# Gastroenterology Volume 157 / Number 4 October 2019 Volume 157 / Number 4 October 2019

## **Contents**

## ON THE COVER

See article by Ding et al, on page 1044, for additional information.



#### IN MEMORIAM

905 Henry T. Lynch, MD (January 4, 1928–June 2, 2019)
C. R. Boland

#### **COVERING THE COVER**

⊳ aga =

907 A. T. Chan and C. S. Williams

#### COMMENTARY

909 Hepatitis C Virus Infection in Patients With Cancer: Impact on Clinical Trial Enrollment, Selection of Therapy, and Prognosis

H. A. Torres, P. Pundhir, and V. Mallet

## MENTORING, EDUCATION, AND TRAINING CORNER

917 How to Advance Research, Education, and Training in the Study of Rare Diseases S. C. Groft, R. Gopal-Srivastava, E. S. Dellon, and S. K. Gupta

#### **EDITORIALS**

922 Is It Prime Time for Proactive Therapeutic Drug Monitoring of Anti-Tumor Necrosis Factor Therapy in Inflammatory Bowel Disease?

K. Papamichael and A. S. Cheifetz

See Assa A et al on page 985.

925 Ver(s)ifying the Efficacy of Vedolizumab Therapy on Mucosal Healing in Patients With Crohn's Disease

L. Gonczi, T. Bessissow, and P. Lakatos

See Danese S et al on page 1007 and Löwenberg M et al on page 997.

Publisher: Gastroenterology (ISSN 0016-5085) is published monthly (semi monthly in January and May) in two indexed volumes by Elsevier Inc, 230 Park Avenue, New York, NY 10169-0901, USA. Periodicals postage paid at New York, NY and additional mailing offices. POSTMASTER: Send address changes to Elsevier, Journal Returns, 1799 Highway 50 East, Linn, MO 65051, USA. 2019 US subscription rates: individual, \$739.00; student and resident, \$282.00. Outside of the U.S. and possessions: individual, \$968.00; student and resident, \$562.00; surface delivery, no additional charge; air mail delivery, add \$78.00. Prices subject to change without notice.

| 927 | Taking a Closer Look at the Biogeography of the Human Gastrointestinal Microbiome |
|-----|---|
|     | M. Engevik and J. Versalovic  |
|     | See Vasapolli R et al on page 1081.   |

929 Intraductal Papillary Mucinous Neoplasms: Attack of the Clones H. K. C. Jacob and S. Banerjee

See Fischer CG et al on page 1123.

## **GASTROENTEROLOGY IN MOTION**

933 Feasibility of Using Hydrogel Spacers for Borderline-Resectable and Locally Advanced

Pancreatic Tumors

T. Kerdsirichairat, A. K. Narang, E. Thompson, S.-H. Kim, A. Rao, K. Ding, and E. J. Shin

## **CLINICAL CHALLENGES AND IMAGES IN GI**

936 A Rare Complication of Peptic Ulcer Disease S. Kabaria, K. G. Patel, and S. Ahlawat

938 "Doctor, I Just Can't Seem to Swallow!"

A. S. Thomas, J. Y. Ro, and G. A. Ergun

940 Abnormal Polypoid Finding During Colonoscopy F. B. Peng, H.-s. Kim, and S. K. Agarwal

942 On The Hot Seat: A Rare Cause of Rectal Pain B. Nunley and C. Truss

## **ELECTRONIC CLINICAL CHALLENGES AND IMAGES IN GI**

For a full list, please see the table of contents online at www.gastrojournal.org.

#### PRACTICAL TEACHING CASES

944 An Unexpected Consequence of a Clinical Trial

D. Bushyhead, R. K. Dorer, and M. Gluck

946 Massive Bleeding and Perforation With Endoscopic Multiple Deep Ulcers in a Patient With Ulcerative Colitis After Colectomy

L. Ye, Z. Jiang, and Q. Cao

## **REVIEWS AND PERSPECTIVES**

## Reviews in Basic and Clinical Gastroenterology and Hepatology

949 Terminology, Molecular Features, Epidemiology, and Management of Serrated Colorectal Neoplasia

S. D. Crockett and I. Nagtegaal

## **ORIGINAL RESEARCH**

## **Full Reports**

## **Clinical—Alimentary Tract**

967 Efficacy of Prophylactic Hemoclips in Prevention of Delayed Post-Polypectomy Bleeding in Patients With Large Colonic Polyps

L. A. Feagins, A. D. Smith, D. Kim, A. Halai, S. Duttala, B. Chebaa, T. Lunsford, J. Vizuete, M. Mara, R. Mascarenhas, R. Meghani, L. Kundrotas, K. B. Dunbar, D. J. Cipher, W. V. Harford, and S. J. Spechler

Randomized, equivalence trial including 1098 patients randomized to prophylactic hemoclipping or no-hemoclipping after removal of large polyps (1cm or bigger) reveals no difference in post-polypectomy bleeding rates.

