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Novel developments in small bowel diseases and intestinal microbiota — presentation at Gastro Update Europe 2018, Prague

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Celiac disease remains the dominant small intestinal pathology. Can celiac disease also be diagnosed in adults without histology as recommended in the 'biopsy-sparing' guidelines for children? A recent study revealed that high anti-tissue transglutaminase and anti-endomisial antibodies in HLA-DQ2/DQ8 symptomatic patients correlated with villous atrophy in over 90%, and that increasing levels of anti-tissue transglutaminase were paralleled by increasing severity of duodenal damage. Despite such findings, duodenal histology (1–2 biopsies in the bulb and 4 biopsies from the second duodenum) is still the gold standard in adults because: anti-tissue transglutaminase antibodies can be false positive, biopsies can rule out coincidental pathologies, comparison of initial biopsies with subsequent biopsies may be useful as up to 30% of adult celiacs may have persistent atrophy despite gluten-free diet, and biopsies are necessary for the diagnosis of complications such as refractory celiac disease and enteropathy-associated T cell lymphoma.

Non-celiac gluten (wheat) sensitivity is a condition in which ingestion of gluten induces gastrointestinal and extra-intestinal symptoms, and complaints occur in the absence of celiac disease or wheat allergy. The clinical picture may overlap with irritable bowel syndrome. So far there are no reliable biomarkers to identify such individuals. The pathogenesis is not completely understood and the culprit molecule is unknown (gluten?, fructans in FODMAPS?, amylase trypsin inhibitors?). In last year's highlights (Gastro Update Europe 2017) it was mentioned that of such gluten-free diet responders, only 14% relapsed upon gluten challenge, raising doubt that gluten is the culprit in the majority of such gluten-sensitive patients. Fructans, rather than gluten, was shown to induce symptoms in such patients with self-reported non-celiac gluten sensitivity. Currently consumption of gluten-free food products is highly promoted in the community without consideration of potentially negative long-term consequences. Indeed, a recent prospective study indicated that high gluten consumption was associated with a decreased risk of coronary heart disease. Avoidance of gluten may result in reduced consumption

of beneficial whole grains, which may affect cardiovascular risk. The promotion of gluten-free diets among people without celiac disease should not be encouraged.

A severe sprue-like enteropathy may occasionally occur in patients treated with Olmesartan (an angiotensin receptor blocker), rarely with telmisartan or valsartan. Results of epidemiological studies however remain conflicting. The incidence appeared to be higher in older patients, those treated for longer periods and those receiving high cumulative doses. Although the absolute rate is low, Olmesartan should always be considered as a potential cause when evaluating patients with enteropathy.

Management of small bowel angiodysplasia remains problematic. Rebleeding occurs in 20–40% despite (optimal ?) endoscopic therapy. A prior meta-analysis suggested that somatostatin analogs could reduce rebleeding and transfusion requirements; this was confirmed in a recent placebo-controlled trial which evaluated the efficacy and safety of pasireotide-LAR in patients with refractory bleeding. A decrease of at least 30% of pRBC transfusion was obtained in 83% with pasireotide-LAR compared to 25% with placebo. New is the emerging role of thalidomide in the treatment of patients with challenging gastrointestinal bleeding. The current therapeutic algorithm is illustrated below [Becq *et al*., Gastrointest Endosc 2017; 86(5): 792–806] (Fig. 1).

A European consensus group recommends fecal microbiota transplantation (FMT) for both mild and severe recurrent clostridium difficile infection, to be carried out also in clinical practice. FMT can be done in different ways. A recent controlled trial compared the effect of oral capsule FMT versus colonoscopy-delivered FMT. Prevention of recurrent infection after a single treatment was obtained in 96%, both for the capsule group and the colonoscopy group. A significantly greater proportion of participants receiving capsules rated their experience as 'not at all unpleasant' (66 vs 44%).

Is fecal microbiota transplantation helpful in ulcerative colitis? Two prior trials, using one donor for every patient, gave rather conflicting outcomes. Recently, a placebo--controlled trial with multi-donor intensive fecal microbiota transplantation was carried out in active ulcerative colitis. Steroid-free clinical remission and endoscopic remission or response was seen in 27% after FMT, *vs* 8% after placebo. Combining all available studies in ulcerative colitis would indicate a 20% increase in combined clinical

