BURIED UNDER FDA REGULATIONS

How have FDA regulations impacted patient accessibility to fecal microbiota transplant (FMT)? Experts debate FDA’s role in regulating this life-saving treatment.

ARTICLES CONTRIBUTED BY

Mark Mellow, MD, FACP, Neil Stollman, MD, FACP, FACC, AGAF, and Colleen Kelly, MD
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Note From the Editor

It is my pleasure to bring you this issue of the AGA Perspectives. Our cover topic tackles the role of FDA in regulating new and emerging treatments. Drs. Mellow, Stollman and Kelly debate the recent interventions of the FDA in regulating fecal microbiota transplant (FMT). This extends well beyond FMT as the FDA plays a critical role in ensuring that drugs and devices are safe and effective. However, an overly regulated process can limit access to potentially life-saving therapies, including FMT, and can have a long-term negative impact on innovation.

Other articles include a diverse array of topics relevant to both the practicing gastroenterologist as well as academic physician. Personalized medicine is an excellent example of how therapies and diagnostics are rapidly moving from the research arena to clinical practice. I think all of us have seen our patients bring genetic reports that may predict specific responses to cancer as well as other gastrointestinal diseases. It is imperative that we inform ourselves with the language of personalized medicine so that we can properly respond to our patient’s questions and further inform them of new opportunities.

Dr. Anna Buchner presents an article on new imaging methods for IBD. The need for improved imaging is highlighted by emerging data that complete mucosal healing is increasingly important to prevent relapse. Furthermore new imaging methods have significantly improved the ability to detect and remove dysplasia without complete colectomy.

Two articles focus on chronic pancreatitis as well as the now widely recognized autoimmune pancreatitis and how to best diagnose it. In our International Corner, we focus on regional variations in dietary patterns and their association with colon cancer prevention. We continue our commitment to trainees and young fellows with Dr. Lena Palmer’s discussion of the new AGA Trainee and Young GI Committee.

Lastly, we close with an introduction to our upcoming president, Dr. Michael Camilleri, whose research has greatly expanded our understanding of functional gastrointestinal diseases.

Michael B. Wallace, MD, MPH
EDITOR
BURIED UNDER FDA REGULATIONS
FDA’s Role in Regulating FMT Is Imperative

Imagine a powerful new biological product derived from human tissue with some inherent risk of transmitting infection. Furthermore, this drug, though effective, has the potential to influence a patient’s risk for developing obesity, type II diabetes, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), autoimmunity, cardiovascular disease and colon cancer. Would FDA regulation of such a product seem unreasonable? Fecal microbiota transplant (FMT) is exactly such an agent. FMT involves administration of fecal material containing billions of intestinal microorganisms from a healthy individual (donor) into a patient (recipient) who then becomes durably colonized with members of the donor’s intestinal flora. While transmission of infectious organisms is an obvious concern, the influence of the human intestinal microbiome in a number of other pathologic conditions is now increasingly being supported in the medical literature.

The U.S. Food and Drug Administration (FDA) is responsible for protecting the public’s health by assuring the safety, efficacy and security of drugs, biological products and medical devices.¹ The FDA has oversight over any substance intended for efficacy and security of drugs, biological products and medical devices.¹ The FDA has oversight over any substance intended for use in the medical literature.

To briefly recap the recent history, the FDA had been essentially silent on fecal microbiota transplant (FMT) for many years, when only a small number of providers were performing, and were somewhat under the radar. Things radically changed on April 25, 2013, when in response to a society query, the FDA released a statement characterizing stool as a ‘drug’ without any approved indications, and thus only able to be utilized in a registered clinical trial, or under the auspices of an individual physician’s investigational new drug (IND) application. In practical terms, this put a complete, immediate and abrupt stop to almost all FMT procedures in this country. A hue and cry ensued, a public workshop occurred, and to their credit, the FDA soon thereafter clarified their position, announcing that they would employ ‘enforcement discretion’ for FMT being performed for multiply recurrent C. difficile infection (R-CDI), with an appropriate patient consent. We were pleasantly surprised by this logical, rational, and at core, compassionate about-face, which reflects well on the FDA’s ability to rapidly pivot based on further evaluation. Further, the FDA has, in essence, made our case for us! After an initial decision that was widely recognized as an appropriate use of a biologic product, for an epidemic illness, for which patients are suffering from recurrent C. difficile infection (R-CDI), the FDA’s ability to rapidly pivot based on further evaluation. Further, the FDA has, in essence, made our case for us! After an initial decision that was widely seen as heavy handed and poorly planned, they have recognized that overall, this is an appropriate use of a biologic product, for an epidemic illness, for which patients generically have no alternative, and that imposition of IND-requiring regulations was inappropriate, and actually harmful.

To elaborate on our position, we believe that in the simplest sense, ‘acceptable’ use of a treatment requires that the treatment be a) efficacious (at least as good as currently available alternative treatments), and b) have a favorable risk/benefit ratio. Regarding efficacy, we now have one published randomized control trial¹, numerous case series²-⁸ and meta-analyses²-⁸ that consistently affirm FMT’s efficacy. We acknowledge that case series can be subject to bias. However, two long-term multicenter reports⁹,¹⁰ (one from Finland and our U.S. experience, involving 10 different centers, totaling 147 patients, after colonoscopic-FMT) reported nearly identical results: 91 vs. 94 percent cure rates, no recurrences in the absence of subsequent antibiotic use and no short-term complications. All of these patients had previously failed multiple ‘standard’ treatment regimens, and we can both personally vouch for the debility and despair these patients have endured for many months, until being truly ‘cured’ with FMT.

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offer assistance. I called CBER who referred me to online guidance documents which were lengthy and directed at the pharmaceutical industry and regulatory experts. It felt like learning another language. This was a long process, consuming hundreds of hours, with enormous administrative requirements. As the holder (sponsor) of an IND, I am legally responsible for monitoring the investigation to ensure it is in accordance with the investigational plan and protocols contained in the IND, and ensuring that the FDA is promptly informed of significant new adverse effects or risks with respect to FMT. I recently worked with other investigators holding INDs for FMT to develop a more user-friendly guidance to researchers on the preparation and submission of IND application. However, the IND process, as it stands, remains burdensome to physician investigators. Furthermore, it is not permissible to charge for an investigational product under an IND, which will certainly impact insurance coverage and any financial incentive to offer this therapy.

FDA regulation of this potent therapeutic is necessary, both to maintain the highest safety standards and to ensure detailed careful monitoring for adverse events. Furthermore, FDA oversight of clinical trials is needed to determine the efficacy of FMT in various indications. Patients deserve protection from the “snake oil salesmen” who might emerge to treat conditions for which few therapeutic options exist and FMT is perceived as something new and hopeful. FMT appears to be safe, with few adverse effects or complications attributed to the procedure yet reported in the medical literature. Transmission of infectious agents, however, is a potential concern, and screening of stool donors for common pathogens, similar to investigations used by blood banks and organ transplant programs, may reduce risk to patients and should be a requirement of any FMT protocol. Exclusion of donors with conditions which could be theoretically transmitted via microbiota is also prudent. FMT is similar to an organ or tissue transplant in that FMT takes whole stool from one person and infuses it into the GI tract of another person with the goal of transplanting and restoring an entire community of beneficial GI flora. Categorizing fecal material as a transplant would require establishments to screen and test donors, to prepare and follow written procedures for the prevention and the spread of communicable disease, and to maintain records of its use. Despite the logic of this argument, the FDA has resisted categorizing FMT as a tissue or transplant because it is not “human” but rather microbial tissue.

