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Editorial

Medical innovation and "complicated" relationships of the digestive system

The second Number of IDEA journal is dedicated to three topics of great interest. First of all, innovation in medical techniques series is present with the second review on artificial intelligence and endoscopy. Then, two "complicated" relationships are explored: COVID-19 and gut microbiome and, also, Crohn disease and tobacco smoking (and smoking cessation).

This second of a series of 4 reviews dedicated to artificial intelligence/machine learning and gastrointestinal endoscopy, by Giulio Antonelli and Cesare Hassan, is focused on the detection and characterization of squamous esophageal carcinoma. Very promising results are reported in terms of sensitivity of the artificial intelligence system in squamous cell carcinoma detection.

COVID-19 and its impact on microbiome was analyzed by Jiajun Wu and colleagues, since, apart from fever, non-productive cough, and asthenia, clinical manifestations induced by COVID-19 also include gastrointestinal symptoms. Also, medical advice was sought due to diarrhea as first symptom by some patients. SARS-CoV-2, hence, colonizes human gastrointestinal tract in addition to respiratory tract, resulting in balance disturbance in human microbiomes, especially, respiratory tract microbiome and gut microbiome. The authors suggest that intervention therapy with microbiota products would be favorable to prognosis of COVID-19.

Finally, Giovanni Maconi and colleagues analyzed the main evidences on the effect of cigarette smoking on Crohn's disease onset and its natural history, along with evidences on benefit of smoking cessation on the course of Crohn's disease and impact and therapeutic strategies for smoking cessation in Crohn's disease. Tobacco smoking is one of the major risk factors for developing Crohn's disease and one of the main effectors on its natural history affecting response to therapy, relapse rate, onset of intestinal complications and extraintestinal manifestations and an increased risk of surgery, but a low awareness on these effects still exists, with important difficulties in education on smoking cessation.

Artificial intelligence in the detection and characterisation of squamous esophageal carcinoma: a review of recent literature

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SQUAMOUS ESOPHAGEAL CARCINOMA

Epidemiology

Esophageal carcinoma is the seventh most common cancer diagnosed worldwide, with around 600,000 new cases diagnosed in 2018 and the sixth cancer for mortality, with more than 500,000 deaths every year (1).

This disease is distinguished in two main histological subtypes with distinct etiologies, molecular pathways and histopathological characteristics: adenocarcinoma (EAC), which is typically located in the lower third of the oesophagus and linked to Barrett's oesophagus (characterised by metaplastic epithelium), and squamous cell carcinoma (SCC), which develops in the native oesophageal epithelium (2-4). SCCs are associated with smoking and alcohol consumption. Recent studies have shown that although SCC is the more common type of oesophageal cancer globally, accounting for almost 90% of all cases of esophageal cancer, in high income countries incidence rates of AC have surpassed SCC rates (5).

Many theories have been proposed for the explanation of this epidemiological shift, for example an increasing prevalence of obesity and GORD and a concurrent decline in Helicobacter pylori infection and declines in tobacco smoking prevalence. Unlike EAC, esophageal squamous-cell carcinoma risk increases from 3- to 5- fold in people who consume alcohol (3+ drinks/die), and this risk is synergistically higher with tobacco use. In addition, red meats, fats, and processed foods intake has been associated with an increased risk of both types of esophageal cancer, whereas high intake of fiber, fresh fruit, and vegetables is associated with a lower risk (5-7).

Another condition strongly associated with the development of SCCs is achalasia, an esophageal motility disorder, that increases 10-fold the risk as compared with patients without achalasia (6,8).

Other risk factors proposed include oncogenic human papillomaviruses, with limited evidence.

The precursor lesion for SCC is esophageal squamous dysplasia; patients with mild, moderate, or severe dysplasia have a risk of squamous-cell carcinoma that is increased by a factor of 3, 10, or 30, respectively. Endoscopic screening or non-endoscopic use of balloon brush cytologic testing has been performed in some regions in China and may have merit; these techniques are also recommended for patients with achalasia or those with a history of lye ingestion resulting in stricture, although there are no evidence-based guidelines for the treatment of these patients (9).

Chemoprevention of SCC has been researched in many epidemiological studies, and both low-dose aspirin and statins have shown a significant reduction

in the risk of SCC. On the other hand, no evidence was found in supplementation with vitamins or other integrators (10).

Diagnosis

Diagnosis of SCC is commonly made at a late stage and results in a poor prognosis. However, early endoscopic diagnosis is strongly associated with improved outcomes. The most important prognostic factor is depth of invasion, which is obviously directly proportional to the time of diagnosis. In detail, studies have shown how the risk of metastatic disease increases with every level of invasion, from a negligible 5-year rate of 0.4% for epithelial/lamina propria tumors, to a 36.2% for SM2. Notably, a great difference in 5-year metastatic rate exists between SM1 and SM2 tumors (7.7% vs 36.2%), and this marks the limit between tumors that are treatable with endoscopic resection and tumors that are subsequently sent to surgical resection (11).