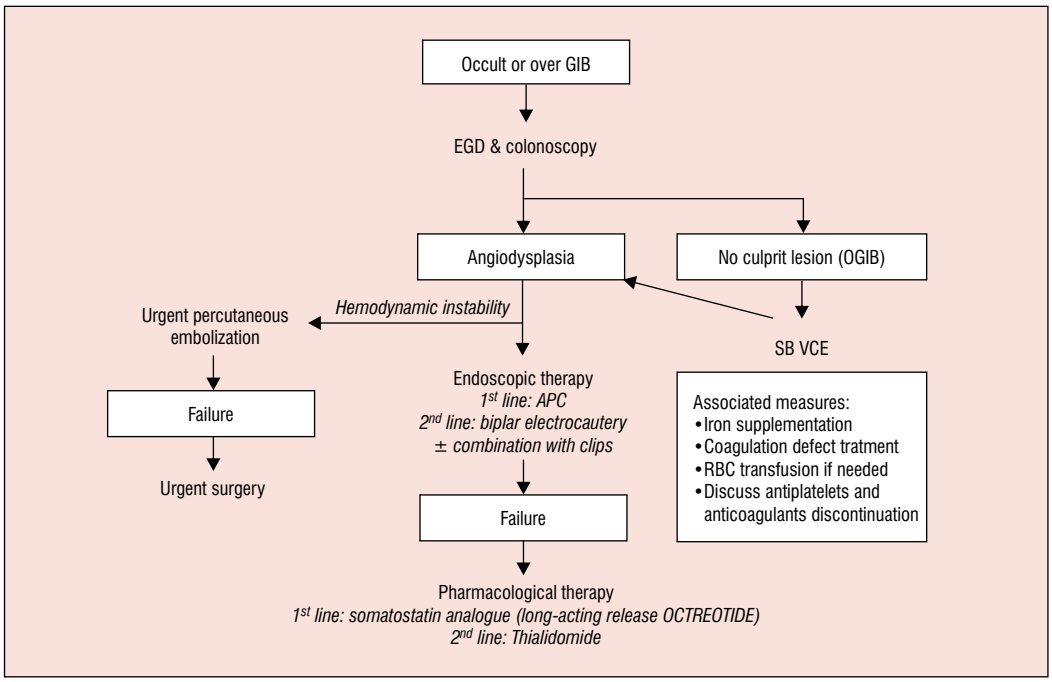

Figure 1. Therapeutic algorithm [Becq *et al.*, Gastrointest Endosc2017; 86(5): 792–806]

remission and endoscopic remission/response. To identify those colitis patients that will respond to FMT and the optimal FMT technology will require substantial further research before such therapy can be used in clinical practice, but the results so far obtained are intriguing and challenging.

Is fecal microbiota transplantation helpful in irritable bowel syndrome? A placebo controlled trial was carried out in patients with diarrhea, or with diarrhea and constipation, scored as moderate to severe. The fecal transplant was administered by colonoscopy to the cecum. A reduction in symptoms after 3 months was observed in 65% after FMT compared to 43% after placebo. Here again, many more studies will be necessary focusing on proper patient selection, proper FMT technology and proper evaluation of the long-term outcome before FMT is ready for prime time therapy.

The 6th Gastro Update Europe is June 14 – 15, 2019 in Budapest (www.gastro-update-europe.eu)

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Novel developments in pancreatic disorders — presentation at Gastro Update Europe 2018, Prague

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Massive hypertriglyceridemia is a well established cause of acute pancreatitis. Less clear is the role of lower triglyceride levels. In an impressive prospective study, sequential triglyceride levels were determined in 116,550 individuals during a mean follow-up of 6.7 years. As shown below, pancreatitis risk increased by 20% when triglyceride levels rose by 100 mg/dl; for comparison, the rising risk of myocardial infarction is also shown [JAMA Intern Med 2016; 176: 1834–1842] (Fig. 2).

The pancreatitis risk is dose-dependent with a postprandial threshold of > 200–300 mg/dl. The true mechanisms by which high triglyceride levels induce pancreatitis needs further study.

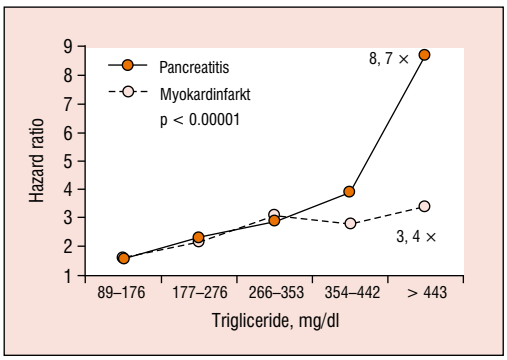

Figure 2. Pedersen *et al.*, JAMA Intern Med 2016; 176: 1834–1842

Also, the visceral adipose tissue mass quantified by CT as area of fatty tissue in cm^2 on day 1 of admission has been shown to be

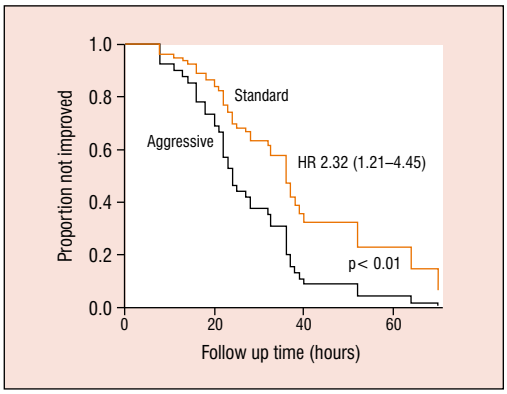

Figure 3. Buxbaum *et al.*, Am J Gastroenterol 2017; 112: 797–803

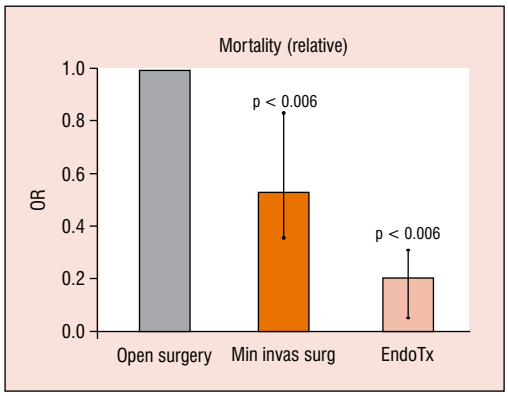

Figure 4. van Brunschot *et al.*, Gut 2018; 67(4): 697–706

an important predictor of pancreatitis severity, and the risk of necrosis and multi-organ failure. Visceral adipose tissue is metabolically highly active. By which mechanism it raises acute pancreatitis severity needs further exploration.

Volume substitution is essential in the management of acute pancreatitis. In a recent prospective study, 60 patients with acute pancreatitis, 'aggressive' hydration with Ringer's lactate solution (20 ml/kg bolus, followed by 3 ml/kg/h continuous infusion) was compared with 'standard' hydration (1.5 ml/kg/h continuous infusion) with protocol adaptation every 12 h, depending on lab and clinical data. As can be seen, early, vigorous and subsequent adequate volume hydration improves the course of pancreatitis. This therapy, which consisted initially in 1–2 L, followed by about 3 L /12 h was well tolerated [A J Gastroent 2017; 112: 797–803] (Fig. 3). One may question whether the volume of 1.5 L in the first 12 h in the standard group was adequate.

