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Editorial

Novel therapeutic approaches in an unpredictable era

This number of the IDEA Journal begins with a review on Artificial intelligence in the detection and characterization of gastric lesions by Giulio Antonelli and Cesare Hassan.

Gastric cancer represents over one million estimated new cases annually, with high mortality due to frequent diagnosis in an advanced stage. Early gastric cancer associated neoplasia is still very often missed at surveillance endoscopy when this is undergone by community or nonexpert endoscopists, because most community endoscopists are rarely confronted with gastric cancer and not trained in recognizing gastric preneoplastic conditions. Deep learning systems autonomously learn to distinguish characteristic features within the images using multiple processing layers, so that CAD systems can recognize discriminative features for neoplastic images that differ from those commonly used and known by the human operator. How they do it and their results are described in the article.

Professor Jørgen Jahnsen clarifies the impact of the introduction of immune checkpoint inhibitors in oncology on the digestive tract. Immune-mediated colitis as a result of immune checkpoint inhibitors treatment is well recognized and can be a serious complication. This condition is usually well treated, but refractory cases can be very challenging. The author recommends a multidisciplinary approach to the Patient and describes the occurrence, clinical course, assessment and treatment of immune-mediated colitis.

The position statement endorsed by the British Society of Gastroenterology Inflammatory Bowel Disease (IBD) section and IBD Clinical Research Group is commented in this Issue, with a focus on the risks associated with immunosuppression and to the increased susceptibility to infection and with questions on reduced effectiveness of some vaccines due to immunosuppressive drugs, with major implications for the safety of immunosuppressed patients in the COVID-19 era. The position paper strongly supports SARS-CoV-2 vaccination for patients with IBD.

Finally, a comment to the paper of Losurdo et al. on the link of small intestinal bacterial overgrowth (SIBO) and some gastroenterological and extra-digestive diseases summarized SIBO causes (a frequent complication of abdominal surgery, structural problems, or medical conditions that slow the passage of food) and consequences (watery diarrhea, bloating, abdominal pain and distension, malnutrition and deficit of vitamins and minerals. Conflicting evidences are highlighted by the authors, triggering the need for thoughtful investigations.

Artificial intelligence in the detection and characterisation of gastric lesions: a review of recent literature

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INTRODUCTION

Gastric cancer represents over 1 million estimated new cases annually and the fifth most diagnosed malignancy worldwide. Mortality from gastric cancer is high as it is frequently diagnosed in an advanced stage, making it the third most common cause of cancer-related deaths, with 784.000 deaths globally in 2018 (1). Some countries show a much higher incidence and mortality from gastric cancer, like regions of East Asia, Eastern Europe, and South America. Males show an incidence of gastric cancer two times higher than females (2).

Despite a steady decline in incidence rates in most countries, more gastric cancer cases in the future are expected due to generally higher median age. Improved living conditions have contributed to reduce Helicobacter Pylori prevalence, considered the major risk factor in developing gastric cancer (3). In high incidence areas the implementation of nationwide gastric cancer screening programmes have also led to reductions in gastric cancer mortality. H pylori infection is the most well described risk factor for gastric cancer. Chronic infection of the gastric mucosa leads to stepwise inflammation progression from atrophic gastritis and intestinal metaplasia (4). The majority of the population infected with H pylori remain asymptomatic. Treatment of H pylori can reduce the risk of transformation to gastric cancer, but the magnitude of risk reduction depends on the degree of pre-existing damage at the time of eradication (5). According to current recommendations, eradication of H pylori should be done in the following risk populations: pan-gastritis and corpus predominant gastritis, first-degree relatives of patients with gastric cancer, and previous gastric neoplasia (6). Risk factors beyond H pylori for non-cardia gastric cancer are older age, low socio-economic status, cigarette smoking, alcohol consumption, familial predisposition, previous gastric surgery, pernicious anaemia, and living in a population at high risk (2,5). Salted food intake might increase the risk of H pylori infection and could also act synergistically to promote the development of gastric cancer. Therefore, dietary modification involving less salt and salted food intake is one possible strategy to prevent gastric cancer. Gastric cancer risk might be decreased with a high intake of fruit and vegetables (7). In contrast to distal gastric cancer, a positive association between gastrooesophageal reflux disease and proximal (cardia type) gastric cancer has been shown (8).

Detection improvement

However, early gastric cancer associated neoplasia is still very often missed at surveillance endoscopy, when this is undergone by community or non-expert endoscopists (9). This is because majority of

community endoscopists are rarely confronted with gastric cancer and are not trained in recognizing gastric preneoplastic conditions such as atrophic gastritis or intestinal metaplasia, and are unfamiliar with the subtle changes associated (10). Furthermore, in the context of advanced endoscopic imaging (11) many other features related to gastric preneoplastic conditions may be learned. In this setting, both classroom-based and online training modules have been proposed, to a certain extent of success, to improve diagnostic capabilities of both expert and non-expert endoscopists (12).