## 977 Clip Closure Prevents Bleeding After Endoscopic Resection of Large Colon Polyps in a Randomized Trial

H. Pohl, I. S. Grimm, M. T. Moyer, M. K. Hasan, D. Pleskow, B. J. Elmunzer, M. A. Khashab, O. Sanaei, F. H. Al-Kawas, S. R. Gordon, A. Mathew, J. M. Levenick, H. R. Aslanian, F. Antaki, D. von Renteln, S. D. Crockett, A. Rastogi, J. A. Gill, R. J. Law, P. A. Elias, M. Pellise, M. B. Wallace, T. A. Mackenzie, and D. K. Rex

Endoscopic clip closure of the mucosal defect following resection of large colon polyps reduces risk of post-procedure bleeding.

# 985 Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased Clinical Remission in Children With Crohn's Disease Compared With Reactive Monitoring

A. Assa, M. Matar, D. Turner, E. Broide, B. Weiss, O. Ledder, A. Guz-Mark, F. Rinawi, S. Cohen, C. Topf-Olivestone, R. Shaoul, B. Yerushalmi, and R. Shamir

## See editorial on page 922

In a controlled trial involving children with Crohn's disease treated with adalimumab, proactive drug level monitoring resulted in higher remission rates and better disease control.

## 997 Vedolizumab Induces Endoscopic and Histologic Remission in Patients With Crohn's Disease

M. Löwenberg, S. Vermeire, N. Mostafavi, F. Hoentjen, D. Franchimont, P. Bossuyt, P. Hindryckx, T. Rispens, A. de Vries, C. J. van der Woude, S. Berends, C. A. Ambarus, R. Mathot, E. Clasquin, F. Baert, and G. D'Haens

## See editorial on page 925

Vedolizumab treatment induces endoscopic and histologic features of remission in patients with CD. Endoscopic outcomes are related to serum levels of vedolizumab. A cut-off serum level was found that correlates with optimal endoscopic outcomes.

# 1007 Endoscopic, Radiologic, and Histologic Healing With Vedolizumab in Patients With Active Crohn's Disease

S. Danese, W. J. Sandborn, J.-F. Colombel, S. Vermeire, S. C. Glover, J. Rimola, J. Siegelman, S. Jones, J. D. Bornstein, and B. G. Feagan

#### See editorial on page 925

Vedolizumab improves several different measures of inflammation with good safety in patients with active CD.

# 1019 Effects of Ustekinumab on Histologic Disease Activity in Patients With Crohn's Disease K. Li, J. R. Friedman, D. Chan, P. Pollack, F. Yang, D. Jacobstein, C. Brodmerkel, C. Gasink, B. G. Feagan, W. J. Sandborn, P. Rutgeerts, and G. De Hertogh

Intravenous ustekinumab induction results in histologic improvement in CD. Subcutaneous maintenance treatment every 8 weeks leads to continued benefit. Ustekinumab clinical and endoscopic efficacy are accompanied by microscopic scale improvement.

# Approaches to Integrating Biomarkers Into Clinical Trials and Care Pathways as Targets for the Treatment of Inflammatory Bowel Diseases

P. S. Dulai, L. Peyrin-Biroulet, S. Danese, B. E. Sands, A. Dignass, D. Turner, G. Mantzaris, J. Schölmerich, J.-Y. Mary, W. Reinisch, and W. J. Sandborn

There is a lack of understanding on how biomarkers should be studied, validated, and integrated in clinical care for IBD. We have provided a framework for future biomarker research.

# Gastroenterologist-Level Identification of Small-Bowel Diseases and Normal Variants by Capsule Endoscopy Using a Deep-Learning Model

Z. Ding, H. Shi, H. Zhang, L. Meng, M. Fan, C. Han, K. Zhang, F. Ming, X. Xie, H. Liu, J. Liu, R. Lin, and X. Hou

A CNN-based algorithm provided a rapid reading time and high sensitivity for detection of SB abnormalities using CE, which may significantly reduce the cost of clinical application of SB-CE and thereby change the reading pattern for SB-CE.

