

GUT HEALTH

SCIENTIFIC NEWSLETTER



No. 2 2021

EDITOR OF THE MONTH



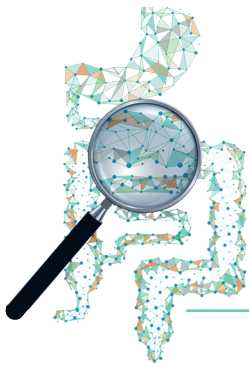
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The COVID-19 pandemic has disrupted our lives in profound and unprecedented ways. In the face of this crisis, it's important to remember that even the smallest acts of care can make a difference. Support from our family, friends and colleagues are now of greater importance than ever. Together we can adapt to an ever-changing world. During these circumstances it feels good to go back to basics and read some of the new insights our colleagues recently published. Below you find some of the IBD article I found interesting this spring.

Lina Vigren



Clinical outcome after anti-tumour necrosis factor therapy discontinuation in 1000 patients with inflammatory bowel disease:

THE EVODIS LONG-TERM STUDY PUBLISHED IN ALIMENT PHARMACOL THER
MAY 7 2021 BY MARIA JOSÉ CASANOVA ET AL.

The long-term outcome of patients after antitumour necrosis factor alpha (anti-TNF) discontinuation is not well known and the study assess the risk of relapse in the long-term after anti-TNF discontinuation. It is an observational, retrospective, multicenter study with a total of 1055 patients. The median follow-up time was 34 months and the incidence rate of relapse was 12% per patientyear (95% confidence interval [CI] = 11-14). The cumulative incidence of

relapse was 50% (95% CI = 47-53): 19% after one year, 31% after 2 years, 38% after 3 years, 44% after 4 years and 48% after 5 years of follow-up. Of the 60% patients retreated with the same anti-TNF after relapse, 73% regained remission. Of the 75 patients who did not respond, 48% achieved remission with other therapies. Of the 190 patients who started other therapies after relapse, 62% achieved remission with the new treatment.

COMMENT

This was an extension of the evolution after anti-TNF discontinuation in patients with inflammatory bowel disease (EVODIS) study including Crohn's disease or ulcerative colitis patients treated with anti-TNFs in whom these drugs were withdrawn after achieving clinical remission (Harvey-Bradshaw index ≤ 4 points in Crohn's disease, a partial Mayo score ≤ 2 in ulcerative colitis and the absence of fistula drainage despite gentle finger compression in perianal disease). And it seems to be safe since half of the patients are still in remission after 5 years and those who relaps, in many of them, retreatment was effective and if not, many of them responded to other therapies

New European guidelines on microscopic colitis has been published.

EUROPEAN GUIDELINES ON MICROSCOPIC COLITIS; UNITED EUROPEAN GASTROENTEROLOGY AND EUROPEAN MICROSCOPIC COLITIS GROUP STATEMENTS AND RECOMMENDATIONS BY STEPHAN MIEHLKE ET AL.

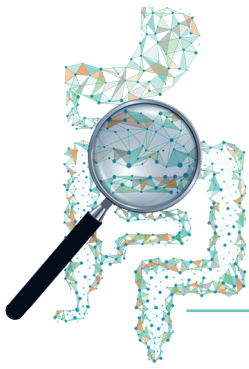
Microscopic colitis is a chronic inflammatory bowel disease characterised by normal or almost normal endoscopic appearance of the colon, chronic watery, nonbloody diarrhoea and distinct histological abnormalities, which identify three histological subtypes, the collagenous colitis, the lymphocytic colitis and the incomplete microscopic colitis. These guidelines provide information on epidemiology and risk factors

of microscopic colitis, as well as evidence-based statements and recommendations on diagnostic criteria and treatment options, including oral budesonide, bile acid binders, immunomodulators and biologics. Recommendations on the clinical management of microscopic colitis are provided based on evidence, expert opinion and best clinical practice.