Reasons for the late diagnostic stage are multiple. First, the prevalence of this disease, especially in the Western setting, is low and in reduction, thus resulting in a reduced familiarity of community endoscopists for these lesions. Second, for the same reasons, the possibility of undergoing a structured training in lesion detection and characterisation is limited. Third, it is known that white-light imaging is suboptimal in detecting these lesions (12,13).

Advanced endoscopic imaging, and in particular blue light imaging techniques (Narrow Band Imaging, Blue Light Imaging, etc) has shown promising results in improving SCC detection and characterisation, enhancing microvascular and mucosal structures and increasing the visibility of these subtle lesions (14). Before the widespread use of blue light technologies, lugol chromoendoscopy was considered the standard-of-care, but recently blue light technologies have been shown to significantly increase detection rate as compared to lugol and have been consequently upgraded to gold-standard (15). Nevertheless, the issues concerning prevalence of the disease and training in its detection are still hampering optimal detection rates outside referral centers. Studies have shown how non-expert endoscopists are suboptimal in the detection of SCC as compared to experts, and even in expert hands, a significant inter-observer agreement on the endoscopic findings has been reported (16).

As previously discussed in the setting of Barrett's Esophagus related neoplasia surveillance, this uncertain terrain is ideal for the development of Artificial Intelligence (AI) systems that can aid the clinician in detecting suspect lesions and guide the right diagnostic choices (17). After the implementation of Convolutional Neural Networks, deep learning systems have shown a good performance in visual tasks and have been applied to the detection and characterisation of many gastrointestinal neoplastic and pre-neoplastic conditions (18). In the setting of esophageal SCC, many systems are under various stages of development. Some have already been

SCC detection				
Study	**System and validation**	**Sensitivity**	**Specificity**	**Accuracy**
Cai 2019 (20)	CNN/Images	97	95	84
Guo 2019 (19)	CNN/Images+Videos	98	95	95
Horie 2019 (21)	CNN/Images	77	79	79
Ohmori 2019 (22)	CNN/Images	100	63	77
Fukuda 2020 (12)	CNN/Videos	91	51	53
SCC Characterization				
Tokai 2019 (23)	CNN/Images	84	-	81
Nakagawa 2019 (24)	CNN/Images	90	95	91
Zhao 2019 (25)	CNN/Images	87	84	89
All numbers are percentages (%) unless otherwise stated. CNN: Convolutional neural network				

Table 1. Summary of the available literature

tested in a real-time setting, but most of them have been tested against still, selected images, leaving some doubts on their current applicability in clinical practice. In addition, a limited number of AI systems have been developed to determine SCC invasion depth, potentially guiding therapeutic choices (endoscopic vs surgical resection).

Most AI systems for esophageal SCC have been developed in the Eastern setting, probably due to the higher prevalence of disease in this area.

In the next sections, we will give a brief overview of currently existing AI systems for the detection and characterisation of esophageal SCC.

A summary of existing literature is available in Table 1.

AI for the detection of esophageal SCC

Currently, only 5 papers have been published regarding detection of esophageal SCC (12,19-22). In detail, all 5 of them come from the Eastern setting, three from Japan (12,21,22) and two from China (19,20).

Among these studies, 3 studies (20-22) have undergone external validation with still images and 2 with videos (12,19).

Given the higher clinical relevance of the studies using a video validation set, we will focalise on the latter. This kind of systems seem to be more ready to be available for clinical practice, and in the future, it is desirable that all validation studies for AI detection systems are proven against videos, even better if in a clinical, real-life setting. This is mainly because this kind of validation is the closest to the actual real life scenarios in which it is foreseeable that the systems will be used in.

The first AI system for the detection of esophageal SCC to be tested on videos was the result of a multi-center effort (19), the only one in which Western centers were involved, although in minority. Four endoscopic centers (Shanghai and Chengdu, China; Rialto, California; Meerut, India) contributed to the creation of an image training database composed by a total of 2770 NBI images of precancerous lesions and early Esophageal SCCs in 191 cases and 3703 NBI images of noncancerous lesions in 358 cases (among them, normal esophagus, esophageal varices, ectopic gastric mucosa, esophagitis).

Interestingly, the authors and developers chose to validate this system on 4, separate datasets, 2 still image libraries and 2 video libraries, encompassing both magnifying and non-magnifying endoscopic images. The authors also chose to divide malignant and benign images separately in the datasets. Suboptimal quality images were excluded from the validation sets.

All validation images and videos were also tested against expert endoscopists, blind to the final diagnosis, to benchmark the performance of the AI system. In addition, all validation images and videos were collected on consecutive cases and later in time compared to the training sets. This, also according to the authors, should increase the quality of the validation tests.

