

## Contents

### ON THE COVER

See article by D'Haens et al on page 624 for additional information.



### COVERING THE COVER

587 *A. T. Chan and C. S. Williams*

### COMMENTARIES

590 **Toward More Accurate Nomenclature for Fatty Liver Diseases**

*M. Eslam, A. J. Sanyal, and J. George*

594 **Opportunities for Innovation and Improved Care Using Telehealth for Nutritional Interventions**

*H. Knotowicz, A. Haas, S. Coe, G. T. Furuta, and P. Mehta*

### MENTORING, EDUCATION, AND TRAINING CORNER

598 **How to Foster Academic Promotion and Career Advancement of Women in Gastroenterology**

*E. M. Zimmermann*

### EDITORIALS

602 **Are Phosphodiesterase-5 Inhibitors a New Frontier for Prevention of Colorectal Cancer?**

*M. Jovani and A. T. Chan*

See Huang W et al on page 672.

604 **Safety and Complications of Long-Term Proton Pump Inhibitor Therapy: Getting Closer to the Truth**

*D. A. Corley*

See Moayyedi P et al on page 682.

607 **Will Science Sway Beliefs About Gluten?**

*E. P. Halmos and P. R. Gibson*

See Croall ID et al on page 881.

Video

Related article in CGH

Hot Papers From New Investigators

CME quiz

Editorial accompanies this article

Additional online content available

Cover

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.

**CLINICAL CHALLENGES AND IMAGES IN GI**

- 610** **Gastroparesis Mimicry: Thinking Beyond the Pylorus**  
*B. Nunley, H. Collins, and F. Weber*
- 612** **An Unusual Cause of Esophageal Varices**  
*R. Agrawal, M. Majeed, and S. Gandhi*
- 614** **An Unusual Cause of Colonic Ulceration**  
*H. S. De Lil, M. A. Lantinga, and H. A. M. Sinnige*
- 616** **A Rare Complication of a Rare Disease**  
*L. J. Nayak, A. R. Sondhi, and M. Westerhoff*

**ELECTRONIC CLINICAL CHALLENGES AND IMAGES IN GI**

For a full list, please see the table of contents online at [www.gastrojournal.org](http://www.gastrojournal.org).

**PRACTICAL TEACHING CASES**

- 619** **An Unusual Cause of Acute Pancreatitis in a Young Woman**  
CME *T.-W. Yang, C.-M. Peng, and M.-C. Tsai*
- 622** **What Is the Peri-Pancreas Cystic Lesion?**  
*Y. Gao, B. Cai, and Y. Miao*

**REVIEWS AND PERSPECTIVES****Reviews in Basic and Clinical Gastroenterology and Hepatology**

- 624** **Fecal Microbial Transplantation for Diseases Beyond Recurrent *Clostridium Difficile* Infection**  
GOV *G. R. D'Haens and C. Jobin*

**ORIGINAL RESEARCH****Full Reports****Clinical—Alimentary Tract**

- 637** ***Bifidobacterium breve* Bif195 Protects Against Small-Intestinal Damage Caused by Acetylsalicylic Acid in Healthy Volunteers**  
WWW *B. Mortensen, C. Murphy, J. O'Grady, M. Lucey, G. Elsaft, L. Barry, V. Westphal, A. Wellejus, O. Lukjancenko, A. C. Eklund, H. B. Nielsen, A. Baker, A. Damholt, J. E. T. van Hylckama Vlieg, F. Shanahan, and M. Buckley*  
The risk of damage to the intestine from frequent intake of aspirin can be reduced by a specific bacteria (probiotic) preparation.
- 647** **Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses**  
CME WWW *D. Piovani, S. Danese, L. Peyrin-Biroulet, G. K. Nikolopoulos, T. Lytras, and S. Bonovas*  
Among 71 previously reported potential risk factors for inflammatory bowel disease, only nine harmful and seven protective associations showed moderate/high epidemiologic credibility.
- 660** **Right-Sided Location Not Associated With Missed Colorectal Adenomas in an Individual-Level Reanalysis of Tandem Colonoscopy Studies**  
CME WWW *K. Zimmermann-Fraedrich, S. Sehner, D. K. Rex, T. Kaltenbach, R. Soetikno, M. Wallace, W. K. Leung, C. Guo, I. M. Gralnek, E. C. Brand, S. Groth, G. Schachschal, H. Ikematsu, P. D. Siersema, and T. Rösch*  
Although screening colonoscopy appears to be less effective at reducing the risk of right-sided colon cancers, the current study did not find that this was related to the likelihood of "missing" precancerous polyps during colonoscopy.
- 672** **Use of Phosphodiesterase 5 Inhibitors Is Associated With Lower Risk of Colorectal Cancer in Men With Benign Colorectal Neoplasms**  
E WWW *W. Huang, J. Sundquist, K. Sundquist, and J. Ji*  
**See editorial on page 602**  
Among men diagnosed with a precancerous polyp in a large population-based study, those using phosphodiesterase 5 inhibitors were at lower risk of colorectal cancer.

