long-term therapy is currently unclear. Budesonide 3–6 mg/d is presumably safe as a long-term therapy.

**Small Bowel Bacterial Overgrowth (SIBO)**

SIBO syndrome: diarrhea, steatorrhoea, 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 (M. Crohn, radiogenic, after operation)

**Intestinal stasis – dysmotility**

Diabetic autonomic neuropathy, sclerodermatitis, amyloidosis, idiopathic intestinal pseudo-obstruction, after radiotherapy, M. Crohn

**Hypo-/anacidity**

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: >105 CFU/mL. *(contraindication: 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 (2 x 250 mg/d), norfloxacin (2 x 400 mg/d), metronidazole (3 x 250 mg/d), trimethoprim/sulfamethoxazole (2 x 160/800 mg/d), doxycycline (2 x 100 mg/d), amoxicillin/clavulanic acid (2 x 500 mg/d), rifaximin (1200 mg/d) – not yet available in Switzerland

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

### Intestine

#### Bacterial overgrowth

**Positive H₂-Lactulose Breath Test**

<table>
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<tr>
<th>Time (min)</th>
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<th>CH₄-content</th>
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<tr>
<td>0</td>
<td>Baseline</td>
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</tr>
<tr>
<td>30</td>
<td></td>
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<tr>
<td>60</td>
<td></td>
<td></td>
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<tr>
<td>90</td>
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<tr>
<td>120</td>
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<tr>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
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</table>

**Assessment:** The H₂ concentration of expired air rose within 60 min >20 ppm above baseline. Flatulence, abdominal pain and increased abdominal sound were detected.

**Diagnosis:** State consistent with bacterial overgrowth

**Negative H₂-Lactulose Breath Test**

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**Assessment:** The H₂ concentration of exhaled air rose within 120 min >20 ppm above baseline. There was no abdominal pain detected.

**Diagnosis:** No signs for bacterial overgrowth
**IBD Therapy**

**Treatment algorithm for mild to moderate ulcerative colitis**

- **Acute flare**
  - No evidence for infectious disease
  - Left-sided
    - Non-acceptance of topical therapy
      - Oral 5-ASA
        - Adequate response
        - Maintenance therapy
    - Acceptance of topical therapy
      - Topical therapy (5-ASA and/or steroids)
        - Add on
        - Inadequate response
      - Oral 5-ASA
        - Adequate response
        - Maintenance therapy 5-ASA
    - Extensive
      - Oral 5-ASA
        - Adequate response
      - Inadequate response
        - Dosage increase
        - Oral steroids

[Rogler et al, Aktuelle Therapieoptionen, Unimed Verlag, 2. Auflage, Kapitel 6.2. Seite 93]
### Treatment algorithm for moderate to severe ulcerative colitis

#### Active ulcerative colitis of any extent not responding to 5-ASA

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<td><strong>Topical treatment and / or oral 5-ASA</strong></td>
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<td>2–4 weeks</td>
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<tr>
<td><strong>0.75–1 mg/kg oral Prednisone-equivalent</strong></td>
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<tr>
<td>Failure</td>
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<td>- Consider iv steroid treatment</td>
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<td>- Exclude infection</td>
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<td>- Full blood count (incl. lymphocytes)</td>
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<td>5-ASA 2–4 g/d</td>
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<td>Tapering</td>
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<td>Full AZA dose during ≥ 12 weeks and Fail to taper CS within ≤ 16 weeks or Relapse within 12 weeks after CS discontinuation</td>
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<td>Full AZA dose during ≥ 12 weeks and Fail to taper CS within ≤ 16 weeks or Relapse within 12 weeks after CS discontinuation</td>
<td></td>
</tr>
<tr>
<td>Steroid-refractory</td>
<td></td>
</tr>
<tr>
<td>Steroid-dependent</td>
<td></td>
</tr>
<tr>
<td>AZA 2–2.5 mg/kg / 6-MP 1–1.5 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

[Manz et al, SMW 2011]
Intestine
IBD Therapy

Treatment algorithm for moderate to severe ulcerative colitis

Steroid-dependent ulcerative colitis

- **0.75 – 1 mg/kg oral Prednisone-equivalent**
  - Fail to taper within ≤ 16 weeks or Relapse within 12 weeks after Steroid discontinuation
  - Check compliance to 5-ASA
  - Monitor blood
  - Exclude infection
  - Measure TPMT

- **AZA 2 – 2.5 mg/kg**
  - Full AZA/6-MP dose during ≥ 12 weeks and Fail to taper CS within ≤ 16 weeks or Relapse within 12 weeks after CS discontinuation
  - Check compliance to AZA/6-MP
  - Exclude infection
  - Blood count (incl. lymphocytes)
  - Gastrointestinal intolerance or flu-like syndrome
  - No signs of pancreatitis
  - Check compliance and dose
  - Liver transaminases

- **AZA failure**

- **6-MP 1 – 1.5 mg/kg**

- **Infliximab 5 – 10 mg/kg (or oral Tacrolimus)**

- **Refractory to treatment**

- **Consider surgery**

[Manz et al, SMW 2011]
Steroid-refractory ulcerative colitis

0.75 – 1 mg/kg oral Prednisone-equivalent within 2 – 4 weeks
- Exclude infection

Need for rapid induction of remission

AZA-naïve

iv Steroids

No response within ≤ 2 weeks
iv Ciclosporin 2 mg/kg and PCP prophylaxis

No response within ≤ 2 weeks
AZA 2 – 2.5 mg/kg / 6-MP 1 – 1.5 mg/kg (Oral Ciclosporin for 3 months)

Response within ≤ 2 weeks

Infliximab 5 mg/kg
No response after 2 infusions or no remission after 8 – 10 weeks
Infliximab 10 mg/kg

Prior AZA failure

No need for rapid induction

AZA 2 – 2.5 mg/kg / 6-MP 1 – 1.5 mg/kg
No remission at full dose within 10 – 12 week or loss of remission
Infliximab 5 – 10 mg/kg (+/- AZA)

Infliximab failure

Infliximab (+/- AZA) failure

Consider surgery

Treatment failure
Successful treatment

* 3rd line immunosuppressive therapy restricted to specialized centers

[Manz et al, SMW 2011]
## Treatment algorithm for moderate to severe ulcerative colitis

### Acute (fulminant) ulcerative colitis

<table>
<thead>
<tr>
<th>Patient with acute symptoms defined by Truelove and Witts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>iv Steroids</strong></td>
</tr>
<tr>
<td><strong>AZA-naïve patient</strong></td>
</tr>
<tr>
<td><strong>Prior AZA failure</strong></td>
</tr>
<tr>
<td><strong>Day 3–7 assessment:</strong></td>
</tr>
<tr>
<td><code>- Sustained fever?</code></td>
</tr>
<tr>
<td><code>- Bloody diarrhea (&gt; 4x daily)?</code></td>
</tr>
<tr>
<td><code>- Elevated CRP?</code></td>
</tr>
<tr>
<td><strong>iv Ciclosporin 2–4 mg/kg</strong></td>
</tr>
<tr>
<td><strong>Infliximab 5 mg/kg, 3 infusions w0, w2, w6</strong></td>
</tr>
<tr>
<td><strong>Infliximab 5 mg/kg, 3 infusions w0, w2, w6</strong></td>
</tr>
</tbody>
</table>

### Day 3–7 assessment:

- **Sustained fever?**
- **Bloody diarrhea (> 4x daily)?**
- **Elevated CRP?**

### Treatment failure

- **iv Ciclosporin 2–4 mg/kg**
- **Infliximab 5 mg/kg, 3 infusions w0, w2, w6**
- **Infliximab 5 mg/kg, 3 infusions w0, w2, w6**

### Successful treatment

- **Check CsA trough level**
- **No improvement within 5–7 days or deterioration**
- **Surgery or Infliximab**
- **Surgery or 3rd line immunosuppression**

### Treatment failure

- **Clinical improvement**
- **CsA trough level**
- **No improvement within 7–10 days or deterioration**
- **Oral Ciclosporin for 3 months Start AZA 2–2.5 mg/kg before discharge**
- **Surgery or Infliximab**
- **Surgery or 3rd line immunosuppression**

### Surgery or 3rd line immunosuppression

- **Continue Infliximab 5 mg/kg every 8 weeks**
- **Surgery or 3rd line immunosuppression**

* Exclude low Mg/Cholesterol
** 3rd line immunosuppressive therapy restricted to specialized centers

[Manz et al, SMW 2011]
Treatment algorithm for maintenance of remission of ulcerative colitis

In remission
- 5-ASA, topical or systemic or in combination; 1.5g or 3g

Relapse
- Colectomy

Relapse
- Chronic active cause (steroid-dependency)
  - Azathioprin
    - Relapse
    - Cylcosporin? Tacrolimus? Infliximab?

No Remission

[Roiger et al, Aktuelle Therapieoptionen, Unimed Verlag, 2. Auflage, Kapitel 6.2. Seite 97]
**Therapy algorithm for Crohn’s disease based on ECCO Consensus and IBD Ahead treatment recommendations*.**

**Dosage of Therapeutics**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>Mesalazine 3 – 4.5 g/d</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Budesonide 9 – 12 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prednisone 0.75 – 1 mg/kg/d</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressors</td>
<td>Azathioprine (AZA) 2 – 2.5 (max. 3) mg/kg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-Mercaptopurine (6-MP) 1 – 1.5 mg/kg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate (MTX) 15 – 25 mg, 1 x / week</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Metronidazole 1000 – 1500 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin 1000 mg/d</td>
<td></td>
</tr>
<tr>
<td>Biologics</td>
<td>Adalimumab (HUMIRA®) Subcutaneous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 0: 160 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 2: 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 4: 40 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Then every 2 weeks: 40 mg</td>
<td></td>
</tr>
<tr>
<td>Infliximab (Remicade®)</td>
<td>Infusion over 1 – 2 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 0: 5 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 2: 5 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 6: 5 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Then every 8 weeks: 5 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Certolizumab Pegol (Cimzia®)</td>
<td>Subcutaneous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 0: 400 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 2: 400 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 4: 400 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Then every 4 weeks: 400 mg</td>
<td></td>
</tr>
</tbody>
</table>

* This therapy algorithms in Crohn’s disease have been developed in the context of an Abbott Advisory Board Meeting in 2012 by Prof. C. Braegger, Dr. Ph. de Saussure, Prof. F. Froehlich, Dr. C. Gaia, Prof. F. Michetti, PD Dr. C. Mottet, Prof. G. Rogler, Prof. B. Sauter, PD Dr. A. Schöpfer, Prof. F. Seibold, Prof. A. Straumann, PD Dr. S. Vavricka and is based on ECCO Guidelines and IBD Ahead Consensus Publication 2011.

**Moderately active localised ileocaecal Crohn's disease***

1. **Step 1 Induction therapy**
   - **Response:** Tapering of steroids
   - **Evaluation of effectiveness after 1 – 2 weeks**

2. **Step 2 Maintenance therapy**
   - **Response:** No medication
   - **Response:** Tapering of steroids
   - **Monitoring every 10 – 12 weeks**
   - **Primary non-response**
   - **Intolerance**
   - **Non-response**

3. **Step 3 Relapse therapy/Therapy failure**
   - **Consider surgery**
   - **anti-TNF**
   - **anti-TNF**
   - **Consider surgery**
   - **Multiple predictors for severe course**

* Moderately active localised ileocaecal Crohn’s disease: CDAI >150-300, no previous surgeries/Therapeutic pathway: is valid for luminal Crohn’s disease, no stenosis, no fistulas.

# This data refers to ECCO statements.
Severely active localised ileocaecal Crohn's disease

- **Prednisone + AZA/6-MP/MTX**
  - Evaluation of effectiveness after 1–2 weeks
  - Response: Tapering of Prednisone

  - Relapse within 12 weeks during tapering of steroids
  - No response after 2–4 weeks

- **AZA/6-MP/MTX**
  - Monitoring every 10–12 weeks. For therapy failures:

  - **Anti-TNF + AZA/6-MP/MTX**
    - Monitoring every 10–12 weeks
    - Response: Tapering of Prednisone
    - Primary non-response
      - Intolerance
    - Steroid-dependent
    - Steroid-refractory
      - Steroid-intolerant

- **Anti-TNF**
  - Reduction of interval
  - Dosage increase

- **Consider surgery**

- **Alternative anti-TNF**

- **Response**

- **Therapy failure**

- **Induction therapy**

- **Maintenance therapy**

- This data refers to ECCO statements.