The AI system showed an impressive overall sensitivity of 98.04% and specificity of 95.03% for the image sets, and a an overall sensitivity of 96.1% and specificity of 99.99% for the video sets. Interestingly, the sensitivity dropped to 60.8% in the non-magnifying videos, while the specificity of 99.9% was reached with 30 non magnifying videos and only 3 magnifying videos.

Authors speculate that the drop in sensitivity in the image library is due to the fact that in non-magnifying videos, motion artifacts occur and could affect and blur the imaging features and therefore the system could receive insufficient details to trigger a detection signal.

The other AI system for the detection of esophageal SCC validated on video images comes from a Japanese multi-center group (12) that has published the 3 Japanese papers on the subject.

This system was trained from a large library including a total of 862 videos and 25,910 images from 2,289 patients. Among these, 1,831 were cancer cases and 458 were non-cancerous cases. The developers divided this library for training and internal validation and calibration, and after tested the system on 144 videos, previously never encountered by the AI. The 144 videos were also benchmarked by 13 board certified expert endoscopists. To reduce any possible bias all videos were cut to a similar length between 5 and 9 seconds.

In the validation set, the sensitivity, specificity, and accuracy of AI in SCC detection was 91%, 51%, and 63%, respectively. Expert endoscopists showed sensitivity, specificity, and accuracy of 79%, 72%, and 75%, respectively. The sensitivity of the AI

system was significantly higher than that of the experts, but its specificity was significantly lower, while interobserver agreement among the experts for detecting SCC was "fair", using kappa agreement.
Interestingly, this system was also trained for the characterization of SCCs' depth of invasion using only the magnification endoscopy videos. The sensitivities, specificities, and accuracy were, respectively, 86%, 89%, and 88% for the AI system and 74% (95% CI, 0.69–0.79; p<0.01), 76% (95% CI, 0.69–0.83; p<0.01), and 75% (95% CI, 0.71–0.79; p<0.01) for the expert endoscopists.

AI for the characterization of esophageal SCC

The previous system is the only system currently reported in literature that has been validated with videos (although not in real time) for characterization of depth of invasion of esophageal SCC. Three other papers (23-25) have reported performance of AI characterisation systems on still images, and their performances are summarised in Table 1.
Overall, characterization performances of AI systems, although still showing promising results, seem to be still less optimal than those shown with detection.

CONCLUSIONS

In conclusion, current evidence on AI systems for detection and characterization of SCC is promising, although its implementation in clinical practice seems a bit further away than systems developed for other gastrointestinal pre-cancerous conditions.

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Microbiome Alterations and Interventions in COVID-19 Patients

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ABSTRACT

Propagation of novel coronavirus (SARS-CoV-2) emerging in December 2019 has led to infection of large population in a short time, resulting in thousands of deaths. SARS-CoV-2-induced pneumonia readily progressing toward severe or critical illness, threatening patients' life. Apart from fever, non-productive cough, and asthenia, clinical manifestations induced by COVID-19 also include gastrointestinal symptoms. Some people even sought medical advice due to diarrhea as first symptom, indicating that SARS-CoV-2 will colonize human gastrointestinal tract in addition to respiratory tract, resulting in balance disturbance in human microbiomes, especially, respiratory tract microbiome and gut microbiome. The gut microbiome is the largest microbiome in human body and disturbance of its balance causes damage to gut immune barrier. Alteration of microbiota structure or translocation of microbiota may lead to systemic inflammation or sclerosis, resulting in multiple tissue/organ injury, and eventually, lung injury further worsens as well. Intervention therapy with microbiota products would be very favorable to prognosis of COVID-19.

Since December 2019, a novel coronavirus has spread quickly across China, the epidemic has been progressing rapidly, making tens of thousands of people infected, and thousands of people have died. On Feb. 7, 2020, the National Health Commission of the People's Republic of China named the pneumonia due to infection with this coronavirus "novel coronavirus pneumonia" (NCP). On Feb. 11, 2020, the International Committee on Taxonomy of Viruses (ICTV) named this virus "severe acute respiratory syndrome-related coronavirus 2", i.e., SARS-CoV-2; and on the same day, WHO named the disease caused by this virus "coronavirus disease 2019", i.e., COVID-19.

COVID-19 has an incubation period of normally 1-14 days, with most patients showing signs and symptoms within 3-7 days. Its primary clinical symptoms include fever, asthenia, and non-productive cough, and some patients progress quickly to severe symptoms or even critical illness due to not timely treatment or concurrent underlying disease. Severely or critically ill patients present dyspnea and/or hypoxemia, and, in serious cases, the illness progresses rapidly to acute respiratory distress syndrome (ARDS), pyemia, incorrigible metabolic acidosis, coagulation dysfunction, etc. In severely or critically ill patients, because of continuous lung injury, hypoxemia is complicated by hypercarbia due to residence of carbon dioxide, and it triggers excessive systemic inflammatory response syndrome

(SIRS) and multiple organ failure (MOF). Hence, compensated shock or shock may occur, or even life may be threatened (1).