The therapy of acute necrotising pancreatitis has changed from early emergency open surgery and necrosectomy, to late elective and strictly selective minimally invasive approaches, alongwith endoscopic interventions. The success of such paradigm shift was shown in a large retrospective multicenter study involving 1,980 patients with acute necrotising pancreatitis. Mortality was 2 fold higher when open surgery was compared to minimally invasive surgery, and mortality was 5 fold higher when open surgery was compared to endotherapy. As shown below, the overall reduction in relative mortality illustrates definite progress in the management of this dreadful disease [Gut 2018; 67: 697–706] (Fig. 4).

Thus, the initial therapeutic approach should focus on early adequate volume substitution and conservative non-surgical management even with infected necrosis to avoid massive intervention trauma in the early phase. During the further course of the disease with/without infected necrosis, intervention should be selective and rather delayed, minimizing iatrogenic trauma as far as possible and exploring first the endotherapeutic possibilities. Note that 50–70% of patients may achieve full recovery without any intervention, even with infected necrosis.

Early cholecystectomy for acute biliary pancreatitis is associated with a lower risk of relapsing acute pancreatitis (particularly in the presence of small gallstones) and is the current standard, cost effective strategy. A recent American study involving over 17,000 patients showed a reduction of acute pancreatitis relapse from 13% to 3% with respectively delayed/absent cholecystomy (22% of patients) and early cholecystectomy (78% of patients). Thus cholecystectomy should be performed within 4 weeks after biliary acute pancreatitis, and whenever possible even during the same hospital stay. It provides effective protection against imminent relapse and does not interfere with recovery from acute pancreatitis.

Prevention of post-ERCP is of major clinical importance and is often carried out with rectal administration of NSAIDs 30 min prior to ERCP. In a recent study 372 patients were evaluated, comparing diclofenac 100 mg, indomethacin 100 mg, and naproxen 500 mg. The overall pancreatitis rate was 8.6% with the lowest rate after diclofenac or indomethacine and the highest rate after naproxen, which might therefore be ineffective. Vigorous hydration using lactated Ringer's solution may also prevent post-ERCP pancreatitis. In a large prospective study involving 510 patients, standard hydration (infusion of 1.5 ml/kg/h during ERCP and for 8 h after ERCP) was compared to vigorous hydration (bolus of 10 ml/kg pre- and post ERCP plus infusion of 3 ml/kg/h during and for 8 h after ERCP). Overall pancreatitis dropped from 9.8 to 4.3% and hyperamylasemia from 16.1 to 6.7% when standard was compared to vigorous hydration.

In a randomized controlled trial involving 192 patients at high risk for post ERCP pancreatitis, vigorous lactated Ringer's solution was combined with or without indomethacine and resulted in a drop of pancreatitis rate from 19% to 6% respectively, indicating that combination should be considered especially for risky situations.

The diagnosis of autoimmune pancreatitis remains difficult in many patients; the clinical presentation is highly variable, IgG4 levels may not be elevated, especially in Europe, typical aberrations in imaging studies are seen in less than 30% and the contribution of EUS-guided histology/cytology is uncertain. A recent study involving 50 patients with suspected autoimmune pancreatitis revealed that EUS-FNA with a 22 gauge needle was diagnostically not effective in most patients, contributing to diagnostic accuracy in only 16%. Convincing clear-cut response to corticosteroids remains the most reliable criterion. A recent study evaluated the relapse prevention in 49 patients after induction of remission with prednisolone 0.6 mg/kg/d for 12 w followed by tapering. In the control 'cessation' group, steroids were terminated after 6 m and in the 'maintenance' group prednisone 5–7.5 mg/d was continued for 3 y. In the control cessation group, relapse occurred in 58% compared to 23% in the predisone maintenance group. Maintenance steroid therapy with the lowest effective dose may therefore be appropriate.

Pancreatic cancer	IPMN 1° non-low risk 9 studies, n = 825	IPMN 1° low risk 10 studies, n = 2411
1 year	2,0%	0,02%
3 year	5,7%	1,4%
5 year	9,8%	3,1%
10 year	25%	7,8%

Figure 5. Choi *et al.*, Clin Gastroenterol Hepatol 2017; 15: 1509–1520

The debate continues with respect to the proper strategy for patients with intraductal papillary mucinous neoplasia (IPMN). A recent meta-analysis was performed related to the course of non-resected IPMN shown below [Clin Gastro Hepatol 2017; 15: 1509–1520] (Fig. 5).

Several strategies and guidelines for branch-duct IPMN have been published. Surveillance with MRI and/or EUS is usually advised for operable patients with no worrisome features or high risk factors; surveillance is recommended after 6–12 m during the first y and after 6–24 m (~yearly) from the second y on for over 5 y. Surveillance should be carried out at shorter intervals for cysts > 2–3 cm or if relevant changes occur (cyst growth > 3 mm; changes in cyst cytology, CEA, serum CA19-9, new diabetes). Surgery is to be considered if worrisome features or high risk factors develop. Note that risk never ceases, even after surgery, and therefore surveillance should be continued also post-surgery. Keep in mind that ultimately the fitness of the patient turns out to be overall more important than worrisome features and risk factors.