Colonic disease

- **Mild disease**
  - Mesalazine topical or p.o.

- **Moderate to severe disease**
  - Prednisone + AZA/6-MP/MTX

- **Response**

- **Therapy failure**:
  - After min. 12 weeks

- **Induction therapy**

- **Maintenance therapy**

- **Step 1**
  - Response
  - Steroid dependent
  - Steroid-refractory
    - Steroid-intolerant

- **Step 2**
  - Response unsatisfactory or loss of response
  - Primary non-response
    - Intolerance

- **Step 3**
  - Alternatives
    - Anti-TNF
    - Reduction of interval
    - Dosage increase

- **Consider surgery**

- This data refers to ECCO statements.
**Intestine**

**IBD Therapy**

**Extensive small bowel disease***

- **Prednisone + AZA/6-MP/MTX**
  - Evaluation of effectiveness after 1–2 weeks

  **Response**
  - Tapering of Prednisone
  - **AZA/6-MP/MTX + anti-TNF**

  **Non-response**
  - 2–4 weeks
  - Steroid-refractory
  - Steroid-intolerant

  **Worsening of symptoms**

  **Step 1** Induction therapy

  **Step 2** Maintenance therapy

  **Step 3** Relapse therapy

  **Response**
  - 10–12 weeks

  **Non-response**
  - Unsatisfactory or loss of response

  **Step 1** Induction therapy

  **Step 2** Maintenance therapy

  **Step 3** Relapse therapy

* **Extensive small bowel disease**: >50cm or >1 segment affected, with or without colonic involvement.

# This data refers to ECCO statements.

---

**Fistulating Disease**

**Symptom-free perianal fistula**

- Therapy optional

**Simple perianal fistula***

- Exclude perianal abscess or treat immediately if present (9F)

- **Antibiotics** (Metronidazole or Ciprofloxacin) and/or
- **Seton** or Fistulotomy

**Complex perianal fistula***

- **AZA/6-MP and/or anti-TNF**
  - **Seton**
  - **Antibiotics** and/or
  - **Anti-TNF**

**Simple fistula**: Perianal fistula without branching

**Complex Fistula**: Perianal branched fistula system

**Seton**: Non-cutting Seton

# This data refers to ECCO statements.
Screening before anti TNF-Therapy

Contra-indications of anti-TNF\(\alpha\) therapy with respect to findings during screening before treatment.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>If yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Suspicion of abscess confirmed on MRI and abdominal- CT</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>2. Flare of colitis</td>
<td></td>
</tr>
<tr>
<td>a. <em>Clostridium difficile</em> toxin positive in stools</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>b. CMV infection proven by biopsies</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>3. Cardiac failure NYHA III or IV</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>4. Neurological disease</td>
<td>Use with caution</td>
</tr>
<tr>
<td>5. Chronic liver disease</td>
<td>Use with caution</td>
</tr>
<tr>
<td>6. History of malignancy</td>
<td>Use with caution</td>
</tr>
<tr>
<td>7. Positive interferon-gamma assay for tuberculosis and/ or chest X-ray prior to a 4 week-treatment with isoniazide (prevention with isoniazide 300mg/day over 9 Months)(^\text{a})</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>8. Positive HIV, uncontrolled disease</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>9. Positive HBV serology(^\text{a})</td>
<td></td>
</tr>
<tr>
<td>a. elevated liver enzymes</td>
<td></td>
</tr>
<tr>
<td>b. normal liver enzymes</td>
<td></td>
</tr>
<tr>
<td>c. isolated anti-HBc Ab</td>
<td></td>
</tr>
<tr>
<td>10. Negative Varicella zoster virus history and VZ serology</td>
<td></td>
</tr>
<tr>
<td>11. Recurrent urinary tract infections</td>
<td>Urine analysis</td>
</tr>
<tr>
<td>12. Patient has travelled to or lived in a tropical area</td>
<td>Evaluate for parasites in stools</td>
</tr>
<tr>
<td>13. Abnormal complete blood cell count or CRP</td>
<td>Further evaluations</td>
</tr>
<tr>
<td>14. Abnormal transaminases levels</td>
<td>Further evaluations</td>
</tr>
<tr>
<td>15. Women: last gynaecological examination &gt;1 year</td>
<td>Obtain exam</td>
</tr>
</tbody>
</table>


**Vaccinations and anti-TNF\(\alpha\)-Therapy**

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Dose(s)</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance of routine vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria-tetanus vaccine ± pertussis ± inactivated poliomyelitis</td>
<td>1</td>
<td>Maintenance: every 10 years (1 dose) Combined vaccine available</td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>1</td>
<td>Revaccination annually (1 dose)</td>
</tr>
<tr>
<td>23-valent pneumococcal vaccine</td>
<td>1</td>
<td>Maintenance: every 5 years (1 dose)</td>
</tr>
<tr>
<td>Vaccinations to be discussed before initiating an anti-TNF(\alpha) therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B vaccine</td>
<td>3</td>
<td>0, 1 and 6 months</td>
</tr>
<tr>
<td>Additional dose(s) if anti-HBs Ab &lt; 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella vaccine</td>
<td>2</td>
<td>0 and 1 months</td>
</tr>
<tr>
<td>In patients with negative serology and temporarily off ISS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tick borne-encephalitis vaccine</td>
<td>3</td>
<td>0, 1 and 6 months</td>
</tr>
<tr>
<td>Maintenance every 10 years if continuing residence in endemic area (1 dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papilloma virus vaccine</td>
<td>3</td>
<td>0, 2 and 6 months</td>
</tr>
<tr>
<td>Recommended for women &lt; 25 year-old with normal Pap smear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinations for travellers (depending on risk of exposure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A vaccine</td>
<td>2</td>
<td>0 and 6 months</td>
</tr>
<tr>
<td>Combined HAV-HBV vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typhoid (non oral) vaccine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Poliomyelitis (non oral) vaccine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Japanese encephalitis vaccine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4-valent ACWY meningococcal vac.</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rabies vaccine</td>
<td>3</td>
<td>0, 1 and 4 weeks</td>
</tr>
<tr>
<td>Live vaccines contra-indicated in patients on ISS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined measles-mumps-rubella</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral poliomyelitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral typhoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow fever</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IBD Therapy**

**Intestine**

**IBD Therapy**
Intestine

IBD Therapy

Monitoring of efficacy and safety\(^4\), \(^7\)

Recommendations for general IBD monitoring\(^4\)

<table>
<thead>
<tr>
<th>Mandatory</th>
<th>Clinical examination:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of bowel movements per day</td>
</tr>
<tr>
<td></td>
<td>Level of abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Extra-intestinal symptoms</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Other medications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Imaging to be discussed according to clinical symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endoscopy</td>
</tr>
<tr>
<td></td>
<td>CT scan or MRI</td>
</tr>
<tr>
<td></td>
<td>Check on vaccination status</td>
</tr>
<tr>
<td></td>
<td>Calprotectin(^7)</td>
</tr>
</tbody>
</table>

Fecal calprotectin for the management of Crohn’s disease\(^7\)

<table>
<thead>
<tr>
<th>Monitoring disease activity</th>
<th>Faecal calprotectin levels correlate well with endoscopic and histological disease activity. In Crohn's disease, the correlation is better for colonic than for ileal disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring response to treatment</td>
<td>Low faecal calprotectin levels after treatment indicate response of endoscopic disease activity better among adult than paediatric patients.</td>
</tr>
<tr>
<td>Establishing mucosal healing</td>
<td>Mucosal healing seems to indicate controlled IBD activity. It has been associated with sustained clinical remission as well as reduced rates of hospitalisation and surgical resection. Data on faecal calprotectin as a surrogate marker of MH are emerging, but the evidence is not yet conclusive.</td>
</tr>
<tr>
<td>Prediction of IBD relapse</td>
<td>Faecal calprotectin levels &lt;150 µg/g indicate IBD remission with a low risk of relapse. Reports from prospective intervention studies using calprotectin-guided therapy strategies to investigate the long-term outcome of IBD are not yet available.</td>
</tr>
</tbody>
</table>

Risk for severe disease course: predictive factors

Patients with poor prognosis benefit most of an early therapeutic begin with immunosuppressiva or biologics (5F)\(^1\)

<table>
<thead>
<tr>
<th>Predictive factors</th>
<th>Disease course</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– Chronically active disease</td>
<td>L Beaugerie et al.; Gastroenetro 2006; 130:650-56</td>
</tr>
<tr>
<td></td>
<td>– Hospitalization</td>
<td>C Loly et al.; Scand J Gastroenterol 2008; 43:948-54</td>
</tr>
<tr>
<td></td>
<td>– Surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Steroid-dependence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Complex perianal disease</td>
<td>C Loly et al.; Scand J Gastroenterol 2008; 43:948-54</td>
</tr>
<tr>
<td></td>
<td>– Resection of colon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Small bowel resection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Stoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Penetrating disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Colonectomy</td>
<td>M Allez et al.; Am J Gastroenterol 2002; 97:947-53</td>
</tr>
<tr>
<td></td>
<td>– Surgery, fistula and abscesses</td>
<td>E Lindberg; Gut 1992; 33: 779-782</td>
</tr>
</tbody>
</table>

### Intestine
#### IBD Therapy

## Treatments during pregnancy

<table>
<thead>
<tr>
<th>Class of product</th>
<th>Products</th>
<th>FDA Classification</th>
<th>Pregnancy</th>
<th>Breast Feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Prednisolone, Budesonide</td>
<td>C</td>
<td>1st Trimester: a slightly increased risk of palatoschisis cannot be excluded if used during sensitive phase between 8–11 weeks of pregnancy. 2nd–3rd Trimester / Perinatal: depending on the duration of treatment, dose and indication, a intra-uterine growth retardation, prematurity delivery, transient hypoglycaemia, hypotonia and electrolyte abnormality in the newborn have been shown.</td>
<td>No risk for the breastfed baby, even if high-dose treatment over a short period of time.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Metronidazole, Ciprofloxacin</td>
<td>B</td>
<td>C</td>
<td>1st Trimester: No risk reported for the breastfed baby, not even if high dose treatment for a short period of time, no evidence for mutagenic or carcinogenic effects if intra-uterine exposure. 2nd–3rd Trimester / Perinatal: No evidence for fetotoxic risk.</td>
</tr>
<tr>
<td>Immuno-modulators</td>
<td>Azathioprine, 6-MP</td>
<td>D</td>
<td></td>
<td>1st Trimester: no teratogenic risk in &gt;1500 pregnant women treated orally 2nd–3rd Trimester / Perinatal: on several occasions a reduced birth weight and an increased number of premature births have been observed. 1st Trimester: teratogenic potential with a variable pattern of malformations; dose-dependent. A dose &lt;10mg/week does not seem to be teratogenic. 2nd–3rd Trimester / Perinatal: can lead to intra-uterine growth retardation, bone marrow suppression and in very rare cases foetal intra-uterine death.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td>X</td>
<td></td>
<td>1st Trimester: no teratogenic effect in &gt;100 assessed pregnancies. 2nd–3rd Trimester / Perinatal: Only individual case reports of exposure during 2–3 trimester. Placental transfer presumed in case of more mature placenta.</td>
</tr>
<tr>
<td>TNF-α Antibody</td>
<td>Adalimumab</td>
<td>B</td>
<td></td>
<td>1st Trimester: no teratogenic effect in &gt;100 assessed pregnancies 2nd–3rd Trimester / Perinatal: Only individual case reports of exposure during 2–3 trimester. Placental transfer presumed in case of more mature placenta.</td>
</tr>
<tr>
<td>Infliximab</td>
<td></td>
<td>B</td>
<td></td>
<td>1st Trimester: No data available, but experience from company registries and case reports: no embryotoxic risk. 2nd–3rd Trimester / Perinatal: only case reports. In case of a more mature placenta, transfer to the foetus via an active process can reach maternal therapeutic serum concentrations.</td>
</tr>
<tr>
<td>Certolizumab</td>
<td></td>
<td>B</td>
<td></td>
<td>1st Trimester: Potential concern that Fab’ fragment can pass the placenta by passive diffusion 2nd–3rd Trimester / Perinatal: Only case reports. Probably lower placental transfer compared to other anti-TNFα antibodies (shown in rats).</td>
</tr>
</tbody>
</table>

**Category A:** Appropriate and well-controlled studies have not shown any risk to the foetus during the first three months of pregnancy (and there is no sign of risk in the later weeks of pregnancy).