Conventional chromoendoscopy with application of dyes (indigo carmine, methylene blue, acetic acid, or hematoxylin) has consistently been associated with the detection of gastric preneoplastic or neoplastic conditions or lesions with high accuracy. In a recently published meta-analysis including 10 studies, 699 patients, and 902 lesions, the pooled sensitivity, specificity, and area under the curve (AUC) of dye-CE were 0.90 (95% CI0.87-0.92), 0.82 (95%CI 0.79-0.86), and 0.95, respectively, these results being significantly better than WLE alone (13). However, dye-CE is cumbersome and significantly lengthens endoscopic procedures. This favors virtual CE which is available at the touch of a button.

Several studies focused on the role of virtual CE in the diagnosis of gastric precancerous conditions. A systematic review showed that most studies addressed narrow-band imaging (NBI) (mainly with magnification). The pooled sensitivity and specificity for the diagnosis of IM were 86% and 77%, and for dysplasia/early cancer these values were 90% and 83%, respectively (14). However, the authors concluded that few studies addressed interobserver reliability and that there was no validated classification.

A more recently developed and attractive option is Artificial Intelligence (AI) or machine learning, especially after the successful application of Convolutional Neural Networks (15,16).

In contrast to human-derived methods, deep learning systems autonomously learn to distinguish characteristic features within the images using multiple processing layers. In this way, CAD systems can recognise discriminative features for neoplastic images that differ from those commonly used and known by the human operator. In addition, a CAD system developed with deep learning techniques can acquire such a fast image processing rate to be able to be used in real time during an endoscopical examination. In the setting of gastric neoplastic and preneoplastic conditions, this can mean both identifying possible dysplastic tissue (demarcation line, etc.) as well as target the operators' biopsies to the spots where intestinal metaplasia or atrophic gastritis can be present with the higher probability (15).

AI SYSTEMS FOR THE DETECTION OF GASTRIC NEOPLASIA

A recent meta-analysis addressed the standalone performance of AI in detecting early gastric cancer (EGC)(15). The pooled results of the 6 studies (17-22) on EGC detection, total number of images used for training was 15,354. Total number of images used for testing was 10,622.

The pooled prevalence of GAC was 55% (Confidence Interval (CI) 47-63%). Overall, AI had sensitivity 90% (CI 84-94%), specificity 88% (CI 81-93%), positive predictive value 90% (CI 84-94%), negative predictive value 88% (CI 81-93%), Likelyhood ratio+ 7.5 (CI 4.4-13.5), and Likelyhood ratio- 0.110 (CI 0.061-0.195).

Interestingly, authors underwent different estimates of AI performance based on different prevalence of disease. This to better picture the impact of AI in the broad spectrum of real life clinical practice, from in a tertiary referral center in a country with a high incidence of gastric neoplasia, to a community based endoscopy center in a low incidence country. In absolute terms, at 55% of cancer prevalence, a positive result of AI would increase the disease probability to 90%, whereas a negative result would decrease the disease probability to 12%. Additional analyses according to hypothesized 1% and 10% pre-test prevalence of GAC (i.e. low- and high-volume endoscopy centers) showed that for a low volume center, a positive result of AI would increase the disease probability to 8%, whereas a negative result would decrease the disease probability to 0.1%.

When considering a high-volume center, with a 10% pre test probability of GAC, a positive result

of AI would increase the disease probability to 46%, whereas a negative result would decrease the disease probability to 1%.

AI for preneoplastic conditions and other future implications

Other interesting studies not included in the meta-analysis researched AI systems that could detect the presence of preneoplastic conditions.

A recent study by Guimares et al. (23) tested a system approach for the diagnosis of atrophic gastritis developed and trained using real-world endoscopic images from the proximal stomach. The model achieved an accuracy of 93% (area under the curve (AUC): 0.98; F-score 0.93) in an independent data set, outperforming expert endoscopists. This study had the strength of using real-world images, although the training and testing sets were both quite limited in number. Nevertheless, having reached a high performance, this algorithm could be improved and tested in a real world live setting in the context of a randomized controlled trial so to test its actual potential.

Another interesting publication addressed the issue of incomplete stomach exploration and the presence of blind spots during upper GI endoscopy (17). In detail, the authors exploited an activation map to proactively track suspicious cancerous regions and built a grid model for the stomach to indicate the existence of blind spots on unprocessed upper GI endoscopy videos. In the task of classifying gastric locations into 10 or 26 parts, the DCNN achieved an accuracy of 90% or 65.9%, similar to that of expert endoscopists. In real-time unprocessed upper GI endoscopy videos, the AI system achieved automated performance for detecting EGC and monitoring blind spots.

This system was also tested in the context of a randomized controlled trial with excellent results (24). In detail AI monitored blind spots with an accuracy of 90.40% in real upper GI endoscopy videos. A total of 324 patients were recruited and randomised. 153 and 150 patients were analysed in the AI group and control group, respectively. Blind spot rate was lower in AI group compared with the control (5.86% vs 22.46%, $p<0.001$), and the mean difference was -15.39% (95% CI -19.23 to -11.54).

