CHIEF'S CORNER

Anil K. Rustgi, MD
T. Grier Miller Professor of Medicine & Genetics
Chief, Division of Gastroenterology

The gastroenterology team at the University of Pennsylvania School of Medicine and University of Pennsylvania Health System is nationally recognized for clinical research and state-of-the-art care for our patients. In this issue, I wish to highlight some of the recent achievements and honors awarded our GI faculty.

Kyong-Mi Chang, MD: W.W. Smith Charitable Trust award for her pioneering research in viral hepatitis C. Also elected into the American Society of Clinical Investigation (ASCI).

Linda Greenbaum, MD: American Liver Foundation grant for research in liver regeneration.

David Kaplan, MD: Veterans Administration research career development grant for research in hepatitis C and liver cancer.

David Katzka, MD: Appointed to chair the American Gastroenterology Association's (AGA) CME committee.

Michael Kochman, MD: American Society of Gastrointestinal Endoscopy (ASGE) award for research in combined endoscopic/surgical approaches (NOTES).

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James Lewis, MD, MSCE: National Institutes of Health (NIH) K24 (Mid-career Investigator Award in Patient-Oriented Research) career mentorship award.

Gary Lichtenstein, MD: Course director of the Fifth Penn Inflammatory Bowel Disease Symposium, March 23 - 24, 2007.

Michael Pack, MD: Elected to a permanent NIH study section.

K. Rajender Reddy, MD: Principal Investigator of the National Institutes of Health trial on silymarin as a therapy for hepatitis C (Penn is one of four participating centers nationwide). **www.synchtrials.org**

Ben Stanger, MD, PhD: Published a key study in the January 28, 2007 issue of *Nature*, "Organ size is limited by the number of embryonic progenitor cells in the pancreas but not the liver."

Gary Wu, MD: Published an important study in the November 2006 issue of *Journal of Clinical Investigation*, "Absence of bacterially induced RELMß reduces injury in the dextran sodium sulfate model of colitis."

Yu-Xiao Yang, MD, MSCE; David Metz, MD; James D. Lewis, MD, MSCE, *et al*: Published an important study in the December 27, 2006 issue of the *Journal of the American Medical Association (JAMA)*, "Long-term proton pump inhibitor therapy and risk of hip fracture."

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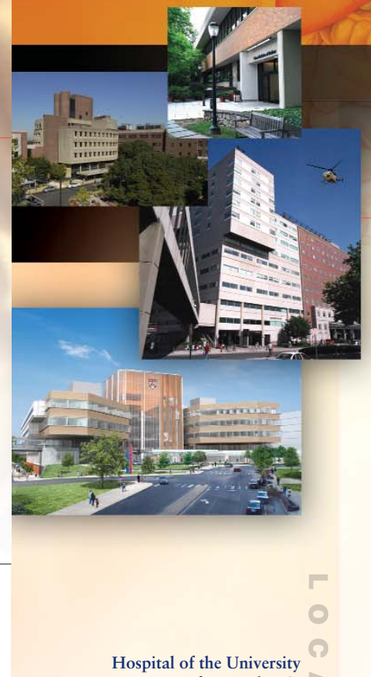
University of Pennsylvania Health System
Penn Digestive & Liver Center

GASTROENTEROLOGY NEWSLETTER



INFLAMMATORY BOWEL DISEASE:
Minimizing Infectious Complications of Immunosuppressant Use

Faten Aberra, MD, MSCE

Infection, a leading complication of inflammatory bowel disease (IBD) and its treatment, has been cited in population studies as a cause of death among IBD cohorts in the United States and Europe. Treatment of IBD commonly requires immunosuppressants such as corticosteroids, 6-mercaptopurine, azathioprine, infliximab, methotrexate, and cyclosporine. A variety of investigations have shown a strong association between immunosuppressant use and infection in patients with IBD.

Corticosteroids

A critical part of IBD treatment since the 1960s, corticosteroids have been linked to numerous side effects, including infection risk, that increase with long-term use.

Penn physicians have initiated several studies to examine the implications of corticosteroid use in patients with IBD. These include an investigation of the risk of postoperative infectious complications in IBD patients treated with corticosteroids and/or 6-mercaptopurine/azathioprine prior to elective intestinal surgery. This study revealed an increased risk for postoperative infections in patients on corticosteroids at the time of surgery. The risk increase was dose dependent, suggesting that corticosteroids should be tapered to the lowest dose possible prior to surgery.

A study published by Penn Professor of Medicine Gary Lichtenstein, MD, et al, found that corticosteroid use was associated with more serious infections in patients with Crohn's disease treated with infliximab. The study utilized a national registry of Crohn's disease patients, and reinforced the importance of minimizing the duration and dose of corticosteroids. Dr. Lichtenstein is Director of the Center for Inflammatory Bowel Diseases at the University of Pennsylvania.

