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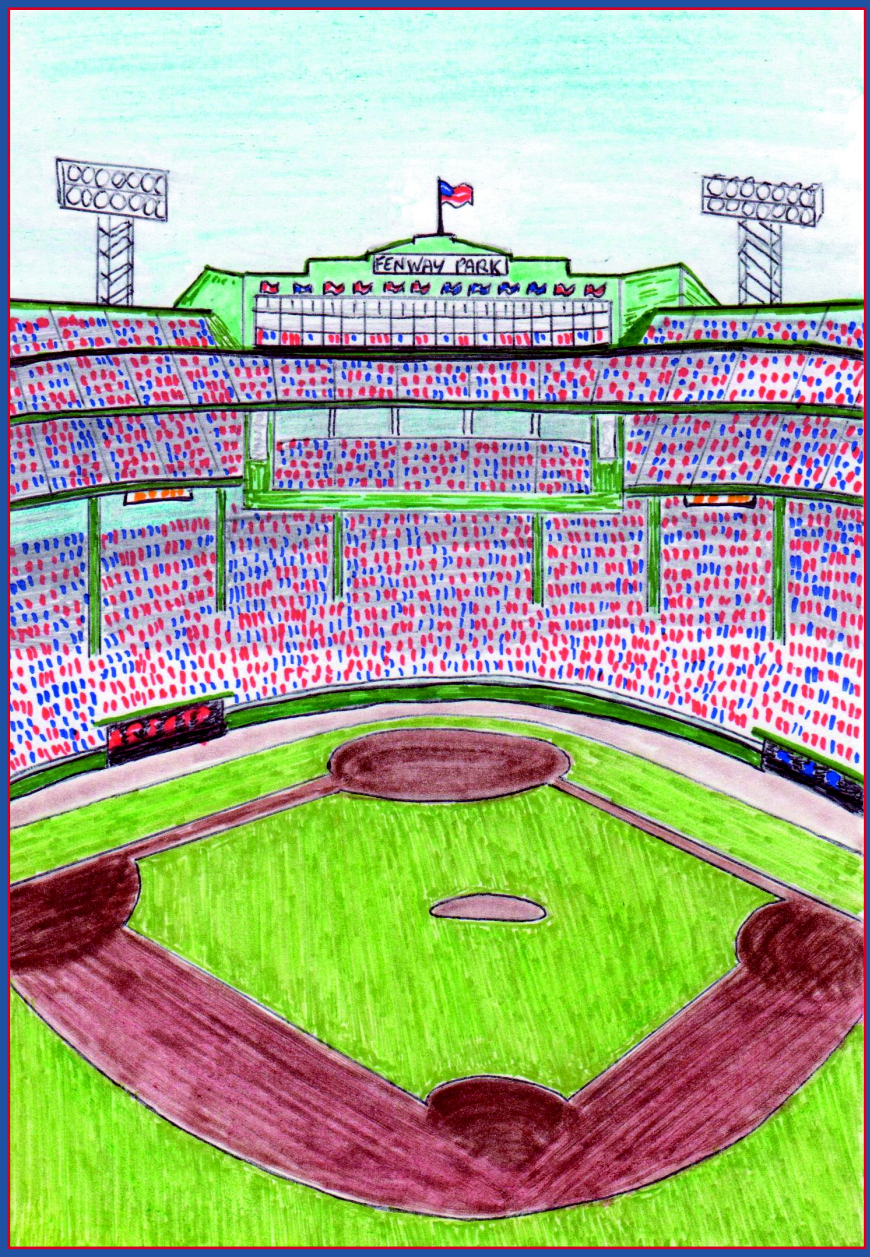


# Inflammatory Bowel Disease (Part II)

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*Cover:* "Fenway Park" drawing on paper by Sophie Lowery, a Charletown, MA-based artist who has exhibited in RI. Her acrylic paintings feature landscapes and seascapes of New England and her native France. Her website is http://www.loweryart.com. Reproductions of antique medical illustrations are available on her other website http://www.AntiqueAnatomy.com.

**Medicine & Health RHODE ISLAND**

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## COMMENTARIES



## CONTRIBUTIONS

**SPECIAL FOCUS: Inflammatory Bowel Disease (Part II)**
***Guest Editors: Samir A. Shah, MD, FACG, and Edward R. Feller, MD, FACG***



## COLUMNS



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# Commentaries

## Why People In RI Won't Drive Far: A Scientific Explanation

**People in RI don't like to drive long** distances. It's not that they don't like to drive. They do. But if you ask them to drive several miles, the common response is, "I can't do that. It's too far."

When we started recruiting for DATATOP in the late 1980s, the first study ever done to attempt to slow progression of **Parkinson's disease (PD),** it got national press because it was, potentially, a landmark study. It was the first study of any progressive neurological disorder in which the goal was to slow disease-progression. Someone in Newport called me, asking to be in the study. "Will you come down to Newport?" "No, you'll have to come to Providence." "How often?" "Every three months." "That's too far. If you come to Newport I'll be happy to participate."

Ten percent of adults who were born in Woonsocket have never been to Providence; 18% have never been to Boston (informal estimates).

I recently saw a patient from Oklahoma who was visiting his daughter in RI. He wanted me to be his Parkinson's disease doctor. I suggested finding someone close to home. He asked me to recommend someone. I said that I didn't know anyone in Oklahoma, so I asked him to name the large cities nearby in other states. "Dallas is only a five hour drive. Do you know anyone there?"

It has been noted time and time again that Rhode Islanders refuse to drive "long distances." In most studies (references available on request) this distance is usually about 10 miles but has been as far as 13. It is widely believed that this is learned behavior; however, we have observed that children born of native Rhode Islanders (defined as being born in RI and raised in the state until age 16), who were adopted and raised in families outside of RI, even taken out of the state within days of birth, never having met their biological parents, still won't drive more than 10 miles, on average.

Letters from the early 1800s suggest that this phenomenon was well-recognized, although transportation difficulties made this behavior less deviant in those days. Jebediah Culls, for example, notes in a letter, that the drive in his horse-drawn cart from Newport to Middletown might take him over 2 hours, which was "way too far" to consider, despite not having seen his son or grandchildren in over a year. Mary Chace noted with grief that her daughter, Elizabeth, had settled "wicked far" away, so that she and her husband may not ever see the daughter again, although the Indians in the region considered the distance less than a day's walk. The number of offspring produced by just these two families was 25, with almost all surviving into adulthood.

At ten polling stations in the 2008 presidential election, the RI Deviant Behavior Study Group distributed the **RI Travel Questionnaire (RITQ)** to all voters who had at least one parent born in RI. Respondents did not have to have been born in RI. The RITQ asked respondents to record on a visual analog scale how far they considered certain distances, from 10 to 100 miles using increments of 10 miles, and then from 25 to 500 miles using increments of 25 miles (very near, near, not too far, far, very far, too far). They were than asked how likely they would be to drive 25, 50 or 75 miles in each of three situations: (1) to take their child to a soccer game, (2) to visit a close friend in the hospital, (3) to see the only doctor in the world who could save them from some dread disease. The same questionnaire was given to other RI voters whose parents were both born outside of RI but who grew up in RI. The questionnaire finally was given to voters at 10 polling places in Ohio whose parents were not born in RI and who themselves had never been to RI.

We found that a surprising 50% of people born to at least one RI native were willing to drive 75 miles if their life depended on it. Twenty percent would visit a friend in the hospital at 75 miles, and 80% would take their child to a soccer game at that distance. In comparison to the two non-"native" groups, these numbers were significantly different statistically. Both those living in RI but not of RI "stock" and those who had no RI interactions endorsed driving 75 miles to save their lives at 100%, whereas 90% would visit a friend in the hospital and 40% would drive 75 miles to see a child's soccer game. When the driving distance was 50 miles, the numbers for RI "natives" and the two control populations were similar to those for 75 miles, but at 25 miles the number changed considerably so that 85% of RI natives would drive 25 miles to save their lives, and to visit a friend in the hospital , while 60% would travel this distance to see the soccer game, vs 100%, 100% and 75% (p values not significant) for people in Ohio without a relationship to RI.

These data suggested a genetic explanation for native RIers' reluctance to drive. Using very new statistical techniques we found that a single abnormal gene could explain the driving limitation as well as why RI natives give driving directions based on physical markers that often were removed (like demolished buildings or trees that had been cut down) years before.