COMMENT

Microscopic colitis is a subgroup of the inflammatory bowel diseases. These guidelines may support you in improve knowledge about the entity and in how to clinical manage patients with microscopic colitis.





Increased risk of stroke among patients with inflammatory bowel disease:

TA PRISMA-COMPLIANT META-ANALYSIS PUBLISHED IN BRAIN BEHAV MAY 7 2021 BY YAO CHEN ET AL.

There have been conflicting results in previous studies on the association between inflammatory bowel disease (IBD) and stroke so the authors did a meta-analysis to investigate this.

They found that IBD was associated with an elevated risk of stroke (OR/RR = 1.21, 95% CI 1.08 to 1.34, I² = 83.6%, $p < .001$). Both Crohn's disease (CD) and ulcerative colitis (UC) were associated with a higher

risk of stroke (CD: OR/RR = 1.25, 95% CI 1.03 to 1.52, I² = 86.1%, $p < .001$; UC: OR/RR = 1.09, 95% CI 1.04 to 1.15, I² = 54.7%, $p = .051$). Subgroup study showed that IBD was related to an elevated risk of stroke in both Caucasian and Asian groups (Caucasian group: OR/RR = 1.13, 95% CI 1.05 to 1.23, I² = 44.6%, $p = .094$; Asian group: OR/RR = 1.36, 95% CI 1.07 to 1.74, I² = 92.5%, $p < .001$).

COMMENT

For a long time there have been indication of a higher thromboembolic activity in active inflammatory bowel disease and this meta-analysis indicate that IBD patients have a slightly higher risk for stroke.

Association Between Portal Vein Thrombosis and Pouchitis in Patients with Ulcerative Colitis.

DIG DIS SCI 2021 MAY 4 2021 BY ASLAM SYED ET AL.

Pouchitis is the most common long-term complication in patients requiring colectomy ileal pouchanal anastomosis with medically refractory ulcerative colitis or colitis-associated neoplasia. A previous small case series suggests association between portal vein thrombosis (PVT) and ischemic pouchitis. This study evaluated the association between PVT and other demographic and clinical factors and pouchitis by using a population-based database, to search medical records between 1999 and 2020. They identified 7900 patients with ileal pouchitis (7.5%) and 97,510 with pouch construction without pouchitis. In mul-

tivariate binary logistic regression, adjusted odds ratio (aOR) for the risk of pouchitis in patients with PVT was 10.78 (95% confidence interval [CI] 7.04-16.49, $P < 0.001$). Other significant factors associated with pouchitis included male gender (aOR 1.11, 95% CI 1.02-1.21, $P = 0.018$), deep vein thrombosis (aOR 1.46, 95% CI 1.23-1.72, $P < 0.001$), and the use of non-steroidal anti-inflammatory drugs (aOR 1.37, 95% CI 1.28-1.45, $P < 0.001$). Smoking was a protective factor (aOR 0.30, 95% CI 0.33-0.36, $P < 0.001$). Further sub-analysis showed a higher prevalence of younger patients with PVT and pouchitis

COMMENT

They address risk factors for pouchitis in patients with ulcerative colitis. Portal Vein Thrombosis seems to be an independent risk factor associated with pouchitis but is a potentially manageable perioperative complication, and intervention may reduce the risk of pouchitis



Postoperative Survival in Colitis-associated Colorectal Cancer With Ulcerative Colitis in Japan:

A MULTICENTER ANALYSIS BY AKIRA SUGITA ET AL PUBLISHED IN ANTICANCER RES MAY 2021 ;41(5):2681-2688.