A review of the inflammatory and noninflammatory bowel disease literature concerning infection risk with corticosteroid use suggests that 10 mg prednisone daily for less than two weeks is best for reducing potential infectious complications. Tapering the dose of corticosteroid during this brief period is a matter of practitioner preference. Adrenal suppression may occur as early as five days or as late as three weeks for prednisone doses greater than 20 mg daily. If a patient has been on chronic corticosteroid preoperatively it is likely best to reduce the corticosteroid to the lowest dose to control disease.

Infliximab

Patients with IBD receiving infliximab should complete PPD testing to evaluate for exposure to tuberculosis; a chest X-ray should be completed in subjects with high suspicion for tuberculosis. Unfortunately, PPD testing is far from perfect in the IBD population due to anergy, likely from immunosuppressants other than infliximab. In one study, 71 percent were anergic. A positive PPD skin test in IBD patients on immunosuppression is ≥ 5mm. In patients with latent TB infection, isoniazid therapy for at least six months in adults and nine months in children should be given. Treatment with rifampin may be considered if isoniazid is not tolerated or the patient is suspected of having isoniazid-resistant latent

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2007 GASTROENTEROLOGY NEWSLETTER

ESOPHAGEAL CANCER:

Penn Advances Care Through a Team Approach

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The University of Pennsylvania Health System and University of Pennsylvania School of Medicine are dedicated to advancing knowledge of the factors that cause esophageal cancer and using this knowledge to improve diagnosis and therapy of this cancer.

Esophageal cancer is the seventh leading cause of cancer death in the Western world, and is diagnosed in more than 15,000 persons in the United States each year. Most cases are one of two major types: squamous cell carcinoma (SCC) or adenocarcinoma (AD). The risk factors for esophageal SCC include chronic cigarette-smoking and/or alcohol consumption. These factors can be exacerbated by certain nutritional deficiencies. Esophageal AD is the result of chronic gastro-esophageal acid reflux. Chronic exposure to acid in the esophagus can lead to a condition called Barrett's esophagus, in which precancerous and cancerous lesions develop. Obesity, alcohol use, and cigarette smoking can exacerbate esophageal AD; bile reflux from the duodenum has also been implicated in the disease. Both esophageal SCC and AD can be present in families, although this is not the common situation.

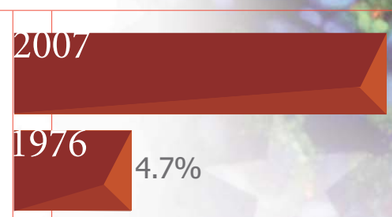
Staging and Diagnosis

Endoscopic diagnosis, staging, and therapy are key components in the appropriate management of patients with esophageal cancer. The evaluation of these patients often begins with an upper endoscopy to evaluate abnormal findings on x-ray imaging, dysphagia, or reflux symptoms. During the endoscopy, biopsies are taken to make a tissue diagnosis. Adjunctive vital stains such as Lugol's Solution and methylene blue may be used to help define the extent of the lesion and to aid in the selection of appropriate candidates for endoscopic therapy.

Endoscopic ultrasound (EUS) is a valued diagnostic tool for esophageal cancers. At the University of Pennsylvania Health System, the use of EUS is orchestrated by a team of nationally renowned physicians, including Drs. Greg Ginsberg, Michael Kochman and Nuzhat Ahmad.

EUS is often used in conjunction with cross-sectional imaging (e.g. CT scan) to aid in the staging evaluation and to determine candidacy for surgical and endoscopic therapy. EUS-guided fine-needle aspiration (FNA) provides biopsy samples of the lymph nodes and accurately determines the metastatic spread of tumor, which may allow for neoadjuvant therapy or preclude surgical resection. EUS-FNA can also aid in documentation of extraluminal tumor recurrence.

Patients who have dysphagia post-resection may have either anastomotic strictures or tumor recurrence. Endoscopic dilation can relieve the stricture. Among patients who are not candidates for surgery endoscopy, localization for brachytherapy and restoration of luminal patency with dilation and esophageal endoprosthetic placement can aid in tumor management.



Based on SEER information, the 5-year survival rate for esophageal cancer in the U.S. increased from 4.7 % in 1976 to 14.9 % in 2007.

Esophageal Cancer 5-Year Survival

At the University of Pennsylvania Health System, the treatment of esophageal cancer involves an outstanding group of dedicated gastroenterologists, medical oncologists, radiologists, radiation oncologists, surgeons, pathologists, nutritionists, speech therapists, and social workers, and other team members.