Despite the clear need for regulation of FMT, the FDA must remain somewhat flexible in its approach to such regulation with the understanding that FMT is a field in evolution. Replacement of the complex community of microorganisms that constitutes stool cannot be regulated as a “drug” per-se. It is not possible to provide exact dosing/colonization data for this product, which is highly variable among individual donors. Just as there are no artificial liver, stem cells or oocytes, there is no in-vitro formulation yet available which approximates the complexity of the human intestinal microbiome and the efficacy of wild-type species. Modification of the regulatory process to better fit the unique aspects of FMT and other microbiota-based therapeutics is something the FDA could do to make the pathway for physicians and investigators clearer. This process must also be applicable to the development of products that are sure to emerge within the next few years as we learn to manipulate the microbiota to treat CDI and other diseases. It is not reasonable to expect clinicians to navigate the regulatory process without direction. At the least, publication of a simplified FDA guidance for physicians and investigators with required elements of an IND clearly described would facilitate compliance with regulatory requirements. Current standard elements of an IND, including “chemical name and structure” and “chemistry/manufacturing data,” are questionable relevant to the administration of minimally modified human stool by individual physicians while focus on the indication, route of administration and dosing regimen is certainly appropriate. Publication of standard donor screening and required laboratory testing guidelines would help doctors develop safe treatment protocols. Those with interest in developing a commercial preparation of FMT should be required to follow good manufacturing practices, yet these would be overly burdensome to a physician or institution treating small numbers of patients. Requiring that serious adverse events (e.g., deaths, infections) related to FMT be reported is clearly beneficial and another function of regulatory oversight. A well-designed national FMT registry would enable outcomes of FMT-treated patients to be tracked and help address long-term safety concerns. Such a registry would also serve as enormous source of data for future research. The public must be able to trust that the risk-to-benefit ratio of a therapy has been considered and that all necessary measures are in place to ensure safety. FDA regulation of FMT, though imperfect at present, is the best way to accomplish that goal.

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It is somewhat telling that, in our impression, the entire tenor of an FDA symposium on FMT seemed to turn favorably after an impassioned presentation of a patient’s personal experience with R-CDI. While single patient testimonials are obviously a poor way to make national health-care policy, those who have treated R-CDI patients can attest to the fact that her story was prototypical, not atypical.

Regarding risks, there are certainly potential safety concerns, including transmission of an undiagnosed infectious agent, complications from the procedure itself and potential unknown future consequences of biome alteration, particularly immunologic. Fortunately, to date, no documented short-term complications have been reported, but the long-term safety remains unclear; particularly, FMT’s effects on the course of auto-immune and inflammatory disorders. This was a topic raised by many participants at the FDA’s symposium and public hearing, and establishment of a national registry has been suggested. We favor a government funded study evaluating long-term outcomes after FMT with appropriate comparators. It is interesting that those voicing the greatest concern about such risks of FMT were generally infectious disease specialists, who have a deservedly healthy and appropriate respect for the capacity of microbes to do harm and that major changes to our microbial populations must be viewed with caution. However, metagenomic analyses have shown that these patients already have marked alterations in their biome, which is why they relapse (rather than having traditionally ‘resistant’ organisms).

Further, expert consensus clinical guidelines have been published, giving newly adopting practitioners clear guidance on the procedure. That being said, there are many areas of practitioners clear guidance on the procedure. That being said, there are many areas of practitioners clear guidance on the procedure. Further, based on our personal experience, we don’t believe the procedure is actually all that hard to do safely (although it is certainly time consuming and poorly reimbursed). As we mentioned, there are now concrete guidelines available as to appropriate technique, and, of course, FDA themselves have essentially agreed with us, although they chose the term ‘enforcement discretion’ rather than overt ‘approval’. FMT for R-CDI is a now well-established procedure, is highly efficacious, has a well-established short-term safety outcome and has a relatively well-established standardized technique. It is appropriate for practitioners to provide this in their community, without the nearly insurmountable burden of an IND requirement.

We recognize that there are still many unanswered questions about this emerging technology, and numerous issues will require further study and clarification. For example, what is the best transplantable material? Individually identified donors versus pre-screened donor stool versus manufactured synthetic stool? Investigations into this question, and their ultimate application, absolutely should be performed under the FDA’s watchful eyes, as should the application of FMT for all other indications, such as IBD, for which the data in support is far less extensive and less compelling than that for R-CDI. We do indeed favor FDA involvement in this emerging microbial transplant research, but we are saying quite specifically that for FMT for R-CDI, direct case-by-case FDA oversight was shown to be problematic, likely harmful and is no longer necessary.

It is appropriate for practitioners to provide FMT in their community, without the nearly insurmountable burden of an IND requirement.

REFERENCES


Physicians have always prided themselves in providing personalized health care. It therefore comes as a surprise to some to hear the term “personalized medicine” being used to describe a particular type of care. The term personalized medicine is currently used to describe the tailoring of medical treatment to the individual characteristics of each patient based on molecular, genomic and related -omic (pharmaco-genomics, epigenomic, proteomic, metabolomic ...) data. Other terms that are used include individualized medicine and precision medicine. Personalized medicine is about predicting, diagnosing and treating a disease based on each person’s unique clinical, genetic, genomic and environmental information. Often considered akin to “genomic” medicine, the interest in personalized medicine surged with the sequencing of the human genome in 2003.

Personalized medicine is a potentially transformational event in the practice of medicine; however, there still are considerable regulatory, reimbursement and technological hurdles to overcome before personalized medicine realizes its full potential. It is not to be confused with “genetic medicine”, which is an established field of medicine mostly examining mono-genetic disorders with more predictable and known inheritance pattern (e.g. sickle cell anemia, cystic fibrosis). Next generation sequencing techniques such as whole genome or exome sequencing and RNA-seq now allow a better understanding of more complex disorders such as cancer, heart disease and diabetes, which are believed to involve complex interactions between environmental factors and the human genome. The area that has impacted the clinical practice most at this time is pharmaco-genomics, using genomic data to deliver the right drug at the
The advantages offered by personalized medicine potentially include:

1. Predicting and preventing disease.
2. Early interventions to slow progression.
3. Developing more targeted therapies with better individual side-effect profile.
4. Enhance a patient’s ability to make more informed decisions.
5. Eventually reduce health-care costs by choosing the right drug earlier, reducing side effects, pursuing earlier and more accurate diagnosis and targeted therapies.

right dose at the right time, with targeted therapy for cancer also rapidly expanding. Gene panels based on next generation sequencing for disease areas (e.g. medications, cancer, cardiovascular) or specific diseases (e.g. colorectal cancer) are entering the practice at an increasing rate and will likely dominate the market for a few years before the widespread use of whole genome/exome sequencing.

