

Gastroenterology

www.gastrojournal.org

Vol. 151, No. 4

October 2016

Contents

ON THE COVER



Please see editorial by Denson and Klein on page 593; articles by Levine et al on page 698; Chuang et al on page 710; and Li et al on page 724 for more information.

COVERING THE COVER

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

COMMENTARY

574 Toward a Comprehensive New Classification of Portal Vein Thrombosis in Patients With Cirrhosis

S. K. Sarin, C. A. Philips, P. S. Kamath, A. Choudhury, H. Maruyama, F. G. Nery, and D. C. Valla

MENTORING, EDUCATION, AND TRAINING CORNER

578 How to Succeed in Academic Gastroenterology

J. I. Allen, T. C. Wang, W. S. Cohen, and V. H. Shah

EDITORIALS

582 After the Direct-acting Antivirals Are Gone, There Is Still Work to Be Done in the Liver

P. Y. Kwo and M. A. Lacerda

See Gambato M et al on page 633.

584 RNA Editing: Another Level of Somatic Mutagenic Activity in Gastric Cancer

V. Blanc and N. O. Davidson

See Chan THM et al on page 637.

Video Related article in CGH

CME quiz

Editorial accompanies this article

Additional online content available

Cover

Publisher: *Gastroenterology* (ISSN 0016-5085) is published monthly (semi monthly in May and June) in two indexed volumes by Elsevier Inc, 230 Park Avenue, New York, NY 10169. Periodicals postage paid at New York, NY and additional mailing offices. POSTMASTER: Send address changes to GASTROENTEROLOGY, Elsevier Health Sciences Division, Subscription Customer Service, 3251 Riverport Lane, Maryland Heights, MO 63043. 2016 US subscription rates: Individual, \$658.00; student and resident, \$251.00. 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.

- 587 Hepatitis C Drugs: Is Next Generation the Last Generation?
J.-M. Pawlotsky
See Gane E et al on page 651.
- 590 Shifting Paradigms: What Is the True Prevalence and Clinical Course of Primary Sclerosing Cholangitis?
R. K. Weersma and K. D. Lindor
See Lunder AK et al on page 660.
- 593 Granulocyte-Macrophage Colony Stimulating Factor Bioactivity and Mucosal Homeostasis in Crohn's Disease: A Role for Genetic Variation
L. A. Denson and C. Klein
See Levine AP et al on page 698; and See Chuang L-S et al on page 710.

CLINICAL CHALLENGES AND IMAGES IN GI

- 597 Velvety-Red Esophageal Mucosa and Dysphagia: Coincidental or Causal?
J. H. Tabibian, R. Tondon, and M. L. Kochman
- 599 Not Just Another Case of Right Iliac Fossa Pain
T. C. Chua, M. Marroquin-Harris, and G. Vasica
- 601 An Elderly Woman With Facial Erythema and Hematemesis
R. Hashimoto and A. Chonan
- 603 Unusual Esophageal Foreign Body
F. Wuestenberghs and P. Druez

ELECTRONIC CLINICAL CHALLENGES AND IMAGES IN GI

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

PRACTICAL TEACHING CASE

- 605 An Unusual Cause of Splenomegaly
M. Sharma, P. Soman, and A. Patil

REVIEWS AND PERSPECTIVES

Brief Review

- 607 Regulation of Transdifferentiation and Retrodifferentiation by Inflammatory Cytokines in Hepatocellular Carcinoma
F. Cabillic and A. Corlu

Reviews in Basic and Clinical Gastroenterology and Hepatology

- 616 Inflammation and the Intestinal Barrier: Leukocyte-Epithelial Cell Interactions, Cell Junction Remodeling, and Mucosal Repair
A.-C. Luissint, C. A. Parkos, and A. Nusrat

ORIGINAL RESEARCH**Brief Report**

- 633 Hepatitis C Virus RNA Persists in Liver Explants of Most Patients Awaiting Liver Transplantation Treated With an Interferon-Free Regimen**

M. Gambato, S. Pérez-del-Pulgar, C. Hedskog, E. S. Svarovskia, D. Brainard, J. Denning, M. P. Curry, M. Charlton, N. Caro-Pérez, M. C. Londoño, G. Koutsoudakis, and X. Forns

See editorial on page 582.