A more complex AI system was reported by Choo and colleagues (25), who attempted to train a deep learning system to categorise in five different categories stomach endoscopy images: the 5 categories were advanced gastric cancer, early gastric cancer, high grade dysplasia, low grade dysplasia and non-neoplastic images. The latter contained any form of gastritis, intestinal metaplasia or any other gastric images not included in the other four. The results were both presented in a binary of 5-way form. The binary (neoplastic or non neoplastic) form showed a good performance, with accuracy, sensitivity, and specificity in classifying gastric cancer were 81.9% (95%CI 79.3%-84.6%), 75.9% (95%CI 79.3%-84.6%), and 85.3% (95%CI 79.3%-84.6%), respectively. The 5 way performance was a little lower for some categories like high grade dysplasia, and was highest for lesions with AGC (range 0.802-0.855), and lowest for lesions with HGD (range 0.491-0.522). Of note, the per-category sensitivity was highest for lesions with non-neoplasm (range 74.2%-92.2%); however, it was lowest for lesions with HGD (range 0-10.3%).

CHARACTERIZATION OF GASTRIC CANCER

Characterization of gastric cancer has many pitfalls even for expert endoscopists. It is a domain in which not many groups have yet attempted to develop AI systems that can help to estimate grade of differentiation and/or invasion depth for early gastric cancer.

However, a preliminary experience reported by Zhu and colleagues (26) showed the results of a CNN based system in determining invasion depth of gastric cancer.

They constructed a training database from retrospectively reviewing endoscopic images and pathologic examination results from 790 patients and prepared a test dataset from 203 patients between. As should be for a unbiased test set, the patients and the images were totally unrelated, although coming from the same center. As we have reported elsewhere (15), ideally a test set should extract images from different centers so its results can be fully generalizable.

Overall, with a threshold value of .5, sensitivity was 76.47% and specificity 95.56%. The overall accuracy of the AI system was 89.16%. Positive and negative predictive values were 89.66% and 88.97%, respectively. When comparing it to 17 benchmarking endoscopists of different experience, the overall accuracy, sensitivity, specificity, positive predictive value, and negative predictive values of the 17 endoscopists were 71.49%, 87.80%, 63.31%, 55.86%, and 91.01%, respectively. The AI system achieved significantly higher accuracy (by 17.25%; 95% CI, 11.63-22.59) and specificity (by 32.21%; 95% CI, 26.78-37.44) than the endoscopists.

CONCLUSIONS

In conclusion, stomach neoplastic and preneoplastic conditions seem the territory in which AI systems are still in an earlier stage of development as compared to other GI endoscopy domains like colon or Barrett's Esophagus.

However, the early performances are promising. We can expect a high number of studies in the near future, especially from those countries where prevalence of disease permits a higher number of training images for the CNN systems. In this particular setting it seems that the need for multicenter efforts to build large training datasets is at its highest.

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Immune Checkpoint Inhibitor-Induced Colitis

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Immunotherapy with the introduction of immune checkpoint inhibitors represents a paradigm shift in cancer treatment and has led to a significantly improved prognosis for a number of cancers. However, the intended stimulation of the immune system has also led to the development of immune-related side effects, which can potentially affect almost all organ systems. The digestive tract is often involved, with immune-mediated colitis being the most common. This condition is usually well treated, but refractory cases can be very challenging. A multidisciplinary approach to the patient of different specialties will usually be required. Here the occurrence, clinical course, assessment and treatment of immune-mediated colitis is described.

INTRODUCTION

The recent development and approval of immune checkpoint inhibitors has been a major advancement in cancer therapy that has substantially improved the prognosis for patients suffering from a variety of malignancies including malignant melanoma, non-small cell lung cancer, kidney cancer, head and neck cancer and Hodgkin's lymphoma.

Immune checkpoints are regulatory inhibitory pathways that contribute to immune homeostasis by modulating the intensity and duration of the immune response. Two of the best described immune checkpoints, essential in maintaining self-tolerance and in preventing autoimmunity by inhibition of auto reactive T-cells, are the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1(PD-1/PD-L1) axes.

One of the mechanisms used by cancer cells to overcome the patient's immune system is to express checkpoint proteins that bind to the negative regulatory T-cell receptors PD-1 and CTLA-4. Antibodies that are targeting CTLA-4 (ipilimumab) and PD-1(nivolumab, pembrolizumab) or its ligand PDL1 (atezolizumab, avelumab, durvalumab) will block these negative interactions between T-cells, antigen presenting cells and tumour cells and a reactivation of the T-cell response to tumour cells occurs.

Upon activation of T cells, there is also an increased risk of an immune-induced inflammation in normal tissue as a consequence of impaired self-tolerance. These side effects can potentially affect all organ systems, but the gastrointestinal tract, liver and endocrine organs are most often involved.

In clinical trials, 70-90% of patients develop immune-mediated adverse reactions during the first three months of immunotherapy with checkpoint inhibitors (1). However, these events can occur at any time, even after the end of treatment. Adverse reactions associated with immunotherapy are graded as mild (grade 1), moderate (grade 2), severe (grade 3) or life-threatening (grade 4) and are defined on the basis of specific parameters according to the organ system involved (Table 1). The majority of side effects are mild and easy to treat, but in some cases they can be fatal (2). Serious side effects (grade 3-4) usually require hospitalization and discontinuation of immunotherapy.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Mild	Moderate	Severe	Life-threatening	Death
Colitis	Asymptomatic, clinical or diagnostic observations only; intervention not indicated	Abdominal pain, mucus or blood in stool	Severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs	Consequences, urgent intervention indicated	Death

Table 1. The National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE), version 4