The infrastructure and expertise needed to develop a personalized medicine program with application into clinical care is considerable (sequencing, conversion of huge data sets into actionable reports, calling variants as significant or not, storage and retrieval of genomic data, etc.), and this has limited personalized/individualized medicine approaches to integrated, tertiary-care academic medical centers. As our understanding of how to handle these complex and large datasets improves and as commercial entities develop a similar expertise, we will likely see diffusion of personalized/individualized medicine into primary care, especially in pharmacogenomics, cancer care and for diagnostic dilemmas. It however is absolutely critical to realize that the terms personalized and/or individualized do not only apply to data, they equally apply to patients, well persons and their relatives. Therefore, it is critical to have an in-depth discussion with the patient, preferably by a specialized genomic counselor, before proceeding with large gene panels or whole genome/exome sequencing to share decision making as the data gained through such analysis can have profound effects on their current and future care and on the well-being of their family members.

Within gastroenterology and hepatology, already there exist examples of how personalized medicine is used today. These include the use of routine thiopurine methyltransferase phenotyping and EMR-based algorithms to guide thiopurine use in IBD, the absence or presence of human anti-chimeric antibodies in guiding anti-TNF use in IBD, and detection of IL28B polymorphisms in predicting response to pegylated interferon-α plus ribavirin treatment in hepatitis C. Additional applications from genomics include the recent introduction of a 17-gene panel for patients with suspected hereditary colon cancer and the targeting of specific chemotherapy for cholangiocarcinoma. In addition to the host genomics and epigenomics, an individual’s microbiome and study of microbiota genomics and its effect on host should also be considered as a part of personalized medicine. There is significant interest in the role of gut microbiota on various luminal and other complex disorders including obesity, diabetes, rheumatoid arthritis and many other diseases. Studies of intestinal microbiome will likely become an integral part of personalized medicine and the gastroenterology community has an opportunity to play a significant role.

We are still at the beginning of the journey to deliver personalized/individualized medicine, a journey which will likely shape medicine for the coming decades. Many challenges remain including:

• Establishing an agreed upon depth threshold for adequate sequencing.
• Further reductions in the cost of sequencing and bioinformatics.
• Creating guidelines for the validation of tests based on next generation sequencing.
• Identifying patient population likely to benefit from individualized care.
• Generating, interpreting, visualizing and storing genome sequencing data that can be used for clinical care.
• Developing user-friendly support tools and practice guidelines.
• Getting insurance reimbursement for genomic testing.
• Ethical issues surrounding routine genomic sequencing and obtaining future health-care coverage.
• Psychological impact of having knowledge of genomic predictors and its impact on medical and personal decisions.

We believe that a careful selection of patients, diseases and drug targets will guide future research, early discovery and clinical practice. Additionally, institutional and extramural support and funding to conduct research on best ways to establish personalized medicine programs will be critical to achieve success in this area. We are privileged to be at the dawn of personalized/individualized medicine where the interface of our genomic discoveries and technological advancements are helping us realize the dream of achieving a model of medicine which is individualized to each patient and their illness.
Optical Imaging Technologies in Inflammatory Colitis

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Dr. Buchner has no relevant conflicts to disclose.

We are currently entering an era where our endoscopic tools with optical imaging may have potential in future not only to better detect, characterize and diagnose lesions in the settings of inflammatory colitis conditions, but also to predict behavior of the disease and measure functions of cells at a molecular level with response to drugs.

REFERENCES

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy allows in vivo histopathological imaging of intestinal mucosa at cellular and subcellular levels during endoscopy. CLE is based on tissue illumination with a low-power laser allowing 10,000 times magnification. To obtain images, fluorescence contrast is required, most commonly intravenous fluorescein. CLE is performed using one of two FDA-approved devices: endoscope-based CLE (eCLE) and a standalone through-the-scope probe CLE system (pCLE). In the settings of inflammatory colitis’ conditions, CLE systems should be used in combination with dye-based chromoendoscopy for detection and characterization of subtle mucosal lesions. This technique can have an important role in assessing the extension and the activity of disease and in targeting biopsies, improving the detection of dysplasia. Kiesslich and colleagues showed that using chromoendoscopy with endomicroscopy, the detection of neoplasia increased 4.75 fold with 50 percent fewer biopsies required.1 The presence of dysplastic changes in the settings of UC/Crohn’s colitis could be predicted by endomicroscopy with high accuracy, sensitivity and specificity of 97.8, 94.7 and 98.3 percent respectively.1 Another study by Gunther et al.2 concluded that, in the setting of IBD-related colitis, the targeted biopsies guided by eCLE led to much higher detection of dysplasia as compared to random biopsies protocol alone. Interestingly, a study by a Dutch group3 evaluated the feasibility and diagnostic accuracy of pCLE for dysplasia detection during surveillance colonoscopy in patients with long-term IBD; it did not reveal as optimistic results with the estimated accuracy, sensitivity and specificity of 81, 65 and 82 percent respectively. The prolongation of the procedure by 30 minutes, as well as the presence of good and excellent qualities of images only in 69 percent of patients with the use of pCLE were noted. Thus, future research should evaluate whether increased experience with these tools improves their ease of use and whether real-time diagnosis is associated with greater diagnostic accuracy.

CLE techniques play a role in assessing inflammatory activity in colonic mucosa and help to distinguish among various types of colitis. Neumann and colleagues,4 in their recent study of CLE and chromoendoscopy in Crohn’s, proposed a Crohn’s Disease Endomicroscopic Activity Score (CDEAS) to evaluate Crohn’s colitis activity in vivo based on typical inflammatory findings such as increased colonic crypt tortuosity, enlarged crypt lumen, microerosions, augmented vascularization and increased cellular infiltration within lamina propria. The inflammation activity of ulcerative colitis was also assessed using CLE by Li and colleagues.5 Their endomicroscopy evaluation of crypt architecture and fluorescein leakage correlated well with traditional histology.

Furthermore, optical imaging with CLE has been applied to investigate mechanisms of inflammation in IBD including bacterial interaction with the immune system and visualization of intramucosal enteric bacteria in vivo and loss of intestinal barrier. Ralph Kiesslich and colleagues have been evaluating the concept of cell shedding and increased epithelial gaps with bacteria penetration into the intestinal mucosa in predicting relapse of IBD. In IBD patients in clinical remission, increased cell shedding with fluorescein leakage was associated with subsequent relapse within 12 months after endomicroscopic examination.6
Endocytoscopy

Endocytoscopy is based on the technology of light-contact microscopy. It may provide up to 1100X magnification. These endoscopes can be easily passed through an accessory channel of the conventional therapeutic endoscope. This method uses topical staining such as methylene blue or cresyl violet. A recent pilot study by Neumann and colleagues showed that endocytoscopy can discriminate mucosal inflammatory cells during colonoscopy and thus may have a potential to assess disease activity.

Optical Coherence Tomography

Optical coherence tomography is another novel, high-resolution cross-sectional imaging modality with 2.5-3.5 mm depth of penetration that can generate images of colonic mucosa, muscularis mucosa, and submucosa and muscularis propria. Its potential role is to distinguish between ulcerative colitis and Crohn’s disease colitis. Bo Shen and colleagues investigated OCT imaging during colonoscopy and found it helpful in the differentiation of ulcerative colitis and Crohn’s colitis. The clinical application of this technology has major limitations including longer duration of real-time OCT colonoscopy, prolonged additionally by necessity of reviewing and interpreting OCT images at a later time, and the actual spatial resolution which does not allow a real-time diagnosis during colonoscopy.