**Category B:** Reproductive studies carried out in animals have not shown any risk to the foetus; however no appropriate or well controlled study exists in pregnant women. **Category C:** Reproductive studies carried out in animals have shown a harmful effect for the foetus; however no appropriate or well controlled study exists in humans. The use of this medication in pregnant women can however be justified when the potential benefit to the latter outweighs the potential risks. **Category D:** Data on the secondary effects coming from observations or clinical or post-marketing studies carried out in humans clearly show risks for the human foetus. The use of this medication in pregnant women can however be justified when the potential benefit to the latter outweighs the potential risks. **Category X:** Studies carried out on animals or on humans have showed malformations in the foetus and/or, on the basis of data on the secondary effects coming from clinical or post-marketing observations, show risks for the human foetus, the risks outweighing by far the potential benefits.
Intestine

**Clostridium difficile therapy**

**Initial episode**
Preferred: metronidazole 500 mg orally three times daily or 250 mg four times daily for 10 to 14 days
Alternative: vancomycin 125 mg orally four times daily for 10 to 14 days

**First relapse**
Confirm diagnosis (see text)
If symptoms are mild, conservative management may be appropriate
If antibiotics are needed, repeat treatment as in initial episode above

**Second relapse**
Confirm diagnosis (see text)
Tapering and pulsed oral vancomycin (below), with or without probiotics (Saccharomyces boulardii 500mg orally twice daily). The probiotics may be overlapped with the final week of the taper and continued for two additional weeks in the absence of antibiotics.

- 125 mg orally four times daily for 7 to 14 days
- 125 mg orally twice daily for 7 days
- 125 mg orally once daily for 7 days
- 125 mg orally every other day for 7 days
- 125 mg orally every 3 days for 14 days
Alternative: fidaxomicin 200mg orally twice daily for 10 days

**Subsequent relapse**
Confirm diagnosis (see text)
Vancomycin 125 mg orally four times daily for 14 days, followed by rifaximin 400 mg twice daily for 14 days
Alternative: fidaxomicin 200 mg orally twice daily for 10 days

**Celiac disease**

**Presenting symptoms of adult celiac patients**

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

[Modified from Zipser RD et al. Digestive Diseases and Sciences 2003]

**Diagnostics in celiac disease**

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Intention</th>
<th>Preferred procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>asymptomatic people</td>
<td>screening</td>
<td>serology antiamoebial antibodies or tissue transglutaminase antibodies</td>
</tr>
<tr>
<td>unspecific symptoms</td>
<td>case finding</td>
<td>serology antiamoebial antibodies or tissue transglutaminase antibodies</td>
</tr>
<tr>
<td>strong suspicion of celiac disease</td>
<td>diagnostic</td>
<td>duodenal biopsy</td>
</tr>
</tbody>
</table>

Intestine
Celiac disease

Range of clinical presentations in celiac disease

Silent celiac disease
- patients who do not complain of any symptoms and do not seek medical advice
- most of these patients are relatives of patients with known celiac disease or members of the general population found to be positive in the search for antiendomysial antibodies or tissue transglutaminase antibodies

Minor celiac disease
- patients complaining of trivial, transient, or apparently unrelated symptoms (i.e. dyspepsia, abdominal discomfort and bloating, mild or occasional altered bowel habit without malabsorption mimicking irritable bowel syndrome, unexplained anemia, isolated fatigue, cryptic hypertransaminasemia, infertility, peripheral and central neurologic disorders, osteoporosis, short stature, dental enamel defects, dermatitis herpetiformis) or of isolated symptoms of autoimmune diseases often reported in association with celiac disease
- most of these patients are biopsied after a positive search of antiendomysial antibodies or tissue transglutaminase antibodies

Major celiac disease
- patients complaining of frank malabsorption symptoms (i.e. diarrhoea which is often nocturnal and with incontinence, steatorrhoea suggested by loose discoloured, greasy, and frothy stools that are difficult to flush away, weight loss and other features of malnutrition, cramps, tetany, and peripheral oedema due to electrolyte and albumin depletion); symptoms of other autoimmune diseases may be associated
- most of these patients are biopsied only on the basis of symptoms

[Modified from Di Sabatino A et al. Lancet 2009]
## Intestine
### Constipation therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Active pharmaceutical ingredient</th>
<th>Example</th>
<th>Indication</th>
<th>Mechanism of action</th>
<th>Dose / maximum recommended dose</th>
<th>Commonest adverse events</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bulk laxative</strong></td>
<td>Psyllium Sterculiae gum</td>
<td>Metamucil®, Laxiplant® soft Colosan® mite, Normaco I*</td>
<td>Stool softener in constipation, for long term use</td>
<td>Increases colonic residue, stimulating peristalsis; Natural fibers that undergo bacterial degradation, increases colonic residue, stimulating peristalsis</td>
<td>Titrate up to ~20g; should be taken with plenty of water to avoid intestinal obstruction</td>
<td>Bloating and flatus, especially at the onset of treatment</td>
<td>Ileus, acute constipation, stool impaction</td>
</tr>
<tr>
<td><strong>Osmotic laxative/poorly absorbed sugars</strong></td>
<td>Lactulose Lactitol</td>
<td></td>
<td>Symptomatic treatment of constipation, for regular use</td>
<td>Colonic retention of water, due to osmotic effect of poorly absorbed sugars, stimulating peristalsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactulose</td>
<td>Duphalac® Importal®</td>
<td>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</td>
<td>Lactulose: 15–45 ml once or twice (initial 3 days), then dose reduction to 10–25 ml Lactitol: 30 ml (= 20g) once a day (initial 4–5 days), then reduce to maintenance dose 15 ml (10g) once daily</td>
<td>Gas and bloating, especially at the onset of treatment</td>
<td>Ileus, abdominal pain of unknown origin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polyethylene glycol / Macrogol</td>
<td>Movicol® Transipeg®</td>
<td>Organic polymers that are poorly absorbed and not metabolized by colonic bacteria</td>
<td>6–36 g once or twice a day, can be mixed with noncarbonated beverages</td>
<td>Bloating and cramping (less than other poorly absorbed sugars)</td>
<td>Ileus, IBD, toxic megacolon, bowel perforation</td>
<td></td>
</tr>
</tbody>
</table>

**Stimulant laxative**

Stimulates intestinal motility or secretion, effect within 6–12 hours
## Intestine
### Constipation therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intestine</th>
<th>Acute constipation, for occasional use</th>
<th>Converted by colonic bacteria to their active form; colonic stimulation by active secretion of electrolytes into the umen and inhibition of reabsorption</th>
<th>12–150 mg daily before bedtime</th>
<th>Ileus, spastic constipation, abdominal pain of unknown origin, hypokalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthraquinones</strong></td>
<td>Senna</td>
<td>Purseannid®, X-Prep®, Liquid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diphenyl-methane derivatives</strong></td>
<td>Bisacodyl</td>
<td>Dulcolax®, Bisacodyl, Prontolax®</td>
<td>Acute constipation, for short term use or prolonged use under medical supervision</td>
<td>Hydrolyzed by endogenous esterases; stimulates directly active secretion of water and electrolytes into the lumen and inhibition of water and electrolyte reabsorption</td>
<td>5–10 mg every night</td>
</tr>
<tr>
<td></td>
<td>Sodium picosulfat</td>
<td>Laxoberon®</td>
<td>Acute constipation, for short term use or prolonged use under medical supervision in opioid induced constipation</td>
<td>Hydrolyzed to its active form by colonic bacterial enzymes; affects only the colon</td>
<td>5–10 mg every night</td>
</tr>
<tr>
<td><strong>Prokinetic agents</strong> (Benzofuran)</td>
<td>Prucaloprid</td>
<td>Resolor®</td>
<td>Chronic constipation in woman after failure of dietary restrictions and 2 laxatives within 9 months, prescribed only by gastroenterologists</td>
<td>Selective, high affinity 5-HT4 (serotonin) receptor agonist, altering colonic motility patterns</td>
<td>1–2 mg once daily, stop if no effect with 2 mg daily within 4 weeks</td>
</tr>
</tbody>
</table>

### 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

### Abdominal cramping, pain, nausea

### Headache, abdominal pain, nausea, diarrhea

### Ileus, spastic constipation, abdominal pain of unknown origin, hypokalemia
Intestine
Mid Gl Bleeding

Main causes of mid gastrointestinal bleeding:

<table>
<thead>
<tr>
<th>Bleeding source</th>
<th>Frequency:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiodysplasia</td>
<td>20–60%</td>
</tr>
<tr>
<td>Ulcerations (IBD, NSAIDs etc.)</td>
<td>10–40%</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>1–10%</td>
</tr>
</tbody>
</table>

[Elia 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 capsule enteroscopy 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

Lower Gl Bleeding

Causes of lower gastrointestinal bleeding:

<table>
<thead>
<tr>
<th>Bleeding source</th>
<th>Frequency:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diverticula</td>
<td>30%</td>
</tr>
<tr>
<td>Colitis (ischemic, IBD)</td>
<td>15%</td>
</tr>
<tr>
<td>Carcinoma, Polyps</td>
<td>13%</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>10%</td>
</tr>
<tr>
<td>Anorectal diseases</td>
<td>11%</td>
</tr>
<tr>
<td>Upper gastrointestinal bleeding</td>
<td>10%</td>
</tr>
<tr>
<td>Unknown</td>
<td>2–8%</td>
</tr>
</tbody>
</table>

[Elia GH et al.: Gastrointest Endosc 2004]

Important facts to remember:
- Overall mortality of lower GIB 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
- 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]
Intestine

Polyps

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.)
### Intestine
#### Polyps

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Polyp histology &amp; secondary criteria</th>
<th>Colonoscopy interval</th>
<th>Colonoscopy interval when findings normal</th>
</tr>
</thead>
</table>
| I             | Tubular adenoma  
• 1–2 polyps and  
• size ≤ 1 cm and  
• no high-grade dysplasia and  
• negative family history (1st degree relatives) | 5 y                  | stop surveillance                        |
|               | 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 | 3 y                  | 5 y                                      |
| II            | 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 | ≤3 months for examination of the polypectomy site; then 3 y | 5 y                                      |
| III           | pT1/carcinoma in situ within the polyp  
• polypectomy endoscopically not complete or  
• resection margins histologically not free of carcinoma  
• poorly differentiated or undifferentiated (G3-G4) or  
• invasion of lymphatic and/or venous vessels |                                      |                                          |
| IV            | Hyperplastic polyps  
proximal to the rectosigmoid or size > 1 cm or > 20 polyps | 3 y                  | 5 y                                      |

→ *surgical resection generally indicated*
Intestine

CRC

Recommendations for surveillance after curative surgery for colo-rectal 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

<table>
<thead>
<tr>
<th>Months postoperatively</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination &amp; CEA levels</td>
<td>quarterly within 1st year</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CT scan of chest &amp; abdomen</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>In case of rectal cancer: rectosigmoidoscopy &amp; EUS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

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
**HNPCC – Amsterdam criteria**

1. There should be at least 3 relatives with an HNPCC-associated cancer (colorectal, endometrium, small bowel, ureter, renal pelvis)
2. One should be a 1st degree relative of the other two
3. At least two successive generations should be affected
4. FAP should be excluded in the colorectal cancer case(s), if any
5. Tumors should be verified by pathological examination

[Adapted from Vasen HF et al. Gastroenterology 1999]

**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, 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]
## Characteristic features of High Risk Colorectal Cancer

<table>
<thead>
<tr>
<th>Condition/Inheritance</th>
<th>Gene</th>
<th>Lifetime cancer risks</th>
<th>%</th>
<th>Nonmalignant features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lynch-Syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>autosomal-dominant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hMLH1 &amp; 2</td>
<td>子宫</td>
<td>50–80</td>
<td></td>
<td>physical or nonmalignant features – besides</td>
</tr>
<tr>
<td>hMSH6</td>
<td>子宫</td>
<td>40–60</td>
<td></td>
<td>keratoacanthomas and sebaceous adenomas/carcinomas – are rare</td>
</tr>
<tr>
<td>hPMS2</td>
<td>子宫</td>
<td>11–19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EpCAM</td>
<td>子宫</td>
<td>9–12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>子宫</td>
<td>2–7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>子宫</td>
<td>4–5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUTYH</td>
<td>子宫</td>
<td>3–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td>子宫</td>
<td>1–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMAD4</td>
<td>子宫</td>
<td>1–3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMPR1A</td>
<td>子宫</td>
<td>&gt; 50</td>
<td></td>
<td>hyperplastic polyps, sessile serrated polyps, traditional serrated adenomas and mixed adenomas</td>
</tr>
</tbody>
</table>