Since the work on this project is evolving we can share only preliminary results on its molecular biology, awaiting confirmation. We have found a remarkable similarity between the gene thought to confer driving conservatism in RI drivers with a gene thought to allow homing pigeons to return to their home, although this gene has not yet been found in other birds or primates. How this gene could have evolved is unclear but one, currently theoretical, explanation is based on the old homily, "ontogeny recapitulates phylogeny," suggesting that evolutionary developments are not necessarily unique and may reoccur even in different species. When these changes lack survival advantages they fail to propagate.

In this case we can conclude that advantageous or not, the gene is unlikely to spread very far.

[April Fool]

**– Joseph H. Friedman, MD**

**Disclosure of Financial Interests**

Joseph Friedman, MD, Consultant: Acadia Pharmacy, Ovation, Transoral; Grant Research Support: Cephalon, Teva, Novartis, Boehringer-Ingelheim, Sepracor, Glaxo; Speakers' Bureau: Astra Zeneca, Teva, Novartis, Boehringer-Ingelheim, GlaxoAcadia, Sepracor, Glaxo Smith Kline, Neurogen, and EMD Serono.

# The Elements of Medicine: Faith, Hope and Credence

**The technical vocabulary of the medical profession is both vast** and intimidating: Vast, as found in the standard English language medical dictionary of about 1,600 pages with an estimated 86,000 words; and intimidating because most of those words are constructed of Latin or Greek roots, prefixes and suffixes. In general, Latin roots have been reserved for normal physiologic phenomena and standard anatomic structure while Greek roots have defined pathologic states.

English, more than most languages, is an accretive tongue with numerous additions to the mother vocabulary through successive invasions of Britain by Celts, Angles, Saxons, Jutes, Romans, Danes, Norman French – and finally, the Americans in the 1940s, each incursion bringing new and enriching words. English, it turns out, is like any other language – but only more so. Thus English, perhaps the most linguistically impure of languages, provides a wide selection of words, some elitist, some vernacular, for virtually every basic term or situation.

With all of these linguistic riches, people nevertheless seem to fall back upon the older, more primitive Germanic words when they feel themselves medically imperiled. Thus, when your head is pounding and ready to spin off to the southwest, you will complain about a splitting headache but never describe it as an acute, bilateral cephalalgia. The two most precious medically-related words in the entire language – heal and health – were both bestowed upon the earlier English by the Anglo-Saxons with not a trace of Classical language origins. Both words convey the sense of completeness, togetherness, to make whole. This kind of comprehensive healing transcends and is distinguished from the customary patient-physician transaction where a specific problem, say a fractured ankle bone, is brought to the physician who then exploits his/her medical education, cumulative experience and technical equipment to repair the damage. The patient leaves, satisfied that the immediate problem has been attended to expeditiously; but whether he feels healed in the sense of being made whole again is another matter. There are many who bless the high rate of cure achieved by modern medicine while expressing, *soto voce*, that the experience felt more like a business transaction than a healing interlude.

Medical historians, particularly those who have also practiced medicine, have been astonished by the clinical successes achieved by occasional physicians in centuries past. Certainly their understanding of the mechanics of disease had been rudimentary; their drugs at best were non-poisonous; and their surgical skills no better than abjectly primitive. Yet cures were indeed achieved, cures which the skeptics called faith-healing in those burdened by imaginary ills. But surely not all were psychosomatic disorders; and while the ill-defined illnesses may have been illusory, certainly the sincerity of the patient's gratitude was tangible. And in today's medical encounters, in contrast, the patients have invested their faith in the machinery of medicine rather than the practitioners of medicine.

Benjamin Rush, one of the five physicians who signed the Declaration of Independence, once declared: ""I have frequently prescribed remedies of doubtful efficacy . . . but never till I have worked up my patients into a confidence bordering upon certainty, of their probable good effects."

William Osler, the most prominent physician of the 20th Century, remarked: "Faith in us, faith in our drugs and methods, is the great stock in trade of the profession." In Osler's iconic textbook (which has guided medical students for over four generations), he said that three factors will lead to therapeutic success: A strong personality in whom the patient has faith; a healing environment rich in symbols such as a shrine, a sanctuary, or for those in medicine, a hospital with skilled nursing care; (Osler, who founded the Johns Hopkins Hospital and Medical School, referred to the institution as Saint Johns Hopkins.) The third factor was the patient's "active belief in the assurance of the physician."

Medicine, before the era dominated by MRIs and other intrusive paraphernalia, still had its visible symbols: the well-worn stethoscope, the pocket watch to determine the patient's pulse, and most of all, the atmosphere of optimism, equanimity, assurance and self-confidence emanating from the physician. The physician's ambience was not marginal; it was all.

In the formative days of Johns Hopkins Hospital, Osler was called to see a mortally ill boy named Billy O. The urgent call came when Osler was presiding over the medical school graduation, and in his haste to arrive at the child's bedside, he neglected to remove his ceremonial robes. This then was how the child had first envisioned him; and for the next forty days, Osler visited Billy daily, always wearing his academic robes. Osler talked at length with Billy, fed him with his own hand, and somehow urged Billy's body to heal itself. Billy recovered, although Osler had no explanation.

In medicine's quest for meaning, its search for plausibility, and its insistent demand for rational explanations, it recognizes intuitively that there must be more operative elements than the intricacies of the immune system, the endocrine glands, the hereditary equipment and other wondrous modalities governing mortal encounters between illness and its victim. Somehow, somewhere, passions must influence the capacity of the body to confront its disorders.

If not blind faith, then certainly some faith in the healer's skills exerts a role in the subtle negotiations that culminate in either healing or non-healing. The physician, as custodian of the healing adventure, must be assertive and have faith in the process - until such time when a pharmaceutical company devises a pill to activate the patient's sense of confidence in himself and his physician.

– Stanley M. Aronson, MD

**Disclosure of Financial Interests**

Stanley M. Aronson, MD, has no financial interests to disclose.

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# Inflammatory Bowel Disease (Part II)

*Samir A. Shah, MD, FACG, and Edward R. Feller, MD, FACG*

**Last month's issue on Inflammatory bowel disease (IBD)** introduced the RI-specific **OSCCAR** (**Ocean State Crohn's and Colitis Area Registry**) study, and reviewed IBD epidemiology, medical treatment, imaging advances, surgery for **ulcerative colitis** (**UC**), and surgery for **Crohn's disease** (**CD**). As noted in last month's issue, IBD includes UC and CD and is distinct from **Irritible Bowel Syndrome** (**IBS**) though some symptoms may overlap.

This issue continues the focus on IBD. The lead article highlights specific emergencies/presentations in a case-based format; in the next two articles, bone disease in IBD and steroids' effects on bone health are reviewed; next nutrition and pediatric issues in IBD treatment are discussed; the final article reviews reproductive issues in IBD. Our hope is that these two issues will (1) provide a practical update for all clinicians involved in caring for patients with IBD and (2) publicize the OSCCAR study, which is gathering groundbreaking information on IBD. This inception cohort of IBD patients not only gives us data on the incidence of IBD in the US, but allows us to examine clinical factors, genes, and bowel flora. Thus we may be able to improve risk stratification of IBD patients to target therapy and achieve better outcomes for our patients.