Studies have shown that, in addition to direct injury of the lungs by the pathogen, intrinsic microecosystem of the lungs and its susceptibility to the pathogen are associated with disease severity, and alterations of lung microbiota structure may alter responses of immune system to the virus and pathogens of secondary infection, leading to acute exacerbation of the disease and further mortality rise. A deep knowledge of lung microbiome, including secondary infection due to microbiome imbalance and bacteria that have significant impact on mucous immune system, can be of paramount importance in predicting effectively prognosis of the disease and in preventing complications and decreasing mortality. Apart from lung microbiome, human gut microbiome could be also very important in predicting progress and prognosis of COVID-19.

Gut microbiome is the largest microbiota in human body, and in the feces of 50% of COVID-19 patients, virus nucleic acid can be detected, and live virus can be isolated, indicating that, when a microorganism is in the pathological state, the virus can survive in disturbed intestinal microecoenvironment. This is why most of COVID-19 patients have respiratory tract symptoms infection complicated by digestive symptoms, such as nausea, vomiting, and diarrhea. Also, in some patients, the first symptom is diarrhea and, among these digestive symptoms, gastrointestinal side-effects due to early use of antivirus drugs are also included. Disruption of gut microbiome structure, dysbiosis, and reduction in dominant microflora such as gut lactobacillus, bifidobacteria, and other probiotics lead to opportunistic infections in COVID-19 patients, who present digestive symptoms. Immune barrier based on stable gut microbiome plays an important role in microorganism protection: close connection between the digestive tract and the respiratory tract can be called "gut–lung axis", destruction of gut microbiome structure lead to bacterial translocation and endotoxin spread, resulting in septicemia, and gut microbial translocation may give rise to substantial proinflammatory cytokines, eventually resulting in acute lung injury (ALI) or ARDS (2).

SARS-COV discovered in 2003 and SARS-CoV-2 discovered in 2019 have about 80% homology in nucleotide sequence. Both viruses infect target cells via human angiotensin converting enzyme 2 (ACE2). As a receptor, ACE2 has independent functions of rennin–angiotensin system (RAS), is highly expressed in the heart and kidneys, expressed to variable extents in lungs and small intestines, and barely expressed in the colon, though ACE2 deficiency increases susceptibility to colitis. ACE2 is vital to neutral amino acid transporter present in the gut and transport of gut amino acids may affect composition and structure of gut microbiota. For example, reduced tryptophan level results in decreased activity of small intestine mTOR pathway, where mTOR is a serine/threonine kinase, mTOR signaling pathway is able to promote metabolism and participate in cell apoptosis and autophagy, and abnormal activation of mTOR leads to impaired expression of antimicrobial peptide in the cells in intra-intestinal microbiome, and further alterations of gut flora composition and structure. Microbiota transplantation test demonstrates that alteration of gut microbiota is an important cause of increased susceptibility leading to colitis. This is why acute inflammatory diarrhea occurs after SARS-COV-2 attacks gut-expressed ACE2 receptor (2,3).

In studies on SARS and COVID-19, it has been found that the viruses infect human and cat tissues and organs in vitro only and cats show gut microbiota structure similar to humans. Feline gut virus test can be referred to human being. Feline coronavirus (FCOV) is extensively present in the gut of healthy cats and it is able to induce feline infectious peritonitis (FIP). FIP is caused by FCOV, while FCOV is normally present in the gut, its reproduction within gut epithelial cells may give rise to mutations, and the mutated genes lose tropism towards gut epithelial cells and obtain the capability of reproduction in macrophages. Regardless of mutation, FCOV is transmittable.

In recent medical research based on microbes in feline feces, cats were classified into three groups:

- one consists of healthy cats,
- the other consists of cats infected with FCOV that do not progress to peritonitis, and
- the third group consists of cats infected with FCOV that progress to peritonitis.

Results indicated that gut microbes are involved in the progression of the systemic disease and able to affect immune responses to viral diseases. Therefore, the presence or absence of infective disease progression may be related to gut microbiota balance (4).

In regard to the progressive disease of COVID-19 patients, one term "cytokine storm" is frequently mentioned. SARS-COV-2 triggers systemic inflammatory response, resulting in a substantial release of proinflammatory cytokines, which forms a cytokine storm after having accumulated to a certain order of magnitude and acts on various tissues and organs to result in a new round of injuring, and the continuation of such a vicious cycle leads to disease progression and worsening. Lung manifestations of COVID-19 patients are often complicated by injuries of other organs, for example, heart injury manifested as mild elevation of troponin, increased transaminases and total bilirubin in the liver, and coagulation dysfunction primarily manifested as increased D-Dimer. Severely or critically ill patients often develop a multiple organ dysfunction syndrome (MODS), when the above parameters increase more significantly. After SARS-COV-2 invades the human body three cases can follow:

1. the virus coexists with the body immune system without clinical manifestation, this is commonly known as virus-carrying state, and it is infectious.