The aim of the study was to analyze the postoperative survival of colitis-associated colorectal cancer (CAC) with ulcerative colitis (UC), and the risk factors affecting it. 88 hospitals were asked to participate and reported CAC patients up until January, 2006. The 5-year postoperative overall survival (OS) of 170 CAC patients was 74.2% which was similar to sporadic colorectal cancer in Japan (72.1%). Pathologic TNM stage, histological type, type of surgical

procedure (proctocolectomy, segmental resection), and preoperative cancer surveillance were statistically significant factors for OS. By Cox regression analysis, pathologic TNM stage and proctocolectomy were statistically significant prognostic factors for OS. In CAC with UC, the postoperative OS was similar to sporadic colorectal cancer. Pathologic TNM stage and proctocolectomy were confirmed as important prognostic factors.

COMMENT

Postoperative survival study in Japan confirm that colitis-associated colorectal cancer in UC have the same prognosis as sporadic cancer.

JAK1 inhibition and inflammatory bowel disease.

RHEUMATOLOGY (OXFORD) MAY 2021; 5;60 BY CLARE HARRIS AND J R FRASER CUMMINGS.

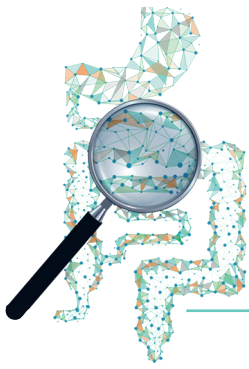
Primary non-response and secondary loss of response remain a significant issue with the currently available treatment options for a significant proportion of patients with inflammatory bowel disease (IBD). There are multiple unmet needs in the IBD treatment algorithm and new treatment options are required. As an answer to this new therapeutic targets are being identified. The JAK-STAT pathway has been extensively studied. Tofacitinib, a JAK1 inhibi-

tor, is now licensed for use in the induction and maintenance of ulcerative colitis and there are a large number of molecules currently under investigation. These new small molecule drugs (SMDs) will challenge current treatment pathways at a time when clinical therapeutic outcomes are rapidly evolving and becoming more ambitious. This is a review of the current JAK1 inhibitors in IBD including the current evidence from clinical trials.

COMMENT

A review of the published experience of the new JAK1 inhibitor in inflammatory bowel disease. A new per-oral alternative.





Conjugal inflammatory bowel disease: a systematic review and European survey.

ANN GASTROENTEROL. 2021;34(3):361-369 BY MARIA PIA COSTA-SANTOS ET AL.

The frequency of inflammatory bowel disease (IBD) is increased after marriage to an individual with the disease. Importantly, the offspring of these couples have a significant risk for developing the disease. A systematic literature search was conducted on studies reporting on couples with IBD and their offspring. Concomitantly, a cross-sectional survey was conducted of couples where both members were affected with IBD. 20 reports of IBD in couples were identified. Of these, 66% were concordant regarding IBD type and 66% were diagnosed after cohabitation.

The overall prevalence of IBD in the offspring of these couples was 29%. The survey identified 58 couples with IBD, with 62% being concordant regarding IBD type; 42.9% were diagnosed prior to cohabitation, in 12.5% one spouse was diagnosed before and the other after cohabitation, and in 44.6% the onset of disease occurred after cohabitation for both. The prevalence of IBD in children born from these couples was 10%. The probability of developing disease in the progeny was 2% at 10 years, 12% at 15 years, and 16% at 20 years of age.

COMMENT

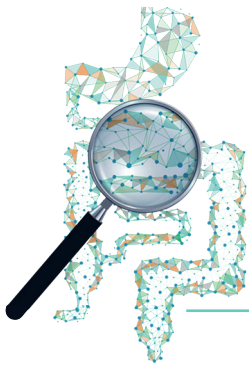
This study gives us some new insights in conjugal inflammatory bowel disease and was written by well-known IBD researchers. IBD in couples occurs mostly after marriage to an individual with disease or after many years of cohabitation. In a modern cohort, the risk for the progeny was around 16% by the age of 20 in this study, lower than previously reported.

Clinicopathologic Characteristics and Neoplasia Risk of Colorectal Inflammatory Polyposis in Inflammatory Bowel Disease.