Treatment

During the last two decades, the overall survival of esophageal cancer patients has continuously improved because of a better understanding of the disease and development of new anti-cancer agents. A multidisciplinary approach to the treatment of patients with esophageal cancer is the key to success.

Early stage lesions verified with EUS are amenable to endoscopic therapy, often with curative intent with thermal ablative technologies or endoscopic mucosal resection (EMR). It has been demonstrated that preoperative chemotherapy or chemoradiation therapy in patients with locally advanced disease may improve the rates of surgical resection, as well as overall survival. Nutrition and psychosocial support are essential for patients to maintain a good quality of life.

For distant metastatic disease, newer systemic chemotherapy agents (eg, paclitaxel, docetaxel, gemcitabine, irinotecan, and oxaliplatin) have improved overall response rates by 50 to 60 percent, and have extended median survival to 10 to 14 months with gains in quality of life. A recently formed patient advocacy board helps patients navigate the issues underlying esophageal cancer.

Clinical Trials in Esophageal Cancer

The National Cancer Institute funds an innovative program project entitled "Mechanisms of Esophageal Carcinogenesis" (Anil K. Rustgi, MD, Principal Investigator; Dr. Wafik El-Deiry; Dr. Meenhard Herlyn). It is the only study of its type in the U.S. designed to bring advances in basic science research to the bedside. Through the development and characterization of new model systems in the research, it is hoped that patients and their families can benefit.

RESOURCES

For Penn's GI division academic website:
www.uphs.upenn.edu/gastro
For the Penn Abramson Cancer Center website:
www.pennhealth.com/abramson
For Penn's cancer information:
www.oncolink.org
For the NCI program project on esophageal cancer at Penn:
www.uphs.upenn.edu/gastro/nci_project

INFLAMMATORY BOWEL DISEASE:

Minimizing Infectious Complications of Immunosuppressant Use

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tuberculosis. Patients treated for latent-TB may be considered for infliximab therapy.

Azathioprine, 6-mercaptopurine, and methotrexate

Patients using azathioprine, 6-mercaptopurine, and methotrexate should be routinely monitored for leukopenia, which may affect the severity of infection. Cases of leukopenia have also been reported in patients using infliximab, although the mechanism is not known. The risk of infection in leukopenic versus non leukopenic IBD patients using these medications is not known. Patients in endemic regions for opportunistic infections such as histoplasmosis should be routinely screened for symptoms.

Other Infectious Complications in IBD

Pneumocystitis carinii

Only a few cases of *P. carinii* have been reported in IBD treated patients, based on findings in other diseases treated with similar immunosuppressants. Patients on multiple chronic immunosuppressants may be considered for PCP prophylaxis. Trimethoprim/sulfamethoxazole 160/800mg PO three times per week is recommended. In endemic regions of histoplasmosis or coccidioidomycosis, prophylaxis has not been routinely recommended in patients on multiple immunosuppressant medication, but may be considered.

Tuberculosis

In patients using anti-inflammatory or immunomodulator therapy, there should be a low threshold for obtaining a chest X-ray among those presenting with cough or other respiratory symptoms, a urine analysis at minimum for any new urinary symptoms, or cross-sectional imaging for new perianal/rectal pain.

Vaccination

Published immunization guidelines provide parameters for the vaccination of patients with IBD receiving immuno-suppressant therapy. According to these guidelines, immunization with live vaccines (including measles, mumps, rubella, live attenuated influenza and smallpox) is contraindicated in patients with IBD receiving immunosuppressants. The rabies, typhoid, varicella, BCG, and yellow fever vaccines should also be avoided in patients receiving chronic immunosuppression.

IBD Immunization Guideline Recommendations

- Influenza trivalent inactivated vaccine is preferred over the live attenuated vaccine in patients receiving immunosuppression.
- Varicella virus vaccine should not be administered to persons receiving immunosuppressive therapy due to the potential for an extensive associated rash or disseminated disease. This contraindication does not apply to patients receiving corticosteroid-replacement therapy.
- Patients recently exposed to primary varicella infection who have not had varicella should be considered for vaccine within five days of exposure.
- Although patients on immunosuppression have been shown to have a decreased immune response to vaccines, they should still be vaccinated.
- Periodic vaccines to be considered include the influenza and pneumococcal vaccines. Vaccines for hepatitis A and B may be considered based on the individual's risk.

IBD

Nationally recognized physicians within the IBD section of the division of gastroenterology at the University of Pennsylvania Health System provide services at the Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, and Penn Medicine at Radnor.

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Christopher Gasink, MD
Gary Wu, MD