## 682 Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin

*P. Moayyedi, J. W. Eikelboom, J. Bosch, S. J. Connolly, L. Dyal, O. Shestakovska, D. Leong, S. S. Anand, S. Störk, K. R. H. Branch, D. L. Bhatt, P. B. Verhamme, M. O'Donnell, A. P. Maggioni, E. M. Lonn, L. S. Piegas, G. Ertl, M. Keltai, N. C. Bruns, E. Muehlhofer, G. R. Dagenais, J.-H. Kim, M. Hori, P. G. Steg, R. G. Hart, R. Diaz, M. Alings, P. Widimsky, A. Avezum, J. Probstfield, J. Zhu, Y. Liang, P. Lopez-Jaramillo, A. K. Kakkar, A. N. Parkhomenko, L. Ryden, N. Pogosova, A. L. Dans, F. Lanus, P. J. Commerford, C. Torp-Pedersen, T. J. Guzik, D. Vinereanu, A. M. Tonkin, B. S. Lewis, C. Felix, K. Yusoff, K. P. Metsarinne, K. A. A. Fox, and S. Yusuf, for the COMPASS Investigators*

See editorial on page 604

Pantoprazole is not associated with any adverse event when used for three years, with the possible exception of an increased risk of enteric infections.

### Clinical—Liver

## 692 Amino Acid Substitutions in Genotype 3a Hepatitis C Virus Polymerase Protein Affect Responses to Sofosbuvir

*P. A. C. Wing, M. Jones, M. Cheung, S. DaSilva, C. Bamford, W.-Y. Jason Lee, E. Aranday-Cortes, A. Da Silva Filipe, J. McLauchlan, D. Smith, W. Irving, M. Cunningham, A. Ansari, E. Barnes, and G. R. Foster*

A genetic alteration in HCV genotype 3 affects its response to treatment with specific drugs. Patients might be tested for this form of HCV to assess treatment options.

## 705 Liver Fibrosis and Metabolic Alterations in Adults With alpha-1-antitrypsin Deficiency Caused by the Pi\*ZZ Mutation

*K. Hamesch, M. Mandorfer, V. M. Pereira, L. S. Moeller, M. Pons, G. E. Dolman, M. C. Reichert, C. V. Schneider, V. Woditsch, J. Voss, C. Lindhauer, M. Fromme, I. Spivak, N. Guldiken, B. Zhou, A. Arslanow, B. Schaefer, H. Zoller, E. Aigner, T. Reiberger, M. Wetzel, B. Siegmund, C. Simões, R. Gaspar, L. Maia, D. Costa, M. Bento-Miranda, J. van Helden, E. Yagmur, D. Bzdok, J. Stolk, W. Gleiber, V. Knipel, W. Windisch, R. Mahadeva, R. Bals, R. Koczulla, M. Barrecheguren, M. Miravittles, S. Janciauskiene, F. Stickel, F. Lammert, R. Liberal, J. Genesca, W. J. Griffiths, M. Trauner, A. Krag, C. Trautwein, and P. Strnad, on behalf of the European Alpha1-Liver Study Group*

In a large, multinational cohort of individuals with alpha1 antitrypsin deficiency, a substantial portion of people had an increased risk of liver fat deposits and potential liver disease.

### Clinical—Pancreas

## 720 Cross Validation of the Monoclonal Antibody Das-1 in Identification of High-Risk Mucinous Pancreatic Cystic Lesions

*K. K. Das, X. Geng, J. W. Brown, V. Morales-Oyarvide, T. Huynh, I. Pergolini, M. B. Pitman, C. Ferrone, M. Al Efishat, D. Haviland, E. Thompson, C. Wolfgang, A. M. Lennon, P. Allen, K. D. Lillemoe, R. C. Fields, W. G. Hawkins, J. Liu, C. F.-d. Castillo, K. M. Das, and M. Mino-Kenudson*

The authors validated the ability of a specific antibody to detect high-risk pancreatic cystic lesions with high levels of sensitivity and selectivity.