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Novel gastroduodenal developments — presentation at Gastro Update Europe 2018, Prague

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Gastroesophageal reflux disease (GERD, NERD) remains the dominant esophageal pathology. In selected patients, especially those with persistent symptoms, ambulatory pH-impedance monitoring and high resolution manometry may be of value in determining the reflux burden and the reflux-symptom association, but this usually requires referral to an expert center. Acid suppression remains the mainstay of therapy both for GERD and NERD, but anti-reflux surgery (although less frequently performed) still has a definite role in case of persistent symptoms, also for NERD, especially if the esophagogastric junction is compromised. Once daily PPI, preferably before breakfast, remains the standard occasionally upregulated to twice daily. Important novel competitors for PPIs are the pCABs (potassium competitive acid blockers), already available for clinical use in Japan and Korea. pCABs such as Vonoprazan are not acid-sensitive, do not require gastric coating, and provide rapid, strong and long lasting acid suppression from day ,1 with so far superior results in GERD, H. Pylori eradication therapy, prevention of bleeding, etc. compared to PPIs without significant side effects. Reflux symptoms can also be improved, not only by co-administration of alginates, but also with ESOXX, a novel hyaluronic acid-chondroitin sulphate bioadhesive mucosal protective.

Inappropriate use of PPIs continues at a high rate which is disappointing and frankly unacceptable! This was again stressed in a recent systemic review, showing that 43% initiation of long-term PPI therapy in hospital was inappropriate. What a waste of resources.

The list of PPI-related adverse effects, shown in the highlights of the 2017 update (Gastro Update Europe 2017), is essentially unchanged also with respect to variability in interpretation of their clinical relevance. Novel are population-based studies from Hong Kong and Sweden, indicating that the risk of gastric cancer during prolonged PPI therapy at least doubles compared to controls; also after *H. Pylori* eradication for those that were infected [Gut 2018; 67: 28; BMJ Open 2017; 7: e017739]. Speculative mechanisms for these alarming (?) findings might include PPI-induced dysbiosis with potential nitrosamine formation in the presence of ongoing hypergastrinemia. Long-term PPI use was also shown to increase the risk of esophageal adenocarcinoma, also in non-GERD patients [Cancer Epidemiol 2018; 53: 172]. Despite the shortcomings and criticisms voiced in the literature, such novel information is quite shocking and should remind us all of the old adage: drugs should be given in the lowest effective dose and for the shortest appropriate time. Finding the right balance

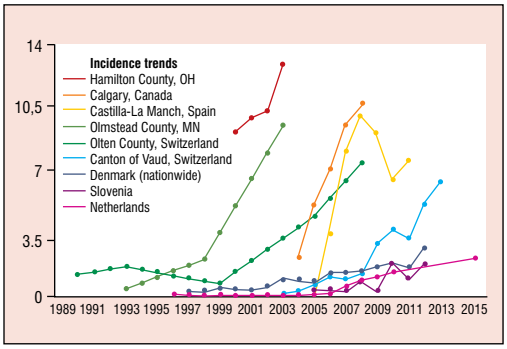

Figure 6. Dellon, Hirano, Gastroenterology 2018; 154(2): 319–332

between benefit and risk will remain a delicate medical enterprise.

Why the incidence of eosinophilic esophagitis (EoE) continues to rise as shown below, apparently quite in parallel with the rising PPI consumption, remains enigmatic despite many hypotheses (Fig. 6).

Recently, Spechler [Cur Gastroent Rep 2018; 20: 26] hypothesized that increasingly consumed PPIs (especially in children) prevent pepsin proteolysis of potentially allergenic proteins because of gastric pH rise > 4.5 (instead of rapid acid-peptic hydrolysis to small non-allergenic peptides). Moreover, PPIs facilitate gastric absorption of peptide fragments because of enhanced PPI-induced permeability, ultimately leading to systemic exposure and sensitization. Further oral intake of those allergens after sensitization exposes the esophageal mucosa which may induce a Th2-geared inflammatory eosinophilic response.

Early diagnosis of EoE remains of upmost importance as progression from an inflammatory to a fibrostenotic phenotype occurs quite rapidly if left untreated. With each additional year of undiagnosed EoE, the risk of stricturing has been shown to increase by 9%. Suspicion for EoE, prompting endoscopy and histology, should be raised when a patient presents with: a history of atopy, history of food impaction, PPI refractory symptoms and either peripheral eosinophilia or elevated IgE levels. For diagnosis at least 6 biopsies should be obtained from different locations, focusing on areas of mucosal abnormality. Recent studies confirmed that none of the standard allergy tests can accurately predict the actual specific food triggers. The common triggers remain wheat, milk and egg, alone or in combination. Investigations with food exclusion/rechallenge with repetitive histological assessment remain an effective strategy but is difficult and hardly carried out in clinical practice. The same can be said for elemental diet (e.g. Neocate, Nutricia, Netherlands) which has been clearly shown to decrease inflammation and to improve symptoms, but such therapy is impractical in adults if prescribed long-term. The main therapy after a trial with PPI is based on topical corticosteroids. Budesonide oral suspension has been shown to be effective in improving symptoms and endoscopic severity scores. Also novel and quite effective is budesonide orodispensible 1mg tablets, given BID (already available in Germany). Topical steroids may increase the risk of candidiasis. Also novel is an anti-IL-13 monoclonal antibody shown to be effective in steroid refractory cases.

European guidelines on EoE management have recently been published (Fig. 7).

It was again confirmed that *H. Pylori* infection doubles the risk of peptic ulcer bleeding in aspirin/NSAID users with even further risk increase in users of combined anti-platelet therapy. Bleeding risk did not increase in patients on anticoagulants, SSRIs or corticosteroids. Eradication therapy is therefore indicated particularly in long-term users of mucosa-damaging drugs. Although not-covered at the meeting, it may be worthwhile to mention the additional protective effect of PPIs in long-term aspirin/NSAID users. However, insufficiently recognized by clinicians is that PPIs only protect the gastroduodenum but may aggravate damage further down in the intestinal tract; this is especially so for entero-hepatic circulating NSAIDs.

It was also again confirmed in a mega Chinese controlled trial that after endoscopic resection of early gastric cancer patients had lower rates of metachronous gastric cancer, shown below together with more improvement of corpus mucosal atrophy if *H. Pylori* was eradicated (Fig. 8).