ARCH PATHOL LAB MED 2021 MAY 4 BY YIHONG R MA AND ALEXANDROS D POLYDORIDES .

Inflammatory polyps (IPs) in inflammatory bowel disease may have been associated in the past with increased neoplasia risk. Additionally, colonic mucosa in filiform polyposis and giant inflammatory polyposis may be difficult to visualize during endoscopic surveillance, perhaps contributing to early colectomy in these patients. In this study they examine the clinicopathologic characteristics and significance of IPs and inflammatory polyposis in inflammatory bowel disease. 336 resections from inflammatory bowel disease patients were identified (212 [63.1%] male; mean age, 40.3 years; 175 [52.1%] with ulcerative colitis), including 78 with rare/few (<10) IPs, 141 with multiple (≥ 10) IPs, and 117 with inflammatory polyposis (including 30 with filiform polyposis/giant inflammatory poly-

posis) and compared them with 100 controls without IPs along various parameters, including overall and occult (unexpected) dysplasia. No increased neoplasia were found in resections with IPs compared with controls, given similar age, disease duration, degree of inflammation, anatomical extent of colitis, prevalence of primary sclerosing cholangitis, and tissue sampling. Increasing numbers of IPs and inflammatory polyposis were significantly associated in multivariate analysis with ulcerative and indeterminate colitis ($P = .003$) and shorter disease duration ($P = .01$), but also, and independently, with lower rates of dysplasia overall, including all grades ($P = .001$) and advanced neoplasia ($P = .04$). There were no instances of occult dysplasia (any grade) among inflammatory polyposis cases. ►



COMMENT

The presence of IPs per se, and inflammatory polyposis in particular (including filiform polyposis and giant inflammatory polyposis), should not according to this study be considered an independent risk factor for the development of neoplasia in inflammatory bowel disease patients, outside the context of disease duration and inflammatory burden.

Effect of Therapeutic Drug Monitoring vs Standard Therapy During Infliximab Induction on Disease Remission in Patients With Chronic Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial.

JAMA 2021 MAY 4;325(17):1744-1754 BY SILJE WATTERDAL SYVERSEN ET AL.

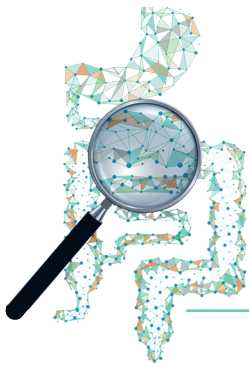
Proactive therapeutic drug monitoring (TDM), defined as individualized drug dosing based on scheduled monitoring of serum drug levels, has been proposed as an alternative to standard therapy to maximize efficacy and safety of infliximab and other biological drugs. However, whether proactive TDM improves clinical outcomes when implemented at the time of drug initiation, compared with standard therapy, remains unclear. This study assess whether TDM during initiation of infliximab therapy improves treatment efficacy compared with standard infliximab therapy without TDM.

Randomized, parallel-group, open-label clinical trial of 411 adults with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn disease, or psoriasis initiating infliximab therapy in 21 hospitals in Norway were included during 2017–2019.

Patients were randomized 1:1 to receive proactive TDM with dose and interval adjustments based on scheduled monitoring of serum drug levels and anti-drug antibodies (TDM group; n = 207) or standard infliximab therapy without drug and antibody level monitoring (standard therapy group; n = 204) and the primary end point was clinical remission at week 30. Among 411 randomized patients (mean age, 44.7 [SD, 14.9] years; 209 women [51%]), 398 (198 in the TDM group and 200 in the standard therapy group) received their randomized intervention and were included. Clinical remission at week 30 was achieved in 100 (50.5%) of 198 and 106 (53.0%) of 200 patients in the TDM and standard therapy groups, respectively (adjusted difference, 1.5%; 95% CI, -8.2% to 11.1%; P = .78). Adverse events were reported in 135 patients (68%) and 139 patients (70%) in the TDM and standard therapy groups, respectively.