The presence of non-functional HCV-RNA, or a down regulation of the intrahepatic IFN pathway unable to clear residual HCV-RNA, might explain the persistence of residual HCV-RNA in liver explants of most HCV-infected patients treated on the waitlist.

Full Reports**Clinical—Alimentary Tract**

- 637 ADAR-Mediated RNA Editing Predicts Progression and Prognosis of Gastric Cancer**

T. H. M. Chan, A. Qamra, K. T. Tan, J. Guo, H. Yang, L. Qi, J. S. Lin, V. H. E. Ng, Y. Song, H. Hong, S. T. Tay, Y. Liu, J. Lee, S. Y. Rha, F. Zhu, J. B. Y. So, B. T. Teh, K. G. Yeoh, S. Rozen, D. G. Tenen, P. Tan, and L. Chen

See editorial on page 584.

RNA editing is found to have a major, previously unobserved role in GC disease and progression. ADAR1 enzymatic inhibition or the potential restoration of ADAR2 activity may be therapeutic opportunities.

Clinical—Liver

- 651 High Efficacy of ABT-493 and ABT-530 Treatment in Patients With HCV Genotype 1 or 3**

Infection and Compensated Cirrhosis

E. Gane, F. Poordad, S. Wang, A. Asatryan, P. Y. Kwo, J. Lalezari, D. L. Wyles, T. Hassanein, H. Aguilar, B. Maliakkal, R. Liu, C.-W. Lin, T. I. Ng, J. Kort, and F. J. Mensa

See editorial on page 587.

The once-daily combination of ABT-493 and ABT-530 without RBV for 12 weeks is sufficient to achieve high rates of SVR12 in patients with GT1 or GT3 infection and compensated cirrhosis.

Clinical—Biliary

- 660 Prevalence of Sclerosing Cholangitis Detected by Magnetic Resonance Cholangiography in**

Patients With Long-term Inflammatory Bowel Disease

A. K. Lunder, J. R. Hov, A. Borthne, J. Gleditsch, G. Johannessen, K. Tveit, E. Viktil, M. Henriksen, Ø. Hovde, G. Huppertz-Hauss, O. Høie, M. L. Høivik, I. Monstad, I. C. Solberg, J. Jahnsen, T. H. Karlsen, B. Moum, M. Vatn, and A. Negård

See editorial on page 590.

Using MRC analysis of patients with long-term IBD, prevalence of PSC was found to be almost 4-fold higher than that detected based on symptoms.

Basic and Translational—Alimentary Tract

- 670 Duodenal Bacteria From Patients With Celiac Disease and Healthy Subjects Distinctly Affect Gluten Breakdown and Immunogenicity**

A. Caminero, H. J. Galipeau, J. L. McCarville, C. W. Johnston, S. P. Bernier, A. K. Russell, J. Jury, A. R. Herran, J. Casqueiro, J. A. Tye-Din, M. G. Surette, N. A. Magarvey, D. Schuppan, and E. F. Verdu

Small intestinal bacteria exhibit distinct gluten metabolic patterns in vivo, increasing or reducing gluten peptide immunogenicity. This may modulate autoimmune risk in genetically susceptible persons and underlie the reported association of dysbiosis and celiac disease.



684

Deletion of Polycomb Repressive Complex 2 From Mouse Intestine Causes Loss of Stem Cells

M. A. J. Koppens, G. Bouanova, G. Gargiulo, E. Tanger, H. Janssen, P. Cornelissen-Steijger, M. Blom, J.-Y. Song, L. F. A. Wessels, and M. van Lohuizen

PRC2 function is essential for maintenance of adult LGR5-positive intestinal stem cells.

698

Genetic Complexity of Crohn's Disease in Two Large Ashkenazi Jewish Families

A. P. Levine, N. Pontikos, E. R. Schiff, L. Jostins, D. Speed, NIDDK Inflammatory Bowel Disease Genetics Consortium, L. B. Lovat, J. C. Barrett, H. Grasberger, V. Plagnol, and A. W. Segal

See editorial on page 593.

The genetic basis of Crohn's disease is complex, with a role for common and rare genetic variants. These findings demonstrate the value of family studies and the importance of the innate immune system in the pathogenesis of CD.