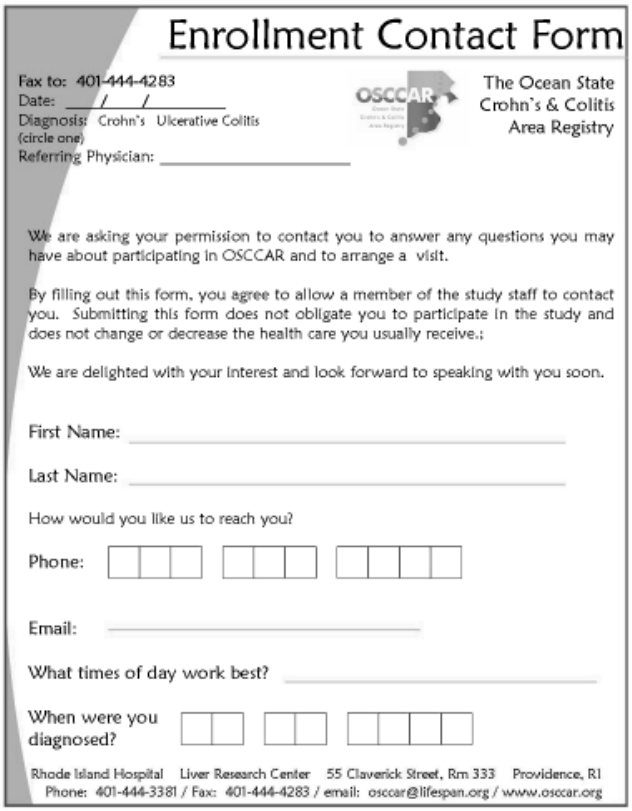
*Samir A. Shah, MD, FACG, is Clinical Associate Professor of Medicine, Warren Alpert Medical School of Brown University.*

*Edward R. Feller, MD, FACG, is Clinical Professor of Medicine and Community Health, Warren Alpert Medical School of Brown University, and Director, Division of Gastroenterology, at Miriam Hospital.*

### Disclosure of Financial Interests

Samir A. Shah, MD, FACG. Speaker's bureau: Abbott, Elan, Procter&Gamble, Prometheus, UCB.

Edward R. Feller, MD, FACG, has no financial interests to disclose.



Enrollment Contact Form

Fax to: 401-444-4283
Date: ___/___/_____
Diagnosis: Crohn's Ulcerative Colitis (circle one)
Referring Physician: _____

OSCCAR
The Ocean State Crohn's & Colitis Area Registry

We are asking your permission to contact you to answer any questions you may have about participating in OSCCAR and to arrange a visit.

By filling out this form, you agree to allow a member of the study staff to contact you. Submitting this form does not obligate you to participate in the study and does not change or decrease the health care you usually receive.;

We are delighted with your interest and look forward to speaking with you soon.

First Name: _____

Last Name: _____

How would you like us to reach you?

Phone: ☐☐☐ ☐☐☐ ☐☐☐☐

Email: _____

What times of day work best? _____

When were you diagnosed? ☐☐ ☐☐ ☐☐☐☐

Rhode Island Hospital Liver Research Center 55 Claverick Street, Rm 333 Providence, RI
Phone: 401-444-3381 / Fax: 401-444-4283 / email: osccar@lifespan.org / www.osccar.org

Patient self referral form.

Enrollment Contact Form

Fax to: 401-444-4283
Today's Date: ___/___/_____
Diagnosis: Crohn's Disease Ulcerative Colitis (circle one)
Referring Physician, RN, or NP:

OSCCAR
The Ocean State Crohn's & Colitis Area Registry

Completed by: _____

Please complete this form once you have spoken with your patient (or their guardians if patient is a child) about OSCCAR and he/she has indicated it would be ok for someone from the study to contact them.

When we call your patient, we will answer any questions they may have about participating in OSCCAR and if they are interested, we will schedule a visit.

By providing your patient's information below, he/she is in no way obligated to participate in the study.

Patient's First Name: _____

Patient's Last Name: _____

Guardian's Name (if patient is a minor): _____

Estimated date of diagnosis: _____/_____/_____

Patient/Guardian's Phone Number: ☐☐☐ ☐☐☐ ☐☐☐☐

Rhode Island Hospital Dept. Pedi GI 593 Eddy Street MPS 148 Providence, RI 02903
Phone: 401-444-4143 / Fax: 401-444-4283 / email: osccar@lifespan.org / www.osccar.org

Health care professional referral form.

# Inflammatory Bowel Disease Potpourri: A Vignette-Based Discussion

*Manuel Y. Lam, Edward R. Feller, MD FACG, John R. Lonks, MD, Samir A. Shah, MD, FACG*

**Crohn's disease (CD) and ulcerative colitis** (UC) can cause abdominal pain, diarrhea, rectal bleeding and a variety of systemic manifestations. Most patients require chronic medical therapy and are managed in the outpatient setting. Some present with signs and symptoms from an uncomplicated exacerbation of IBD; others present with clinical features that seem unrelated to IBD or its medications. However, these manifestations may be associated with an acute, severe, sometimes life-threatening complication that requires prompt intervention. We describe a few clinical vignettes to showcase several common and not so common emergencies and medical complications in IBD.

**Case 1.** *A 43-year-old man with a long-standing CD presents to his primary care physician with the complaint of right hip pain and a slight limp. His surgical history is significant for resection of a small bowel stricture and enterocutaneous fistula 4 years ago. His post-operative course was uncomplicated, and he declined treatment with 6-mercaptopurine. Several weeks ago, he began to have abdominal cramping and diarrhea, which rapidly improved after prednisone was started at a walk-in clinic. His doctor wants to avoid NSAIDs because in the past they led to flare-up of his Crohn's; the patient has also tried acetaminophen without relief. Instead, the physician makes an orthopedic referral. X-ray of the hip is normal. A CT scan demonstrates a psoas abscess in the right iliopsoas region. He is hospitalized and intravenous ampicillin/sulbactam and vancomycin were started. A percutaneous drain was inserted into the abscess and left in situ for several days. Culture grew* Escherichia coli *and* Bacteroides fragilis. *He is discharged on oral amoxicillin/clavulanic acid, and his condition improves.*

In contrast to a patient who presents with an acute perforation of the bowel and free air in the abdomen, a patient with fistulizing CD, as in this case, commonly presents with an encapsulated intra-abdominal abscess. Intestinal contents may leak through transmural sinus tracts into surrounding structures, very commonly the iliopsoas muscle, which is anatomically contiguous to the ileocecal junction. It has been estimated that over one-third of patients with CD will develop a fistula during the course of their disease,[1] and over half of those will develop an intra-abdominal abscess.[2]

The clinical manifestations of an intra-abdominal abscess are often difficult to distinguish from an exacerbation of CD. Patients in either scenario may present with abdominal pain and tenderness, fever, and an elevated white blood cell count. Corticosteroids may blunt the inflammatory response, masking the typical signs and symptoms of infection, including fever. Generally, patients with CD, especially those on corticosteroid therapy, presenting with increased abdominal pain or fever should have abdominal and pelvic CT or MR enterography. Those patients with hip/groin pain or difficulty with hip flexion must have deep pelvic and groin imaging to exclude an iliopsoas abscess complicating fistulizing CD. Aseptic necrosis of the hip secondary to steroid use must also be considered. A delay in diagnosis may result in increased morbidity and mortality and longer hospital stays.[3]

A combined medical and surgical approach is the therapy of choice in these cases. Initially, management includes broad-spectrum antibiotics and percutaneous drainage. However, since an abscess is formed via a perforation of the bowel wall, nearly 50% of those patients managed medically ultimately require subsequent resection of the fistula and affected bowel segment.[4]

*A week later, the patient returns to the ER with diarrhea and abdominal pain. CT reveals new thickening in the transverse, descending and sigmoid colon.* Stool *Clostridium difficile toxin test is negative. Steroids and empiric oral metronidazole are started. The next day, a flexible sigmoidoscopy shows nonspecific inflammation and ulcers. No pseudomembranes are seen. However, stool aspirate sent for C. difficile toxin test and sigmoid biopsy confirms the diagnosis of C. difficile. The steroids are discontinued, Metronidazole is changed to oral Vancomycin with rapid improvement in symptoms.*

Infection with enteric pathogens account for approximately 10% of relapses in patients with IBD; *Clostridum difficile* has been implicated in more than half of these infections [5]. Infection with *C. difficile* may trigger a flare of IBD requiring hospitalization[6] and increase the risk of colectomy (20% in one series).[7] The incidence and severity of *C. difficile* infection appears to be increasing among patients with IBD, resulting in increased morbidity and mortality.[7,8] Contrary to past reports that hospitalized patients were primarily susceptible to infection, the majority of IBD patients actually contract *C. difficile* in the outpatient setting. The most significant risk factor seems to be a prior history of colitis itself independent of previous antibiotic treatment. Therefore, all patients presenting with relapse of IBD should be evaluated for *C difficile*.