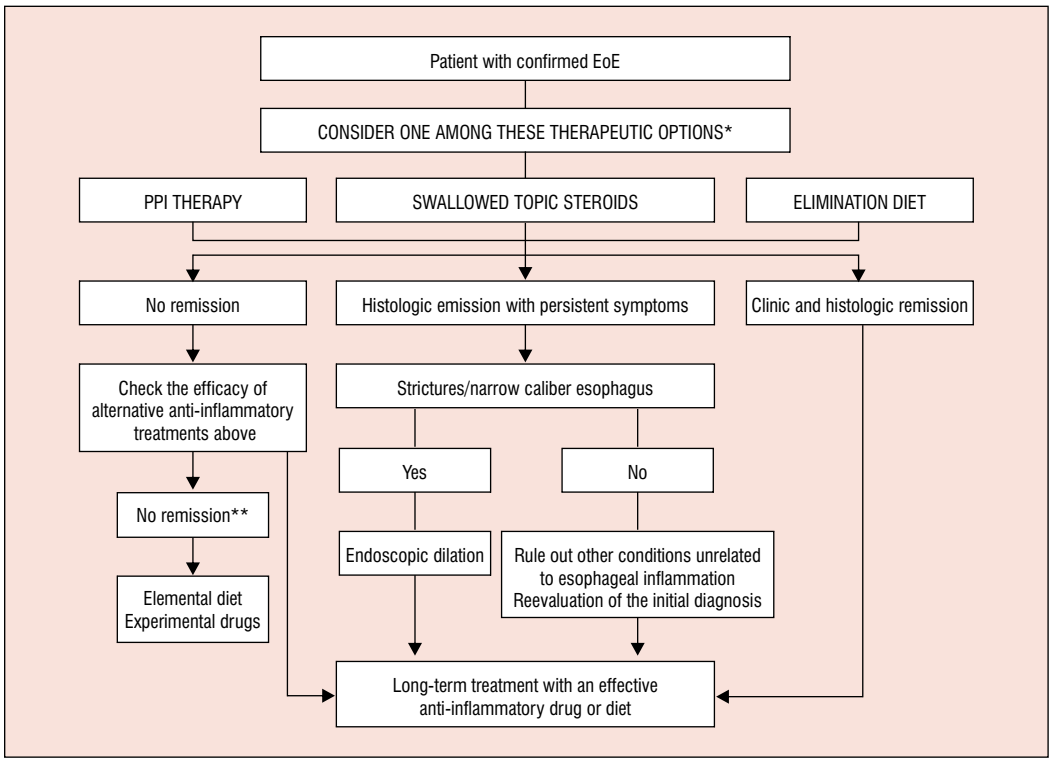

Figure 7. Lucendo *et al.*, United European Gastroenterol J. 2017; 5(3): 335–358. *In patients with persistent symptoms under anti-inflammatory therapy, endoscopic dilation should be considered; ** Refer the patient to an EoE center

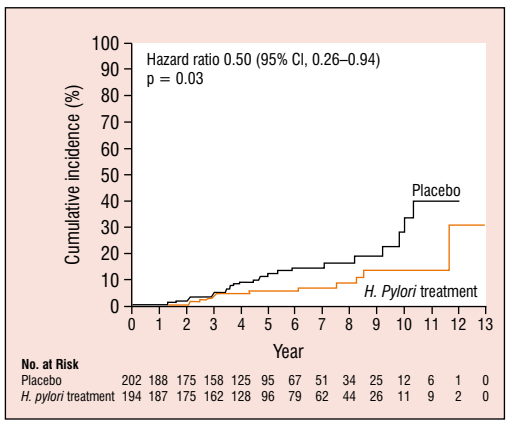

Figure 8. Choi *et al.*, N Engl J Med 2018; 378(12): 1085–1095

However, *H. Pylori* eradication was not protective in all patients. *H. Pylori* eradication may fail to prevent metachronous gastric cancer in those with advanced atrophy, intestinal metaplasia and a(hypo)chlorhydria, indicating a 'point of no return'. As it is not really possible to predict where and when the 'point of no return' is reached, patients with precancerous lesions may still benefit from *H. Pylori* eradication which may slow down the progression to more advanced disease as shown in a recent study. Particularly patients with so-called 'incomplete-type of intestinal metaplasia' are at high cancer risk with ongoing *H. Pylori* infection.

Useful prediction of gastric cancer risk has been shown to be possible by measuring pepsinogen 1 and anti-*H. Pylori* whole cell or CagA antibody levels. If the latter are positive, gastroscopy should be performed. Increasingly discussed is the question whether gastroscopy should be combined with screening colonoscopy during the same examination. An additional reason for combining gastroscopy with colonoscopy is the recognition that the risk of (advanced) colonic adenoma appears to be increased in H. Pylori infected individuals, particularly with gastric atrophy (hypergastrinemia?). This is further supported by a recent Korean study, finding a 1.34 fold higher prevalence of advanced colorectal cancer in *H. Pylori* seropositive patients.