COMMENT

Proactive therapeutic drug monitoring in this studied patient group compared to standard therapy in Norway did not seem to improve clinical remission rates over the 30 weeks. They suggest that these findings do not support routine use of therapeutic drug monitoring during infliximab induction and should maybe only be used in selected patients.



Perioperative Safety of Tofacitinib in Surgical Ulcerative Colitis Patients.

COLORECTAL DIS. 2021 MAY 3 BY AMY L LIGHTNER ET AL.

Literature regarding monoclonal antibodies and increased postoperative complications in inflammatory bowel disease remains controversial. No study has previously investigated tofacitinib. This study sought to determine preoperative exposure to small molecule inhibitors, tofacitinib, and postoperative outcomes. A retrospective review of all adult patients exposed to tofacitinib within 4 weeks of total abdominal colectomy for medically refractory ulcerative colitis at four inflammatory bowel disease referral centers 2018–2020 was conducted. Data collected included patient demographics and 90-day postoperative morbidity, readmission and reoperation rates. Fifty-three patients (32 male; 60%) with ulcerative colitis underwent a total abdominal colectomy (n=50 laparoscopic; 94%) for medically refractory disease.

Previous monoclonal antibody exposure included infliximab (n=34), adalimumab (n=35), certolizumab pegol (n=5), vedolizumab (n=33), and ustekinumab (n=10). Twenty seven (51%) patients were on concurrent prednisone at a median dose of 30 mg po daily (range, 5-60 mg). There were no postoperative deaths. Ninety day postoperative complications included ileus (n=7; 13.2%), superficial surgical site infection (n=4; 7.5%), intra abdominal abscess (n=2; 3.8%), and venous thromboembolism (VTE) (n=7; 13.2%). Locations of VTE included portomesenteric venous thrombus (PMVT) (n=4), internal iliac vein (n=2), and pulmonary embolism (PE) (n=1). Nine (17%) patients were readmitted to hospital and 5 (9%) patients had a reoperation.

COMMENT

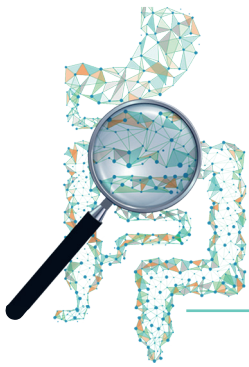
Food and Drug Administration recently issued a black box warning of an increased risk of VTE in medically treated ulcerative colitis patients taking tofacitinib in line with that preoperative tofacitinib exposure might induce an increased risk of postoperative VTE events. Maybe we should take into consideration prolonged VTE prophylaxis after surgery in these patients?

Approach to the management of recently diagnosed inflammatory bowel disease patients: a user's guide for adult and pediatric gastroenterologists.

GASTROENTEROLOGY 2021 APR 30;S0016-5085(21)00734-4 BY MANASI AGRAWAL ET AL

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), can cause significant morbidity and lead to complications such as strictures, fistulas, infections, and cancer. In children, IBD can also result in growth impairment and pubertal delays. IBD is highly heterogenous, with severity ranging from mild to severe and symptoms ranging from mild to debilitating. Delay in IBD diagnosis, especially in CD, is common and associated with

adverse outcomes. Early diagnosis and prompt institution of treatment are the cornerstones for improving outcomes and maximizing health. Early diagnosis requires a low threshold of suspicion and red flags to guide early specialist referral at the primary provider level. While the armamentarium of IBD medications is growing, many patients will not respond to treatment and the selection of first line therapy is critical. Risk stratification of disease severity, based on ►



► clinical, demographic and serological markers, can help guide selection of first-line therapy. Clinical decision support tools, genomics and other biomarkers of response to therapy and risk of adverse events are the future of personalized medicine. After starting appropriate therapy, it is important to confirm remission using objective end-points (treat-to-target) with continued control of inflammation with adjust-

ment of therapy using surrogate biomarkers (tight control). Last, IBD therapy extends far beyond medications, and other aspects of the overall health and well-being of the patient are critical. These include preventive health, nutrition, psycho-behavioral support, addressing patients' concerns around complementary therapy and medication adherence, prevention of disability, and ensuring open communication.