*C. difficile* may be difficult to distinguish from an IBD relapse given the similar symptoms (diarrhea, abdominal pain, and low grade fever). In fact, typical pseudomembranes may not be seen on endoscopy, especially if the patient is im-

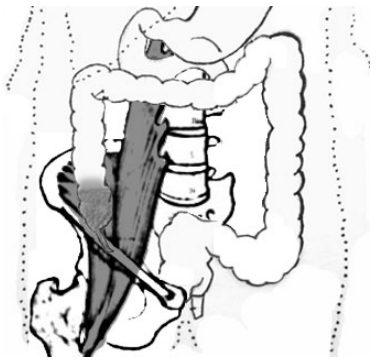


**Diagram:** The iliopsoas muscle is anatomically contiguous to the ileocecal junction.

munosuppressed. Furthermore, failure to promptly diagnose *C. difficile* infection in patients with IBD can lead to inappropriate treatment with corticosteroids and worsening of colitis. Therefore, it is important to exclude *C. difficile* infection in patients with apparent exacerbations of IBD.[7,8] Colonic biopsy and stool aspirate for *C. difficile* toxin testing should be done if initial stool tests for *C difficile* are negative. Oral vancomycin is superior to oral metronidazole for severe *C. difficile*. [9]

**Case 2.** *A 31-year-old woman with ileal Crohn's complicated by perianal disease presents to her internist with fever, chest pain, malaise and a dry cough. She has been in remission on infliximab therapy for one year. Of note, she had a negative PPD and normal CXR prior to starting treatment. Recently, she visited her family in Ohio. No family members were sick. She had not been on antibiotics recently. The internist orders a chest x-ray, which shows upper lobe haziness. He orders urine antigen test for Histoplasmosis and sends the patient for direct hospital admission. The infectious disease and pulmonary consults confirm Histoplasmosis. Infliximab is discontinued. She is started on amphotericin B and subsequently improves.*

**Tumor necrosis factor (TNF)** plays a critical role in host defense and granuloma formation. Thus, a possible adverse event following the use of TNF-alpha inhibitors is the development of granulomatous infections, such as tuberculosis and histoplasmosis.

Tuberculosis is the opportunistic infection most strongly associated with TNF-alpha inhibitors. A Spanish database of over 1500 patients treated with TNF-alpha inhibitors estimates an annual TB incidence of 1% following initiation of infliximab, an incidence rate up to 90 times higher than what is expected in the general Spanish population .[10] A United States registry of over 10,000 rheumatoid arthritis patients with over 16,000 person-years of follow-up estimates that the incidence rate of TB before infliximab became available was 6.2 cases per 100,000 person-years. Among infliximab-treated patients, there is an eightfold elevation in risk to as high as 52.5 per 100,000 person-years .[11] However, once TB screening was instituted before initiation of TNF-alpha inhibitors, the incidence rate waned.[10]

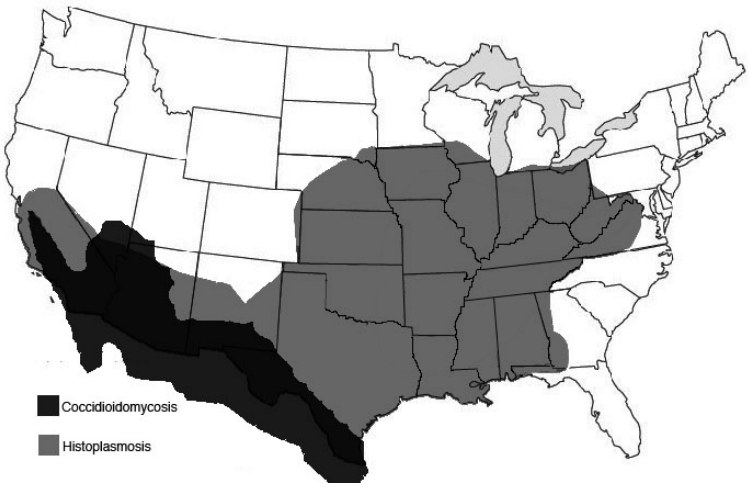
Most cases of TB were reported within 3 months of initiating TNF-alpha inhibitors; this would suggest that most cases were caused by reactivation of latent infection rather than newly acquired infection. According to the **Centers for Disease Control and Prevention (CDC),** patients should be evaluated for latent infection with a tuberculin skin test before initiating anti-TNF-alpha therapy. However, a negative tuberculin skin test does not exclude the possibility of latent infection. Initiation of empiric treatment in consultation with an infectious disease specialist should be considered in high-risk groups (eg., prisoners, homeless, previous resident of or traveler to a high-prevalence country, etc.) before therapy with a TNF-alpha inhibitor.[12]

Clinicians should consider TB in any patient on anti-TNF-alpha agents who has a febrile or respiratory illness. Both extrapulmonary and disseminated TB are also more common in patients treated with TNF-alpha inhibitors than in immunocompetent patients .[13] A few cases of TB enteritis mistaken for an IBD flare have been treated with infliximab, resulting in death.[14] If active TB is diagnosed, anti-TNF-alpha therapy should be temporarily discontinued until treatment for active TB has been initiated and the patient's condition has improved.[12]

In addition to TB, invasive opportunistic fungal infections are important considerations in any patient undergoing treatment with anti-TNF-alpha therapy. In 2008, **the Food and Drug Administration (FDA)** issued a warning about the risk for pulmonary and disseminated histoplasmosis, coccidioidomyscosis, blastomycosis, aspergillosis, candidiasis, cryptococcosis, and other invasive fungal infections in patients taking TNF-alpha inhibitors. The FDA identified 240 reports of patients diagnosed with histoplasmosis who had been treated with TNF-alpha inhibitors. There was a delay in diagnosis and treatment in 21 of these cases, resulting in 12 deaths among these 21 patients.[14]

Among cases of histoplasmosis and coccidioidomycosis in the United States, (1) most patients resided or travelled in endemic regions, and (2) nearly all were concurrently on immunosuppressive agents.[15,16] These patients should be advised to have a low threshold for seeking medical attention. Typical signs and symptoms of possible systemic fungal infection include fever, malaise, sweats, weight loss, cough, shortness of breath, pulmonary infiltrates on chest x-ray, or shock. In these patients, clinicians should be vigilant to stop anti-TNF-alpha therapy; start a complete diagnostic workup in consultation with an infectious disease specialist; and consider empiric antifungal treatment until the pathogens are identified. At this time, there are no recommendations for baseline testing for *Histoplasma capsulatum* or *Coccidioides immitis* in residents of endemic areas before initiation of anti-TNF-alpha therapy.

*Histoplasma capsulatum* is found worldwide. In the United States, Histoplasmosis is endemic in the Ohio and Mississippi River valleys. Histoplasmosis is acquired through inhaling conidia, usually found in the soil of these endemic regions.




Map: Distribution of Regions Endemic with Histoplasmosis and Coccidioidomycosis in the United States.

*Coccidioides immitis* is a dimorphic fungus found in the southwestern United States (Arizona, California, Nevada) and parts of Central and South America.

**Case 3.** *A 54-year-old man with long-standing UC had done well for many years on mesalamine alone until a bout of gout treated with indomethacin sixteen months ago flared up his colitis. He required two courses of steriods and the eventual addition of azathioprine to wean off the steroids. He now presents to his family physician with a second bout of gout in his left great toe. He is treated with colchicine, which improves his pain. He is referred to a rheumatologist. At his evaluation, he forgets to bring his list of medications. He is prescribed allopurinol, which he immediately fills at a 24-hour pharmacy near the office. Three weeks later, his gastroenterologist calls to discuss a depressed WBC on routine blood work. His azathioprine is temporarily stopped. Given the gout, a joint decision is made with the rheumatologist to continue allopurinol. Two weeks later, his WBC is normal, and azathioprine is restarted* at one-third the previous dose with serial blood work monitoring.

**Azathioprine** (**AZA**) is a pro-drug, converted *in vivo* to the active metabolite 6-mercaptopurine (6-MP). AZA and 6-MP are both active purine synthesis inhibitors, which inhibit the proliferation of cells, especially leukocytes. The typical doses used in inflammatory bowel disease are 2.0-2.5 mg/kg for AZA and 1.0-1.5 mg/kg for 6-MP.

