Gastro Update Europe 2018

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The following congress review outlines a selection of important novel gastrointestinal and hepatological achievements presented at the recent Gastro Update Europe in Prague. The selected topics reflect what the faculty considered to be essential to be communicated to the astute busy gastroenterologist in clinical practice, who wants to stay abreast of clinically important developments in this rapidly changing scientific world. Whenever appropriate a personal note or comment will be included to further raise the educational level of these highlights. Given the narrative nature of this review, the conclusions drawn are expert-based and speculative.

Novel Gastroduodenal Developments: Peter Malfertheiner (Germany)

Gastroesophageal reflux disease (GERD, NERD) remains the dominant oesophageal 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 centre. 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 oesophago-

gastric junction is compromised. Once daily PPI, preferably before breakfast, remains the standard occasionally upregulated to twice daily. Important novel competitors for PPIs are the potassium competitive acid blockers, already available for clinical use in Japan and Korea. Potassium competitive acid blockers 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, and so on 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 and this trend 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

Meeting report of Gastro Update Europe 2018, June 15 – 16, 2018, Prague, Czech Republic. This meeting report has been published in full or in part in the following journals: Gastroenterologie a hepatologie, Central European Journal of Gastroenterology and Hepatology, Arab Journal of Gastroenterology, and Gastroenterologia Kliniczna.

Keep in mind!

- **True increase in incidence**
- **Select patients and adopt biopsy protocol**
- **Causes undefined**
 - PPI responsive esophageal eosinophilia not a distinct entity
- **PPI initial therapy**
 - If PPI fails, topical steroids
 - Special galenic form, now available, since June 15, 2018

Fig. 1. Take-home message: EoE – P. Malfertheiner.

2017) is essentially unchanged also with respect to variability in interpretation of their clinical relevance. Novel are the 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 [1, 2]. 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 oesophageal adenocarcinoma, also in non-GERD patients [3]. 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 between benefit and risk will remain a delicate medical enterprise.

Why the incidence of eosinophilic esophagitis (EoE) continues to rise is apparently quite in parallel with the rising PPI consumption and remains enigmatic despite many hypotheses [4] (Fig. 1).

Recently, Spechler [5] 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 oesophageal mucosa that 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 stric-

turing has been shown to increase by 9%. Suspicion for EoE, prompting endoscopy and histology, should be raised when a patient presents with the following details: a history of atopy, history of food impaction, PPI refractory symptoms and either peripheral eosinophilia or elevated IgE levels. For the purpose of 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/re-challenge with repetitive histological assessment remain an effective strategy but are difficult and hardly carried out in clinical practice. The same can be said for elemental diet (e.g., Neocate, Nutricia, the Netherlands), which has been clearly shown to decrease inflammation and to improve symptoms, but such therapy is impractical in adults if prescribed for a 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 orodispersible 1 mg 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.

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 antiplatelet 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 there were lower rates of metachronous gastric cancer, together with more improvement of corpus mucosal atrophy if *H. pylori* was eradicated [6] (Fig. 2).

However, *H. pylori* eradication was not protective in all patients. *H. pylori* eradication may fail to prevent metachronous gastric cancer in those with advanced at-

- *H. pylori* gastritis is an infectious disease
 - Screen and treat:
 - Consider regional gastric cancer risk
 - Bismuth-based quadruple first choice
 - Concomitant, an alternative first line
 - PPI triple only in areas of low Clari-R
- In case of failure:
 - Established second-line therapies
 - Increased acid suppression
 - Susceptibility-based treatment
 - Rescue therapies available
- Gastric microbiome beyond *H. pylori*!
 - The probiotic option

Fig. 2. Take-home message: *H. pylori* infection – P. Malfertheiner.

rophy, 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.

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, levofloxacin) 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 10 days bismuth quadruple therapy (O-BMT), 10 day concomitant therapy and 14 day 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 favours the selection of bismuth quadruple therapy as a first-line therapy, as shown in the recent Maastricht V/Florence consensus report [7].

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Novel Developments in Small Bowel Diseases and Intestinal Microbiota: Sherine Khater (France)

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-endomysial 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. In spite of 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 of the following reasons: 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

- FMT is recommended as treatment option for recurrent CDI
- FMT has the potential to be effective in the management of UC and IBS
- Need for standardization of the optimal technique of FMT application

Fig. 3. Take-home message: FMT – S. Khater.

gluten may result in the 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 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 analogues could reduce re-bleeding 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 thalido-mide in the treatment of patients with challenging gastrointestinal bleeding [8] (Fig. 3).

A European consensus group recommends faecal 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 FMT helpful in ulcerative colitis? Two prior trials, using 1 donor for every patient, gave rather conflicting outcomes. Recently, a placebo-controlled trial with multi-do-

nor intensive FMT 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 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 FMT helpful in irritable bowel syndrome? A placebo-controlled trial was carried out in patients with diarrhoea, or with diarrhoea and constipation, scored as moderate to severe. The faecal 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.