COMMENT

Colombels and Ungaros team suggest how to manage recently diagnosed IBD.

A comparison of intravenous methylprednisolone and hydrocortisone for the treatment of acute inflammatory bowel disease.

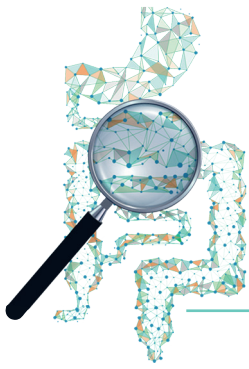
J GASTROENTEROL HEPATOL 2021 MAY 3 BY CAMERON SCHAUER ET AL.

Despite widespread recommendations and use of intravenous corticosteroids (IVCS) for the treatment of acute flares of ulcerative colitis and Crohn's disease, limited evidence exists comparing outcomes of the two most common regimens, intravenous methylprednisolone (IVMP) and intravenous hydrocortisone (IVHC). IVHC has stronger mineralocorticoid effects compared to IVMP and may cause higher rates of hypokalaemia. This multicenter cohort in study New Zealand aimed to determine differences in clinical outcomes including requirement for inpatient rescue therapy, bowel resection and rates of hypokalaemia in patients admitted with an acute flare of IBD where the protocol at each institution is either IVMP 60 mg

daily or IVHC 100 mg four times daily. 359 patients were included. 129 (35.9%) patients receiving IVMP and 230 (64.1%) patients receiving IVHC. IVMP treatment was associated with a greater requirement for rescue therapy than IVHC (36.4% vs 19.6%, $p=0.001$; odds ratio [OR]= 2.79; 95% confidence interval [CI], 1.64-4.75, $p<0.001$), but also reduced rates of hypokalaemia (55.8% vs 67.0%, $p=0.04$; OR=0.49; 95% CI, 0.30-0.81, $p=0.005$). There was no difference between treatment groups for the median length of admission (5 days, interquartile range, IQR 3-8), median duration of IVCS treatment (3 days, IQR 2-5) or bowel resection within 30 days of admission (12.4% vs 11.7%; OR=1.04).

COMMENT

Interesting comparison of treatment with two different corticosteroids during an acute flare of IBD.



Rectal Cancer Risk and Survival After Total Colectomy for IBD: A Population-Based Study.

RECTUM. 2021 MAY;64(5):583-591 BY ANDERS MARK-CHRISTENSEN ET AL.

Patients undergoing total colectomy for IBD may develop cancer in the rectal remnant, but the association is poorly understood. This nationwide population-based study in Denmark 1977–2013 aimed to examine the risk and prognosis of rectal cancer after total colectomy for IBD.

Patients with IBD undergoing total colectomy were included and they examined the incidence of rectal cancer among patients with IBD and total colectomy and compared cancer stage to that of other patients with rectal cancer in Denmark. 4703 patients with IBD were identified (1026 Crohn's disease; 3677 ulcerative colitis) who underwent total colectomy with a rectal remnant. During 29,725 years of follow-up,

30 rectal cancers were observed, compared with 8 rectal cancers expected (standardized incidence ratio = 3.6 (95% CI, 2.4-5.1)). Cancer stage distributions were similar. Risk of rectal cancer 35 years after total colectomy was 1.9% (95% CI, 1.1%-2.9%). Five years after rectal cancer diagnosis, survival was 28% (95% CI, 12%-47%) and 38% (95% CI, 37%-38%) for patients with and without IBD and a rectal remnant. The adjusted mortality rate ratio 1 to 5 years after a rectal cancer diagnosis was 2.5 (95% CI, 1.6-3.9). Median time from last recorded nondiagnostic proctoscopy to rectal cancer diagnosis for patients with IBD and total colectomy was 1.1 years.