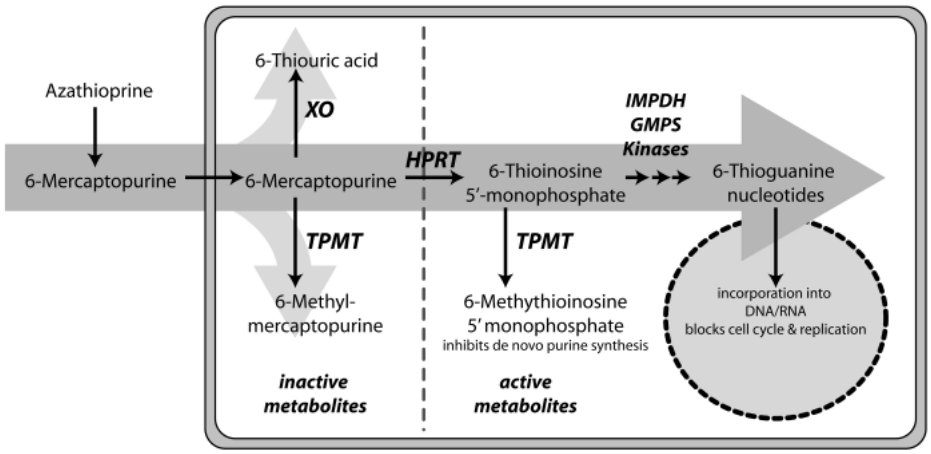



Diagram: Metabolism of Azathioprine
XO = xanthine oxidase, TPMT = thiopurine methyltransferase, HPRT = hypoxanthine phosphoribosyltransferase; IMPDH = inosine monophosphate dehydrogenase, GMPS = guanosine monophosphate synthetase

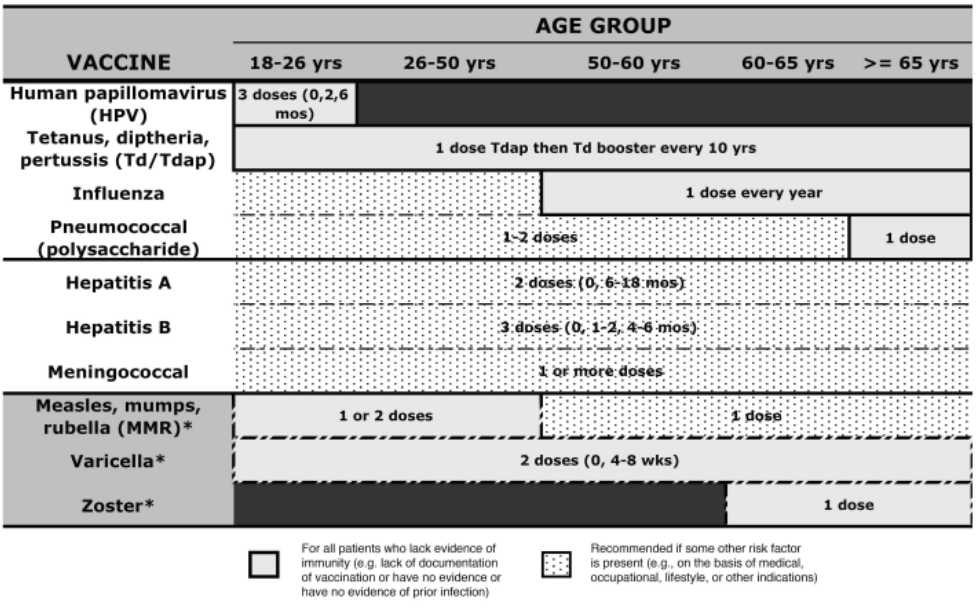



Table: Immunization Guidelines for Immunocompetent Adults, by vaccine and age group
Adapted from CDC's Recommended Adult Immunization Schedule [21]
* Live vaccines should be avoided in *immunocompromised* children and adults with IBD.

However, lack or inhibition of either of these enzymes causes 6-MP to be preferentially metabolized to produce higher levels of 6-TG, which then leads to bone marrow suppression. Thus, it is important to consider drug-drug interactions. For example, allopurinol inhibits XO. Thus, concomitant use of allopurinol and AZA/6-MP should be avoided.[17] However, if the patient has severe gout and allopurinol must be used, a reduced azathioprine dose by at least 50% may be used.

6-MP is further metabolized along the competing routes catalyzed by xanthine oxidase (XO), thiopurine methyltransferase (TPMT) and hypoxanthine-guanine phosphoribosyltransferase (HGPRT). HGPRT produces thioguanine nucleotides, such as 6-thioguanine (6-TG), which are incorporated into both the RNA and DNA of rapidly dividing cells inducing cell cycle arrest and cell death. Bone marrow suppression secondary to AZA or 6-MP correlate with elevated 6-TG levels. Conversely, XO and TPMT deactivate 6-MP and render several inactive metabolites, including 6-thiouracil (6-TU) and 6-methylmercaptopurine (6-MMP), respectively.

| General Recommendations for Immunosuppressed IBD patients | |
|---|---|
| Tetanus, diphteria, pertussis | 1 dose Tdap then Td booster every 10 years |
| Human papillomavirus | 3 doses for women < 26 yo |
| Influenza | Annually |
| Pneumococcal | 1-2 doses |
| Hepatitis A | Consider in all patients |
| Hepatitis B | Consider in all patients |
| Meningococcal | If risk of exposure |
| **Avoid live vaccines!** | |
| Measles Mumps Rubella | |
| Varicella | |
| Zoster | |
| Yellow Fever | |
| Oral typhoid | typhoid Vi is safe. |
| Smallpox | |
| Adenovirus | |
| Bacille Calmette-Guerin | |

Table: General Recommendations for Immunosuppressed Adults with Inflammatory Bowel Disease

AZA/6-MP is eventually discontinued in many of these patients. Similarly, TPMT genotype or phenotype testing may be assessed in all patients before starting AZA or 6-MP to prevent toxicity by identifying patients with low or absent TPMT enzyme activity.[18,19] Approximately, 11% are heterozygous, have low TPMT ezyme activity, and thus require lower dosing. One in 300 is homozygous for TPMT genetic mutations, has no activity, and should not receive AZA or 6-MP.

Regardless of testing for enzyme activity or metabolite assays, all patients must receive frequent monitoring of **complete blood count (CBC)** and **liver function tests (LFTs)**—weekly CBCs for the first month and eventually CBCs and LFTs every 2-3 months when on a stable dose regimen.

***Several months later, he is doing well. He asks his primary care doctor during his annual physical exam whether he should receive a flu shot. Since the patient is immunosuppressed on azathioprine, his doctor informs him that a flu shot is safe and recommended along with a pneumonia vaccine.***

Recombinant and inactived vaccines are safe in patients on either an immunosuppressant (i.e. AZA, 6-MP, MTX, or steroids) or an anti-TNF agent (infliximab, adalimumab, certolizumab pegol). However, live vaccines should be **not** be used in an IBD who is on treatment with:[20]

1. glucocorticoids (prednisone 20 mg/d equivalent) for 2 weeks or more and within 3 months of stopping,
2. effective doses of 6-MP/AZA and within 3 months of stopping,
3. methotrexate and within 3 months of stopping,
4. an anti-TNF agent and within 3 months of stopping, or
5. significant protein-calorie malnutrition.

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**Discussion of off-label usage of drug:** Metronidazole is not FDA-approved for treatment of *Clostridium difficile.*

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# Bone Disease In the Inflammatory Bowel Disease Population

*Jeanette Smith, MD, and Sheldon Lidofsky, MD*

**Bone disease, an under-diagnosed manifestation of Inflammatory Bowel Disease IBD**, warrants special consideration. Osteoporosis/osteopenia commonly affects 30-50% of IBD patients. The quiescent nature of this disease makes it extremely challenging to diagnose and treat. Patients with osteoporosis and osteopenia are asymptomatic unless they suffer a fracture. In the past, bone health has been overlooked due to the other pressing issues and complications that arise in this population. However, screening, preventive efforts and active treatment are essential. Because bone disease can significantly reduce health and quality of life, clinicians should be aware of bone disease in all patients with IBD.

## Definition and Epidemiology of Osteoporosis.

The **World Health Organization (WHO)** defines osteoporosis as a "systemic skeletal disease characterized by low bone mass and architectural deterioration of bone, with a consequent increase in bone fragility and susceptibility to fracture." [1] It has often been thought of as an older person's disease. However, in the IBD population it can occur at any age. Studies have shown that approximately 30% of patients with inflammatory bowel disease have low bone density, with a mean bone density on average 10% lower than normal age matched controls.[2,3] The overall relative risk of fracture is 40% greater in IBD patients compared to the general population.[4]

The prevalence of bone disease in patients with **Crohn's disease (CD)** or **Ulcerative Colitis (UC)** is thought to be equal.[4] Thus, patients with UC and CD should be evaluated and treated similarly.