2. The body is infected with a certain amount of viruses that impair human organs and shows certain clinical symptoms and signs. After having invaded the human body, unlike other viruses, SARS-COV-2 also invades lymphocytes, in particular, T lymphocytes, resulting in a decrease in T lymphocytes. A substantial number of viruses leads to the death of T lymphocytes, compromising body immunity; in addition, the virus is able to produce directly viremia and to spread to organs across the body, resulting in a vicious cycle.

3. SARS-COV-2 and the body repel each other, which may induce cytokine storm and lead to MOF, primarily manifested as increased IL-6 and IL-8 and decreased IL-10. Cytokines can be generated by various impaired organs. The lungs produce cytokines mainly because SARS-COV-2 infection causes interstitial lung disease, leading to substantial neutrophil infiltration and release of elastase and cytokines, resulting in vicious cycle. Under hypoxic conditions, endothelial injury leads to substantial release of cytokines while initiating coagulation function to aggravate hypoxia and induce continuous cytokine release, eventually resulting in vicious cycle. In regard to gut, gut epithelial cells–dendritic cells (DC) conversion and differentiation occurs: following hypoxia, gut epithelial cells are converted into DC cells capable of presenting antigens. A large quantity of antigens are presented to gut submucosal lymphocytes to release a lot of cytokines, which converge in lymphatic vessels and then flow back to the lungs to aggravate their injuries, and gut hypoxia, especially shock, lead to serious alteration of gut microbiome, breaking the balance between microbiome and body, resulting in variation of microbial abundance. As described above, both alveolar endothelium and gut epithelium are the main places to produce substantial cytokines, where the gut epithelium-derived cytokines have the greatest share, and eventually, all such cytokines lead to further lung injury. In response to this outcome, prevention and remedy should be carried out on time (6).

Severely or critically ill patients suffer ischemia, hypoxia, or shock, and, in particular, their guts will suffer serious injury due to rich blood supply and depletion of substantial oxygen gas, so that edema, exudation, and inflammatory response occur, resulting in gut microenvironment disorder. Dynamic balance of gut microbiome is closely related with gut microenvironment, loss of microbiome balance and destruction of microbiota structure lead to translocation of gut microbes, and when dominant gut microflora no longer play inhibitory effect against other bacteria, opportunistic infections with various microbes occur, and after substantial reproduction of pathogenic microbes inducing such opportunistic infections, the resulting metabolites are able to wander across the body to develop SIRS and release a large amount of cytokines, resulting in cytokine storm to impair crucial organs such as heart, liver, kidneys, and lungs, in particular, further lung injury leads to exacerbated ischemia

and hypoxia, further making the disease more severe or critical.

In consideration of these factors, microbiome products such as probiotics are used to stabilize gut microbiota, alleviate microenvironmental inflammation, inhibit production of substantial cytokines, and reduce output of toxic metabolites, meanwhile gut immune barrier and autoimmune mechanism are known to mitigate invasion capability of internal or external bacteria or viruses, and antagonize them from colonizing the gut for growth and reproduction, to contain SIRS effectively (5,6).

For COVID-19 patients, current therapy is an integrated therapy focusing on "Four-Anti's and Two-Equilibria". It enables effective improvement in survival rate and reduction in mortality. "Four-Anti's and Two-Equilibria" means anti-virus, anti-shock, anti-hypoxemia, anti-secondary-infection, maintenance of fluid and electrolyte equilibria and acid-base equilibrium, and maintenance of in vivo microbiome equilibrium. This treatment strategy is a summary of experience accumulated by the First Affiliated Hospital, Zhejiang University School of Medicine during rescue and treatment of patients with H7N9 avian influenza, but it remains applicable to clinical rescue and treatment of COVID-19 patients. Moreover, as pointed out in Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7) issued by National Health Commission and National Administration of Traditional Chinese Medicine of the People's Republic of China, microbiome products can be administered to severely or critically ill patients. For different patients, individual therapies should be customized. For many patients, gut microbiome disturbance may occur in the early stage, including decreased probiotics such as gut lactobacillus and bifidobacteria, and increased enterobacillus. After gastrointestinal function assessment for these patients, nutrition support is given and high dose of gut microbiome regulator is added to correct gut microbiome imbalance to minimize bacterial translocation and secondary infection (1).