Risk factor	Colitis
Drug	Combination therapy > anti-CTLA-4 > anti-PD-1
Dosing	Dose-dependent toxicity with anti-CTLA-4
NSAID usage	Suggested with anti-CTLA-4
Co-morbidity	Great risk of relapse in patients with inflammatory bowel disease especially with anti-CTLA-4
Gut microbiome	Various bacterial strains in the intestinal flora promote / inhibit risk
Tumour	Increased risk in malignant melanoma compared with non-small cell lung- and kidney cancer

Table 2. Risk factors for development of immune-mediated colitis due to immune checkpoint inhibitors

IMMUNE-MEDIATED COLITIS

Immune-mediated colitis as a result of treatment with immune checkpoint inhibitors is well recognized and can be a serious complication. It is the most common cause of hospitalization, discontinuation of immunological cancer treatment and death among all patients who develop immune-related adverse reactions (2). The incidence varies between the different checkpoint inhibitors and is most often seen with combination therapy. The pathogenesis of immune-mediated colitis is not fully understood, but recent studies have focused on the interaction between regulatory T cells and the intestinal flora. Similar to inflammatory bowel disease where a dysbiosis can trigger the intestinal inflammation, it seems that the intestinal flora also has an important and central role in a colitis that occurs as a result of immunotherapy (3). There are evidence indicating that the diversity and composition of the intestinal flora are important for both the treatment response of the cancer therapy and the risk of developing immune-related side effects. However, a more detailed knowledge of how the various bacterial strains can affect these conditions is unknown and further research is needed to map the interaction between the gut microbiome and the immune system. Although there are clear similarities with inflammatory bowel disease, immune-mediated colitis is considered a separate disease entity. Usage of non-steroidal anti-inflammatory drugs (NSAIDs) have been described as a risk factor for development of immune-mediated colitis and case series have demonstrated an increased occurrence of this side effect in patients with an established diagnosis of inflammatory bowel disease (Table 2).

Figure 1. Endoscopic features of immune-mediated colitis due to immune checkpoint Pathophysiol Sep 2019)