## Normal Bone Development

Normal adult bone is comprised of metabolically active cells (osteoblasts and osteoclasts) along with a non-living extracellular matrix of collagen and calcium salts.[5] Bone strength is determined by these collagenous proteins and mineralized osteoid. It has been accepted that bone mass is the single best predictor of in vivo bone strength and fracture risk.[1] Adult bone is constantly being remodeled to maintain strength. Osteoclasts direct the timing and location of bone resorption, whereas osteoblasts secrete, mineralize and form the new osteoid. The osteoclasts require weeks to resorb bone, whereas the osteoblasts need months to produce new bone. Therefore, any process that increases the rate of bone remodeling results in a net bone loss over time. Furthermore, in periods of rapid remodeling, bone is at an increased risk for fracture because the newly produced bone is less densely mineralized.[5]

Bone mass peaks by the third decade of life and slowly decreases afterward. The failure to attain optimal bone strength by this point is one factor that contributes to osteoporosis. Therefore, nutrition and physical activity are important during growth and development. Genetic factors play a principal role in determining an individual's peak bone strength. Ethnicity and gender also have an influence on the development of osteoporosis. The risk of developing osteoporosis is higher in Caucasian women compared to other groups.[1]

## Development of Bone Disease in IBD

The pathogenesis of bone disease in IBD is multifactorial. Patients are at increased risk for development of bone disease due to nutritional deficiencies in Vitamin D and calcium, decrease in gonadal function, disease-related inflammatory activity and most commonly as a result of medications, especially glucocorticoid therapy. Glucocorticoid-induced bone disease is such a significant component of osteoporosis and osteopenia in the IBD population that it will be discussed separately (see next article by Lidofsky and Smith).

Vitamin D, calcium and parathyroid hormone help to maintain normal bone homeostasis. Insufficient dietary calcium or impaired intestinal absorption of calcium due to small bowel disease can lead to secondary hyperparathyroidism. Parathyroid hormone is secreted in response to low serum calcium levels and increases calcium resorption from bone, decreases renal calcium excretion, and increases renal production of 1,25-dihydroxyvitamin D all in an attempt to raise the serum calcium level. This active hormonal form of vitamin D optimizes calcium and phosphorous absorption from the gut, inhibits parathyroid hormone synthesis, and plays a minor role in bone resorption. Vitamin D deficiency has been estimated to occur in 30-60% of patients with CD and can result in secondary hyperparathyroidism via decreased intestinal calcium absorption.[6] In CD, Vitamin D and calcium deficiency are the result of malabsorption from uncontrolled small bowel inflammation, malabsorption secondary to significant bowel resection, poor nutritional intake and patient's avoidance of dairy products.

Amenorrhea and hypogonadism are also very common in IBD patients and can contribute to decreased bone mineral density. They occur due to the inhibitory effects the chronic inflammatory illness has on the pituitary gonadal axis and the use of glucocorticoids.

**Bone mineral density (BMD)** is still significantly reduced in many patients in the absence of nutritional deficiencies, gonadal dysfunction or treatment with glucocorticoids implying that there are other causes of bone disease in these patients.

Inflammation has emerged as the principal pathophysiological mechanism responsible for bone loss in IBD. It is be-

**TABLE 1. Criteria for Osteoporosis/Osteopenia**

| |
|---|
| T-score of -1 to -2.5 SD indicates osteopenia |
| T-score of less than -2.5 SD indicates osteoporosis. |
| T-score of less than -2.5 SD with fragility fracture(s) indicates severe osteoporosis |

Adapted from WHO.

lieved that bone resorption may be increased in IBD patients without a compensatory increase in bone formation. The cause of excess bone resorption is not fully understood. One possibility is increased intestinal production of cytokines that stimulate bone resorption. In CD, the main inflammatory cytokines are interferon gamma, TNF alpha and IL-6. In particular, TNF alpha and IL-6 have been shown to stimulate osteoclast activity, leading to increased bone resorption and net bone loss. Maintenance treatment with TNF alpha antagonists, such as infliximab, is associated with improvement in bone mineral density, thus implicating a role for TNF alpha in bone loss.[7, 8]

## Detection of Bone Disease

Bone disease can be evaluated by diverse modalities including blood, urinary testing and bone imaging. All patients with IBD should be screened for osteoporosis with a complete blood count, serum alkaline phosphatase, creatinine, calcium, 25-OH vitamin D, testosterone level and protein electrophoresis. This testing will screen for the other causes of low bone density. There are specific biochemical markers of bone formation (bone-specific alkaline phosphatase, osteocalcin, and type I procollagen peptides) and bone resorption (urinary deoxypyridinoline, cross-linked N- and C-telopeptide).[9] These markers of bone turnover may be elevated in high bone turnover states and may be useful for monitoring and predicting response to therapy. However, currently these markers are used by bone disease specialists. Their clinical utility in osteoporosis management needs further study before recommendations are made to include them in routine testing.

**Dual-energy x-ray absorptiometry (DEXA)**, a radiological study used to establish or confirm a diagnosis of osteoporosis/osteopenia, is considered the gold standard for bone mineral measurement. The measurement depends on the ability of bone to block the transmission of energy. DEXA is used to calculate BMD at the hip and spine. Measurements at these sites are the best predictors of fracture risk. DEXA measurements are reported as T-scores and Z-scores. T-scores represent the number of **standard deviations (SD)**s from the mean bone density values in healthy young adults, whereas Z-scores represent the number of SD from the normal mean value for age- and sex-matched controls. Z scores should be used in place of T scores when evaluating pre-menopausal women and men younger than age 50. The WHO defines a normal T-score value as within 1 SD of the mean bone density value in a healthy young adult. For each SD reduction in BMD, the relative fracture risk is increased 1.5-3 times.[1] It is important to interpret these tests with caution. A DEXA scan cannot differentiate low bone mineral density as osteopenia or osteoporosis from metabolic bone disease or osteomalacia (Vitamin D deficiency).

**Insufficient dietary calcium or impaired intestinal absorption of calcium due to small bowel disease can lead to secondary hyperparathyroidism**

Alternative imaging modalities for diagnosis of bone disease include conventional radiographs, quantitative CT scanning, peripheral DEXA and quantitative ultrasonography. Plain radiography is not sensitive. Approximately 30-80% of bone mineral must be lost before radiographic lucency becomes apparent on radiographs.[10]

The 2003 Guidelines from both the **American College of Gastroenterology (ACG)** and **American Gastroenterological Association (AGA)** recommend the selective screening of IBD patients with DEXA scanning. They specify the use of DEXA in patients in the postmenopausal state, ongoing corticosteroid treatment, cumulative prior use of corticosteroid exceeding 3 months, history of low trauma fracture and age over 60.[4,11]

## Prevention and Treatment of Bone Disease in IBD

All patients with IBD should utilize preventive measures to ensure bone health, including low impact exercise regimens, institution of adequate calcium and vitamin D, and education regarding smoking cessation and minimal alcohol consumption.

Physical activity is very important to bone health. The benefit of a low impact exercise program on bone mineral density has been shown in patients with CD after a one year intervention. Patients who exercised 2 times per week demonstrated an increase in their bone mineral density compared to controls.[12] Patients can be referred to a physical therapist to assist in developing an exercise regimen and for instruction on proper technique.

It has been accepted that calcium and vitamin D are essential, but frequently not sufficient for prevention and treatment of osteoporosis. The supplementation of calcium and vitamin D has been shown to have a modest effect on reducing fracture occurrence.[13] The AGA recommends Vitamin D 800 IU/day and calcium 1000-1500mg/day to minimize bone loss.

Patients with IBD who are receiving appropriate vitamin D and calcium supplements should have measurement of bone density every two years. Patients who continue to lose bone on this regimen should be considered for antiresorptive therapy.[4]

Antiresorptive agents, including bisphosphonates (both oral and intravenous), the **selective estrogen-receptor modulator (SERM)** raloxifene, calcitonin, and the anabolic agent teriparatide, are currently used for osteoporosis treatment.[10, 13] There are no comparative data on the relative efficacy of the different antiresorptive drugs in patients with IBD.