Maintaining stable microbiomes, in particular gut microbiome, aids in regulating immunocompetence of the patients and reducing effectively mortality of severely or critically ill patients. In addition to essential anti-virus therapy, attention should also be paid to nutrition support therapies, such as oral feeding; for those failing to be orally fed, enteral nourishment can be conducted to nourish gut epithelium to improve gut mucosal barrier and immune function and maintain gut microbiome. Antibacterial agents should be properly used to prevent secondary infection. As COVID-19 is a viral disease, prophylactic use of antibacterial agents is not recommended for mild and normal patients, while for severely ill patients, decision should be discreetly made based on specific situation, and once infection occurs, pathogen of the infection should be identified as soon as possible. Virus infection may result in compromised cell immune function, and improper use of glucocorticoids or broad-spectrum antibiotics may lead to secondary fungal infection, where candida infection or pulmonary aspergillus infection should be guarded against. Microbiome regulators should be used in treatment. The experience in rescue and treatment of H7N9 avian influenza with microbiome regulators suggests that:

- patients have lower risk of secondary infection,
- all-cause digestive symptoms in the patients are relieved,
- probability of gut microbiota translocation decreases,
- dominant bacteria in the gut increase, so as to antagonize proliferation of harmful bacteria in the gut, mitigate toxin production, promote growth of gut epithelium, and repair and potentiate its immune barrier effect.

In cases of serious hypoxemia, cytokine storm, secondary severe infection, shock-induced tissue perfusion disorder, or even MOF, artificial liver-based blood purification therapy can be used to reduce circulating toxins and improve prognosis. Researchers find that fecal microbiota transplantation is a novel therapy, that is obviously superior to antibiotics and plays an important role in treatment of Clostridium difficile infection.

Evidence shows that viruses remain detectable in feces when no more virus can be detected in the respiratory tract, indicating the presence of fecal-oral transmission of viruses, which partially explains why COVID-19 patients present digestive symptoms (1,7,8).

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Smoking habit, health risk of smoking awareness and smoking cessation in Crohn's disease patients

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ABSTRACT

Crohn's disease (CD) is a chronic inflammatory disease associated with a long-term morbidity, accounting for a high burden to patients and health care system. Its etiology is complex and involves environmental, immunological and genetic factors. Tobacco smoking is one of the major risk factors for developing CD and one of the main effectors on its natural history affecting response to therapy, relapse rate, onset of intestinal complications and extraintestinal manifestations and an increased risk of surgery. Benefits of smoking cessation have been consistently reported. However, a low awareness of the detrimental effect of smoking in CD still exists and difficulties of educational and smoking cessation programs are reported.
In this review we summarize the main evidences on the effect of cigarette smoking on disease onset and its natural history, along with evidences on benefit of smoking cessation on the course of CD and impact and therapeutic strategies for smoking cessation in CD.

Crohn's disease (CD) is a chronic inflammatory disease that may affect the whole gastrointestinal tract. Its incidence varies from 6 to 8 per 100 000 and the prevalence is 130–200 per 100 000 (1-3). Crohn's disease occurs mainly between the second and fourth decades of life, with a relapsing and remitting course, characterized by flares of disease activity requiring medical therapy and/or surgery, and quiescent periods of variable duration. It is associated with a long-term morbidity, several visits, diagnostic exams and, frequently, a lifelong treatment, accounting for a high burden to patients and health care system (4).
The etiology of CD is complex and involves environmental, immunological and genetic factors (5). Among environmental factors, tobacco smoking is one of the major risk factors for developing CD and one of the main effectors on its subsequent natural history. Despite literature data show inconsistent definition of smoking habit, particularly in earlier reports. More recent reports consider an active smoker a patient with a consumption of more than 7 cigarettes per week for at least 6 months, while nonsmokers are patients who have never smoked or smoked fewer than seven cigarettes weekly, and former smokers are individuals who have quit smoking for more than 6 months.
In this review we summarize the main evidences

on the effects of cigarette smoking on disease onset and its natural history, along with evidences on the benefits of smoking cessation on the course of CD.

EFFECTS OF SMOKING ON CD AND ITS NATURAL HISTORY

Risk for CD

The correlation between smoking and increased risk of CD has been identified more than 30 years ago (6,7). The most recent meta-analysis on the topic including 9 studies, but with lack of consistency of the definition of the smoking status, showed that current smokers had increased risk of CD (OR 1.79; 1.4 to 2.22, p<0.001), while former smokers had not a significantly different risk compared with patients who had never smoked (OR 1.30; 0.97 to 1.76, p<0.08) (8). Interestingly, smokers and heavy smokers in particular seemed to have higher risk of small bowel and ileocolonic CD (9).

There are several pathogenetic hypotheses regarding the role of smoking on disease onset and its course (Table 1). Smoking may affect the role of immune system and inflammatory cascade, increasing the production of proinflammatory cytokines, such as TNF-alpha or TNF-alpha receptors, and decreasing levels of anti-inflammatory cytokines. Moreover, it effects gut motility, mucus production, gut permeability and intestinal blood flow and determines a prothrombotic condition mediated by platelet activation (9-13).