### Familial adenomatous polyposis (FAP)

| **autosomal-dominant**|       |                        |    |                                                                                       |
| **APC**              |子宫 | 100                    |    | 100s to 1000s of colorectal adenomas gastric fundic glands and duodenal adenomatous polyposis |
|                      |      | 4–12                   |    | congenital hypertrophy of the retinal pigment epithelium; epidermoid cysts; osteomas    |
|                      |      | < 1                    |    | dental abnormalities                                                                   |
|                      |      | 1–2                    |    | desmoid tumors                                                                         |

### Attenuated FAP

| **autosomal-dominant**|       |                        |    |                                                                                       |
| **APC**              |子宫 | 70                     |    | <100 colonic adenomas                                                                   |
|                      |      | 4–12                   |    | upper gastrointestinal polyposis similar to FAP                                         |
|                      |      | 1–2                    |    | other non-malignant features are rare in attenuated FAP                                  |

### MUTYH-associated polyposis

| **autosomal-recessive**|       |                        |    |                                                                                       |
| **MUTYH**             |子宫 | 80                     |    | colonic phenotype similar to attenuated FAP; duodenal polyposis                        |
|                      |      | 4                      |    |                                                                                       |

### Peutz-Jeghers syndrome

| **autosomal-dominant**|       |                        |    |                                                                                       |
| **STK11**            |子宫 | 54                     |    | mucocutaneous pigmentation                                                             |
|                      |      | 39                     |    | gastrointestinal hamartomatous (Peutz-Jeghers) polyps                                   |
|                      |      | 11–36                  |    | (Peutz-Jeghers) polyps                                                                 |
|                      |      | 29                     |    |                                                                                       |
|                      |      | 21                     |    |                                                                                       |
|                      |      | 15                     |    |                                                                                       |
|                      |      | 13                     |    |                                                                                       |
|                      |      | 9                      |    |                                                                                       |
|                      |      | <1                     |    |                                                                                       |

### Juvenile polyposis syndrome

| **autosomal-dominant**|       |                        |    |                                                                                       |
| **SMAD4**            |子宫 | 39                     |    | gastrointestinal hamartomatous (juvenile) polyps                                      |
| **BMPR1A**           |子宫 | 21                     |    | features of hereditary hemorrhagic telangiectasia; congenital defects                  |
|                      |      | 39                     |    |                                                                                       |
|                      |      | 21                     |    |                                                                                       |

### Hyperplastic polyposis

| **inheritance unknown**|       |                        |    |                                                                                       |
| **?**                 |子宫 | > 50                   |    | hyperplastic polyps, sessile serrated polyps, traditional serrated adenomas and mixed adenomas |

[Adapted from Jasperson KW et al. Gastroenterology 2010]
## Intestine
### High risk colorectal cancer conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cancer</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lynch-Syndrome</strong></td>
<td>colon</td>
<td>colonoscopy every 1–2y, start at 20–25y</td>
</tr>
<tr>
<td></td>
<td>endometrium/ovary</td>
<td>consider prophylactic hysterectomy &amp; bilateral salpingooophorectomy after childbearing complete; gynecological cancer screening</td>
</tr>
<tr>
<td></td>
<td>upper urinary tract</td>
<td>consider annual urinalysis, beginning at 30–35y</td>
</tr>
<tr>
<td></td>
<td>upper GI tract other</td>
<td>consider EGD (incl. side view endoscope) every 1–2y, start at age 30–35y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>annual physical examination including skin (sebaceous carcinoma ?)</td>
</tr>
<tr>
<td><strong>Familial adenomatous polyposis (FAP)</strong></td>
<td>colon</td>
<td>colonoscopy every 1–2y, start at 10–12y (for attenuated FAP at 18–20y)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prophylactic colectomy when polyps become unmanageable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(if remaining rectum or ileal pouch, screen every year)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EGD every 1–3y, start at 20–25y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>annual physical examination, including skin</td>
</tr>
<tr>
<td><strong>MUTYH-associated polyposis</strong></td>
<td>colon</td>
<td>colonoscopy every 2–3y, start at 25y</td>
</tr>
<tr>
<td></td>
<td>duodenum</td>
<td>prophylactic colectomy when polyps become unmanageable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EGD every 1–3y, start at 20–25y</td>
</tr>
<tr>
<td><strong>Peutz-Jeghers syndrome</strong></td>
<td>colon</td>
<td>colonoscopy every 2–3y, start with symptoms or latest at 18–20y</td>
</tr>
<tr>
<td></td>
<td>breast</td>
<td>annual mammogram &amp; breast MRI, start at 25y</td>
</tr>
<tr>
<td></td>
<td>pancreas</td>
<td>MRCP and/or EUS every 1–2y, start at 30y</td>
</tr>
<tr>
<td></td>
<td>stomach/small bowel</td>
<td>EGD and abdominal CT with oral contrast every 2–3y, start at 10y</td>
</tr>
<tr>
<td></td>
<td>cervix/uterus/ovary</td>
<td>annual pelvic examination, pap smear and transvaginal US, start at 18y</td>
</tr>
<tr>
<td></td>
<td>testses</td>
<td>annual testicular examination, start at 10y</td>
</tr>
<tr>
<td><strong>Juvenile polyposis syndrome</strong></td>
<td>colon</td>
<td>colonoscopy every 2–3y, start with symptoms or latest at 18–20y</td>
</tr>
<tr>
<td></td>
<td>stomach</td>
<td>EGD every 1–3y</td>
</tr>
<tr>
<td><strong>Hyperplastic polyposis</strong></td>
<td>colon</td>
<td>colonoscopy every 1–2y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prophylactic colectomy when polyps become unmanageable</td>
</tr>
</tbody>
</table>

[Adapted from Jasperson KW et al. Gastroenterology 2010]
**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

**rx**
- 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 – 2mg IV (over 2-3 min) under cardiovascular monitoring (atropine bedside!)
- **CONTRAINDICATIONS:** bronchial asthma, recent myocardial infarction, beta-blockers, bradyarrhythmias, hyperthyreosis
- If no response...

**endoscopic decompression**
- At the latest if cecum > 12cm
- If no response...

**surgery or PEC**
- Endoscopic: percutaneous endoscopic colostomy (PEC)
- Surgery: cecostomy or colectomy
**Intestine**

**Diverticulitis**

### Classification and management

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


### Diverticulitis

**Diagnosis:**
- CT has highest sensitivity and specificity for diverticulitis
  [Lohrmann D: Eur J Radiol 2005]
- Classifications of Hansen/Stock and Hinchey correlate to prognosis
  [Kaiser AM: Am J Gastroenterol 2005]

**Important facts to remember:**
- Serious course in immunocompromised patients
- Avoid opiates, steroids, ASS, NSAID
  [Humes DJ: Gut 2011; Strate LL: Gastroenterology 2011]
- Controversial efficacy of fiber supplementation
  [Peery AF: Gastroenterology 2012]
### Differential Diagnosis

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

### $\alpha$-1-AT-Clearance

Formula: $\alpha$-1-AT-Clearance (ml/d) = \[ \frac{\text{Stool volume}}{\text{H9251}} \times \frac{\text{Stool } \alpha\text{-1-AT}}{\text{Serum } \alpha\text{-1-AT}} \]

*Normal values.* <24 ml/d without diarrhea; <56 ml/d with diarrhea. **Interpretation.** In the case of marked albumin loss syndrome, values exceeding 200 ml/d are possible. **Sources of error**

- Diarrhoea
- $\alpha$-1-Antitrypsin is degraded at gastric pH levels <3.5 (so the test is of limited value in Ménétrier’s disease).
- Blood in faeces leads to misleading high $\alpha$-1-antitrypsin levels.
### Diagnosis Evaluations

#### Table 20–3. Useful laboratory tests in evaluation of intestinal malabsorption.

<table>
<thead>
<tr>
<th>Test</th>
<th>Impaired intraluminal Digestion</th>
<th>Mucosal Disease</th>
<th>Lymphatic Obstruction</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool fat (qualitative, quantitative)</td>
<td>Increased (concentration usually &gt; 9.5%)</td>
<td>Increased (concentration usually &lt;9.5%)</td>
<td>Increased</td>
<td>False-negative result if inadequate ingestion of dietary fat or recent barium ingestion; false-positive result with castor oil or mineral oil ingestion</td>
</tr>
<tr>
<td>Stool elastase</td>
<td>Low in moderate and severe pancreatic exocrine insufficiency</td>
<td>May be low due to dilution</td>
<td>Usually normal</td>
<td>Low specificity for pancreatic disease if small intestinal disease is present</td>
</tr>
<tr>
<td>Stool ova and parasites and specific parasitic antigens</td>
<td>May be positive in parasitic biliary cholangiopathy</td>
<td>May diagnose Giardia, Isospora, cryptosporidia, microsporidia, tapeworms Lactulose and glucose breath hydrogen test</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Serum carotene</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Low values may occur in normal subjects who ingest little dietary carotene</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>May be normal or increased in patients with untreated lipoprotein abnormality</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Usually normal, except with bacterial overgrowth</td>
<td>Often decreased</td>
<td>Often decreased</td>
<td></td>
</tr>
<tr>
<td>Prothrombin activity</td>
<td>Decreased if severe</td>
<td>Decreased if severe</td>
<td>Decreased if severe</td>
<td>May also be decreased in liver disease but parenterally administered vitamin K should induce normalization if caused by malabsorption</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>Usually normal if pancreas is the cause</td>
<td>Decreased</td>
<td>Decreased</td>
<td>May reflect hypoalbuminemia</td>
</tr>
<tr>
<td>Serum 25-OH vitamin D</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Serum iron</td>
<td>Normal</td>
<td>Often decreased</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Serum folate</td>
<td>Normal</td>
<td>Often decreased</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Xylose absorption</td>
<td>Normal, except with bacterial overgrowth</td>
<td>Abnormal, unless disease confined to distal small intestine</td>
<td>Normal</td>
<td>Requires normal gastric emptying and renal function</td>
</tr>
<tr>
<td>Lactose absorption (lactose tolerance test or breath hydrogen after lactose load)</td>
<td>Normal, except in some instances of bacterial overgrowth</td>
<td>Increase in plasma glucose &lt;20 mg/dL; increased breath H₂</td>
<td>Normal</td>
<td>May be abnormal in all categories if patient has primary intestinal lactase deficiency; requires normal gastric emptying</td>
</tr>
<tr>
<td>Vitamin B₁₂ absorption (Schilling test)</td>
<td>Decreased in bacterial overgrowth and exocrine pancreatic insufficiency</td>
<td>Decreased in extensive ileal disease</td>
<td>Normal</td>
<td>Requires good renal function</td>
</tr>
<tr>
<td>Lactulose and glucose breath hydrogen test</td>
<td>Early appearance of H₂ in breath in bacterial overgrowth</td>
<td>Normal</td>
<td>Normal</td>
<td>Requires normal gastric emptying; false-positive results may occur in patients with rapid small intestinal transit</td>
</tr>
<tr>
<td>Secretin/cholecystokinin stimulation tests</td>
<td>Abnormal in chronic pancreatic exocrine insufficiency</td>
<td>Normal</td>
<td>Normal</td>
<td>Relatively low sensitivity, cumbersome and labor intensive</td>
</tr>
<tr>
<td>IgA anti-tissue transglutaminase and IgA antiendomysial antibody</td>
<td>Absent</td>
<td>Present in celiac sprue</td>
<td>Absent</td>
<td>Lower sensitivity in infants and all ages in mild disease, false negative results in IgA deficiency</td>
</tr>
<tr>
<td>Endoscopic intestinal biopsy</td>
<td>Normal except in severe bacterial overgrowth</td>
<td>Often abnormal</td>
<td>Often abnormal</td>
<td>May miss patchy mucosal disease</td>
</tr>
<tr>
<td>Wireless capsule endoscopy</td>
<td>Usually normal</td>
<td>Often abnormal</td>
<td>Often abnormal</td>
<td>Labor intensive, cannot biopsy lesions, may obstruct strictured intestine</td>
</tr>
</tbody>
</table>
Intestine

Lactose intolerance

**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, M. Crohn, 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**

1. **Symptoms lactose intolerance** → **Lactose H2-AT Breath test**
   - **Lactose H2-AT Breath test**
     - **LCT 13910**
       - **Gene test+ H2-AT+** → **Primary LI**
       - **Gene test- H2-AT-** → **Secondary LI bacterial overgrowth**
     - **LCT 13910**
       - **Gene test+ H2-AT-** → **False negative Breath test asymptomatic deficiency**
       - **Gene test- H2-AT+** → **No LI**