### Basic and Translational—Alimentary Tract

## 731 RNA-Binding Protein HuR Regulates Paneth Cell Function by Altering Membrane Localization of TLR2 via Post-transcriptional Control of CNPY3

*L. Xiao, X.-X. Li, H. K. Chung, S. Kalakonda, J.-Z. Cai, S. Cao, N. Chen, Y. Liu, J. N. Rao, H.-Y. Wang, M. Gorospe, and J.-Y. Wang*

Studies in mice, intestinal organoids, and human intestinal tissues demonstrate that RNA-binding protein HuR regulates Paneth cell function by altering TLR2 localization via posttranscriptional control of chaperone protein CNPY3.

## 744 Intestinal PPAR $\alpha$ Protects Against Colon Carcinogenesis via Regulation of Methyltransferases DNMT1 and PRMT6

*Y. Luo, C. Xie, C. N. Brocker, J. Fan, X. Wu, L. Feng, Q. Wang, J. Zhao, D. Lu, M. Tandon, M. Cam, K. W. Krausz, W. Liu, and F. J. Gonzalez*

The authors identified preventative effects of intestinal PPAR $\alpha$  in colon carcinogenesis and potential strategies for colon cancer prevention and treatment.

**Basic and Translational—Liver****760 Analysis of Liver Cancer Cell Lines Identifies Agents With Likely Efficacy Against Hepatocellular Carcinoma and Markers of Response**

www

*S. Caruso, A.-L. Calatayud, J. Pilet, T. La Bella, S. Rekik, S. Imbeaud, E. Letouzé, L. Meunier, Q. Bayard, N. Rohr-Udilova, C. Péneau, B. Grasl-Kraupp, L. de Koning, B. Ouine, P. Bioulac-Sage, G. Couchy, J. Calderaro, J.-C. Nault, J. Zucman-Rossi, and S. Rebouissou*

Liver cancer cell lines might be used in screens to identify drugs with efficacy against hepatocellular carcinoma. The cells can then be analyzed to identify factors associated with effective anti-cancer response and patients' tumors might be tested for these factors.

**777 Inhibiting Interleukin 11 Signaling Reduces Hepatocyte Death and Liver Fibrosis, Inflammation, and Steatosis in Mouse Models of Nonalcoholic Steatohepatitis**

www

*A. A. Widjaja, B. K. Singh, E. Adami, S. Viswanathan, J. Dong, G. A. D'Agostino, B. Ng, W. W. Lim, J. Tan, B. S. Paleja, M. Tripathi, S. Y. Lim, S. G. Shekeran, S. P. Chothani, A. Rabes, M. Sombetzki, E. Bruinstroop, L. P. Min, R. A. Sinha, S. Albani, P. M. Yen, S. Schafer, and S. A. Cook*

Neutralizing antibodies that inhibit part of the immune system signaling might be developed to treat complications of fatty liver disease.

**793 Aryl Hydrocarbon Receptor Signaling Prevents Activation of Hepatic Stellate Cells and Liver Fibrogenesis in Mice**

www

*J. Yan, H.-C. Tung, S. Li, Y. Niu, W. G. Garbacz, P. Lu, Y. Bi, Y. Li, J. He, M. Xu, S. Ren, S. P. Monga, R. F. Schwabe, D. Yang, and W. Xie*

Activation of hepatic stellate cells (HSCs) is key to liver fibrosis formation. This study showed that drug activation of the aryl hydrocarbon receptor can prevent HSC activation and liver fibrosis.

**807 Hepatocellular Carcinomas With Mutational Activation of Beta-Catenin Require Choline and Can Be Detected by Positron Emission Tomography**

www

*A. Gougelet, C. Sartor, N. Senni, J. Calderaro, L. Fartoux, M. Lequoy, D. Wendum, J.-N. Talbot, A. Prignon, J. Chalaye, S. Imbeaud, J. Zucman-Rossi, T. Tordjmann, C. Godard, P. Bossard, O. Rosmorduc, G. Amaddeo, and S. Colnot*

A specific metabolic feature of some hepatocellular carcinomas can be identified by PET imaging. These liver tumors might be susceptible to specific treatments or dietary therapies.

**Basic and Translational—Pancreas****823 Regulation of pH by Carbonic Anhydrase 9 Mediates Survival of Pancreatic Cancer Cells With Activated KRAS in Response to Hypoxia**

www

*P. C. McDonald, S. C. Chafe, W. S. Brown, S. Saberi, M. Swayampakula, G. Venkateswaran, O. Nemirovsky, J. A. Gillespie, J. M. Karasinska, S. E. Kalloger, C. T. Supuran, D. F. Schaeffer, A. Bashashati, S. P. Shah, J. T. Topham, D. T. Yapp, J. Li, D. J. Renouf, B. Z. Stanger, and S. Dedhar*

This study identifies a critical genetic vulnerability of certain pancreatic cancers; a novel new strategy targeting this vulnerability may be a new treatment of patients with pancreatic cancer.