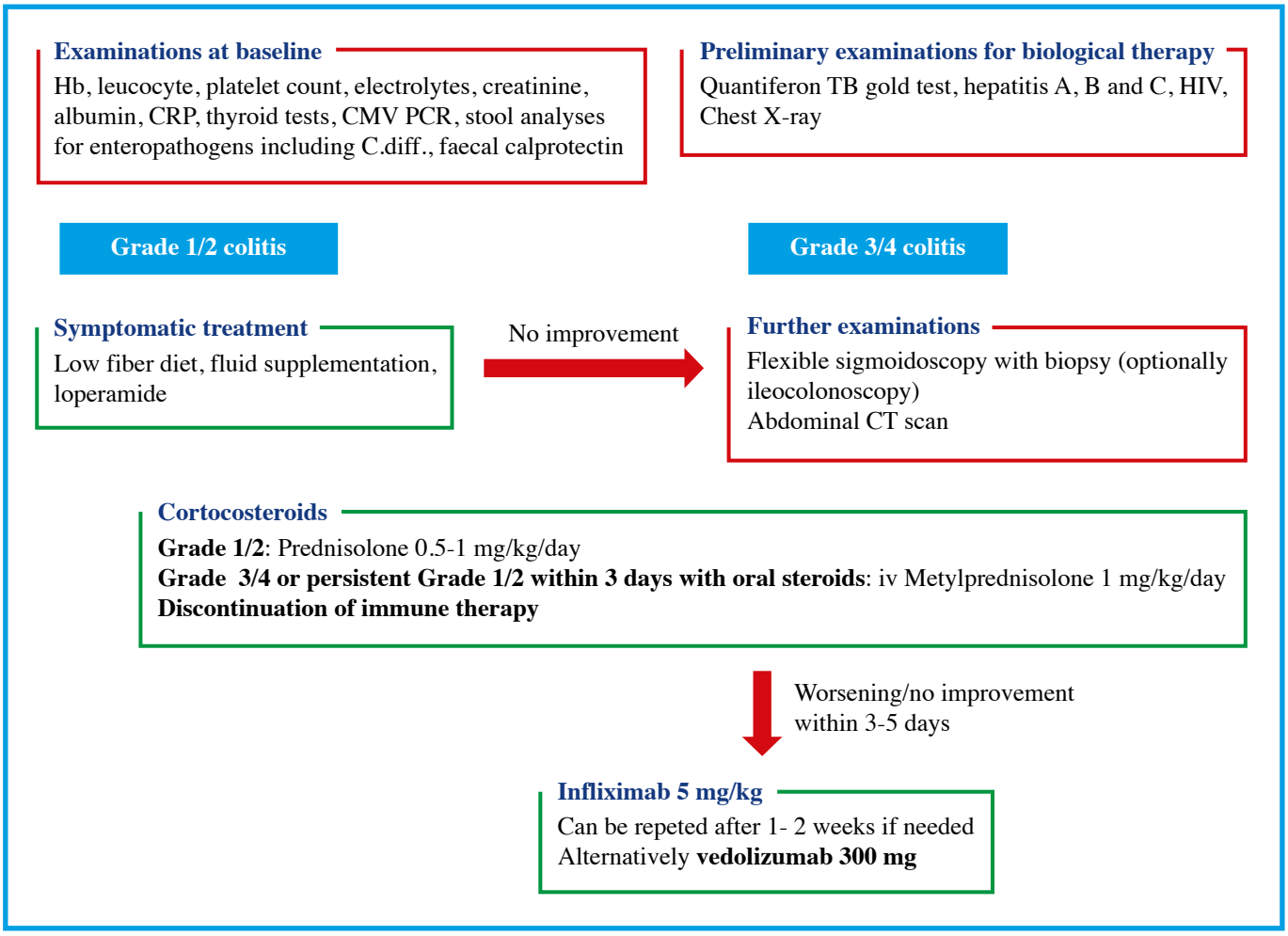

Figure 1. Algorithm for the investigation and treatment of immune mediated-colitis due to immune checkpoint inhibitors

INVESTIGATION

Faecal calprotectin is a very sensitive marker for active inflammation in the digestive tract and should be measured immediately in patients who develop symptoms suggestive of immune-induced colitis. Furthermore, it is very important to rule out an infection that may give a similar symptom picture. This includes the common pathogenic intestinal bacteria including Clostridium difficile and various viruses (Figure 1). It is also important to take the necessary preliminary samples for biological treatment. It often takes a few days before the results are available, and they should be in place before any biological treatment is given. Endoscopic examination with biopsies is considered the gold standard for diagnosing and assessing disease activity of immune-mediated colitis. Flexible sigmoidoscopy will usually be sufficient as the left side of the colon is affected in almost all cases (4). The endoscopic appearance has many features in common with inflammatory bowel disease and will vary greatly depending on the severity of the inflammation (Figure 2). The whole spectrum can be seen from only slight redness and edema of the mucous membrane to widespread and deep ulcerations that indicate a more severe disease. The most common histological findings are acute inflammatory, diffuse changes with infiltration of neutrophils and eosinophilic granulocytes in the lamina propria and formation of crypt abscesses. (5) More chronic changes with infiltration of mononuclear cells, granulomas and destruction of the crypts can also be seen. Cross sectional imaging with an abdominal CT scan should be performed in all patients admitted to hospital with suspected immune-mediated colitis.

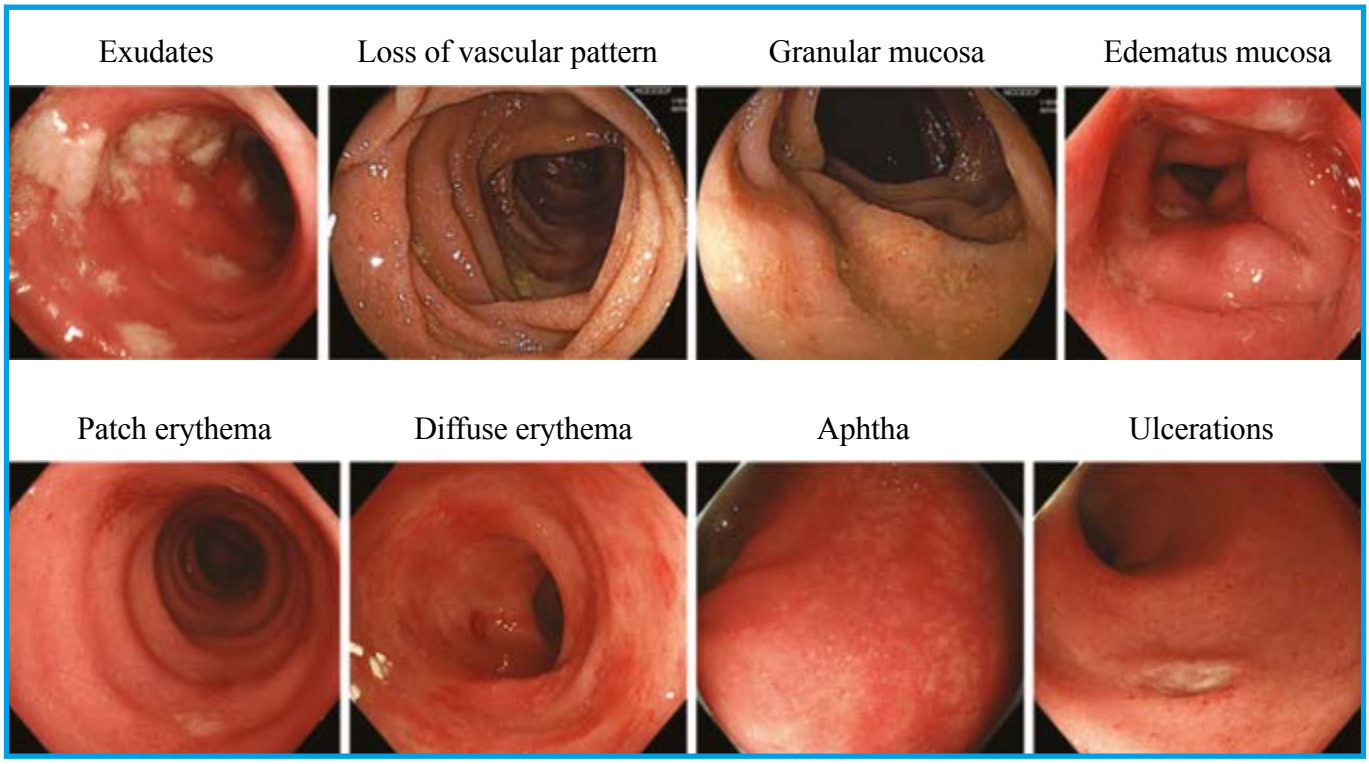

Figure 2. Endoscopic features of immune-mediated colitis due to immune checkpoint inhibitors (mod. from World J Gastrointest Pathophysiol 2019 Sep 10;10(2):17-28)

The examination can provide information about the extension of the colitis and whether there is a dilation of the bowel which can be a serious signal with regard to complications.