Reduced effectiveness of therapies

Current smoking adversely affects the disease course increasing the need for steroids and immunosuppressants and reducing response to therapy. While former meta-analysis did not find any relationship between smoking and response to anti TNF therapy (14), a recent systematic review and meta-analysis including a greater number of studies has been able to show an association between smoking and induction of clinical response or remission with anti-TNF therapy. This meta-analysis included 18 observational studies and 3 randomized controlled trials. Current smokers and non-smokers (never or former) had similar rates of clinical response both in observational studies (RR: 0.96; 95% CI: 0.88, 1.05) and in RCTs (RR: 1.09; 95% CI: 0.84, 1.41). However, when considering only the studies that clearly defined the smoking exposure (e.g., current smokers with ≥5 cigarettes/day for ≥6 months), smokers treated with anti-TNF were less likely to achieve clinical response than non-smokers (RR: 0.63; 95% CI: 0.48, 0.83). Likewise, current smokers were also less likely to achieve clinical remission in observational studies (RR: 0.75; 95% CI: 0.57, 0.98), though this association was not seen in RCTs (RR: 1.04; 95% CI: 0.89, 1.21) (15).

Impact on quality of life

A recent study has investigated the relationship between smoking, CD activity and disease-specific quality of life over time, in 608 patients. After adjustment for age, sex, and disease duration,

Immune system and inflammatory cascade	CNN/Images
	Decreased production of anti-inflammatory cytokines (IL1 beta and IL8)
	Reduced IGA levels
Bowel motility	Reduction of smooth muscle tone and contractile activity (release on nitric oxide)
Intestinal permeability	Increased gut permeability by a possible activation NF-κB (p65) signalling pathway
Blood flow	Changes in microvasculature of bowel (ischemia)
Platelet activation	Pro-thrombotic effect

Table 1. Pathogenetic factor linking smoking habit and Crohn disease

current smokers have significantly increased disease activity and decreased quality of life at the initial visit, compared to former and never smokers (16).

Risk for complication

Smoking worsens the prognosis of Crohn's disease increasing the risk of penetrating and fibrostenotic complications (9,11,17). However, not all studies come to the same conclusions (18,19). A recent cooperative Swiss study that has examined the risk factors for the development of fistulae and stenosis in CD patients showed that smoking has a trend towards a higher risk for developing non-perianal fistula and stenosis, with a significant correlation and univariate but not at multivariate analysis. However, this study did not have information on the number of cigarettes smoked per day and on the duration of current smoking (20). Moreover, it has been observed that chronic skin disorders and joint manifestations were more prevalent in smoker than in non-smoker CD patients (21).

Risk for disease flares and surgery

A recent meta-analysis has shown that smokers have a greater risk of flares and surgery compared with non-smokers. In particular To et al. (22) showed that smokers, compared with nonsmokers, have 55-85% higher rates of flares of disease activity and twofold higher clinical recurrence rates after surgery. The same meta-analysis showed a 54-68% increase in the need for first surgery and a twofold or greater increase in rates of second surgery for smokers compared with non-smokers with an OR = 1.68 (95% CI, 1.33-2.12) and OR = 2.17 (95% CI, 1.63– 2.89), respectively. These results have been observed in another meta-analysis (23) that showed that current cigarette smokers have an increased risk of first surgery compared to non-smokers (pooled HR 1.27, 95% CI 1.08 to 1.49). However, both studies showed that the risk of surgery for first and second surgery disappeared in former smokers when compared with non-smokers (pooled HR 1.11, 95% CI 0.95 to 1.30). Interestingly, one of these meta-analyses showed in a subgroup analysis based on patient recruitment that current smoking increased the risk of surgery in population-based studies (HR 1.48, 95% CI 1.15 to 1.90), but not in patients recruited from tertiary-care centers (HR 1.17, 95% CI 0.94 to 1.46).

The effect of smoking has been also evaluated in a cooperative prospective Spanish multicenter study, showing that current smokers relapsed more frequently than non-smokers, with an incidence ratio of 1.53 (95% CI: 1.10-2.17), and with an earlier relapse, regardless of anti-TNF or immunosuppressant use (24).

However, despite the number of studies on this topic, the lack of specific data on the definition of smoking does not allow to estimate the risk of relapses and surgery according to the amount of cigarette smoked and particularly differences between light, moderate, and heavy smokers, as well as potential differences in duration of smoking and cumulative exposure to cigarette smoke (e.g., pack years).

PASSIVE SMOKING

The role of passive smoking and CD has been studied in several contexts. The role of passive smoking as risk factor for CD has been investigated in a meta-analysis suggesting that there is not a strong association between childhood passive smoke exposure and the development of CD (25).

The effect of passive smoking on disease course of CD has been far less studied compared to that of active smoking. A Dutch study that investigated with questionnaire 820 IBD patients, including 625 CD, did not show detrimental effects of active smoking on CD, but found that passive smokers needed immunosuppressants and infliximab more frequently than nonpassive smokers (18). The same authors, using a questionnaire, found no detrimental effects of active and passive smoking also on the disease course of CD (26). Opposite results have been found by a more recent Japanese multicenter case-control study, focused on the effect of environmental factors - including passive smoking - in newly diagnosed CD (27). The study showed significantly increased OR (2.49, 1.09-5.73) of CD in patients with passive smoking, with a dose-response relationship, namely with an increased number of cigarettes per day, smoking time per day, and smoking duration (27).