Molecular Imaging

Finally, molecular imaging utilizes fluorescently labeled probes (antibodies or peptides) to highlight abnormal lesions based on their molecular signatures. Molecular imaging relies on visualization of biological properties of a lesion rather than just assessing its gross appearance, and also assessing the potential response to targeted therapy and visualize the interracial interaction of targeted drugs within the lesion. The recent in vivo human study by Schmidt et al. assessed the role of nano- and microscaled-particles for drug targeting to inflamed intestinal mucosa in patients with IBD. In this experiment there was a notable accumulation of microparticles in ulcerated mucosal lesions whereas nanoparticles were hardly visible in mucosal surface of all patients.

We are currently entering an era where our endoscopic tools with optical imaging may have potential in the future not only to better detect, characterize and diagnose lesions in the settings of inflammatory colitis conditions, but also to predict behavior of the disease and measure functions of cells at a molecular level with response to drugs. However, the available tools are not yet the standard of care and further studies are necessary to establish their benefits and their ease of use. We can certainly hope that in time these new tools will help us to diagnose dysplasia, assess inflammatory activity and guide the therapies of our patients with inflammatory colitis conditions.
In this guest column, at the invitation of AGA’s president, Anil K. Rustgi, MD, AGAF, I would like to explore the issue of care coordination between generalist physicians and subspecialists, using internists and gastroenterologists as my case in point. I am an internist at University of California, San Francisco (UCSF). While I focus on HIV, my patient panel runs the full gamut of internal medicine and I have ample opportunity to collaborate with my GI colleagues. Undoubtedly, my most common referral to GI is for screening colonoscopy but even in my “smallish” practice, I have many patients with serious chronic disorders of the liver and gut, including ulcerative colitis, hepatitis C, HIV-HBV co-infection with cirrhosis and recurrent iron deficient anemia with intermittent guaiac-positive stools in elderly patients.

As a resident in internal medicine, I was taught that there were four reasons to consult a subspecialist:

1. The patient presents a true diagnostic dilemma.
2. A procedure is required that internists don’t do.
3. There is a diagnostic or therapeutic decision to be made that requires more experience-derived judgment than a non-subspecialist can possess.
4. The patient has an interesting finding, an unusual presentation or a rare disease that the fellows should have a chance to see.

These still seem like pretty good rules to me. But many teachers have commented that residents are partitioning their patients, delegating their problems to the relevant subspecialist. Anemia? Heme consult. Ulcerative colitis? GI. Of course, this apportioning of the patient creates all kinds of problems: consultants from different subspecialties may make conflicting recommendations, access to subspecialists for patients who truly need subspecialty input is impaired, patients can’t figure out who their doctor is, to name just a few. And then there are problems in the other direction: the subspecialist schedules a follow-up appointment when I was just asking a question, the subspecialist refers our patient to another subspecialist for a problem I was managing, the subspecialist makes a host of medication changes without letting me know the rationale.

How can we work together to make the ever-increasing coordination and collaboration our patients require work better while we are getting busier and busier? The solution is not likely to be found in increasing individual effort. Rather we need systematic and structural approaches.

At UCSF we are experimenting with structured consultation/referral forms and what Justin Sewell, a UCSF gastroenterologist, has called “preconsultation exchange.” Both of these approaches have similar goals:

1. To “right-size” the intensity of the subspecialist’s involvement.
2. To make sure that the patient arrives at the subspecialty appointment with the studies needed to address the clinical question.
3. To ensure that both the referring physician and the consultant have a shared understanding of what the consultant is being asked to do and who is responsible for what going forward.

Structured referrals are electronic templates within our EHR. When I indicate that I would like to refer a patient to GI, I am offered a drop-down menu of scenarios, such as “abdominal pain” and “hepatic mass.” Once I have selected the circumstance, the subspecialist makes a host of medication changes without letting me know the rationale.

How can we work together to make the ever-increasing coordination and collaboration our patients require work better while we are getting busier and busier? The solution is not likely to be found in increasing individual effort. Rather we need systematic and structural approaches.

Structured referrals are electronic templates within our EHR. When I indicate that I would like to refer a patient to GI, I am offered a drop-down menu of scenarios, such as “abdominal pain” and “hepatic mass.” Once I have selected the circumstance, the template “coaches” me to provide results of relevant tests. If I refer a patient for advice about the further evaluation of patient with elevated transaminases, the template will auto-populate with the results of pertinent tests I have already obtained and remind me that I should order an antinuclear antibodies test and an
The day-long meeting, attended by 23 societies including the AGA, focused on exactly this issue. Meanwhile, the increasing focus on value-based payment structures, including bundled payments and shared savings, will reward both the referring physician and the subspecialist for effective, high-value referrals and consultations.

One last thing — and it is a sore point among many internists, as our gastroenterology colleagues surely know — when we refer a complex patient for a nuanced expert opinion and the patient is seen by a nurse practitioner (NP) or physician assistant (PA), rather than a physician. Before I take this further, let me say that in the years that I worked in the AIDS clinic at San Francisco General Hospital (SFGH) my favorite consultant for difficult points of HIV management was a PA. What I know about learning in the workplace has convinced me that the right individual, regardless of their formal training, can develop true expertise and nuanced judgment. But not everyone does. If having thought about a patient long and hard and deciding that I want to the opinion of Dr. Doe, I want Dr. Doe’s opinion, just as I would look for my PA colleague when I was working at SFGH. While several factors provoke the referring physician’s irritation when she refers a patient to a gastroenterologist and the patient is seen by an NP, the solution is simple: forging shared expectations prior to the visit, expectations that are shared by the referring doctor, the consultant and the patient.

I greatly appreciate the opportunity to write a guest column for AGA Perspectives and look forward to your comments. Let’s continue the conversation.
**DEXILANT WORKS A SECOND SHIFT TO HELP SHUT DOWN ACID PUMPS**

Conclusions of comparative efficacy cannot be drawn from this information.

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**Indications for DEXILANT (dexlansoprazole)**

- Healing all grades of erosive esophagitis (EE) for up to 8 weeks
- Maintaining healing of EE and relief of heartburn for up to 6 months
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks

**Important Safety Information**

- **DEXILANT** is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity and anaphylaxis have been reported with DEXILANT use.
- Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy.
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea.
- Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs.
- Most commonly reported adverse reactions were diarrhea (4.9%), abdominal pain (4.0%), nausea (2.9%), upper respiratory tract infection (1.9%), vomiting (1.9%), and flatulence (1.6%).
- Do not co-administer atazanavir with DEXILANT because atazanavir systemic concentrations may be substantially decreased. DEXILANT may interfere with absorption of drugs for which gastric pH is important for bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole). Patients taking concomitant warfarin may require monitoring for increases in international normalized ratio (INR) and prothrombin time. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Concomitant tacrolimus use may increase tacrolimus whole blood concentrations. DEXILANT may increase serum levels of methotrexate. Please see adjacent brief summary of prescribing information for DEXILANT. See prescribing information for DEXILANT for a complete list of adverse reactions.

**References:**

1. DEXILANT (dexlansoprazole) package insert, Takeda Pharmaceuticals America, Inc.
Published observational studies suggest that PPI therapy like DEXILANT may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see Adverse Reactions].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Bone Fracture

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (≥1 year). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the conditions being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [see Adverse Reactions].

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see Adverse Reactions].

Concomitant use of DEXILANT with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients [see Drug Interactions].