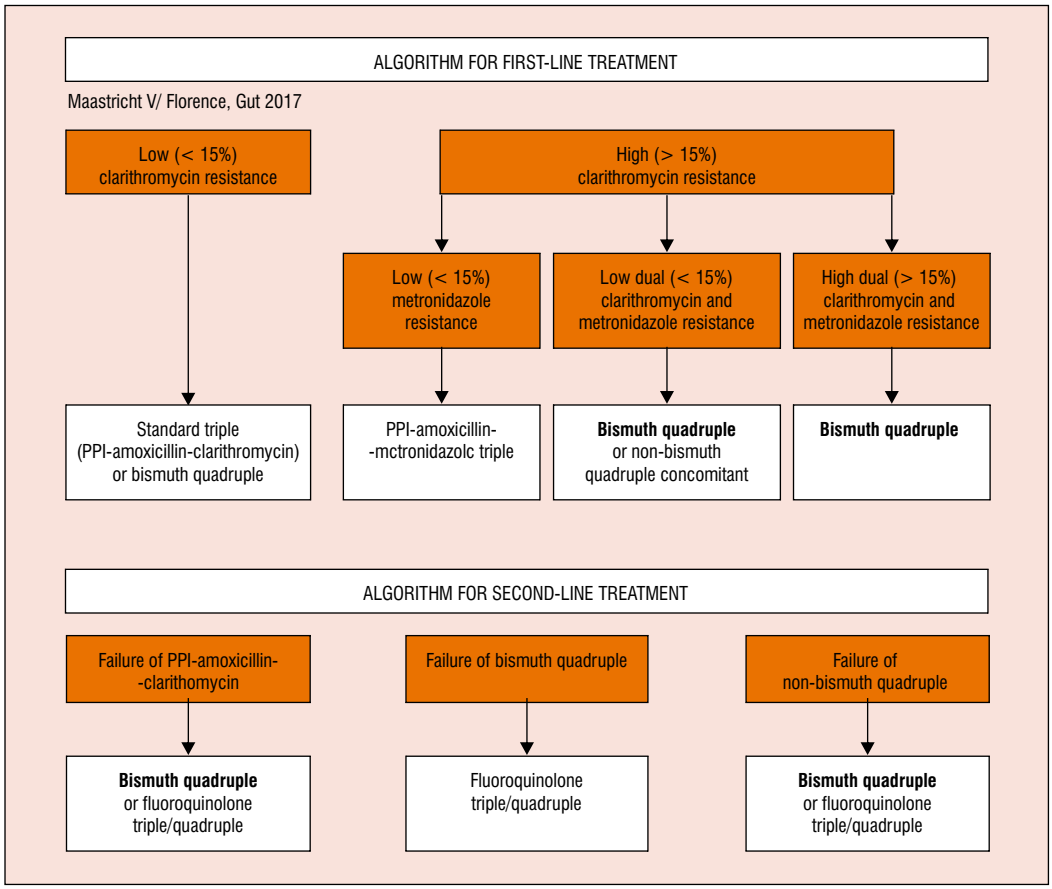

Figure 9. Malfertheiner *et al.*, Gut 2018; 66: 6–30

Clarithromycin resistance has been rising in many countries over the past decades, reaching 30% in Japan and Italy, 40% in Turkey and 50% in China. Other antibiotics (metronidazole, levofloxacine) showed a similar, though usually lower trend. Re-interest in bismuth quadruple therapy is rising. In a recent large scale Chinese study *H. Pylori* eradication rates with 10d bismuth quadruple therapy (O-BMT), 10d concomitant therapy and 14d standard triple therapy were respectively 90%, 86%, and 84%.

Ideally, antimicrobials prone to resistance should be avoided for mass application to lower additional resistance selection pressure on pathogens other than *H. Pylori*. Bismuth, tetracycline and metronidazole are of lesser importance in managing other bacterial infections. Moreover, resistance does not occur or is of lesser critical importance for metronidazole. All this favors the selection of bismuth quadruple therapy as a first line therapy, as shown in the recent Maastricht V/Florence consensus report [Gut 2018; 66: 6–30] (Fig. 9).

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Novel developments in endoscopy of the proximal microbiota — presentation at Gastro Update Europe 2018, Prague

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Surveillance recommendations, according to ESGE guidelines vary according to the length of the Barrett segment. Surveillance varies from: none for < 10 mm; every 5 y for < 3 cm; every 3 y for < 10 cm; and surveillance in a Barrett expert center if > 10 cm. Difference in expertise between a community hospital and an expert center was analysed in a retrospective multi-centric study involving 198 patients with high-grade dysplasia/adenocarcinoma. Detection of a visible lesion occurred respectively in 60% vs ~90%. In 40% neoplasia was only detected on non-targeted biopsies in community hospitals but was endoscopically detected in 75% by experts.

A new classification using acetic acid chromoendoscopy (PREDICT) has been presented shown below [Gut 2017-314512 /Sep 28 2017] (Fig. 10).

Acetic acid staining using this classification is easy to learn and can improve diagnostic performance in detecting Barrett neoplasia.

A model was developed to determine the risk of malignant progression of Barrett esophagus.The scoring system involved: Barrett length (1 point for each cm); male gender (9 points); smoking (5 points); low-grade dysplasia at baseline (11 points). The model was evaluated retrospectively in a longitudinal follow-up study involving 2,697 Barrett patients. The primary outcome parameter was the development of high-grade dysplasia/early adenocarcinoma during a median 5.9 y follow-up period. In low risk Group (0–10 points) progression risk was 0.13%/y. In the intermediate risk Group (11–20 points) progression risk was 0.73%/y. In the high risk Group (> 20 points) progression risk was 2.1%/y.

Treatment op post-operative esophageal leakage can be: conservative (watch and wait, nil per os, tube feeding); per-endoscopic (OTS-clip, stent, endovac sponge therapy); surgical (anastomosis redo). A recent prospective evaluation of endoscopic vacuum therapy was carried out in 52 patients of which 75% had post-surgical leakage. First line therapy was endoscopic vacuum therapy with intraluminal or intracavitary sponge placement with 2 changes/w and with 100–125 mm Hg negative pressure. Between 1–25 (~6) sponges were used. The defect healed in 94% of those only treated with sponges. Minor (dislocation, bleeding) and major (fatal bleeding) complications occured in respectively 31% and 4% of the patients. In-hospital mortality (bleeding, multi-organ failure, pneumonia) was 10%. Comparative studies are needed to find out which treatment modality is preferable for each anatomical presentation.