TREATMENT

Immune-mediated colitis often debuts acute and rapid progression of the condition can lead to life-threatening complications such as intestinal perforation. It is therefore very important to get started quickly with treatment. Figure 1 shows a proposed algorithm for diagnostic assessments and treatments. In the mildest cases, symptomatic treatment with loperamide and dietary recommendations may be sufficient. The effect of budesonide and 5-ASA preparations in this patient group has also been described. In case of more pronounced symptoms, treatment with corticosteroids should be started, for example Prednisolone 40-60 mg daily. If not rapidly improving, it should be changed to iv methylprednisolone 1 mg / kg / day. Oncologists have recommended higher doses of corticosteroids, but there is no clear evidence that this has any better effect. If there is no clear improvement or worsening of the condition after 3-5 days, treatment with infliximab should be started according to guidelines as for severe ulcerative colitis. An alternative may be vedolizumab, which can also be used if infliximab treatment has failed. Colectomy may be necessary in some patients. It is important to emphasize that these patients often need an interdisciplinary follow-up by an oncologist, gastroenterologist and possibly a gastro surgeon.

SUMMARY

Gastroenterologists must be aware of immune-related side effects including immune-mediated colitis as a result of immunotherapy for various cancers. In the coming years, there will probably be an exponential increase in the use of immunotherapy due to new indications, development of new drugs and combination therapy with these. It is therefore expected that the incidence of immune-related side effects will increase. Most immune-induced side

effects respond well to corticosteroids provided that treatment is started early in the course and with an adequate dose. However, many patients are likely to need other immunosuppressive therapy. So far, there is little evidence that such treatment affects the course of the underlying cancer. A multidisciplinary approach to these patients involving several specialties will often be necessary.

References

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The position statement of the British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group on SARS-CoV-2 vaccination for patients with IBD

Comment to: Alexander JL, Moran GW, Gaya DR, Raine T, Hart A, Kennedy NA, Lindsay JO, MacDonald J, Segal JP, Sebastian S, Selinger CP, Parkes M, Smith PJ, Dhar A, Subramanian S, Arasaradnam R, Lamb CA, Ahmad T, Lees CW, Dobson L, Wakeman R, Iqbal TH, Arnott I, Powell N; Inflammatory Bowel Disease section of the British Society of Gastroenterology and the Inflammatory Bowel Disease Clinical Research Group. SARS-CoV-2 vaccination for patients with inflammatory bowel disease: a British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group position statement. Lancet Gastroenterol Hepatol. 2021 Jan 25:S2468-1253(21)00024-8. doi: 10.1016/S2468-1253(21)00024-8. Epub ahead of print. PMID: 33508241; PMCID: PMC7834976.

Vaccination is a key protective strategy of the world's population from COVID-19, especially in high-risk individuals, such as those with pre-existing health conditions. Inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, is an immune-mediated inflammatory disease, with a global prevalence around 400 cases per 100,000 persons per year and continuously increasing incidence. Being an immune-mediated inflammatory disease, IBD patients often require immunosuppressive therapies, triggering foremost concerns during the COVID-19 pandemic. As noted by Alexander et al. in a position statement endorsed by the British Society of Gastroenterology Inflammatory Bowel Disease (IBD) section and IBD Clinical Research Group, the risks associated with immunosuppression are not limited to increased susceptibility to infection, since immunosuppressive drugs may reduce the effectiveness of some vaccines, with major implications for the safety of immunosuppressed patients in the COVID-19 era.

Three SARS-CoV-2 vaccines are currently approved in the several Countries (Figure 1) and additional vaccines will become available in the future.

Several factors offer some reassurance for persons with IBD regarding vaccination, starting with the robust and comprehensive nature of the regulatory process. Approved SARS-CoV-2 vaccines have been tested in about 19000 patients with safety profiles comparable to other vaccines commonly used in patients with IBD, and have been appraised by multiple independent regulators. For the three currently approved vaccines, immunosuppression is not a contraindication, even though IBD patient groups were not included in phase 3 studies. However, other commonly used vaccines (e.g. influenza, HBV,