COMMENT

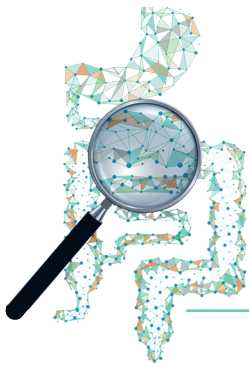
The risk of rectal cancer following after total colectomy for IBD seems to be low although survival following a diagnosis of rectal cancer was poorer for patients with IBD and total colectomy than for patients who had rectal cancer without IBD and total colectomy.

Incidence and Prevalence of Inflammatory Bowel Disease in Norway and the Impact of Different Case Definitions: A Nationwide Registry Study.

CLIN EPIDEMIOL 2021 APR 23;13:287-294 BY SANDRE SVATUN LIRHUS ET AL.

Countries have different diagnostic procedures and treatment regimens for inflammatory bowel disease (IBD) patients. In addition differences in population characteristics, completeness of data, different follow-up time and case definitions can impact on estimates of the incidence and prevalence of IBD. In this study they use hospital and prescription data to estimate incidence and prevalence of Crohn's disease (CD) and ulcerative colitis (UC) from the Norwegian Patient Registry (2008 to 2017) and the Norwegian Prescription Database (2004 to April 2018).

Incidence and prevalence were estimated using different case definitions of an IBD patient, varying the number of IBD-related hospital visits and IBD prescriptions required. The base case definition included patients with at least one IBD hospital visit and two IBD prescriptions or two IBD hospital visits. From 2010 to 2017, 16,758 incident IBD patients fulfilled base case definition, with 6045 diagnosed with CD (36.1%) and 10,713 (63.9%) with UC. For CD, 47.2% of the patients were male while 53.8% of UC patients were male. The base case incidence ►



► varied between 14.1 and 16.0 per 100,000 person-years for CD and 24.7 and 28.4/100,000 person-years for UC patients in the years 2010–2017. When required at least two IBD hospital visits, not utilizing the prescription data, the CD incidence was 22.3 per

100,000 person-years in 2010 and 13.9 per 100,000 person-years in 2017. For UC, the incidence was 47.4 and 20.6 per 100,000 person-years in 2010 and 2017. In 2017, the prevalence of CD was 0.27% (95% CI: 0.26-0.27) and 0.50% (95% CI: 0.490-0.502) for UC.

COMMENT

An interesting way to look at different ways of case incidence and prevalence that are good to keep in mind when we compare results from different studies. The incidence of IBD in Norway seems to be stable during 2010 to 2017 but both the incidence and prevalence of IBD are very high especially compare to other parts of the world.

Endoscopic evaluation of surgically altered bowel in inflammatory bowel disease: a consensus guideline from the Global Interventional Inflammatory Bowel Disease Group.

BY BO SHEN ET AL. IN LANCET GASTROENTEROL HEPATOL 2021 APR 16;S2468-1253(20)30394-0.

The majority of patients with Crohn's disease and a proportion of patients with ulcerative colitis will ultimately require surgical treatment despite advances in diagnosis, therapy, and endoscopic interventions. The surgical procedures that are most commonly done include bowel resection with anastomosis, strictureplasty, faecal diversion, and ileal pouch. These surgical treatment modalities result in substantial alterations in bowel anatomy. In patients with inflam-

matory bowel disease, endoscopy plays a key role in the assessment of disease activity, disease recurrence, treatment response, dysplasia surveillance, and delivery of endoscopic therapy. Endoscopic evaluation and management of surgically altered bowel can be challenging. This consensus guideline delineates anatomical landmarks and endoscopic assessment of these landmarks in diseased and surgically altered bowel.

COMMENT

An approach on how to evaluate and manage endoscopic surveillance after bowel surgery in IBD patients. ■