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Novel Developments in Large Bowel Disorders: Jaroslaw Regula (Poland)

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. Twenty per cent 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 the use of antibiotics may play a role in colorectal cancer pathogenesis. Further support for this concept was recently provided by the long-term follow-up of the Nurses' Health Study. Antibiotic use for >2 months during age 20–39 years 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 years) is a reduced all-cause and especially colorectal cancer-specific death after consuming 4 or more cups of coffee, including decaffeinated [9] (Fig. 4).

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 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 multisliced, 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-years overall and colorectal cancer-specific mortality were indistinguishable (Fig. 5).

Consuming 4 or more cups of coffee
(including decaffeinated) results in:

- **CRC specific death** - **0.48 (0.28–0.83)**
- **All-cause death** - **0.70 (0.54–0.91)**

Inverse association between coffee intake CRC death after diagnosis is observed

Studies are needed to determine the mechanism by which coffee may reduce CRC progression

Hu Y et al., *Gastroenterology* 2018 Mar;154(4):916–926

Fig. 4. Conclusions: coffee intake and CRC mortality after diagnosis – J. Regula.

- Young age onset-CRC suggests a need to perform multigene mutations testing
- Antibiotic use in the past is associated with adenoma risk and may modify the risk of colorectal cancer
- Coffee intake (4 cups or more) improves prognosis in patients with diagnosed CRC
- Intensive follow-up with CT and CEA testing does not improve survival after curative surgery for CRC

Fig. 5. Take-home message – J. Regula.

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

Improvement of the adenoma detection rate through training has now been shown to lead to a decreased risk of interval cancer and to a decrease in 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 (Fig. 6).

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.

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70,124 patients (50–75 years old) with positive FIT test (out of 1,258,039 screenees and after some exclusions);
- have had a colonoscopy with diagnosis:
- 2,191 CRC
- 67,933 no CRC
Time between positive test and colonoscopy was recorded

Corley DA et al. 2017;317;1631

Fig. 6. Study summary – J. Regula.

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Novel Developments in Pancreatic Disorders: Peter Layer (Germany)

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 [10].

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.

Also, the visceral adipose tissue mass quantified by CT as area of fatty tissue in cm² on day 1 of admission has been shown to be 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 [11]. One may question whether the volume of 1.5 L in the first 12 h in the standard group was adequate (Fig. 7).

The therapy of acute necrotising pancreatitis has changed from early emergency open surgery and necrosectomy, to late elective and strictly selective minimally invasive approaches, along with endoscopic interventions. The success of such paradigm shift was shown in a large retrospective multicentre study involving 1,980 patients with acute necrotising pancreatitis. Mortality was twofold higher when open surgery was compared to minimally invasive surgery, and mortality was fivefold higher when open surgery was compared to endotherapy. The overall reduction in relative mortality illustrates definite progress in the management of this dreadful disease [12] (Fig. 8).

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

- Fat as important harming factor for the pancreas:
- **Hypertriglyceridemia (HTG)**
 - AP-risk “dose-dependent”, i.e., not only following massive, but also mild/moderate HTG (postprandial threshold >200–300 mg/dL)
 - Risk for pancreas relatively greater than that for heart
- **Visceral obesity**
 - Day-1-predictor of severity, necrosis, multi-organ failure

Fig. 7. Take-home message: fat and risk of AP – P. Layer.

- **Initially:**
 - Adequate volume substitution from the start
 - Conservative, non-surgical management
 - ... even with infected necrosis!
 - Note: massive intervention trauma in early phase of AP!
- **Further course, with/without infected necrosis:**
 - Intervention strictly selective** and late-elective
 - “Step-up” strategy: avoid/minimize iatrogenic trauma as far as possible
 - Prefer **Endotherapy** to surgery
 - **Note: 50–70% of patients may achieve full recovery **without any intervention**, even with infected necrosis!

Fig. 8. Take-home message: therapy of (necrotizing) pancreatitis – P. Layer.

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 indomethacin 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 indomethacin and resulted in a drop of pancreatitis rate from 19 to 6%, 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/day for 12 week followed by tapering. In the control "cessation" group, steroids were terminated after 6 months and in the "maintenance" group, prednisone 5–7.5 mg/day was continued for 3 years. In the control cessation group, relapse occurred in 58% compared to 23% in the prednisone maintenance group. Maintenance steroid therapy with the lowest effective dose may therefore be appropriate.

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 [13] (Fig. 9).

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 months during the first years and after 6–24 months (~yearly) from the second year on for over 5 years. 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.

- **Fukuoka-negative (FN):** initially low risk of malignancy
 - **Surveillance** initially every ½ year, then yearly
 - **Note: continue for >5 years!** (*new WF/HR often at >5 years!*
Compare AGA-guidelines...)
- **FP worrisome features (WF9):** increased cancer risk
 - **Individually: initial surveillance; consider surgery**
 - **Evaluate morphol., clin. criteria!**
- **FP high risk (HR):** very high cancer risk
 - **Surgery, whenever possible (comorbidity?)**
 - **Risk never ceases, even after surgery!**
 - **i.e.: surveillance should be continued post-OP!**
- **But keep in mind:**
 - **Fitness of patient more important than WF/HR criteria!**

Fig. 9. Practical management of IPMN – P. Layer.