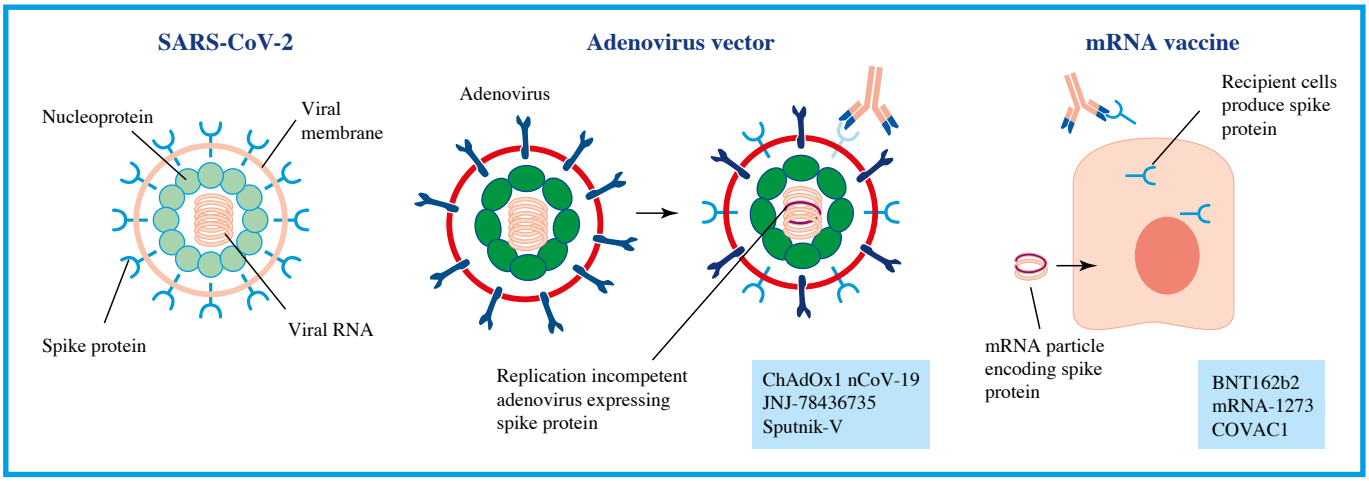

Figure 1. SARS-CoV-2 and currently approved vaccine mechanisms (mod. from Alexander et al. Lancet Gastroenterol Hepatol 2021)

HAV) are also very low risk in patients with IBD, although they were never specifically investigated in IBD patients.

Side-effect profiles from SARS-CoV-2 vaccines are in line with events observed with other commonly used vaccines and common side-effects such as pain or fever can be treated with analgesia or anti-pyretic medication.

Groups of patients with IBD in whom vaccination is not advised or should be considered on the basis of a benefit-versus-risk analysis include people younger than 16-18 years or during pregnancy (while breastfeeding is not a contraindication).

The three approved vaccines are contraindicated if there is a history of hypersensitivity to the active substance or any of the vaccine excipients, while adverse reaction to other medications biologic treatment for IBD is not a contraindication.

Since SARS-CoV-2 vaccines have not been tested in patients with IBD it is not possible to judge whether vaccination will have an effect on IBD disease activity. However, no serious gastrointestinal side-effects to SARS-CoV-2 vaccinations have yet been reported. Furthermore, there are reassuring data from studies of patients with IBD receiving other commonly used vaccinations.

The authors recommendations are summarized in Figure 2.

1. The position paper strongly supports SARS-CoV-2 vaccination for patients with IBD
2. The risks of SARS-CoV-2 vaccination in patients with IBD are anticipated to be very low
3. Concerns may be related to the theoretical risk of suboptimal vaccine responses rather than vaccine side-effects in persons taking IBD indicated immunosuppressive drugs (biologics and small-molecule inhibitors)
4. The position paper recommends that patients with IBD accept whichever approved SARS-CoV-2 vaccination is offered to them
5. It is important that patients with IBD are offered consistent and unbiased advice by the Scientific Societies or Patient Associations

Figure 2. Key messages (mod. from Alexander et al. Lancet Gastroenterol Hepatol 2021)

SIBO and extra-intestinal disorders

Comment to: Losurdo G, Salvatore D'Abramo F, Indellicati G, Lillo C, Ierardi E, Di Leo A. The Influence of Small Intestinal Bacterial Overgrowth in Digestive and Extra-Intestinal Disorders. Int J Mol Sci. 2020 May 16;21(10):3531. doi: 10.3390/ijms21103531. PMID: 32429454; PMCID: PMC7279035.

Small intestinal bacterial overgrowth (SIBO) is defined as an increase of the concentration of colonic-type bacteria in the small intestine, it occurs more often in conditions when parts of the small bowel are not in continuity any more, the so called or "blind loop syndrome". The small bowel physiologically contains a concentration lower than 103 colony forming units (CFU)/mL of mostly Gram-positive organisms. Above the cut off of 105 CFU/mL SIBO is diagnosed and a predominance of Gram-negative and anaerobic bacteria is often observed.

SIBO is frequently a complication of abdominal surgery, structural problems, or medical conditions that slow the passage of food and waste products in the digestive tract. Excess bacteria can cause watery diarrhea, bloating, abdominal pain and distension and, also, malnutrition and deficit of vitamins (B12, D, A, and E) as well as minerals (iron and calcium). According to Losurdo et al. this classifies SIBO as a syndrome that may arise in different clinical contexts, with different implications for diagnosis and treatment, able to mask or worsen the history of some diseases (celiac disease, irritable bowel disease). The authors subsequently explored the links between SIBO and some gastroenterological and extra-digestive diseases in a recent narrative review.