Bisphosphonates are stable analogs of inorganic pyrophosphate that have a high affinity for hydroxyapatite crystals. They bind to sites of active bone resorption and inhibit osteoclastic resorption. Bisphosphonates are approved in the United States for the prevention and treatment of postmenopausal osteoporosis, osteoporosis in males, and steroid-induced osteoporosis. They include etidronate (Didronel), pamidronate (Aredia), aledronate (Fosamax), risedronate (Actonel), ibandronate (Boniva) and clodronate (not available in US). A systematic review of randomized controlled trials evaluating alendronate and risedronate revealed that both increase bone mineral density in the spine

and hip and reduce risk of fracture by 30-50%.[14, 15] There are scant data evaluating the effectiveness of bisphosphonate therapy in IBD patients.

Hormone replacement therapy has been shown to increase bone mineral density in postmenopausal women with IBD. However, in the Women's Health Initiative trial hormone replacement therapy was associated with an increased risk of breast cancer, myocardial infarction, stroke and venous thromboembolic events and is no longer recommended as a treatment of osteoporosis in postmenopausal women. Bisphosphonates should be used instead of estrogen and progestin in postmenopausal women.

SERMs act as weak estrogens in some organ systems, while acting as estrogen antagonists in others. Raloxifene (Evista) is approved for the prevention and treatment of postmenopausal osteoporosis. It was shown to reduce spinal fracture rate, but not effective in prevention of hip fracture.[10, 13]

Calcitonin (Micalcin) acts directly on osteoclasts to inhibit bone resorption. It is available as a subcutaneous injection and an intranasal spray. It has been reported to reduce spinal fractures, but not hip fractures.[10, 13]

Teriparatide is a biological product that contains a portion of the human parathyroid hormone. It is the first approved agent for the treatment of osteoporosis that stimulates bone formation. Teriparatide is approved in the United States for postmenopausal osteoporosis and primary or hypogonadal osteoporosis in men. The major limiting factors are its subcutaneous administration and its cost. There are concerns with prolonged use (>24months) and development of osteosarcoma.[10, 13]

## Conclusion

Bone disease in IBD is preventable and warrants investigation. It is the role of both the gastroenterologist and the primary care physician to evaluate for bone disease in IBD patients and to refer to a specialist when appropriate (endocrinologist or rheumatologist) to ensure adequate prevention and treatment of this silent disease.

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**Discussion of off-label or investigational drug:** Miacalcin



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# Glucocorticoid-Induced Osteoporosis In Inflammatory Bowel Disease

*Sheldon Lidofsky, MD, and Jeanette Smith, MD*

**Systemic glucocorticoid therapy is a mainstay in the treatment** of active **inflammatory bowel disease (IBD).** However, glucocorticoids are associated with multiple side effects, of which bone loss resulting in glucocorticoid–induced osteoporosis and increase in fracture risk are predictable and debilitating complications.

Glucocorticoids exert multiple adverse effects on bone metabolism. They impair osteoblast growth, differentiation and function; reduce intestinal calcium absorption and increase renal calcium excretion, resulting in secondary hyperparathyroidism; and enhance osteoclast bone resorption.[1] Hypogonadism may result from glucorticoid suppression of pituitary function. These drugs also decrease muscle mass and muscle strength, contributing to further bone loss by decreased physical activity.

Bone loss is most pronounced in the first six months of glucocorticoid use, especially in areas of trabecular bone (eg., vertebrae), which are the predominant sites of fracture.[2] The risk of fracture increases rapidly within the first 3 months of glucocorticoid therapy.[3] However, both trabecular bone loss and cortical bone loss do occur over time.[4] During the second year of treatment bone loss continues, but at a slower rate.[4] Recovery after discontinuation of glucocorticoids may occur, but this is related to the dose of glucocorticoid used and its duration of use.[4] Whatever bone mineral has been lost is unlikely to be fully restored. The increased risk of fracture in patients taking glucocorticoids does decline rapidly in the first year off of therapy.[5]

Significant bone loss and risk of fracture are thought to occur when the daily dose of prednisone is >= 7.5 mg. Men and women of all ages, including children, can lose bone while taking long–term glucocorticoid therapy.

Budesonide is a topically acting glucocorticoid that undergoes extensive first-pass metabolism in the liver and thus has low systemic bioavailability. It is available as an oral controlled–release formulation that delivers drug selectively to the ileocolonic region of the gastrointestinal tract and is effective in patients with active ileocecal **Crohn's disease (CD)**. A controlled trial included 272 patients with CD involving the ileum and/or ascending colon who were randomly assigned to once daily budesonide or prednisolone for 2 years at doses adapted to disease activity.[6] Treatment with Budesonide was associated with significantly less loss of bone mass compared with prednisolone in only those patients with active ileocecal CD who were steroid-naïve. This advantage was not seen with budesonide in patients previously exposed to glucocorticoids or those who were glucocorticoid–dependent.

**...steroids have no benefit in maintenance of remission in IBD.**

## General Measures to Prevent and Treat Glucocorticoid-Induced Osteoporosis

Many of the prevention and treatment strategies for glucocorticoid–induced bone loss are similar to those used to prevent and treat other causes of osteoporosis; i.e., lifestyle modifications, calcium and vitamin D supplementation, and in some patients, pharmacologic therapy to minimize further bone loss or increase bone density.

Glucocorticoids should be avoided, if possible, in the treatment of active IBD. If they cannot be avoided, use the lowest possible effective dose for the shortest possible period of time. Budesonide is preferred over other steroids in mild-moderate CD involving the ileum and/or proximal colon. Steroid–sparing agents should be considered, including azathioprine/6–mercaptopurine, methotrexate, and biologic agents (see Treatment of IBD in previous issue). Topical therapies are preferred to systemic therapies, if possible. Surgical intervention should be considered when appropriate (see articles on surgery in IBD in March 2009 *Medicine & Health/Rhode Island* by Pricolo, Sturrock and Klipfel). It is important to emphasize that steroids have no benefit in maintenance of remission in IBD.

If glucocorticoids cannot be avoided, general preventive measures should be initiated, including:

- avoidance of cigarette smoking and excessive alcohol use
- fall prevention measures
- weight–bearing exercises for at least 30 minutes five times weekly
- Calcium and vitamin D supplementation

## Calcium and Vitamin D Supplementation

Glucocorticoids induce negative calcium balance by decreasing calcium absorption and increasing urinary calcium excretion. Calcium replacement may help restore positive calcium balance. The **American College of Rheumatology (ACR)** Task Force on Osteoporosis recommends that patients taking glucocorticoids maintain a calcium intake of 1000–1500 mg/day and Vitamin D intake of 800 IU/day through either diet or supplements.[7]

In one study evaluating calcium and Vitamin D supplementation in patients with rheumatoid arthritis treated with low dose glucocorticoid therapy, those receiving calcium and Vitamin D supplementation gained bone in the LS spine and trochanter at a rate of 0.7% and 0.8% per year, respectively[8] In those patients not receiving calcium or Vitamin D supplementation, bone was lost in the LS spine and trochanter at a rate of 2.0 % and 0.9% per year, respectively.

It is important to assess Vitamin D levels in patients with IBD. If patients are Vitamin D deficient, pharmacologic doses of Vitamin D should be prescribed. Careful monitoring of the serum and urinary calcium concentration is essential in order to prevent the complications of hypercalcemia, hypercalciuria, and nephrolithiasis.

Hydrochlorthiazide may reduce the hypercalciuria associated with glucocorticoid therapy[2] and may represent a good

choice for anti-hypertensive treatment in a hypertensive patient on glucocorticoids.

## Replacement of Gonadal Sex Hormones

Glucocorticoids may reduce the production of sex steroids, resulting in hypogonadism. A significant gain in BMD in estrogen–treated postmenopausal women taking glucocorticoids was demonstrated compared with progressive bone loss in those taking glucocorticoids with no estrogen replacement therapy.[9]

However, long term clinical trials of combined estrogen–progestin therapy in postmenopausal women demonstrated increased risks of breast cancer, myocardial infarction, stroke, and venous thromboembolism.[10] Therefore, estrogen is no longer viewed as a first-line drug for the prevention of postmenopausal osteoporosis.