	Morphological Features	Classification	Barrett's diagnosis
Acetow-hitening	No focal loss of acetowhitening	Absent	Non-neoplastic
	Focal loss of acetowhitening	Present	Neoplastic
Surface Pattern	Uniform evenly spaced pits with normal pit density	Normal	Non-neoplastic
	Compactly packed small pits with increased pit density	Abnormal	Neoplastic
	Focal irregularity or disorganized pits		
	Absent pit pattern		

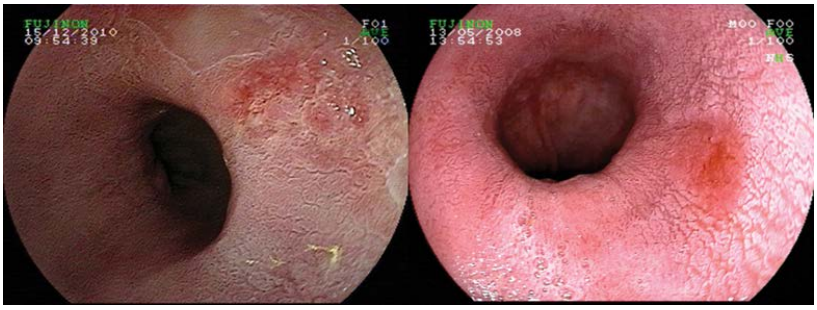

Figure 10. Kandiah *et al.*, Gut 2017 Sep 28. pii: gutjnl-2017-314512

Standard criteria for endoscopic resection of early gastric cancer are: mucosal, G1-2, L0, V0, up to 20 mm. Novel expanded criteria are: submucosal sm1/<500microm or G3, or > 20 mm or < 30 mm in ulcerated lesions. Gradually ESD data from Europe is also becoming available as illustrated by a recent study involving 179 patients with 191 ESDs. ESD was incomplete because of 'non-lifting' in 5%. En-bloc resection and RO-resection were respectively 92% and 76%. Major complications (bleeding, perforation) occurred in 8% and procedure-related mortality was 1%. According to standard and expanded criteria, local recurrence was seen in 0 vs 5%, metachronous lesions in 15 vs 7%, need for surgery in 0 vs 7% and total death/cancer death in (13%/0%) vs (18%/0%). Beyond doubt ESD for early gastric cancer will continue to expand in Europe in parallel with more refined methodology for lesion delineation etc, but for the time being such therapy will be restricted to dedicated expert centers because the patient volume is so far rather limited.

The risk of lymphnode metastasis in early gastric cancer is rather low, as again shown by a meta-analysis of 12 studies involving 9,798 gastrectomised patients. Lymphnode metastasis for standard vs expanded criteria lesions were respectively 0.2% and 0.7%, for differentiated mucosal cancer < 3 cm with ulceration 0.57%, for differentiated mucosal cancer without ulceration 0.27% m, for undifferentiated mucosal cancer < 2 cm 2.6% and for differentiated submucosal cancer < 3 cm 2.5%. It is clear from such data that grade of differentiation and presence of ulceration are important prognostic features.

The role of *H. Pylori* eradication (amoxicillin-clarithromycin-rabeprazole) after gastric ESD for early gastric cancer or high-grade dysplasia was evaluated in a large prospective placebo-controlled trial involving 470 patients, followed-up for a median of 5.9y. In the eradication group (successful in 80%) and the placebo group, metachronous cancer occurred in respectively 7.2% vs 13.4% and improvement of gastric mucosal atrophy in 48.4% vs 15%. Thus the risk for metachronous gastric cancer after successful eradication dropped to an HR of o.32. After ESD, but also after partial gastrectomy for more advanced cancer, *H. Pylori* eradication should be carried out.

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Novel developments in large bowel disorders — presentation at Gastro Update Europe 2018, Prague

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The incidence of colorectal cancer in individuals < 50 years old is on the rise, related perhaps to the obesity epidemic and increased frequency of germline genetic changes. A large retrospective analysis was carried out in 430 young colorectal cancer patients. 20% carried germline mutations associated with cancer predisposition (mostly mutations in Lynch MMR, but also APC gene and other variants). Importantly, half of the individuals with genetic diagnosis did not have a typical family history. Testing with multigene panels for germline sequencing of such individuals is strongly recommended.

Changes in the microbiota after use of antibiotics may play a role in colorectal cancer pathogenesis. Further support for this concept was recently provided by the long-term follow of the Nurses' Health Study. Antibiotic use for > 2 months during age 20–39 y increased the risk for colorectal adenoma to an OR 1.36, and antimicrobial exposure during age 40–59 to an OR 1.69. Obviously, further studies are required to clarify the role of the altered microbial composition after antibiotic use and its duration with respect to the mechanisms of carcinogenesis. Elimination of confounders will be of crucial importance, but in all probability the (altered?) microbiome is involved in colorectal cancer pathogenesis.

Another intriguing finding from the prospective Nurses' Health Study (1984–2012), and from the Health Professionals Follow-up study (1986–2012 — median follow-up 7.8 y) is a reduced all-cause and especially colorectal cancer-specific death after consuming 4 or more cups of coffee, including decaffeinated, per day as shown in Figure 11.

Again, further studies are needed to determine the potential mechanisms by which coffee may reduce colorectal cancer progression with ongoing attention for confounders.