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of DEXILANT was evaluated in 4548 patients in controlled and uncontrolled studies, including 863 patients treated for at least 6 months and 203 patients treated for one year. Patients ranged in age from 18 to 80 years (median age 48 years), with 24% female, 86% Caucasian, 8% Black, 4% Asian, and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of EE, maintenance of healed EE, and symptomatic GERD, which included 896 patients on placebo, 455 patients on DEXILANT 30 mg, 2218 patients on DEXILANT 60 mg, and 1363 patients on lanensoprazole 30 mg once daily.

Most Commonly Reported Adverse Reactions

The most common adverse reactions (≥2%) that occurred at a higher incidence for DEXILANT than placebo in the controlled studies are presented in Table 2.
uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Blood and Lymphatic System Disorders:** autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura

**Ear and Labyrinth Disorders:** deafness

**Eye Disorders:** blurred vision

**Gastrointestinal Disorders:** oral edema, pancreatitis

**General Disorders and Administration Site Conditions:** facial edema

**Hepatobiliary Disorders:** drug-induced hepatitis

**Immune System Disorders:** anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal)

**Infections and Infestations:** Clostridium difficile associated diarrhea

**Metabolism and Nutrition Disorders:** hypomagnesemia, hypotremia

**Musculoskeletal System Disorders:** bone fracture

**Nervous System Disorders:** cerebrovascular accident, transient ischemic attack

**Respiratory, Thoracic and Mediastinal Disorders:** acute renal failure

**Skin and Subcutaneous Tissue Disorders:** generalized rash, leukocytoclastic vasculitis

**DRUG INTERACTIONS**

**Drugs with pH-Dependent Absorption Pharmacokinetics**

DEXILANT causes inhibition of gastric acid secretion. DEXILANT is likely to substantially decrease the systemic concentrations of the HIV protease inhibitors which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, DEXILANT should not be co-administered with atazanavir.

DEXILANT may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole).

**Warfarin**

Co-administration of DEXILANT 90 mg and warfarin 25 mg did not affect the pharmacokinetics of warfarin or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concurrently. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with DEXILANT and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

**Tacrolimus**

Concomitant administration of dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP3A4.

**Clopidogrel**

Concomitant administration of dexlansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of DEXILANT.

**Methotrexate**

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of high-dose methotrexate with PPIs have been conducted [see Warnings and Precautions].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Teratogenic Effects**

- **Pregnancy Category B.** There are no adequate and well-controlled studies with dexlansoprazole in pregnant women. There were no adverse fetal effects in animal reproduction studies of dexlansoprazole in rabbits. Because animal reproduction studies are not always predictive of human response, DEXILANT should be used during pregnancy only if clearly needed.

- A reproduction study conducted in rabbits at oral dexlansoprazole doses up to approximately 9 times the maximum recommended human dexlansoprazole dose (60 mg per day) revealed no evidence of impaired fertility or harm to the fetus due to dexlansoprazole. In addition, reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 40 times the recommended human lansoprazole dose and in pregnant rabbits at oral lansoprazole doses up to 16 times the recommended human lansoprazole dose revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

**Nursing Mothers**

It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for tumorgenicity shown for lansoprazole in rat carcinogenicity studies (see Nonclinical Toxicology), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

Safety and effectiveness of DEXILANT in pediatric patients (less than 18 years of age) have not been established.

**Geriatric Use**

In clinical studies of DEXILANT, 11% of patients were aged 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified significant differences in responses between geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Renal Impairment**

No dosage adjustment of DEXILANT is necessary in patients with renal impairment. The pharmacokinetics of dexlansoprazole in patients with renal impairment are not expected to be altered since dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole.

**Hepatic Impairment**

No dosage adjustment for DEXILANT is necessary for patients with mild hepatic impairment (Child-Pugh Class A). DEXILANT 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

**OVERDOSAGE**

There have been no reports of significant overdose of DEXILANT. Multiple doses of DEXILANT 120 mg and a single dose of DEXILANT 300 mg did not result in death or other severe adverse events. However, serious adverse events of hypertension have been reported in association with twice daily doses of DEXILANT 60 mg. Non-serious adverse reactions observed with twice daily doses of DEXILANT 60 mg include hot flashes, contusion, oropharyngeal pain, and weight loss. Dexlansoprazole is not expected to be removed from the circulation by hemodialysis. If an overdose occurs, treatment should be symptomatic and supportive.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

**Serum Gastrin Effects**

The effect of DEXILANT on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to 8 weeks and in 1023 patients for up to 6 to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with DEXILANT 30 mg and 60 mg doses. In patients treated for more than 6 months, mean serum gastrin levels increased during approximately the first 3 months of treatment and were stable for the remainder of treatment. Mean serum gastrin levels returned to pretreatment levels within one month of discontinuation of treatment. Enterochromaffin-Like Cell (ECL) Effects

There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 653 patients treated with DEXILANT 30 mg, 60 mg or 90 mg for up to 12 months.

During lifetime exposure of rats dosed daily with up to 150 mg per kg per day of lansoprazole, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats [see Nonclinical Toxicology].

**Effect on Cardiac Repolarization**

A study was conducted to assess the potential of DEXILANT to prolong the QT/QTc interval in healthy adult subjects. DEXILANT doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (moxifloxacin) produced statistically significantly greater mean maximum and time-averaged QT/QTc intervals compared to placebo.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg per kg per day, about 1 to 40 times the exposure on a body surface (mg/m²) basis (4-150 kg person of average height [1.46 m² body surface area (BSA)]) given the recommended human dose of lansoprazole 30 mg per day.

Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats [see Clinical Pharmacology].

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg per kg per day
In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 to 600 mg per kg per day, 2 to 80 times the recommended human lansoprazole dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg lansoprazole per kg per day (40 to 80 times the recommended human lansoprazole dose based on BSA) and female mice treated with 150 to 600 mg lansoprazole per kg per day (20 to 80 times the recommended human lansoprazole dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg per kg per day (10 to 80 times the recommended human lansoprazole dose based on BSA).

A 26-week p53 (+/-) transgenic mouse carcinogenicity study of lansoprazole was not positive.

Lansoprazole was positive in the Ames test and the in vitro human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, the in vitro mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. Dexlansoprazole was positive in the Ames test and in the in vitro chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the in vivo mouse micronucleus test.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg per kg per day (40 to 80 times the recommended human lansoprazole dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

**PATIENT COUNSELING INFORMATION**

See FDA-Approved Medication Guide

To ensure the safe and effective use of DEXILANT, this information and instructions provided in the FDA-approved Medication Guide should be discussed with the patient.

Inform the patient to watch for signs of an allergic reaction as these could be serious and may require that DEXILANT be discontinued.

Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea [see Warnings and Precautions].

Advise the patient to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany as these may be signs of hypomagnesemia [see Warnings and Precautions].

Advise the patient to tell their health care provider if they take atazanavir, tacrolimus, warfarin and drugs that are affected by gastric pH changes [see Drug Interactions].