---

Small intestine bacterial overgrowth

**Lactulose H2-Breath Test (bacterial overgrowth)**

**Principle of the lactulose H2-breath test**

The human intestine cannot metabolize lactulose (polysaccharide). 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 (H2, CH4) are transported via the portal venous system through the liver unmetabolized, and are expelled out via the lungs. An increase in the concentrations of H2 and CH4 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.
**Intestine**

**Proctology hemorrhoids**

### Definition

#### Internal hemorrhoids

<table>
<thead>
<tr>
<th>Grade</th>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Protrusion in proctoscope</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Emerging towards outside with pressing; spontaneous reposition</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Spontaneous prolapse without reposition</td>
<td></td>
</tr>
</tbody>
</table>

- Plexus hemorrhoidalis internus
- Normal: hemorrhoidal cushion/padding

#### External hemorrhoids

- Thrombosed external hemorrhoids
- Perianal hematoma caused by vein rupture

- Plexus hemorrhoidalis externus
- Normal: not visible

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

### Proctology fissures

#### Fissure – Drug treatment

<table>
<thead>
<tr>
<th>Nitro-glycerine</th>
<th>Ca-channel blocker</th>
<th>Botulinum toxin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Glyceryl trinitrate 0.2%</td>
<td>Nifedipine 2%</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td>Intrasphincter pressure ↓</td>
<td>Intrasphincter pressure ↓</td>
</tr>
<tr>
<td><strong>Healing rate</strong></td>
<td>27–85%</td>
<td>45–95%</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>0–43%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Advantage(s)</strong></td>
<td>Inexpensive</td>
<td>Inexpensive</td>
</tr>
<tr>
<td><strong>Disadvantage(s)</strong></td>
<td>Headache 20–70%</td>
<td>Compliance</td>
</tr>
</tbody>
</table>

[AGA technical review. Gastroenterology 2003]

---

#### Fissure Therapy

- Nifedipine 2% for 6 weeks + stool regulation
- Stool regulation for further 3 months
- Nifedipine 2% for 6 weeks + stool regulation
- Fissure debridement (and/or Botox)
- Follow-up at 6 weeks
- V-Y flaps + (Botox)

[Hetzer FA et al.: Praxis 2000]
Liver segments

Liver segments I

Anterior view
- Right cranial
- Left cranial
- Caudal
- Lobus caudatus dorsal

Inferior view
- Right cranial
- Ventral left cranial
- Left cranial

Liver segments II

Subcostal cut cranial
- IVb
- III
- II
- IVa

Subcostal cut median
- V
- VI
- VII
- VIII

Subcostal cut caudal
- IVb
- IVa
- I
- VII

Longitudinal cut
- Left lobe lateral
- Left lobe paramedian left
- Both liver lobes
- Right lobe
- Right liver lobe portal vein cut
- Right liver lobe wide lateral

Liver segments

Hepatology

Liver segments

Anterior view
- Right cranial
- Left cranial
- Caudal
- Lobus caudatus dorsal

Inferior view
- Right cranial
- Ventral left cranial
- Left cranial
Hepatopathy

**Hepatopathology**

**Increased transaminases (< 5x ULN)**
- Obesity, alcohol, hepatotoxic medication

**Hematology:** hemoglobin, MCV, MCHC, leucocytes + differentiation, thrombocytes

**Chemistry:** alk. phosphatase, y-GT, bilirubin, ferritin, transferrin saturation, albumin,

**Serology:** hepatitis A (HAV-AB), hepatitis B (HBsAg, HBcAB), hepatitis C (HCV-AB)

**Purely hepatocellular**

- Positive serology

**Cholestatic**

**Laboratory:** ANA, auto-antibodies (SMC, LKM, SLC), ceruloplasmin, α1-Antitrypsin deficiency, transglutaminase-AB, endomysium-AB, serum electrophoresis, genetics (HFE)

**Ultrasound – abdomen**

**Liver biopsy**

**Markedly increased transaminases (> 15x the upper normal value)**
- Hepatic ALAT > ASAT
  - Non-alcoholic fatty liver disease (NAFLD)
  - Non-alcoholic steatohepatitis (NASH)
  - Medication/toxins (see separate list)
  - Chronic hepatitis B/C
  - 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)
  - Macro

**MRCP/ERCP**

**Slightly increased transaminases (< 5x the upper normal value)**
- Hepatic ALAT > ASAT
  - Non-alcoholic fatty liver disease (NAFLD)
  - Non-alcoholic steatohepatitis (NASH)
  - Medication/toxins (see separate list)
  - Chronic hepatitis B/C
  - 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)
  - Macro

**Acute viral hepatitis (A-E, Herpes)**

**Medication/toxins (see separate list)**

**Ischemic hepatitis**

**Autoimmune hepatitis**

**Acute bile duct obstruction**

**Acute Budd-Chiari syndrome**
Hepatopathy

Medication
- Paracetamol
- Alpha-methylidopa
- Amoxicillin/Clavulanic acid
- Amiodarone
- Carbamazepine
- Dantrolene sodium
- Disulfiram
- Etretinate
- Fluconazole
- Gilbenclamide
- Halothane
- Heparin
- Isoniazide
- Ketoconazole
- Labelol
- Nicotinic acid
- Nitrofurantoin
- Non-steroidal antiinflammatories
- Phenylbutazone
- Phenytoin
- Protease inhibitors
- Sulfonamide
- Propylthiouracil
- Statins
- Trazadone
- Valproate
- Zafirlukast

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

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

Toxins
- Tetrachloromethane (CCl4)
- Trichlormethane/chloroform (CHCl3)
- Dimethylformamide (C3H7NO)
- Dimethylnitropropane (C3H7NO2)
- Hydrazine/diamide (N2H4)
- Chlorofluorocarbon (CFC)
- Trichloroethylene (C2HCl3)
- Toluene (C7H8, C6H5CH3)

Hepatopathy

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

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- Chlorofluorocarbon (CFC)
- Trichloroethylene (C2HCl3)
- Toluene (C7H8, C6H5CH3)

Cholestatic Hepatopathy

Unconjugated hyperbilirubinemia
- Gilbert–Meulengracht syndrome
- Neonatal jaundice (ICterus neonatorum)
- Hemolysis
- Hematoma
- Crigler–Najjar syndrome
- Ineffektive erythropoiesis (thalssemia, megaloblastic anemia)

Conjugated hyperbilirubinemia
- Extrahepatic cholestasis
- Hepatitis (viral, autoimmune, alcoholic)
- Liver cirrhosis
- Sepsis
- Toxic hepatitis (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
Hepatopathy

Increased alkaline phosphatase
- Hepatobiliary
  - Bile duct obstruction
  - Primary biliary cirrhosis (PBC)
  - Primary sclerosing cholangitis (PSC)
- Medication (see separate list)
- Hepatitis (viral, autoimmune, alcoholic)
- Liver cirrhosis
- Vanishing bile duct syndrome
- Benign recurrent intrahepatic cholestasis (BRIC)
- 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

Medication/Toxins/Drugs
- Anabolic steroids
- Allopurinol
- Amoxicillin/clavulanic acid
- Captopril
- Carbamazepine
- Chlorpropamide
- Ciproheptadine
- Diltiazem
- Erythromycin
- Estrogens
- Floxuridine
- Fluocinocillin
- Fluphenazine
- Gold salts
- Imipramine
- Indinavir
- Iprindole
- Nevaprin
- Methyltestosterone
- Ecstasy (3,4-methylenedioxy-N-methylamphetamine)
- Oxaprozin
- Pizotyline
- Quinidine
- Tolbutamide
- Trimethoprim/sulfamethoxazole


Ascites-SBP-HRS

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.

<table>
<thead>
<tr>
<th>SAAG &gt; 11 g/L</th>
<th>SAAG &lt; 11 g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver cirrhosis (80%)</td>
<td>Malignant ascites (10%)</td>
</tr>
<tr>
<td>(often hemorrhagic; LDH, lactate, increased cholesterol/triglyceride)</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Ileus, pancreatitis, serositis with collagenosis, peritoneal tuberculosis, mesenteric infarct, chylous ascites, biliary ascites, nephrotic syndrome, exudative enteropathy</td>
<td></td>
</tr>
</tbody>
</table>

Serum Ascites Albumin Gradient (SAAG) = Albumin<sub>serum</sub> – Albumin<sub>ascites</sub>

Therapy
General measures
Salt restriction (in addition, avoid using salt, no convenience foods), fluid restriction to 1 liter/d (only with Na<sup>+</sup> < 125 mmol/L), no NSAR

First-time ascites
1. Spironolactone: initially 100 mg/d, then increase weekly up to 400 mg/d
   Side effects: hyperkalemia (stop at K<sup>+</sup> > 6 mmol/L), gynecomastia
2. Torasemide: with therapy failure (< 2 kg/week weight reduction) initially 40 mg/d, slowly increase up to a maximum of 160 mg/d
   Side effects: hypokalemia, kidney insufficiency
Hepatology

Ascites-SBP-HRS

Recurring ascites
Direct combination spironolactone 100 mg/d + torasemide 40 mg/d. Increase to 400 mg/d + 160 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, kidney insufficiency (creatinine > 180µmol/L)

[Hinet 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/mL ± positive ascites culture (positive in 60%)

**Bacteria**
E. coli (37%), K. 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 48h: 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 2x 400 mg/d as longterm therapy
- Acute gastrointestinal bleeding: ceftriaxone 2 g/d IV for 5 days or norfloxacin 2x 400 mg/d for 7 days

[H Hepatol (2010)]

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
- 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)
Hepatology
Ascites-SBP-HRS

**Therapy**

**General measures**

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

**HRS Typ 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 un-tl max. 14 days
*Cave: tachyarrhythmia, ischemia (cardial, peripheral)*

**Albumin:** 1 g/kg on Day 1 (max. 100 mg/d), thereafter 20-40 g/d serum albumin > 45 g/L
=> stop therapy (lung edema)

Secondary **TIPS** (Transjugular Intrahepatic Portosystemic Shunt)

**HRS Typ II**

Terlipressin + albumin or TIPS, although limited data

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

---

**CHILD-PUGH-Score**

<table>
<thead>
<tr>
<th>Parameter / Points</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT s &gt; contr.</td>
<td>&lt; 4</td>
<td>4 – 6</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>Quick %</td>
<td>&gt; 70</td>
<td>40 – 70</td>
<td>&lt; 40</td>
</tr>
<tr>
<td>INR</td>
<td>&lt; 1.7</td>
<td>1.7 – 2.3</td>
<td>&gt; 2.3</td>
</tr>
<tr>
<td>Bilirubin µmol/l</td>
<td>&lt; 35</td>
<td>35 – 50</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>in PBC µmol/l</td>
<td>&lt; 70</td>
<td>70 – 170</td>
<td>&gt; 170</td>
</tr>
<tr>
<td>Albumin g/l</td>
<td>&gt; 35</td>
<td>28 – 35</td>
<td>&lt; 28</td>
</tr>
<tr>
<td></td>
<td>&gt; 3.5</td>
<td>2.8 – 3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Ascites</td>
<td>none</td>
<td>mild</td>
<td>moderate to severe</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>none</td>
<td>Grades 1–2</td>
<td>Grades 3–4</td>
</tr>
</tbody>
</table>

**Point score**

<table>
<thead>
<tr>
<th>CHILD-Stage</th>
<th>1st year survival rate</th>
<th>2nd year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 – 6</td>
<td>A – compensated</td>
<td>100%</td>
</tr>
<tr>
<td>7 – 9</td>
<td>B – impaired</td>
<td>80%</td>
</tr>
<tr>
<td>10 – 15</td>
<td>C – decompensated</td>
<td>45%</td>
</tr>
</tbody>
</table>