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Novel Developments in Endoscopy of the Proximal Microbiota: Oliver Pech (Germany)

Surveillance recommendations, according to ESGE guidelines vary according to the length of the Barrett segment. Surveillance varies from: none for <10 mm; every 5 years for <3 cm; every 3 years for <10 cm; and surveillance in a Barrett expert centre if >10 cm. Difference in expertise between a community hospital and an expert centre was analysed in a retrospective multicentric 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 [14] (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 years follow-up period. In low-risk group (0–10 points), progression risk was 0.13%/years. In the intermediate-risk group (11–20 points), progression risk was 0.73%/years. In the high-risk group (>20 points), progression risk was 2.1%/years.

Treatment of post-operative oesophageal leakage can be one of the following ways: 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 whom 75% had post-surgical leakage. First-line therapy was endoscopic vacuum therapy with intraluminal or intracavitary sponge placement with 2 changes without and with 100–125 mm Hg negative pressure. Between 1 and 25 (~6) sponges were used. The defect healed in 94% of those only

- Endoscopic surveillance of Barrett's esophagus according to BE length
- Use of acetic acid combined with a training program can improve lesion detection even in Barrett's experienced endoscopists
- Barrett's expert centers are important because Barrett's neoplasia is rare
- Progression risk of Barrett's esophagus can be assessed with a new score according baseline criteria

Fig. 10. Take-home message: Barrett's esophagus – O. Pech.

treated with sponges. Minor (dislocation, bleeding) and major (fatal bleeding) complications occurred 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.

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/<500 microm or G3, or >20 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 and so on, but for the time being such therapy will be restricted to dedicated expert centres 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 the 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 5.9 years. 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 0.32. After ESD, but also after partial gastrectomy for more advanced cancer, *H. pylori* eradication should be carried out.

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About Gastro Update Europe

The 5th edition of this CME-certified event took place in June, updating delegates on recent developments across the broad spectrum of gastroenterology.

European leaders, whose expertise lie in areas, such as endoscopy, hepatology, small bowel diseases, oncology and much more, spent 2 compact days summarizing international literature and presenting the most recent cutting-edge developments. The scientific program and speakers were determined by the Scientific Board: Peter Layer (Israelitisches Krankenhaus, Hamburg, Germany),

Lars Lundell (Karolinska University Hospital, Stockholm, Sweden), Jan Tack (University Hospital, Leuven, Belgium), and Guido Tytgat (Amsterdam UMC, Amsterdam, Netherlands).

In particular, trial and study results published in peer-reviewed journals during the past year were discussed and practical, relevant take-home messages were presented, with the goal of impacting daily patient care in a positive way.

Gastro Update Europe 2019: June 14 and 15, 2019 in Budapest

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1/3 Winning abstracts as decided on by the Scientific Board of Gastro Update Europe 2018

Evaluation of serum prolactin as a potential tumour marker for detection of hepatocellular Carcinoma

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Rationale/Objective: Prolactin is a polypeptide hormone synthesized by anterior pituitary and immune system cells. Prolactin has an established role in molecular carcinogenesis of breast cancer and other malignancies. Increased prolactin, high p-JAK2 expression, and generation of liver cancer cells through PRLR/JAK2 signalling have all been proposed as mechanisms that could contribute to HCC development. The aim of this work is to evaluate serum prolactin as a potential tumour marker in the detection of HCC.

Methods: The study included 40 patients with liver cirrhosis (cirrhotic group) and 40 patients with liver cirrhosis and HCC (HCC group) from Menoufia University Hospitals (Egypt) and 20 healthy volunteers (control group). They underwent laboratory investigations (liver profile, AFP and serum prolactin) and abdominal ultrasonography. HCC is further confirmed by triphasic CT.

Results: AFP of HCC group (458.9 ± 566.6 ng/dL) was significantly higher than cirrhotic group (42.1 ± 16.5 ng/dL) and controls (6.3 ± 2.2 ng/dL; $p = 0.0001$). Prolactin of HCC group (67.7 ± 20.2 ng/dL) was significantly higher than that of the cirrhotic group (35.9 ± 12.1 ng/dL) and control (15.6 ± 4.9 ng/dL; $p = 0.0001$). Prolactin was sig-

nificantly higher in patients with multifocal HCC (85.2 ± 15.5 ng/dL) than in patients with single HCC (62.6 ± 18.6 ng/dL; $p = 0.002$). There was a positive correlation between prolactin and tumour size ($r = +0.82$, $p = 0.0001$). Diagnostic validity of serum AFP at a cut-off level 51 ng/dL for HCC prediction (sensitivity 84%, specificity 65%, area under the curve (0.96) and accuracy 83%). Diagnostic validity of serum prolactin at cutoff level 44.5 ng/dL

for HCC prediction (sensitivity 81%, specificity 78%, area under the curve (0.9297) and accuracy 86%). Diagnostic validity of combined AFP and prolactin for HCC prediction (sensitivity 88%, specificity 90%, and accuracy 89%).

Conclusion: Serum prolactin is considered a promising and potentially complementary biomarker with AFP for early detection of HCC. Significant elevation of prolactin levels is useful for HCC screening in cirrhotic patients.

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