Advise the patient to follow the dosing instructions in the Medication Guide and inform the patient that:

- DEXILANT is available as a delayed-release capsule.
- DEXILANT may be taken without regard to food.
- DEXILANT should be swallowed whole.
- Alternatively, DEXILANT capsules can be administered as follows:
  - Open capsule;
  - Sprinkle intact granules on one tablespoon of applesauce;
  - Swallow immediately. Granules should not be chewed.
  - Do not store for later use.
Chronic pain is the cardinal feature of chronic pancreatitis. Despite extensive research, understanding the cause of pain and, importantly, effective treatments for our patients is lacking. Acute pain generates a behavioral response to prevent further injury, and may activate immune responses to aid in resolution. However, chronic pain can be either maladaptive or salutagenic.

Maladaptive pain persists after resolution of injury, becoming the primary problem. In contrast, salutagenic mechanisms refer to specific modulation of the immune system induced by brain activation. That is, in response to pain, the brain can activate the immune system to assist with repair of a damaged or infected gland.

However, chronic inflammation of the pancreas may lead through sustained altered afferent visceral sensory input to changes in plasticity in the nervous system that eventually can become self-perpetuating, pancreas-independent and account for the disabling chronic pain. Furthermore, through salutagenic mechanisms, inflammation of the pancreatic gland may be perpetuated in an endless cycle. This can also be the result of activation of local pancreatic processes such as persistent stellate cell activation but additional central mechanisms may be at play leading to allodynia and/or hyperalgesia.
The perception of pain can be divided into three sequential anatomic regions based on the pathways that signal pain from the pancreas to the brain. The first area is inflammation within the pancreatic gland activating local nociceptors. The second area is activation of the dorsal root ganglia and dorsal horn within the spinal cord. The third is perception of pain by the brain.

In the first anatomic region, capsaicin-sensitive sensory neurons are activated in response to pancreatic inflammation. With chronic inflammation, sensitization can occur resulting in an exaggerated response leading to increased and persistent pain that may be out of proportion to what would be expected. Nerve growth factor, bradykinin, substance P and mast cells are just a few of the contributors to this process.

In the second anatomic region, transmission of pain impulses is then conducted through the dorsal root ganglion to the dorsal horn in the spinal cord. In the setting of chronic pain, neural remodeling through neuroplasticity within these structures contribute to the sensation of chronic pain and/or exaggerated pain independent of continued inflammation of the pancreas.

In the third region, it is likely that consequences of neural remodeling through neuroplasticity within structures in the brain that regulate proprioception result in the ongoing perception of pain and the response to medications.

Our group has shown that pain is represented in cortical SII within the right hemisphere of the brain in patients with chronic pancreatitis. Administration of a noninvasive method of brain stimulation called repetitive transcranial magnetic stimulation (rTMS) to this region resulted in less pain and decreased narcotic use. Using MR spectroscopy, levels of glutamate and N-acetyl-aspartate, neurometabolites shown to modulate cortical activity in the brain, were increased in response to rTMS and predicted improvement in pain. Although not the only site in the brain responsible for visceral pain perception, cortical SII has been shown to be activated with abdominal visceral pain as seen following esophageal or rectal distention.

A number of important questions remain. Can we better phenotype the etiology of pain in our patients with chronic pancreatitis in order to define which therapies will be efficacious in an individual? Will therapies such as rTMS or a less invasive approach called transcranial direct current stimulation (tDCS) be effective through modulation of central nociception? Will this lead to less immune activation and hence decreased pancreatic inflammation? Will the effects be sustainable or will chronic therapies alone or more likely in combination be required? One could view patients with chronic debilitating pain due to chronic pancreatitis as either “a pain” or instead, as an opportunity to truly alleviate pain and suffering using new technologies and thoughtful stepwise approaches, and to fulfill our oath as physicians.
Autoimmune pancreatitis (AIP) is a very gratifying diagnosis to make, not only because it avoids major pancreatic surgery for a benign disease, but also because it responds dramatically to medical treatment. However, diagnosis of AIP is a complex exercise in pattern recognition, akin to solving a jigsaw puzzle, wherein multiple pieces of evidence (the five cardinal criteria), weighted appropriately, need to fit into specific diagnostic combinations. The HISORt criteria and the more recent International Consensus Diagnostic Criteria (ICDC) highlight the five cardinal features of AIP (viz., characteristic pancreatic imaging, elevated serum IgG4, other organ involvement, typical histopathologic pattern and response to steroids) and their various diagnostic combinations. Here I will discuss the diagnostic role of two of these features: serum IgG4 and pancreatic histology.

In 2001 a landmark paper from Japan suggested that serum IgG4 elevation was highly sensitive and specific for AIP.1 Subsequent Japanese studies showed that other organs affected in AIP, such as retroperitoneum, salivary gland and kidneys, had infiltration with abundant IgG4-positive plasma cells. The term IgG4-related disease (IgG4-RD) has recently been introduced to describe an entity characterized by elevated serum IgG4 levels, tissue infiltration with IgG4+ plasma cells, a characteristic histology and a dramatic response to steroids. Type 1 AIP is the pancreatic manifestation of IgG4-RD.

These developments have given the impression that an elevated serum IgG4 is pathognomonic of AIP. However, the sensitivity of serum IgG4 for the diagnosis of AIP is only 65 to 75 percent. More importantly, in a recent study from Mayo Clinic,2 we found that elevated serum IgG4 is a poor predictor of the diagnosis of IgG4-RD; of more than 6,000 patients who had serum IgG4 measured, 6.5 percent had an elevated value and only 10 percent of those with an elevated serum IgG4 had IgG4-RD. Up to 10 percent of patients with biopsy-proven pancreatic cancer have elevated serum IgG4 levels. Thus, the positive predictive value of serum IgG4 can be as low as 10 percent if measured in a population with a low prevalence of AIP or IgG4-RD.

So, when do we measure serum IgG4 levels and what do we make of elevated levels? Just as it is not good medicine to measure serum CA 19-9 to diagnose pancreatic cancer in a patient with vague abdominal pain, similarly serum IgG4 should not be measured in patients unlikely to have AIP or IgG4-RD. In such patients, an elevated level will likely be a false positive and lead to a lot of unnecessary additional testing and therapy. And even when it is measured appropriately (e.g., in a patient with obstructive jaundice or pancreatic mass), its diagnostic value is determined by how well it fits with the other cardinal features of AIP to form a diagnostic pattern, as
... diagnosis of AIP is a complex exercise in pattern recognition, akin to solving a jigsaw puzzle ...

defined by the ICDC. Thus, serum IgG4 is only an adjunct to diagnosis of AIP; by itself, it is neither necessary nor sufficient to make the diagnosis.

Reduction in serum IgG4 in response to steroids should not be used to diagnose AIP after a steroid trial because even false positive serum IgG4 elevations “respond” to steroid therapy. Serum IgG4 is also not helpful for following patients on therapy as its levels do not correlate with response.

When is a pancreatic biopsy indicated to diagnose AIP? Among the five cardinal features of AIP, only pancreatic histology can independently diagnose AIP, even in the absence of other features. However, it is also the hardest to obtain. Fortunately, 80 percent of type 1 AIP can be diagnosed without pancreatic histology by identifying specific combinations of the other four features. Biopsy is indicated if you suspect type 1 AIP but do not have any or enough collateral evidence of AIP in the form of elevated IgG4 or other organ involvement to meet diagnostic criteria.

Additionally, the only way to definitively diagnose type 2 AIP is by pancreatic histology. Pancreatic biopsy can be obtained by endosonographic guidance, percutaneous CT guidance or intraoperatively. The diagnosis of AIP in small bits of tissue obtained by biopsy is also challenging and requires an experienced pathologist familiar with AIP. In our experience, only a small proportion of AIP need histology for diagnosis.