HCC Hepatocellular carcinoma

Barcelona Clinic Liver Cancer (BCLC)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour characteristics</th>
<th>Associated liver features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A (early HCC)</td>
<td>Single tumour</td>
<td>No portal hypertension and normal bilirubin level</td>
</tr>
<tr>
<td>A1 PST 0</td>
<td>Single tumour</td>
<td>Portal hypertension, normal bilirubin level</td>
</tr>
<tr>
<td>A2 PST 0</td>
<td>Single tumour</td>
<td>Portal hypertension and abnormal level</td>
</tr>
<tr>
<td>A3 PST 0</td>
<td>3 tumours, all &lt; 3cm</td>
<td>Child-Pugh A-B</td>
</tr>
<tr>
<td>A4 PST 0</td>
<td>Single tumour</td>
<td>Child-Pugh A-B</td>
</tr>
<tr>
<td>Stage B (intermediate HCC)</td>
<td>Large multinodular</td>
<td>Child-Pugh A-B</td>
</tr>
<tr>
<td>PST 0</td>
<td>Vascular invasion</td>
<td>Child-Pugh A-B</td>
</tr>
<tr>
<td>Stage C (advanced HCC)</td>
<td>Any</td>
<td>Child-Pugh C</td>
</tr>
<tr>
<td>PST 1-2</td>
<td>Vascular invasion or extrahepatic spread</td>
<td>Child-Pugh A-B</td>
</tr>
<tr>
<td>Stage D (end stage HCC)</td>
<td>Any</td>
<td>Child-Pugh C</td>
</tr>
<tr>
<td>PST 3-4</td>
<td>Vascular invasion or extrahepatic spread</td>
<td>Child-Pugh C</td>
</tr>
</tbody>
</table>

[Bruix and Sherman, Hepatology, 2011]

Barcelona Clinic Liver Cancer (BCLC) Staging and Treatment Strategy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour characteristics</th>
<th>Associated liver features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Single &lt;2cm Carcinoma in situ</td>
<td>No portal hypertension and normal bilirubin level</td>
</tr>
<tr>
<td>PST 0, Child A</td>
<td>Single or 3 nodules ≤3cm PS 0</td>
<td>Portal hypertension, normal bilirubin level</td>
</tr>
<tr>
<td>Early stage (A)</td>
<td>3 nodules ≤3cm</td>
<td>Portal hypertension and abnormal level</td>
</tr>
<tr>
<td>Very early stage (0)</td>
<td>Associated diseases</td>
<td>Child-Pugh A-B</td>
</tr>
<tr>
<td>Intermediate stage (B)</td>
<td>Multinodular, PS 0</td>
<td>Child-Pugh C*</td>
</tr>
<tr>
<td>Advanced stage (C)</td>
<td>Portal invasion, N1, M1, PS 1-2</td>
<td>Child-Pugh C*</td>
</tr>
<tr>
<td>Terminal stage (D)</td>
<td>Portal invasion, N1, M1, PS 1-2</td>
<td>Child-Pugh C*</td>
</tr>
<tr>
<td>Stage D</td>
<td>Portal invasion, N1, M1, PS 1-2</td>
<td>Child-Pugh C*</td>
</tr>
</tbody>
</table>

Abbreviations: OS: Overall survival, PST: Performance status, PEI: percutaneous ethanol injection, RF: radiofrequency ablation

[Modified after EASL Clinical Practice Guidelines, 2011]
In patients with gastroesophageal varices, do not initiate anticoagulation until after adequate prophylaxis for variceal bleeding has been instituted.

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

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

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

TIPS

Indications for TIPS

Efficacy determined by controlled trials
- Secondary prevention variceal 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

Contraindications to TIPS placement

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

Relative
- Hepatoma, especially if central
- Obstruction of all hepatic veins
- Portal vein thrombosis
- Severe coagulopathy (INR 5)
- Thrombocytopenia of 20,000/cm³
- Moderate pulmonary hypertension

Complications of TIPS

Complications Frequency (%)
- TIPS dysfunction
- Thrombosis (10 – 15)
- Occlusion/stenosis (18 – 78)
- Transcapsular puncture (33)
- Intraperitoneal bleed (1 – 2)

Vmax: normal 40 – 60 cm/sec
Hepatopetal mVPmax < 39 cm/s indicates dysfunction
Hepatofugal mVPmax < 28 cm/s indicates dysfunction

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

[Abrahades et al. Am J Gastroenterol 2005
Hepatology

MELD Score

- MELD Risk Score = 10 x [0.957 x loge (creatinine mg/dl)]
- + 0.378 x loge (bilirubin mg/dl)
- + 1.120 x loge (INR)]
- + 0.643 x cause of the cirrhosis (0 = alcohol or cholestatic liver enzyme, 1 = other causes)

\[
\begin{align*}
\text{MELD Score} &= 10 \times \ln(\text{creatinine mg/dl}) + 0.378 \times \ln(\text{bilirubin mg/dl}) + 1.120 \times \ln(\text{INR}) + 0.643 \times \text{cause of the cirrhosis}\smallskip \\
&= \ln(\text{bilirubin / 17.1}) + 3.8 + \ln(\text{creatinine / 88.4}) + 9.6 + \ln(\text{INR}) + 11.2 + 6.4
\end{align*}
\]

\(in = \text{natural logarithm}\)

online: www.unos.org/resources/MeldPeldCalculator.asp?index=98

[Discrimination factor or Maddrey Score (Maddrey, 1988):
DF = 4.6 x (Prothrombin time [TP] - control-TP [sec]) + bilirubin [mg/dl] > 32]

Liver cirrhosis, MELD Score

MELD Score: Model of End Stage Liver Disease

- 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):

\[
\text{MELD Score} = 9.57 \times \ln(\text{Creatinine}) + 3.78 \times \ln(\text{Bilirubin}) + 11.20 \times \ln(\text{INR}) + 6.43
\]

- 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/1calculators-MELD.php

MELD Score

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)
  - 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
Hepatology

Acute Liver Failure

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


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


Hemochromatosis

Target Population

<table>
<thead>
<tr>
<th>Symptomatic**</th>
<th>Asymptomatic*</th>
<th>Adult 1st degree relative of HH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum transferrin saturation and ferritin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS &lt; 45% and normal ferritin</td>
<td>TS &gt; 45% and/or elevated ferritin</td>
<td></td>
</tr>
<tr>
<td><strong>HFE Genotype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Compound heterozygote C282Y/H63D C282Y heterozygote or non-C282Y</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin &lt; 1000 μg/L and normal liver enzymes</td>
<td>Ferritin &gt; 1000 μg/L or elevated liver enzymes</td>
<td></td>
</tr>
<tr>
<td>Exclude other liver or hematologic diseases ± liver biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic phlebotomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver biopsy for HIC and histopathology</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Step 1]

[Step 2]

[Step 3]


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

Wilson Disease

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/24h, > 100 µg/24h)
• 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)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ceruloplasmin:</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.1 g/L = 2</td>
<td>2</td>
</tr>
<tr>
<td>0.1-0.2 g/L = 1</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 0.2 g/L = 0</td>
<td>0</td>
</tr>
<tr>
<td>24-hour urinary copper excretion:</td>
<td></td>
</tr>
<tr>
<td>&gt; 2x ULN = 2</td>
<td>2</td>
</tr>
<tr>
<td>1-2x ULN = 1</td>
<td>1</td>
</tr>
<tr>
<td>Normal = 0</td>
<td></td>
</tr>
<tr>
<td>Presence of Kayser-Fleischer rings:</td>
<td></td>
</tr>
<tr>
<td>Present = 2</td>
<td>2</td>
</tr>
<tr>
<td>Absent = 0</td>
<td>0</td>
</tr>
<tr>
<td>Neurologic symptoms*:</td>
<td></td>
</tr>
<tr>
<td>Severe = 2</td>
<td>2</td>
</tr>
<tr>
<td>Mild = 1</td>
<td>1</td>
</tr>
<tr>
<td>Absent = 0</td>
<td>0</td>
</tr>
<tr>
<td>Liver copper**:</td>
<td></td>
</tr>
<tr>
<td>(no cholestasis present):</td>
<td></td>
</tr>
<tr>
<td>&gt;4 µmol/g = 2</td>
<td>2</td>
</tr>
<tr>
<td>0.8-4 µmol/g = 1</td>
<td>1</td>
</tr>
<tr>
<td>&lt;0.8 µmol/g = -1</td>
<td></td>
</tr>
<tr>
<td>Genetic testing for ATP7B mutations:</td>
<td></td>
</tr>
<tr>
<td>2 chromosomes = 4</td>
<td>1</td>
</tr>
<tr>
<td>1 chromosome =</td>
<td></td>
</tr>
<tr>
<td>Coombs-negative hemolytic anemia:</td>
<td></td>
</tr>
<tr>
<td>Present = 1</td>
<td>2</td>
</tr>
<tr>
<td>Absent = 0</td>
<td>0</td>
</tr>
</tbody>
</table>

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]
Hepatology

Hepatitis B

Diagnosis and progression

<table>
<thead>
<tr>
<th>HBc</th>
<th>HBe</th>
<th>HBs</th>
<th>DNA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>Ag</td>
<td>AB</td>
<td>Ag</td>
<td>AB</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
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</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
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<td>+</td>
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<td>+</td>
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<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Progression

HBV infection → Asymptomatic infection → Healed

10% → Acute hepatitis → Fulminant hepatitis → Cirrhosis → HCC

65% → Chronic hepatitis → HBs carrier

25% → Virus persistence

1% → Fulminant hepatitis

20% → Chronic hepatitis

80% → HBs carrier

Indication for therapy

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

ALWAYS treat patients with liver cirrhosis

Treatment algorithm for HBeAg negative Hepatitis B

Liver cirrhosis?

Yes

NUC with high resistance threshold (Entecavir, Tenofovir)

No

NUC mit normal resistance threshold (Lamivudine, Telbivudine)

Long-term therapy with NUC
Hepatitis B

Treatment

Treatment algorithm for HBeAg positive Hepatitis B

Chronic HBe-antigen positive Hepatitis B

Interferon therapy? (ALAT >3x ULN, HBV-DNA < 2x10^6 IU/mL)

- Yes: pegylated INF
- No: nucleoside / nucleotide analogs

Liver cirrhosis?

- Yes: NUC with high resistance threshold (Entecavir, Tenofovir)
- No: NUC with normal resistance threshold (Lamivudine, Telbivudine)

Seroconversion (HBeAg-, HBeAK+) after 48 weeks?

- Yes: Continue NUC >12 months + HBV-DNA negative
- No: Follow-up at 24 and 48 weeks

Long-term therapy with NUC

Therapy modifications with virological breakthrough

Therapy answer

Primary non-response
(= reduction HBV-DNA <1 log10 IU/mL after 3 months)

- Exclude malcompliance

Partial response
(= HBV-DNA > 20 IU/mL, but reduction > 1log10 IU/mL after 24 weeks)

- Exclude malcompliance
- Change to NUC with higher resistance threshold (Entecavir oder Tenofovir) – change of treatment or additional to the current therapy
- If there is only partial re-sponse after 48 weeks with double therapy, change to Entecavir + Tenofovir.

Viral breakthrough
(= increase HBV-DNA > 1 log10 IU/mL against Na-dir)

- Exclude malcompliance
- Lamivudine / Telbivudine / Entecavir: in addition, Teno-fovir
- If there is only partial response after 48 weeks with double therapy, change to Entecavir + Tenofovir.
Hepatology
Hepatitis B

Pregnancy and Hepatitis B

Mother
- Risk of transmission varies: HBeAg positive (70%), HBeAg negative (2-10%, HBc only (1%))
- With higher virus load (>107 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* (200IE HBsAK always after 0-12 h) immunization postpartum
- Serological control after 7-12 months (HBsAg, HBcAK)

* in Switzerland: Hepatect CP, Hepatitis B Immunoglobulins Behring
### Hepatitis B