**838 Axon Guidance Molecules Promote Perineural Invasion and Metastasis of Orthotopic Pancreatic Tumors in Mice**

www

*N. R. Jurcak, A. A. Rucki, S. Muth, E. Thompson, R. Sharma, D. Ding, Q. Zhu, J. R. Eshleman, R. A. Anders, E. M. Jaffee, K. Fujiwara, and L. Zheng*

This study links the axon guidance pathway to pancreatic cancer invasion toward nerves and also describes a role of axon guidance molecules in pancreatic cancer metastasis.

**CONTINUING MEDICAL EDUCATION (CME)/MOC ACTIVITIES**

- e14 CME Exam 1: An Unusual Cause of Acute Pancreatitis in a Young Woman**
- e16 CME Exam 2: Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses**
- e17 CME Exam 3: Right-Sided Location Not Associated With Missed Colorectal Adenomas in an Individual-Level Reanalysis of Tandem Colonoscopy Studies**

**CLINICAL PRACTICE GUIDELINES**

- 851 AGA Clinical Practice Guidelines on the Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D)**  
*W. Smalley, C. Falck-Ytter, A. Carrasco-Labra, S. Wani, L. Lytvyn, and Y. Falck-Ytter*
- 855 Irritable Bowel Syndrome in Adults (IBS-D): Clinical Decision Support Tool**  
*American Gastroenterological Association*
- 856 AGA Clinical Practice Guidelines on the Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D): Patient Summary**  
*American Gastroenterological Association*
- 858 Spotlight: Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D)**  
*W. Smalley, C. Falck-Ytter, A. Carrasco-Labra, S. Wani, L. Lytvyn, and Y. Falck-Ytter*
- 859 AGA Technical Review on the Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D)**  
*A. Carrasco-Labra, L. Lytvyn, Y. Falck-Ytter, C. M. Surawicz, and W. D. Chey*

**BRIEF COMMUNICATIONS**

- 881 Gluten Does Not Induce Gastrointestinal Symptoms in Healthy Volunteers: A Double-Blind Randomized Placebo Trial**  
*I. D. Croall, I. Aziz, N. Trott, P. Tosi, N. Hoggard, and D. S. Sanders*  
**See editorial on page 607**
- 884 Noninvasive Detection of High-Risk Adenomas Using Stool-Derived Eukaryotic RNA Sequences as Biomarkers**  
*E. K. Barnell, Y. Kang, E. M. Wurtzler, M. Griffith, A. A. Chaudhuri, and O. L. Griffith, and Geneoscopy Scientists*

**SELECTED SUMMARIES**

- 888 Prevention of Biliary Cancer With Statins: Still a Long Way to Go**  
*M. Colombo, F. Turati, and C. La Vecchia*
- 890 Colonoscopy Surveillance Intervals for Small Nonadvanced Adenomas: Does Size Matter?**  
*J. W. Birk and J. C. Anderson*

**CORRESPONDENCE**

- 892 Accurate and Dynamic Monitoring of Pancreatic Endocrine Function Is Required in Discharged Patients With Necrotizing Pancreatitis**  
*L. Gao, L. Ke, and W.-Q. Li*
- 892 Improving Clinical Trial Efficiency in Gastroenterology**  
*C. Ma, L. Guizzetti, and V. Jairath*

- 894 **Reply**  
*M. S. Harris and C. W. Howden*
- 894 **Population Difference and Disease Status Affect the Association Between Genetic Variants and Gene Expression**  
*G. Liu, Y. Hu, and Q. Jiang*
- 896 **Reply**  
*Y. Lu and W. Zheng*
- 897 **Tobacco Smoking and Alcohol Drinking: Two Clinically Significant Risk Factors for Esophageal Squamous Cell Carcinoma**  
*F. Najafi*
- 897 **Reply**  
*M. Sheikh, P. Brennan, and R. Malekzadeh*
- 898 **Future Possibility of Mizagliflozin on Functional Constipation and/or Irritable Bowel Syndrome With Constipation**  
*S. Fukudo and K. Kaku*
- 899 **Historical Data Are Not Relevant to the Diagnostic Performance of Ultrasound in Surveillance for Hepatocellular Carcinoma**  
*K. Khalili*
- 901 **Reply**  
*A. G. Singal*
- 902 **The Transplantation of Fecal Microbiota for Cirrhotic Patients**  
*G.-H. Lo*
- 902 **Reply**  
*J. S. Bajaj and P. M. Gillevet*
- CORRECTION**
- 903 **Correction**

**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