I diagnosed AIP for the first time in 1999. In the early years, the diagnosis of AIP was often made on retrospective review of surgically resected pancreata. Today, it is unusual for me to primarily diagnose AIP because it is being considered and confirmed at many centers across the country. Serum IgG4 and pancreatic histology have certainly helped immensely in this regard. When used judiciously, they can certainly be indispensable diagnostic tools for AIP.

REFERENCES

2. Ngwa et al. Pancreas (accepted for publication)
Before the industrial revolution, human dietary intake was extremely rich in natural compounds obtained from plants and fruits. In particular, the Mediterranean diet has been traditionally characterized by unsaturated fats and a variety of phytochemicals coming from fruits, vegetables, whole grains and virgin olive oil. However, each geographical area has its favorite phytochemicals: in Asia, many phytochemicals present in spices, such as curcumin, and polyphenols in fruits and teas have constituted a central role in the dietary patterns of hundreds of millions of people over the centuries.

The 20th century has been characterized by an incredibly fast-growing change in dietary habits, coming from industrialized world and rapidly expanding throughout the planet. The abrupt switch toward the so-called Western diet (refined grain, animal proteins, low amount of fruits and vegetables, saturated fats) has led to a dramatic modification of the digestion by-products reaching the colon. This dietary modification has significantly contributed to the increase of colon cancer incidence. In fact, it is strongly believed that a westernized dietary pattern is a key contributor to colorectal cancer, which is one of the leading causes of cancer incidence and death worldwide.

In recent years, increased incidence rates have also been observed in countries where dietary habits have protected toward colon cancer development thus far, in particular those rapidly moving toward a Western lifestyle and dietary pattern, including Southern Europe and Japan. To corroborate this hypothesis, recent epidemiological data have confirmed that subjects following a strict
Mediterranean diet are protected from distal colon cancer, indicating that phytochemicals present in plants, fruits, virgin olive oil and fish could have led to strong chemopreventive effects over years of consumption.

To understand the reasons for this beneficial effect it should be remembered that there has been a continuous co-evolution process between the microflora and the human gut which have adapted to the type of phytochemicals ingested, in particular non-digestible phytochemicals which are metabolized into final products with undisputed anti-inflammatory capabilities. The gut microflora have learned how to employ phytochemicals and used them to establish the most favorable host-bacterial relationship. The adoption of the Western diet has rapidly led to the replacement of saprophites with pathogens, which we are now understanding as being critically involved in the development of obesity, metabolic syndrome and ultimately cancer.

Given the difficulties in the development of new synthetic agents suitable for cancer prevention, researchers are now focusing more and more on the use of natural compounds. However, in the search of possible chemopreventive agents, researchers have consistently tried to narrow the epidemiological data to single candidates in order to develop some sort of "magic pill" with disappointing results when applying the molecules in human trials. In the attempt of switching from pharmacological to dietary approach, it is critical to understand that food chemoprevention is a matter of whole diet and not of single molecules or even a single food. To favor the health-promoting equilibrium of the gut microbiota, it is necessary to provide manifold of phytochemicals and non-digestible polysaccharides. Importantly, one key issue is that this process takes a long time to be achieved.

From a molecular standpoint, it is known that colorectal cancer is characterized by a constellation of molecular events leading to at least three different pathways. In the same way, while multiple phytochemicals have redundant activities, it is highly improbable that one of them could have effects on all the pathways involved in colon cancer pathogenesis. On the other hand, the combination of multiple phytochemicals can lead to previously undisplayed molecular effects. Scientists are looking for new ways to demonstrate chemopreventive effects on colon cancer development. Preclinical models are designed to demonstrate positive effects in a very short time, using phytochemical concentrations that cannot be adopted by humans. Promising results have been obtained using the combination of multiple phytochemicals in order to reduce toxicity and enhancing synergisms, thus resembling a more "natural" approach to prevention. In fact, our experience has shown that whole plant and fruit extracts or combination of bioactives exert strong preventive effects toward colon cancer in animal models at concentrations much lower than those obtained using single compounds.

It is time to give up the idea of finding a single compound with anticancer effect; we should focus on more natural ways of preventing colorectal cancer that should be very well received by consumers. Also, food industries must contribute to this effort by designing food rich of phytochemicals and non-digestible polysaccharides tailored to modulate gut microbiota.
There is no way to overlook the challenges facing tomorrow’s gastroenterologists — a shrinking workforce and reimbursement combines with expanding patient loads, educational debt and regulatory requirements to create a perfect storm for my generation of physicians. The AGA has recognized these challenges and created a committee entirely devoted to young gastroenterologists — the AGA Trainee and Young GI Committee. In this AGA Perspectives article, the first in a series focused on trainee and young GI members, I’ll discuss the background of the new committee and the exciting initiatives we have planned to address the needs of our peers.
BACKGROUND

The foundation of the committee began with the realization that retention rates among younger members were declining. This led to a series of interviews and surveys suggesting that the needs of young GI physicians were not being met with current society programs. The AGA Governing Board responded to this research by convening a task force composed of existing young AGA committee members including myself, which met during the 2012 joint committee meetings. Together with senior leadership, we discussed the results of the research, reviewed existing AGA initiatives and compared these to other professional society programs. We identified potential avenues through which to address priority areas and chose to pursue one item for the spring — hosting a fun, casual networking event during Digestive Diseases Week® (DDW) 2013 in Orlando, FL.

The task force noted that several high-quality programs already exist, including the Gastroenterology Training Examination (GTE®), Digestive Diseases Self-Education Program® (DDSEP), the AGA Trainee & Young GI Track at DDW, GI Self-Assessment Modules (GI SAM®), core curriculum chapter highlights, practice skills and academic skills workshops, an online procedure log, the AGA Mentor and Advisor Program, and the newly released online modules, “Are You Ready? What Every GI Fellow Should Know About Choosing a Clinical Practice” and “Going Into Practice — A Guide for the GI Physician.” These programs are valued by existing members; however, lack of coordination between programs, lack of awareness among members and non-members, and lack of long-term engagement of members may limit their impact.

Additionally, the research showed a significant shift in how younger members view the value of professional societies. Increasingly, young physicians are able to meet their professional needs through online or other services. They are therefore less likely to join professional societies due to a decreased perception of value; i.e. the advantages of membership don’t always outweigh the costs. With competition for young gastroenterologists’ time and money, it is important to identify and develop high-value, high-priority services.

FORMING THE INAUGURAL COMMITTEE

Several promising ideas were generated from the task force. The AGA Trainee and Young GI Committee was formed in recognition that implementing these broad-reaching ideas would require dedicated time and resources. The young members of existing AGA committees were in ideal positions to fill this role.

The committee held a pre-meeting teleconference in the weeks leading up to DDW 2013. In Orlando, we convened our first committee meeting in the wee (and I do mean wee) hours to discuss the ideas generated during the task force session as well as to brainstorm additional projects. The excitement carried over to our networking event held at B.B. King’s Blues Club. At the event, we distributed a survey that asked participants to rank items on which they wished us to focus in the coming year. The event was a great success, drawing more than 150 young members and yielding valuable results from the survey.