#### Treatment

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA (PCR)</th>
<th>ALT</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>&gt;20,000 IU/mL</td>
<td>≤2x ULN</td>
<td>Low efficacy with current treatment. Consider treatment when ALT becomes elevated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider treatment in persons &gt;40 years, ALT persistently high normal-2xULN, or with family history of HCC.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider treatment if HBV DNA &gt; 20,000 IU/mL and biopsy shows moderate/severe inflammation or significant fibrosis.</td>
</tr>
<tr>
<td>+</td>
<td>&gt;20,000 IU/mL</td>
<td>&gt;2x ULN</td>
<td>Observe for 3-6 months and treat if no spontaneous HBeAg loss.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider liver biopsy prior to treatment if compensated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Immediate treatment if icteric or clinical decompensation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN-α/pegIFNα, LAM, ADV, ETV, TDF or LdT may be used as initial therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADV not preferred due to weak antiviral activity and high rate of resistance after 1st year. LAM and LdT not preferred due to high rate of drug resistance. End-point of treatment: Seroconversion from HBeAg to anti-HBe.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration of therapy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• IFN-α: 16 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• PegIFNα: 48 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• LAM/ADV/ETV/LdT/TDF: minimum 1 year, continue for at least 6 months after HBeAg seroconversion.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN-α non-responders/ contraindications to IFN-α → TDF/ETV.</td>
</tr>
<tr>
<td>-</td>
<td>&gt;20,000 IU/mL</td>
<td>&gt;2x ULN</td>
<td>IFN-α/pegIFNα, LAM, ADV, ETV, TDF or LdT may be used as initial therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LAM and LdT not preferred due to high rate of drug resistance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADV not preferred due to weak antiviral activity and high rate of resistance after 1st year. End-point of treatment: not defined.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration of therapy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• IFN-α/pegIFNα: 1 year.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• LAM/ADV/ETV/LdT/TDF: &gt;1 year.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFN-α non-responders/ contraindications to IFN-α → TDF/ETV.</td>
</tr>
<tr>
<td>-</td>
<td>&gt;2,000 IU/mL</td>
<td>1-&gt;2x ULN</td>
<td>Observe, treat if HBV DNA or ALT becomes higher.</td>
</tr>
<tr>
<td></td>
<td>≤2,000 IU/mL</td>
<td>≤ULN</td>
<td>Compensated: HBV DNA &gt;2,000 IU/mL-Treat: LAM/ADV/ETV/LdT/TDF may be used as initial therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• LAM and LdT not preferred due to high rate of drug resistance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADV not preferred due to weak antiviral activity and high rate of resistance after 1st year.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HBV DNA &lt;2,000 IU/mL consider treatment if ALT elevated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decompensated: Coordinate treatment with transplant center, LAM (or LdT) + ADV, TDF, ETV preferred. Refer for liver transplant.</td>
</tr>
<tr>
<td>+/-</td>
<td>Detectable</td>
<td>Cirrhosis</td>
<td>Compensated: HBV DNA &gt;2,000 IU/mL-Treat: LAM/ADV/ETV/LdT/TDF may be used as initial therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• LAM and LdT not preferred due to high rate of drug resistance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADV not preferred due to weak antiviral activity and high rate of resistance after 1st year.</td>
</tr>
<tr>
<td>+/-</td>
<td>Undetectable</td>
<td>Cirrhosis</td>
<td>Decompensated: Observe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decompensated: Refer for liver transplant.</td>
</tr>
</tbody>
</table>

[Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal; IFN-α, interferon alpha; pegIFN-α, pegylated interferon alpha; LAM, lamivudine, ADV, adefovir; ETV, entecavir; LdT, telbivudine; TDF, tenofovir disoproxil fumarate]

* Treatment may be considered in patients with HBV DNA 2,000-20,000 IU/mL, particularly if they are older or have cirrhosis. Although several studies including the REVEAL study showed a correlation between serum HBV DNA and clinical outcomes such as HCC, only patients with 1 or both samples at baseline and last follow-up with serum HBV DNA >100,000 copies/mL (20,000 IU/mL) had significantly increased risk of HCC (Chen, JAMA).
Hepatitis B

Treatment

Management of antiviral-Resistant HBV

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 200mg and tenofovir 300mg
$ 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

Hepatitis C

Definitions of virological response patterns

Rapid virological response (RVR) Undetectable¹ HCV RNA at week 4

Extended RVR (eRVR) Undetectable HCV RNA at weeks 4 and 12²

RVR³ Undetectable HCV RNA at week 8³

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» in this paper 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

Telaprevir response-guided therapy in non-cirrhotic treatment-naïve and prior relapse genotype 1 hepatitis C-infected patients

**HCV Therapy GT 1: Telaprevir (Incivo)**

- **Null response**
- **Partial response**
- **Breakthrough**
- **Non response**
- **Relapse**

**Detection limit**

**SVR: 72–75%**

- **Peg-IFN alfa + Ribavirin**
  - Stop treatment at Week 24 if undetectable at Week 4 and 12
  - Peg IFN alfa + Ribavirin if detectable at Week 4 or 12

**Treatment**

- If > 1000 IU/ml at Week 4 or 12: discontinue all drugs
- If detectable at Week 24 or 36: discontinue all drugs

Hepatology

Hepatitis C

HCV Therapy GT 1: Telaprevir (Incivo)

Telaprevir: treatment algorithm in genotype 1 hepatitis C-infected patients with prior partial or null response or cirrhosis

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Telaprevir</th>
<th>Peg-IFN alfa + Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If > 1000 IU/ml at Week 4 or 12: discontinue all drugs
If detectable at Week 24 or 36: discontinue all drugs

Telaprevir – DRESS

DRESS = Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms

When to suspect DRESS – alert criteria:
Onset from 6-10 weeks after first dose
Rapidly progressing exanthema
Prolonged fever (> 38.5°C)
Facial edema

If any DRESS alert criteria are found, the patient should be assessed for the following DRESS confirmation criteria:
Enlarged lymph nodes (at least 2 sites)
Eosinophilia (≥ 700/uL or ≥ 10%)
Atypical lymphocytes
Internal organ involved:
  a. liver: alanine aminotransferase, alkaline phosphatase ≥2x upper limit of normal
  b. Kidney: rise in creatinine ≥ 150% basal level

[ALT: alanine aminotransferase]
**Hepatology**

**Hepatitis C**

**Treatment of chronic hepatitis C**

**Swissmedic Treatment Regimen with Telaprevir (TPV)**

**Genotype 1**

<table>
<thead>
<tr>
<th></th>
<th>TPV PR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive and Relapser</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive HCV RNA (&lt;1’000 IU/ml) at week 4 and/or week 12</td>
<td>TPV PR</td>
<td>PR</td>
</tr>
<tr>
<td>Naive and Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative HCV RNA at weeks 4 and 12</td>
<td>TPV PR</td>
<td>PR</td>
</tr>
<tr>
<td>Part Resp, Null-Resp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative HCV RNA at weeks 4 and 12</td>
<td>TPV PR</td>
<td>PR</td>
</tr>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>

PR = pegylated interferon, TPV = Telaprevir, BOC = Boceprevir

**Stopping rules:**
- HCV RNA >1’000 IU/ml at week 4 or 12
- Positive HCV RNA at week 24

**Swissmedic Treatment Regimen with Boceprevir (BOC)**

**Genotype 1**

<table>
<thead>
<tr>
<th></th>
<th>PR</th>
<th>BOC PR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive</td>
<td></td>
<td>BOC PR</td>
<td></td>
</tr>
<tr>
<td>Positive HCV RNA at week 8 and negative at week 24</td>
<td>PR</td>
<td>BOC PR</td>
<td>PR</td>
</tr>
<tr>
<td>Part Resp, Relapser</td>
<td></td>
<td>BOC PR</td>
<td></td>
</tr>
<tr>
<td>Positive HCV RNA at week 8 and negative at week 12</td>
<td>PR</td>
<td>BOC PR</td>
<td>PR</td>
</tr>
<tr>
<td>Cirrhosis, Null-Resp</td>
<td></td>
<td>BOC PR</td>
<td></td>
</tr>
<tr>
<td>Negative HCV RNA at weeks 8 and 12</td>
<td>PR</td>
<td>BOC PR</td>
<td></td>
</tr>
</tbody>
</table>

**Stopping rules:**
- Positive HCV RNA at week 12 (not for naive or cirrhosis in compendium, but useful for >100=Stop!)
- Positive HCV RNA at week 24
Hepatology

Hepatitis C

**HCV Therapy GT 2/3: Pegylated Interferon alpha/Ribavirin**

- Chronic HCV Infection GT 2/3 (PCR of HCV-RNA before start of therapy)

  - Week 4 HCV-RNA PCR
  - HCV RNA < 15 IU/ml
  - Therapy 16 weeks

  - Therapy 24 weeks
  - Therapy 48 weeks

  - Week 12 HCV-RNA PCR
  - HCV RNA < 15 IU/ml
  - > 2log decline

  - Therapy stop

- Therapy 24 weeks

**Autoimmune hepatitis**

**Simplified diagnostic criteria for autoimmune hepatitis (AIH)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cutoff</th>
<th>Points</th>
<th>Cutoff</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA or SMA*</td>
<td>≥ 1:40</td>
<td>1</td>
<td>≥ 1:80</td>
<td>2</td>
</tr>
<tr>
<td>LKM</td>
<td>≥ 1:40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLA</td>
<td>positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>&gt; ULN</td>
<td>1</td>
<td>&gt; 1.1 x ULN</td>
<td>2</td>
</tr>
<tr>
<td>Histology</td>
<td>Compatible with AIH</td>
<td>1</td>
<td>Typical of AIH</td>
<td>2</td>
</tr>
<tr>
<td>Absence of viral hepatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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]

**Pegylated Interferon**

- **Alfa-2a (Pegasys):** 180 µg/week s.c.
- **Alfa-2b (Peginteron):** 1.5 µg/kg/week s.c.

**Ribavirin:** 800 mg/day p.o.

[DGVS Guidelines 2010]
### Autoimmune hepatitis

#### Indications for immunosuppressive treatment in autoimmune hepatitis

<table>
<thead>
<tr>
<th>Absolute indications</th>
<th>Relative indications</th>
<th>No indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum AST ≥ 10 fold ULN</td>
<td>Symptoms (fatigue, arthralgia, jaundice)</td>
<td>Asymptomatic with normal or near normal serum and γ-globulin levels</td>
</tr>
<tr>
<td>Serum AST ≥ 5 fold ULN and γ-globulin ≥ 2 fold ULN</td>
<td>Serum AST and/or γ-globulin less than absolute criteria</td>
<td>Inactive cirrhosis or mild portal hypertension (portal hepatitis)</td>
</tr>
<tr>
<td>Bridging necrosis or multiacinar necrosis on histology</td>
<td>Interface hepatitis</td>
<td>Severe leucopenia (&lt; 2.5 x 10⁹/L or thrombocytopenia &lt; 50 x 10⁹/L or known complete deficiency of TPMT activity precludes treatment with azathioprine)</td>
</tr>
<tr>
<td>Incapacitating symptoms</td>
<td>Leucopenia (≤ 2.5 x 10⁹/L) Thrombocytopenia ≤ 50 x 10⁹/L</td>
<td>Vertebral compression, psychosis, brittle diabetes, uncontrolled hypertension, known intolerances to prednisone or azathioprine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone (mg/day)</td>
<td>Prednisone (mg/day)*</td>
</tr>
<tr>
<td>Week 1</td>
<td>60</td>
</tr>
<tr>
<td>Week 2</td>
<td>40</td>
</tr>
<tr>
<td>Week 3</td>
<td>30</td>
</tr>
<tr>
<td>Week 4</td>
<td>30</td>
</tr>
<tr>
<td>Maintainance until endpoint</td>
<td>20 and below</td>
</tr>
<tr>
<td>Reasons for preference</td>
<td>Cytopenia Thiopurine methyltransferase deficiency Pregnancy Malignancy Short course (&lt;6 months)</td>
</tr>
</tbody>
</table>

*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]

Abbreviations: AST = aspartate aminotransferase levels; ULN = upper limit of normal range; TPMT = thiopurine methyltransferase.
### Hepatology

#### Liver and pregnancy

#### Biochemical changes during normal pregnancy

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>hemoglobin</td>
<td>↓ (from 2nd trimester)</td>
</tr>
<tr>
<td>white cell count</td>
<td>↑</td>
</tr>
<tr>
<td>platelets</td>
<td>unchanged</td>
</tr>
<tr>
<td>prothrombin time</td>
<td>unchanged</td>
</tr>
<tr>
<td>transaminases (ALT, AST)</td>
<td>unchanged</td>
</tr>
<tr>
<td>alkaline phosphatase (ALP)</td>
<td>↑</td>
</tr>
<tr>
<td>gGT</td>
<td>unchanged</td>
</tr>
<tr>
<td>albumin</td>
<td>↓</td>
</tr>
<tr>
<td>bilirubin</td>
<td>unchanged</td>
</tr>
<tr>
<td>alpha-fetoprotein</td>
<td>↑</td>
</tr>
<tr>
<td>cholesterol</td>
<td>↑</td>
</tr>
<tr>
<td>uric acid</td>
<td>↓</td>
</tr>
</tbody>
</table>