The detrimental effect of passive smoking on disease course has been corroborated by a recent study showing passive smoking increases the risk for intestinal surgeries in patients with CD (28).

SMOKING BEHAVIOR AND SMOKING CESSATION IN CD

Knowledge of the health effects of smoking in CD

Detrimental effect of smoking habit seems also well known in CD patients, although the extent of this information and exact awareness of the negative impact of smoking on their disease is still unclear. A recent study has shown that IBD patients referred in tertiary center in Belgium seem to be informed on the detrimental effects of smoking, but the awareness rate was low (29). However, quite different results have been reported in another French study where the majority of IBD patients were unaware of the effects of tobacco on their disease (30) and even though CD patients were informed on the detrimental effect of smoke on their own disease, only about 50% of patients was aware of it (31).

Variables Associated with Smoking Cessation in CD

On account of the detrimental effect of smoking in CD and the low awareness of this condition, therapeutic education programs of information are recommended, and advice-based anti-smoking strategies are advocated to improve outcome. However, the effectiveness of these programs so far carried out gave conflicting results. A wide Spanish multicenter study showed that most CD smokers patients, well instructed about the risk of smoking and followed prospectively up to 18 months, wished and tried to stop smoking. However, despite supports and pharmacological helps in their attempt to quit smoking, only less than a quarter was smoking free at the end of follow-up. Moreover, the study showed that most patients (88%) tried to quit smoking with no pharmacological therapy and that pharmacological treatment to quit smoking (such as bupropion, varenicline and nicotine) was used in few patients (32). Therefore, the evaluation of knowledge of the risk of smoking on disease progression, the assessment of reasons for smoking cessation or persistence in smoking habit, are utmost important to plan anti-smoking strategies in CD patients (Table 2). Leung at al. showed that patients who report a short time to first cigarette in the morning may have more difficulties in smoking cessation as well as current smokers who have another smoker in the household (33). More important, the main reason for quitting smoking is a strong motivation and, in most cases, the diagnosis of CD and surgery for CD (34). This is what emerges from a study from the Republic of Korea showing that more than 40% of CD patients quits smoking at the time of CD diagnosis, and other factors related with smoking cessation were related with surgery for CD, light smoking and to be a smoker after 18 years of age (34).

Factors related with smoking cessation
Diagnosis of Crohn's disease
Surgery for Crohn's disease
Light smoking
Initiation of smoking after 18 years of age
Factors related with difficulties in smoking cessation
First cigarette early after awaking
Have another smoker in the household
Psychiatric comorbidities (anxiety and depression)

Table 2. Factors related with smoking cessation

Impact of Smoking Cessation in Crohn's Disease

Tobacco smoking in Crohn's disease is, therefore, a potentially modifiable environmental risk factor, and this is supported by studies that show smoking cessation in patients with Crohn's disease is associated with a milder subsequent disease course. Quitting smoking may have a beneficial effect on disease course, particularly for flares of disease activity or need for a second operation with similar relapse incidence compared with non-smokers (24). The most recent studies on this topic showed that smoking cessation after primary ileocolic resection for CD may significantly reduce long-term risk of

surgical recurrence and is associated with less use of immunosuppressive maintenance therapy (35). In particular, on this specific issue, a recent study including 3553 patients with a new CD diagnosis, of whom 1121 (32%) smokers, showed that quitting smoking was able to reduce corticosteroid dependency (36). The authors of this study concluded highlighting the importance of offering early smoking cessation support for CD smokers patients.

Smoking cessation programs for Crohn's disease

By considering what has been stated above, and particularly the benefit of smoking cessation on CD course, the possibility of smoking cessation programs for all CD smokers patients has been suggested. A cost-utility analysis comparing five smoking cessation strategies, namely (i) No Program, (ii) Counseling, (iii) Nicotine Replacement Therapy (NRT), (iv) NRT + Counseling, and (v) Varenicline, showed that every strategy was more cost-effective that No Program and therefore that health-care systems should consider funding smoking cessation programs for CD, as they improve health outcomes and reduce costs (37).

However, very few studies have evaluated the effectiveness of a multidisciplinary smoking cessation program in patients with CD. The few available experience showed that results, despite adopting a multidisciplinary approach, could give a lower success rate compared to that reported in programs for the general population of smokers. Previous experiences reported a success rate ranging for 12% to 23% (32,38). The more recent multicentre prospective interventional study, TABACROHN, reported a success rates of 23% of smoking-free patients after a median 9-month follow-up (32). However, differences in success rate may depend on characteristics of patients as reported and in particular on smoking history and concurrent psychiatric comorbidities. A study performed in our centre found a very low quit smoking rate, related with a high incidence of anxiety and depression in patients with CD. This observation confirms the importance of patients' psychological burden reported in the literature and once more the need for multidisciplinary approach to CD patients (39).

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