SETTING ITEMS INTO MOTION

Based on our initial meeting and the survey we distributed, we identified the following priorities for the coming year:

1. Partner with the GTE subgroup of the AGA Institute Education and Training Committee to create directed, individualized post-exam feedback and remediation.
2. Pilot regional practice skills/"going-into-practice" events targeting fellows who are planning their post-graduate job search.
3. Continue the momentum from DDW 2013 with a second networking event in Chicago at DDW 2014.

We have also partnered with other AGA committees to co-sponsor pertinent sessions at DDW 2014, to enhance the DDW AGA Trainee & Young GI Track, and to contribute to Gastroenterology’s Mentoring, Education and Training (MET) Corner. Finally, we proposed a series on advanced gastroenterology fellowship training which will be featured in the “Fellows Corner” of AGA Perspectives.

GOING FORWARD

The current health-care environment presents quite a challenge to young gastroenterologists, and as members of the trainee and young GI committee, we are deeply committed to affecting positive change for our peers. It is an exciting time to be a member of the AGA, and we look forward to showcasing our new, dynamic programming in the years to come.

ARE YOU READY?
What Every GI Fellow Should Know About Choosing a Clinical Practice

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Passionate about AGA and the Research-Fueled Renaissance in the Understanding of IBS

Michael Camilleri, MD, AGAF
Vice President, AGA Institute; Mayo Clinic College of Medicine, Rochester, MN

I make no apology in claiming that the focus of my passion, clinical work and research is neither trendy, nor easy, nor popular among fellows and gastroenterologists. Yet, functional GI and motility disorders are arguably one of the most relevant groups of disorders bringing patients to gastroenterologists. Some estimate that they account for 50 percent of consultations to gastroenterologists and 25 percent of visits to primary care physicians. There is unmet clinical need, large indirect costs, absenteeism or presenteeism for patients, as well as a “heart sinking” feeling for doctors encountering these patients. Progress in this field has been difficult, and the speed bumps have included focus on symptom-based diagnosis rather than understanding of patho-physiological mechanisms, excessive regulatory focus on patient response outcomes, and lack of funding.

However, I perceive that my own experience has paved the way to shape how clinicians diagnose and care for patients with gastroparesis, dyspepsia, IBS, chronic constipation and diarrhea, and has helped to develop the drugs that are used widely in practice today.

AGA Research Funding Enables Renaissance in IBS Understanding

With research funding from the AGA Research Foundation, my team at the Mayo Clinic has made significant strides in applied, patient-oriented gastroenterology research. In 1992, I received a grant from the AGA Research Foundation and used those resources to develop noninvasive imaging methods to study patho-physiology and to understand mechanisms that modify motor functions of the stomach, small bowel and colon. With these crucial validation studies, our research and diagnostic tests in the field of motility no longer depended on the passage of tubes down the throat, which was uncomfortable, invasive and sometimes so stressful that the observed changes might have been attributable to the psycho-sensory perturbation rather than the disease state.

We introduced these gamma scintigraphic methods into clinical practice and used these measurements as biomarkers of disease and response to therapies in development for colonic motility disorders or IBS. We predicted correctly (current count 12 for 12) which drugs would go on to regulatory approval and
marketing and those which did not make the grade in clinical trials. The approved drugs are: LOTRONEX®, Zelnorm®, AMITZA, Linzess™ and RESOLOR®.

Subsequently, a method was developed and validated to measure gastric volumes noninvasively, and we introduced these tests into clinical practice to assess symptoms of dyspepsia and gastroparesis.

With these validated measurements, I was fortunate to receive funding from NIH to study adrenergic and genetic mechanisms in the control of motor, sensory and autonomic functions in IBS, and the genetic control of gastric motor functions and satiation in obesity.

I was then at a crossroads in my career: I wanted to start to understand the intraluminal and mucosal factors involved in IBS. Fortunately, I received the AGA-Miles & Shirley Fiterman Foundation Joseph B. Kirsner Award for Distinguished Achievement in Clinical Research in Gastroenterology. I was deeply honored to receive this award in the presence of Dr. Kirsner, arguably one of the giants of patient-oriented research in the last century. This award allowed us to investigate intraluminal content (initially bile acids and, more recently, short chain fatty acids and the microbiome) and mucosal barrier and immune functions in order to complement the studies of motility and sensation and comprehensively explore the peripheral functions that could be altered in IBS. As an integrative physiologist, I believe that understanding the inter-relationships of these diverse quantitative traits is essential if we are to have an impact on the diseases that we are trying to cure sometimes, to relieve often and to comfort always.

The work of many groups around the world has demonstrated that there are other peripheral mechanisms that can be targeted to improve current treatment outcomes, including permeability, immune activation, hypersensitivity, bile acids and the microbiome. Just as fecal microbial transplants are having dramatic effects on colonic infections, it is conceivable that the restoration of balance among these intraluminal mechanisms may pave the way for significant advances in patient care.

As gastroenterologists, we are heading for a time when there will be less emphasis on the procedural, and more on the “cognitive” practice. If we are to preserve our place as the preferred caregivers for gastroenterological disorders, we need to make sure that we can offer patients more than another negative colonoscopy.

**Conclusion**

It is now my turn to give and support the renaissance in cognitive gastroenterology. On my first travel to a research meeting in Europe in 1978, my first mentor advised, “Make sure you give to academic gastroenterology at least as much as you take from it.” I am now fortunate to be a servant leader of AGA, and I invite you to join me in supporting the AGA Research Foundation, which plays an important role in mentoring and academic development of young investigators. I am confident this effort will jump-start other gastroenterology trainees’ careers, whether they come from a Mediterranean island (as I do) or somewhere else in the U.S. or the world.
AN OPEN LETTER TO THE GI COMMUNITY

We’re Setting the Record Straight on Colonoscopy

It has been a tough summer for colonoscopy. Reports in the New York Times, USA Today, Washington Post and a study in JAMA Internal Medicine have challenged how colonoscopy is billed to patients and the physician time involved in these procedures.

The gastroenterology societies are educating policymakers and patients that colonoscopy is a good deal and that gastroenterologists provide lifesaving care with integrity.

• Thanks to screening, fewer people than ever before are developing or dying from colorectal cancer. Recent publications continue to demonstrate the sustained benefits of a colonoscopy. The GI community is proud of our role in this public health success story.

• Medicare pays gastroenterologists only $220 on average for our time, expertise and clinical care. That is certainly not excessive for a complex and invasive procedure that prevents cancer and saves lives. Colonoscopy can prevent many cancers, thereby avoiding the high cost of cancer care in many cases.

• Primary care physicians question the gap between payment for cognitive and procedural services, such as colonoscopy. As specialists who provide valuable cognitive services, we recognize that these services may well be underpaid.

The economics of health care in the U.S. are highly complex with many factors driving costs, but payment to gastroenterologists for colonoscopy is not one of them.

As gastroenterologists, we know firsthand that colonoscopy is one of the most effective cancer prevention tools in clinical medicine, preventing the second leading cause of cancer-related deaths in this country.

WORKING TOGETHER

The gastroenterology societies are committed to working together to improve the quality and affordability of health care for all Americans. We support the three-part aim of the National Quality Strategy: better care, affordable care, and healthy people and communities.

There are no easy solutions to the rising costs of medical care in the U.S. Our first priority is providing safe, high-quality care to our patients.