1055 Trends in Mortality From Extrahepatic Complications in Patients With Chronic Liver Disease,
From 2007 Through 2017

D. Kim, A. C. Adejumo, E. R. Yoo, U. Iqbal, A. A. Li, E. A. Pham, G. Cholankeril, J. S. Glenn, and A. Ahmed

Now that hepatitis C virus infection can be treated with direct-acting antiviral agents, death from extrahepatic cancers is increasing in this population. Most patients with fatty liver disease die from cardiovascular disease or diabetes.

## Clinical—Biliary

1067 Imbalance of Genes Encoding Natural Killer Immunoglobulin-Like Receptors and Human Leukocyte Antigen in Patients With Biliary Cancer

M. Cornillet, H. Jansson, M. Schaffer, L. Hertwig, L. Berglin, C. L. Zimmer, H. Johansson, E. Ellis, B. Isaksson, F. F. Gonzalez-Galarza, D. Middleton, K.-J. Malmberg, E. Sparrelid, and N. K. Björkström

In patients with bile duct cancer, the authors found alterations in genes that control activity of immune cells that attack tumors. Altered activities of these immune cells might promote development of bile duct tumors.

## Basic and Translational—Alimentary Tract

1081 Analysis of Transcriptionally Active Bacteria Throughout the Gastrointestinal Tract of

Healthy Individuals

R. Vasapolli, K. Schütte, C. Schulz, M. Vital, D. Schomburg, D. H. Pieper, R. Vilchez-Vargas, and P. Malfertheiner See editorial on page 927

Differences were found in microbial communities along the gastrointestinal tract of healthy individuals. Defined active phylotypes are confined to specific niches. The fecal microbiome does not represent the mucosal microbiome.

1093 Epithelial Indoleamine 2,3-Dioxygenase 1 Modulates Aryl Hydrocarbon Receptor and Notch Signaling to Increase Differentiation of Secretory Cells and Alter Mucus-Associated Microbiota

D. M. Alvarado, B. Chen, M. Iticovici, A. I. Thaker, N. Dai, K. L. VanDussen, N. Shaikh, C. K. Lim, G. J. Guillemin, P. I. Tarr, and M. A. Ciorba

The intestinal protein ID01 mediates a response that protects against inflammation.

## Basic and Translational—Liver

1109 Microbiome Signatures Associated With Steatohepatitis and Moderate to Severe Fibrosis in Children With Nonalcoholic Fatty Liver Disease

J. B. Schwimmer, J. S. Johnson, J. E. Angeles, C. Behling, P. H. Belt, I. Borecki, C. Bross, J. Durelle, N. P. Goyal, G. Hamilton, M. L. Holtz, J. E. Lavine, M. Mitreva, K. P. Newton, A. Pan, P. M. Simpson, C. B. Sirlin, E. Sodergren, R. Tyagi, K. P. Yates, G. M. Weinstock, and N. H. Salzman

The intestinal microbiota of children with NAFLD is altered compared to that of children without it, with increased levels of bacterial proteins that promote inflammation. These microbial features were associated with liver disease severity.

## Basic and Translational—Pancreas

1123 Intraductal Papillary Mucinous Neoplasms Arise From Multiple Independent Clones, Each

With Distinct Mutations

C. G. Fischer, V. Beleva Guthrie, A. M. Braxton, L. Zheng, P. Wang, Q. Song, J. F. Griffin, P. E. Chianchiano, W. Hosoda, N. Niknafs, S. Springer, M. Dal Molin, D. Masica, R. B. Scharpf, E. D. Thompson, J. He, C. L. Wolfgang, R. H. Hruban, N. J. Roberts, A. M. Lennon, Y. Jiao, R. Karchin, and L. D. Wood

See editorial on page 929

Genomic analyses reveal that low-grade precancerous neoplasms in the pancreas arise from multiple independent clones, while selection of a dominant clone leads to neoplastic progression.

## Basic and Translational—Biliary

# 1138 Gene Expression Signatures Associated With Survival Times of Pediatric Patients With Biliary Atresia Identify Potential Therapeutic Agents

Z. Luo, P. Shivakumar, R. Mourya, S. Gutta, and J. A. Bezerra

The liver expression profile of 14 genes at diagnosis predicts the 2-year survival in children with biliary atresia and identifies glutathione metabolism as putative drug target.