Specific bacterial strains may play a role in colorectal carcinogenesis. In an intriguing study, over 13,000 patients with blood culture positive bacteremia were compared with over 32,000 well matched blood culture

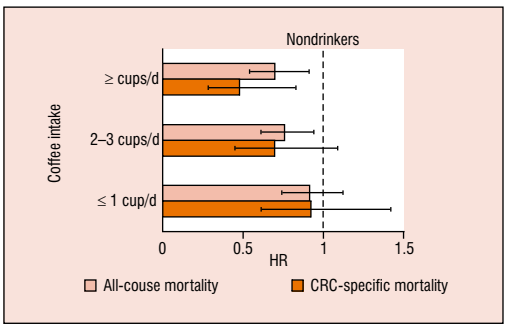

Figure 11. Association between coffee intake after diagnosis of colorectal cancer mortality [Hu *et al.*, Gastroenterology 2018; 154: 916]

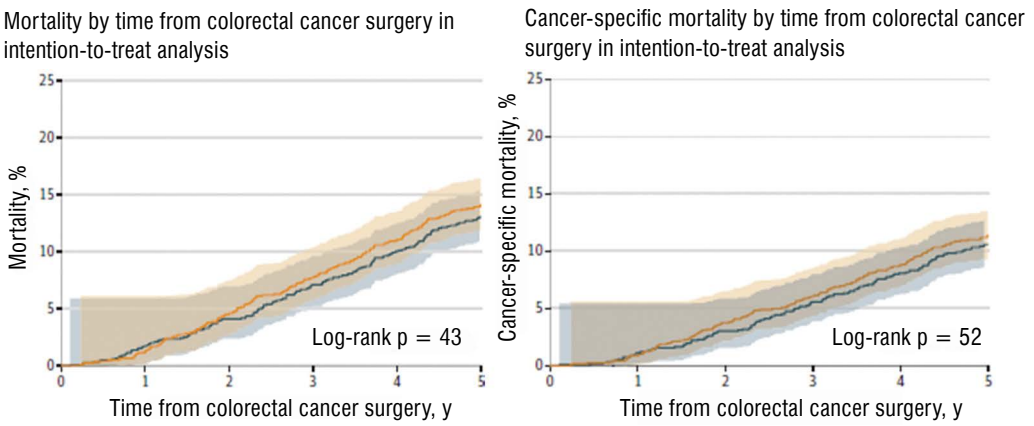

Figure 12. Wille-Jorgensen *et al.*, JAMA 2018; 319: 2095

negative controls. Among the bacteria responsible for bacteremia and sepsis were Bacteroides, Streptococcus, Fusobacterium, Peptostreptococcus, and Clostridium. Many of the bacteremia-positive patients were associated with a later diagnosis of colorectal cancer. The take-home message of that study was that clinicians should evaluate patients with bacteremia with specific species for neoplasia in the large bowel. Apparently cancerous growth in the colon, with disrupted barriers, allows bacterial penetration and ultimately bacteremia.

After therapy for colorectal cancer, routine follow-up is usually performed in clinical practice. To find out if there is an outcome difference between intensive or less intensive follow-up, over 2,509 patients with initial stage II/III colorectal cancer were analysed after intended curative surgery. Intensive follow-up consisted of multi-sliced, contrast-enhanced CT of abdomen and chest, plus CEA at 6, 12, 18, 24, and 36 months. Less intensive follow-up consisted of the same regimen but only at 12 and 36 months. The 5 y overall, and colorectal cancer-specific mortality, were indistinguishable (Fig. 12).

Such outcome is similar to what has been seen for post-therapy gastric cancer follow-up. Such intensive follow-up is very costly, often redundant and medically non-contributory, and should probably be discouraged. However, close monitoring post cancer therapy is so entrenched in clinical practice that a rapid change in attitude is not to be expected. An individualized approach would seem preferable, based upon the

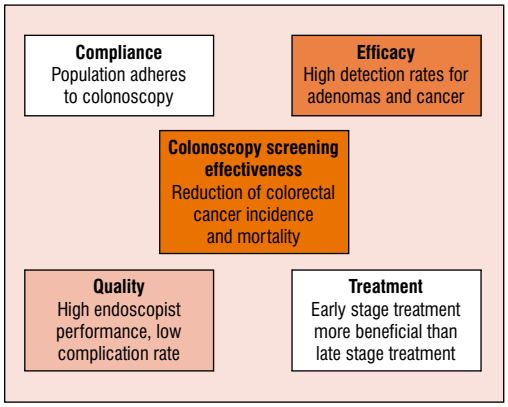

Figure 13. Robertson, Kaminski, Bretthauer, Gut 2015; 64: 982

specific medical situation, but also the psychological make-up of the individual requiring and benefitting from close physician-patient interaction.

Effectiveness of colorectal cancer screening depends on key factors, summarized below (Fig. 13).

Previous studies have shown that the higher the adenoma detection rate, the lower the risk of interval colorectal cancer. Improvement of the adenoma detection rate through training has now been shown to lead to a decreased risk of interval cancer and to decreased cancer death. Colonoscopic improvement is necessary because the interval cancer rate overall stays at around 8%! High detectors remove more neoplastic lesions and they instruct more patients to return at shorter intervals for surveillance endoscopy; both factors contributing to superior results and lower interval cancers.

Colonoscopy should not be delayed after a positive FIT test. In a large American study involving over 70,000 patients with a positive FIT test, 2,191 cancers were detected at colonoscopy. Comparing early colonoscopy (within 30 days) with late colonoscopy (delay over 10 months), after a positive FIT revealed that delayed colonoscopy had a higher risk of colorectal cancer and more advanced disease stages.

A significant complication of diverticular disease is bleeding. Fortunately, spontaneous cessation occurs in ~75%. Colonoscopic attempt at hemostasis is usually the first investigation if bleeding continues. In a systematic review and meta-analysis, involving 384 patients, coagulation was compared to clipping and to band ligation. The endpoints were: initial hemostasis, 30-day bleeding recurrence, and need for embolisation of the feeding artery. Initial hemostasis and early bleeding recurrence occurred at roughly similar rates for banding, coagulation and clipping. Band ligation, however, was most efficient in terms of avoiding surgery and embolization, and should probably become the therapy of choice.

The 6th Gastro Update Europe is June 14 – 15, 2019 in Budapest (www.gastro-update--europe.eu)