#### Pregnancy-related liver diseases

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Onset (trimester)</th>
<th>Symptoms</th>
<th>Therapy</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis Gravidarum</td>
<td>1st</td>
<td>nausea, vomiting, weight loss &gt; 5%, dehydration, electrolyte abnormalities</td>
<td>supportive</td>
<td>0.3 – 1.0</td>
</tr>
<tr>
<td>Pre-Eclampsia/Eclampsia</td>
<td>2nd and/or 3rd</td>
<td>headache, visual disturbances, RUQ pain, hypertension, edema, proteinuria, (with seizures : eclampsia)</td>
<td>supportive, prompt delivery</td>
<td>5 – 7</td>
</tr>
<tr>
<td>HELLP</td>
<td>2nd to 3rd or postpartum</td>
<td>nausea, vomiting, headache, RUQ pain, edema, weight gain</td>
<td>supportive, prompt delivery</td>
<td>0.2 – 0.6</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>3rd</td>
<td>anorexia, nausea, vomiting, headache, RUQ pain, liver failure, encephalopathy</td>
<td>immediate delivery</td>
<td>0.005 – 0.010</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>3rd</td>
<td>pruritus, mild jaundice</td>
<td>ursodeoxycholic acid (10-15 mg/kg), delivery after fetal maturity</td>
<td>0.1 – 0.3</td>
</tr>
<tr>
<td>Liver hematoma or rupture</td>
<td>3rd or postpartum</td>
<td>RUQ pain, pre-eclampsia, hypotension, shock</td>
<td>surgery</td>
<td>1 (in patients with HELLP)</td>
</tr>
</tbody>
</table>

- ONSET: 1st trimester, 2nd trimester, 3rd trimester, postpartum
- THERAPY: supportive, prompt delivery, immediate delivery, surgery
- PREVALENCE: 0.3 – 1.0%, 5 – 7%, 0.2 – 0.6%, 0.005 – 0.010%, 0.1 – 0.3%
## Hepatology

### Liver and pregnancy

### Diagnostic laboratory features in pregnancy-related liver diseases

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ALT</th>
<th>Bilirubin</th>
<th>Bile Acids</th>
<th>Prothrombin Time</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis Gravidarum</td>
<td>2 – 4 x ↑</td>
<td>up to 4 x ↑</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Pre-Eclampsia/ Eclampsia</td>
<td>10 – 50 x ↑</td>
<td>2 – 5 x ↑</td>
<td>=</td>
<td>= / ↑</td>
<td>= / ↓</td>
</tr>
<tr>
<td>HELLP</td>
<td>10 – 20 x ↑</td>
<td>2 – 4 x ↑</td>
<td>=</td>
<td>= / ↑</td>
<td>↓</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>5 – 10 x ↑</td>
<td>6 – 8 x ↑</td>
<td>=</td>
<td>↑</td>
<td>= / ↓</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>1 – 10 x ↑</td>
<td>up to 6 x ↑</td>
<td>↑</td>
<td>= / (↑)</td>
<td>=</td>
</tr>
<tr>
<td>Liver hematoma or rupture</td>
<td>10 – 50 x ↑</td>
<td>2 – 10 x ↑</td>
<td>=</td>
<td>= / ↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
## Disorders severely affected by pregnancy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mechanisms of effect of Pregnancy</th>
<th>Clinical Presentation</th>
<th>Diagnosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis E</strong></td>
<td>particularly severe during pregnancy (especially 3rd trimester), possibly related to immunologic changes</td>
<td>malaise, anorexia, nausea, vomiting, abdominal pain and jaundice</td>
<td>IgM antibody and PCR analysis of blood or feces for hepatitis E</td>
<td>supportive therapy for acute infection may require liver transplant</td>
</tr>
<tr>
<td><strong>Hepatic Adenoma</strong></td>
<td>increased growth of adenoma because of hyperestrogenemia</td>
<td>nausea, vomiting and RUQ pain</td>
<td>abdominal US</td>
<td>observe if size &lt; 5 cm surgery if size &gt; 5 cm or symptomatic or intraslesional hemorrhage</td>
</tr>
<tr>
<td><strong>Budd-Chiari syndrome</strong></td>
<td>thrombosis promoted by increased gestational serum levels of estrogen and decrease in AT III levels</td>
<td>RUQ pain, hepatomegaly and ascites</td>
<td>doppler abdominal US, hepatic venography or MR-angiography</td>
<td>selective thrombolytic therapy, surgical shunt or TIPS anticoagulation with heparin because warfarin is contraindicated in pregnancy</td>
</tr>
<tr>
<td><strong>Splenic artery syndrome</strong></td>
<td>can rupture during pregnancy because of compression by gravid uterus</td>
<td>abdominal pain, pulsatile left upper quadrant mass and abdominal bruit in patient with portal hypertension</td>
<td>abdominal doppler US</td>
<td>surgical removal or angiographic occlusion</td>
</tr>
<tr>
<td><strong>Acute intermittent porphyria</strong></td>
<td>symptoms worsened by hyperestrogenemia</td>
<td>abdominal pain, vomiting, constipation, paresthesias in extremities, mental status changes, tachycardia, and ileus</td>
<td>increased urinary porphobilinogen, and xx-aminolevulinic acid</td>
<td>discontinue precipitating drugs, avoid prolonged fasting, and administer hematin and glucose to prevent attacks</td>
</tr>
<tr>
<td><strong>Choledochal cysts</strong></td>
<td>cyst compression by gravid uterus can lead to cyst rupture or cholangitis</td>
<td>abdominal pain, jaundice, and abdominal mass</td>
<td>abdominal US, may require cholangiography</td>
<td>frequently requires surgery: cystectomy and cholecystectomy with either Roux-en-Y hepaticojejunostomy oder cholecdochoojejunostomy</td>
</tr>
</tbody>
</table>
Hepatology
Liver nodule

Diagnostic algorithm for suspected HCC

Liver nodule

- < 1 cm
  - Repeat US at 3 months
  - Growing/ changing character
  - Stable
  - Investigate according to size

- > 1 cm
  - 4-phase MDCT/ dynamic contrast enhanced MRI
  - Arterial hypervascularity AND venous or delayed phase washout
    - Yes
    - Other contrast enhanced study (CT or MRI)
      - Yes
        - HCC
        - Arterial hypervascularity AND venous or delayed phase washout
          - Yes
            - Biopsy
          - No
  - No
    - Biopsy

Abbreviations: CT, computed tomography; MDCT, multidetector CT; MRI, magnetic resonance imaging; US, ultrasound.

[Bruix and Sherman, Hepatology, 2011]
Hepatology

Alcoholic hepatitis

Therapeutic algorithm for the management of alcoholic hepatitis

Establish disease severity

Low risk: MDF < 32 and 1st week decrease in bilirubin, or MELD < 18 and 1st week decrease in MELD by 2 points

High risk: MDF >= 32, presence of HE, or MELD >= 18

Nutritional assessment/intervention

Nutritional assessment/intervention

Supportive care & follow-up

Consider liver biopsy if diagnosis is uncertain

If steroid contraindications or early renal failure

Prednisolone

Pentoxifylline

Biliary Diseases
Gallbladder polyps

Gallbladder Polyps

<table>
<thead>
<tr>
<th>Polyp on ultrasound</th>
<th>&gt; 2 cm</th>
<th>10 – 20 mm</th>
<th>5 – 10 mm</th>
<th>&lt; 5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>«extended» laparoscopic cholecystectomy</td>
<td>asymptomatic</td>
<td>asymptomatic*</td>
<td>asymptomatic</td>
</tr>
<tr>
<td></td>
<td>no gallstones</td>
<td>galstones</td>
<td>repeat ultrasound at 6 and 12 months</td>
<td>increased in size</td>
</tr>
<tr>
<td></td>
<td>repeat ultrasound every 12 months</td>
<td>stable</td>
<td>stable</td>
<td>reassure</td>
</tr>
</tbody>
</table>

*Symptoms: Biliary type pain, common duct obstruction, cholangitis, or recurrent pancreatitis. Dyspepsia is not an indication for surgery.

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

Gallbladder polyps
Biliary Diseases

**Choledocholithiasis**

*Predictors for choledocholithiasis:*

**Clinical predictor:**
- **Very strong**
  - 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 level 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:**
- **High:** Presence of any very strong predictor or both strong predictors
- **Intermediate:** All other patients
- **Low:** No predictors present

**Management:**
- **High:** Preoperative ERCP
- **Intermediate:** Preoperative EUS or MRCP or laparoscopic ultrasound
- **Low:** Laparoscopic cholecystectomy without cholangiography

[Maple JT et al.: Gastrointest Endosc 2010]

**Choledochal cysts**

*Todani classification of bile duct cysts*

[www.radiopaedia.org]
## Pancreas Cysts

### Pancreas Cysts – Fluid Chemistries and Tumor Markers for Specific Diagnoses of Pancreatic Cystic Lesions

<table>
<thead>
<tr>
<th>Pseudocysts</th>
<th>Chemistry/Tumor Marker</th>
<th>Cutoff Value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystadenomas</td>
<td>Amylase</td>
<td>&gt;5000 U/mL</td>
<td>61–94</td>
<td>58–74</td>
</tr>
<tr>
<td></td>
<td>Lipase</td>
<td>&gt;2000 U/mL</td>
<td>41–100</td>
<td>56–59</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>&lt;5 ng/mL</td>
<td>54–100</td>
<td>77–86</td>
</tr>
<tr>
<td>Mucinous neoplasms</td>
<td>Amylase</td>
<td>&gt;5000 U/mL</td>
<td>42</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Lipase</td>
<td>&gt;2000 U/mL</td>
<td>50</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>&gt;400 ng/mL</td>
<td>13–50</td>
<td>75–100</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>&gt;192 ng/mL</td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>CA 19-9</td>
<td>&gt;50,000 U/mL</td>
<td>15–75</td>
<td>81–90</td>
</tr>
<tr>
<td></td>
<td>CA 19-9</td>
<td>&gt;2900 U/mL</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>CA 125</td>
<td>&gt;9 ng/mL</td>
<td>83</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>CA 72-4</td>
<td>&gt;7 ng/mL</td>
<td>80</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>CA 15-3</td>
<td>&gt;121 ng/mL</td>
<td>19</td>
<td>94</td>
</tr>
</tbody>
</table>

[Catalano et al. Gastrointest Endosc. 2009]
Pancreas

Acute pancreatitis

Ranson’s Criteria
At admission or diagnosis
Age > 55 years
WBC >16,000/mm3
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
PaO2 < 60 mmHg

Scoring 1 point for each criterion
• 0 – 2: Mild
• 3 – 5: Moderate, mortality 10 – 20%
• 6 – 11: Severe, mortality > 50%


Acute pancreatitis

APACHE II Scale
Diagnosis:
Equation includes these factors: age, rectal temperature, mean arterial pressure, heart rate, PaO2, arterial pH, serum potassium, sodium, creatinine, hematocrit, WBC count, Glasgow coma scale score, chronic health status


CT Severity Index (Balthazar Score)
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)

## Pancreas

### Acute pancreatitis

#### Factors causing acute pancreatitis

**Toxic**
- Alcohol
- Scorpion toxin

**Metabolic**
- Hypertriglyceridemia
- Hypercalcemia
- Hyperuricemia
- Celiac disease

**Drugs (with best proof)**
- Azathioprine
- Sulfonylamides
- Thiazides
- Furosemide
- Pentamidine
- Didanosine
- Methylpiperazine
- Tetracycline
- Estrogens
- Valproic acid
- Sulindac
- 6-mercaptopuride
- 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
- Mycoplasmas
- Worms

**Vascular**
- Circulatory shock
- Ischemia-reperfusion
- Embolic
- Hypothermia
- Malignant hyperthermia
- Autoimmune vasculitis

**Hereditary**
- SPINK1
- PRSS1
- CFTR

[Adapted from Waldthaler A et al., Dig Dis. 2010]

### Increase of Amylase and Lipase

#### Causes of Increased Amylase and Lipase Levels

<table>
<thead>
<tr>
<th>Amylase</th>
<th>Lipase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Pancreatic pseudocyst</td>
<td>Pancreatic pseudocyst</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>Pancreatic carcinoma</td>
</tr>
<tr>
<td>Biliary tract disease</td>
<td>Biliary tract disease</td>
</tr>
<tr>
<td>(cholecystitis, cholangitis,</td>
<td>(cholecystitis, cholangitis,</td>
</tr>
<tr>
<td>choledocholithiasis)</td>
<td>choledocholithiasis)</td>
</tr>
<tr>
<td>Intestinal obstruction,</td>
<td>Intestinal obstruction,</td>
</tr>
<tr>
<td>pseudo-obstruction, ischemia,</td>
<td>pseudo-obstruction, ischemia,</td>
</tr>
<tr>
<td>or perforation</td>
<td>or perforation</td>
</tr>
<tr>
<td>Acute appendicitis</td>
<td>Acute appendicitis</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

**Other disorders**

- Renal failure
- Parotitis
- 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]