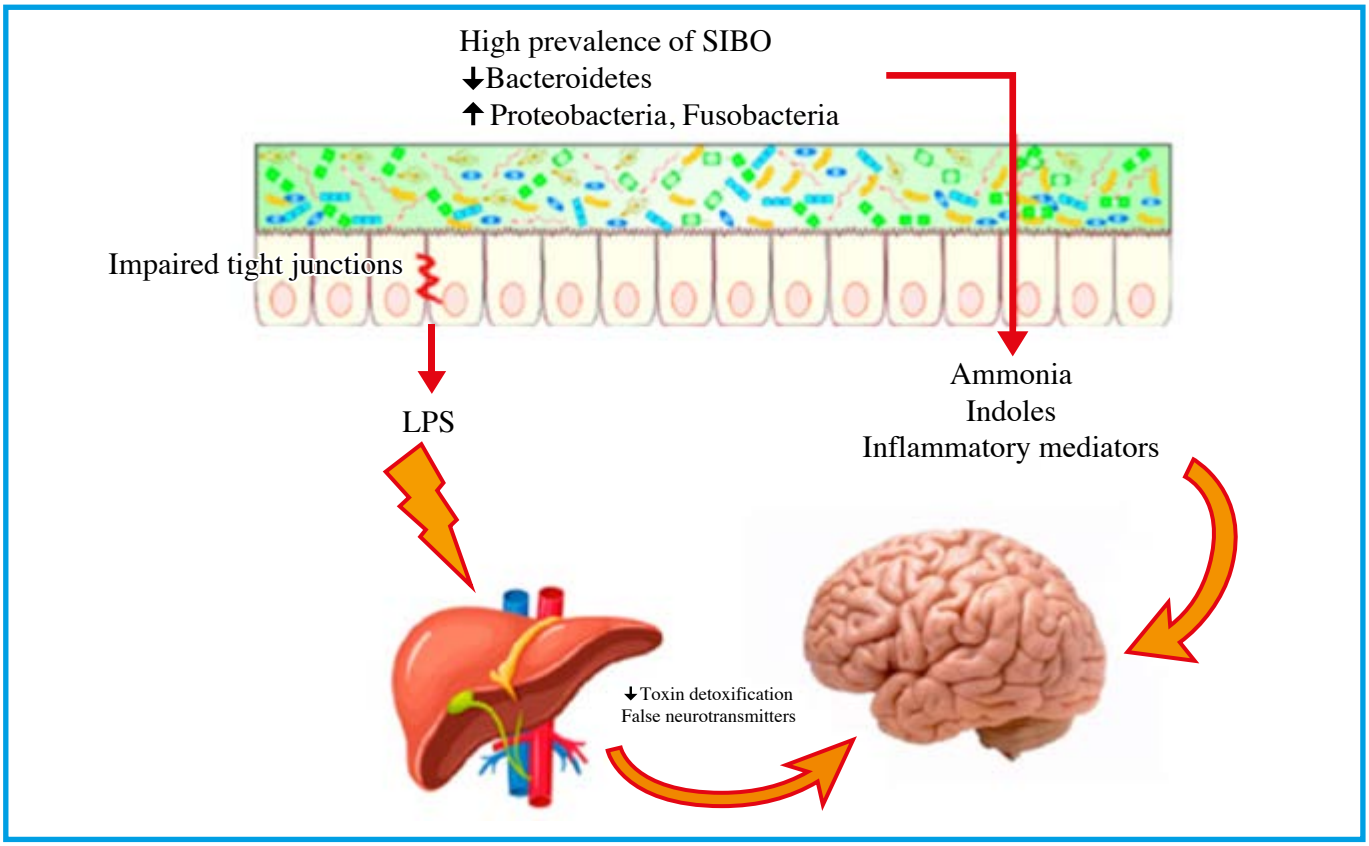

Figure 1. from Losurdo et al.

Numerous factors are linked to SIBO in patients with irritable bowel syndrome (IBS), with female gender, old age, bloating and flatulence as the main manifestations, and diarrhea-predominant IBS. Also, IBS patients may have overlapping functional dyspepsia or be prescribed narcotic drugs inhibiting gut motility.

A much higher risk of SIBO in inflammatory bowel disease (IBD) patients has been demonstrated, linked to fibro-stenotic conditions, previous intestinal surgery, and slow transit time. SIBO could have a relevant impact on IBD symptoms and clinical management.

The importance of SIBO in celiac disease is still debated, due to the extreme heterogeneity in terms of study type, number of patients and diagnostic techniques. However, SIBO should be taken into account in patients with non-responsive celiac disease.

Hepatic encephalopathy (HE) indicates a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of other known brain disease. A direct association between SIBO and HE has been observed, but this is still debated since no connection between SIBO and minimal HE has been reported. The implications of SIBO in HE may be framed in the complex alterations of gut microbiota that can underlie HE, as summarized in Figure 1.

Metabolic syndrome, a disease growing in developed countries, encloses multiple conditions as central obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein. It has a debated link with intestinal microflora and the correlation with SIBO is worth investigating. Also, patients with diabetes may suffer from a visceral neuropathy characterized by slower intestinal transit that could favor SIBO onset.

The authors conclude that evidence regarding extra-intestinal diseases correlation with SIBO is still conflicting and evidence insufficient to draw definitive conclusions and thoughtful investigations are needed.