710

A Frameshift in *CSF2RB* Predominant Among Ashkenazi Jews Increases Risk for Crohn's Disease and Reduces Monocyte Signaling via GM-CSF

L.-S. Chuang, N. Villaverde, K. Y. Hui, A. Mortha, A. Rahman, A. P. Levine, T. Haritunians, S. M. Evelyn Ng, W. Zhang, N.-Y. Hsu, J.-A. Facey, T. Luong, H. Fernandez-Hernandez, D. Li, M. Rivas, E. R. Schiff, A. Gusev, L. P. Schumm, B. M. Bowen, Y. Sharma, K. Ning, R. Remark, S. Gnjatic, P. Legnani, J. George, B. E. Sands, J. M. Stempak, L. W. Datta, S. Lipka, S. Katz, A. S. Cheifetz, N. Barzilai, N. Pontikos, C. Abraham, M. J. Dubinsky, S. Targan, K. Taylor, J. I. Rotter, E. J. Scherl, R. J. Desnick, M. T. Abreu, H. Zhao, G. Atzman, I. Pe'er, S. Kugathasan, H. Hakonarson, J. L. McCauley, T. Lencz, A. Darvasi, V. Plagnol, M. S. Silverberg, A. M. Muise, S. R. Brant, M. J. Daly, A. W. Segal, R. H. Duerr, M. Merad, D. P. B. McGovern, I. Peter, and J. H. Cho

See editorial on page 593.

Intestinal monocytes from carriers of a frameshift mutation in *CSF2RB* had reduced responses to GM-CSF. Enhancing specific phagocyte cell subset function may be a more effective means of developing the novel therapies needed in CD.

724

A Pleiotropic Missense Variant in *SLC39A8* Is Associated With Crohn's Disease and Human Gut Microbiome Composition

D. Li, J.-P. Achkar, T. Haritunians, J. P. Jacobs, K. Y. Hui, M. D'Amato, S. Brand, G. Radford-Smith, J. Halfvarson, J.-H. Niess, S. Kugathasan, C. Büning, L. P. Schumm, L. Klei, A. Ananthakrishnan, G. Aumais, L. Baidoo, M. Dubinsky, C. Fiocchi, J. Glas, R. Milgrom, D. D. Proctor, M. Regueiro, L. A. Simms, J. M. Stempak, S. R. Targan, L. Törkvist, Y. Sharma, B. Devlin, J. Borneman, H. Hakonarson, R. J. Xavier, M. Daly, S. R. Brant, J. D. Rioux, M. S. Silverberg, J. H. Cho, J. Braun, D. P. B. McGovern, and R. H. Duerr

An *SLC39A8*-dependent shift in the gut microbiome could explain its pleiotropic effects on multiple complex diseases including Crohn's disease.

Basic and Translational—Liver

733

Loss of Junctional Adhesion Molecule A Promotes Severe Steatohepatitis in Mice on a Diet High in Saturated Fat, Fructose, and Cholesterol

K. Rahman, C. Desai, S. S. Iyer, N. E. Thorn, P. Kumar, Y. Liu, T. Smith, A. S. Neish, H. Li, S. Tan, P. Wu, X. Liu, Y. Yu, A. B. Farris, A. Nusrat, C. A. Parkos, and F. A. Anania

Intestinal epithelial barrier function and microbial dysbiosis contribute to development of NASH. Restoration of intestinal barrier integrity and manipulation of gut microbiota are potential therapeutic strategies.

- 770 **Genetic Variants in the BMP6 Pro-Peptide May Not Cause Iron Loading and Should Be Interpreted With Caution**
C. J. McDonald, G. Rishi, D. F. Wallace, and V. N. Subramaniam
- 771 **Reply**
Z. Karim, H. Puy, C. Beaumont, L. Gouya, and C. Kannengiesser
- 773 **Clinical and Immunologic Features of Ultra-Short Celiac Disease**
G. Oberhuber and H. Vogelsang
- 773 ***Helicobacter pylori* Eradication?**
A. Donzelli
- 774 **Reply**
Y.-C. Lee, W.-C. Liao, M.-S. Wu, and D. Y. Graham

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

**Sample
mailing
label**

GAST0000101864

JANE DOE
531 MAIN ST
CENTER CITY, NY 10001-001

Your Account Number

1GAST V91-4 1234567-8

JANE DOE
531 MAIN ST
CENTER CITY, NY 10001-001