## CONTINUING MEDICAL EDUCATION (CME)/MOC ACTIVITIES

- e14 CME Exam 1: Hydrogel Spacer for Borderline Resectable and Locally Advanced Pancreatic Cancer: A Feasibility Human Study
- e16 CME Exam 2: An Unexpected Consequence of a Clinical Trial
- e17 CME Exam 3: Epithelial Indoleamine 2,3-Dioxygenase 1 Modulates Aryl Hydrocarbon Receptor and Notch Signaling to Increase Differentiation of Secretory Cells and Alter Mucus-Associated Microbiota
- e18 CME Exam 4: Microbiome Signatures Associated with Steatohepatitis and Moderate to Severe Fibrosis in Children With Nonalcoholic Fatty Liver Disease

## **BRIEF COMMUNICATION**

1153 MET Signaling Overcomes Epidermal Growth Factor Receptor Inhibition in Normal and Colorectal Cancer Stem Cells Causing Drug Resistance

S. P. J. Joosten, T. Mizutani, M. Spaargaren, H. Clevers, and S. T. Pals

## **SELECTED SUMMARIES**

- 1156 Towards Precision Medicine in Nonalcoholic Fatty Liver Disease with PNPLA3 as a Therapeutic Target

  M. Colombo and S. Pelusi
- 1158 Single Dose Aspirin before Fecal Immunochemical Testing Does Not Increase Sensitivity for Advanced Colorectal Neoplasia

  B. Sullivan and J. Roper

## **CORRESPONDENCE**

1160 Treatment of Active Crohn's Disease With an Ordinary Food-Based Diet That Replicates Exclusive Enteral Nutrition

J. J. Ashton and R. M. Beattie

1161 Reply

K. Gerasimidis, V. Svolos, B. Nichols, R. Papadopoulou, C. Quince, U. Z. Ijaz, S. Milling, D. R. Gaya, R. K. Russell, and R. Hansen

- Factors Associated With Survival of Patients With Severe Acute-On-Chronic Liver Failure
  Before and After Liver Transplantation: Unanswered Questions
  N. S. Choudhary, N. Saraf, S. Saigal, and A. S. Soin
- 1163 Reply
  V. Sundaram and R. Jalan
- 1164 Roseburia Species: Prime Candidates for Microbial Therapeutics in Inflammatory Bowel Disease

  R. Kellermayer

- 1165 Reply
  - S. Paramsothy and N. O. Kaakoush
- 1166 Evolving Trends in Machine Liver Perfusion: Comments on Clinical End Points and Selection Criteria
  - Z. Czigany, F. Tacke, and G. Lurje
- 1167 Genome-Wide Association Studies of Drug-Induced Liver Injury Make Progress Beyond the *HLA* Region
  - G. E. B. Wright, B. I. Drögemöller, C. J. D. Ross, and B. C. Carleton
- More Evidence Needed on the Combination of Diclofenac and Sublingual Nitrates in Preventing Pancreatitis After Endoscopic Retrograde Cholangiopancreatography

  Z.-F. Zhang
- 1169 Role of CXCR6-Deficient Natural Killer T Cells and CD4 T Cells in Hepatocarcinogenesis

  H. Tao and X. Chen
- 1170 Reply
  J. C. Mossanen and F. Tacke

## Access to the full content of Gastroenterology Online is available to all subscribers!

AGA members have seamless access to full Gastroenterology content from the AGA Web site. Simply sign in to http://www.gastro.org, visit the Publications section of the Web site, and click on Gastroenterology. You will be directed to the Journal Web site and will have full access to all content without having to supply a different username and password. Members can also visit http://www.gastrojournal.org directly and click on "Activate Online Access." Nonmember subscribers must create an online user account and activate their subscription to access the full text of articles on Gastroenterology Online. To activate your individual online subscription, please visit http://www.gastrojournal.org and click on "Activate Online Access." To activate your account, you

will need your subscriber account or member number, which you can find on your mailing label, (AGA members must use their 10-digit member number, including leading zeros). If you have any questions regarding your online subscription please call Elsevier Customer Service at (800) 654-2452.

Institutional access to Gastroenterology Online will be allowed only by limited site licensing. Further instructions will be available online. Personal subscriptions to Gastroenterology Online are for individual use only and may not be transferred. Use of Gastroenterology Online is subject to agreement to the terms and conditions of use as indicated online.

**AGA Member Number** 

**Your Account Number** 

Sample mailing label

GAST0000101864 JANE DOE

531 MAIN ST CENTER CITY, NY 10001-001 1GAST V91-4 1234567-8
JANE DOE
531 MAIN ST
CENTER CITY, NY 10001-001