The ACR Task Force does recommend oral contraceptive therapy for premenopausal women with oligomenorrhea or amenorrhea while taking glucocorticoids, if no contraindication exists.[7]

Because chronic glucocorticoid therapy can lower serum testosterone levels in men, those who take glucocorticoids regularly should have periodic serum testosterone determinations. Men with low serum levels of testosterone who are receiving glucocorticoids should receive testosterone replacement.[7] If testosterone replacement is to be initiated, assessment for possible prostatic carcinoma with digital rectal examination and PSA at baseline and yearly thereafter should be performed. Prostatic carcinoma is an absolute contraindication to testosterone replacement.

## Bisphosphonates

Anti–resorptive therapy with the bisphosphonates alendronate and risedronate have been shown to be effective for both the prevention and treatment of glucocorticoid–induced bone loss. The effect of alendronate on glucocorticoid–induced osteoporosis was studied in a 2 year trial of 477 men and women on glucocorticoid therapy.[11] Significant increases in mean LS BMD by 2.1 % and 2.9 % were seen with 5 mg. and 10 mg. of alendronate per day, respectively. Femoral neck density significantly increased by 1.2 % and 1.0 % in the respective alendronate groups. Those receiving alendronate had fewer new vertebral fractures compared with placebo.

Risendronate has also been studied among men and women on glucocorticoids and showed significant increases in LS and hip BMD. The relative risk of vertebral fracture was reduced by 70 % .[12]

Oral bisphosphonates have the potential to cause esophageal and gastric ulcers. Osteonecrosis of the jaw is an infrequent, devastating side effect of bisphosphonate therapy.[13] The majority of patients with this side effect received parenteral bisphosphonates in the setting of cancer treatment. It has also been rarely reported in patients receiving oral bisphosphonates. It can be triggered by dental surgery and by ill-fitted dentures.

Bisphosphonates are not approved for use in children. Premenopausal women and young men should not be treated with bisphosphonates in the absence of fracture history or evidence of accelerated bone loss.[4] Caution must be exercised when considering bisphosphonates in premenopausal women. Bisphosphonates cross the placenta, and there is potential for harm to the fetus in women who become pregnant while receiving or who have recently been treated with bisphosphonates.

## Parathyroid Hormone

PTH stimulates bone formation as well as resorption, and intermittent administration stimulates formation of bone more than resorption. Increases in lumbar spine BMD and markers of bone formation have been observed among those treated with PTH.[14] Markers of bone formation increased almost 150 % in the first 3 months of therapy, in contrast to markers of bone resorption, which increased only 100 %.

## Calcitonin

Calcitonin acts directly on osteoclasts to inhibit bone resorption. It causes a gain in bone mass of approximately 4-5 % when given parenterally at a daily dose of 100 IU.[4] This medication has not received approval for use in glucocorticoid-induced osteoporosis. It can, however, be considered in patients who cannot tolerate bisphosphonates.

## Management Approach

The AGA Medical Position Statement[2] recommends obtaining a DEXA scan in any patient with IBD with any of the following characteristics:

- prolonged glucocorticoid use (> 3 months consecutive or recurrent courses)
- history of low trauma fracture
- postmenopausal female or male age > 50
- hypogonadism

| | |
|---|---|
| If T score > -1: | - repeat DEXA in 2-3 years<br>- initiate basic preventive measures:<br>- adequate calcium/vitamin D;<br>- regular weight-bearing exercises;<br>- smoking cessation/ avoidance of excess alcohol;<br>- minimize glucocorticoids;<br>- consider correction of hypogonadism. |
| If T score - 2.5 to -1.0: | - repeat DEXA in 2 years<br>- initiate basic preventive measures (as cited above)<br>- if prolonged glucocorticoids consider bisphosphonates and repeat DEXA in 1 year. |
| If T score <- 2.5/or if vertebral compression fractures regardless of DEXA | - initiate basic preventive measures (as cited above)<br>- look for secondary causes of low bone density*<br>- bisphosphonate therapy; or<br>- refer to bone specialist |

*CBC, serum calcium, alkaline phosphatase, creatinine, 25-OH vitamin D, SPEP, testosterone (males). Additionally, consider TSH, liver profile and celiac antibodies.

## Summary

Osteoporosis secondary to glucocorticoid use is a potentially preventable disorder.

It is the role of the physician to establish and maintain disease remission, minimize the use of glucocorticoids, and initiate measures to prevent and treat bone loss.[4] The essentials of management include lifestyle modifications, nutritional interventions, and pharmacologic therapies. Bisphosphonates should be used when indicated.

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**Discussion of off-label or investigational drug:** Miacalcin


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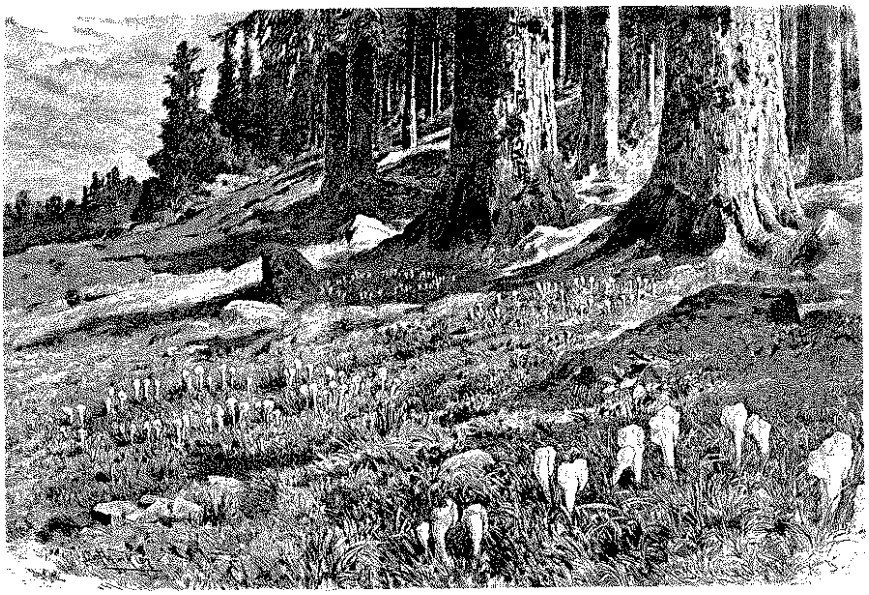

# Nutrition In Inflammatory Bowel Disease

*Neal S. LeLeiko, MD, PhD, Beth Pinkos, RD, Janet Trotta, PNP, David Kawatu, MD*

**An understanding of the pathogenesis of inflammatory bowel disease (IBD)** continues to be the major focus of IBD research.

Environmental factors contribute to the increased incidence of **Crohn's disease (CD)** and the changing incidences of IBD in groups of people who have migrated from areas with low disease incidence to areas of higher incidence. (See "Epidemiology of Inflammatory Bowel Disease and Overview of Pathogenesis," by Bruce E. Sands, MD, MS, and Stacey Grabert, PharmD, MS, in March 2009 *Medicine & Health/Rhode Island*).

It is now widely accepted that IBD represents a dysregulation of the immune response to intraluminal antigens. Evidence to date has failed to identify specific food antigens and has focused on bacterial antigens. Although no specific dietary antigen, toxin or diet product has been linked to IBD, both the lay and scientific communities are interested in this possibility. Studies of pre-illness diet have implicated some dietary components, most notably refined sugars[1] and a high fat diet.[2] The popular appeal of incriminating refined sugar and high fat as signs of "westernization" of diet reinforces the widespread appeal and frequent citation of these theories. The studies, however, have too many methodological problems[3] to be considered useful. Concern about nutritional deficiencies in IBD[4] as well as the role of nutrition in pediatric IBD[5] has been the subject of physician interest for many years.

## Nutritional Deficiencies in IBD

Recommendations for nutrient intake generally cited as "daily values" on most food labels are derived from the **Dietary Reference Intakes (DRI)** published by the Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences.[6] These values are intended as guidelines for healthy individuals and need to be used with caution as reference values for individuals with IBD. The DRIs consist of **Estimated Average Requirements (EAR)**, which should meet the needs of half the healthy individuals in the population based on scientific research; **Recommended Dietary Allowances (RDA)**, a level based on the EAR, adjusted to meet the requirements of 97-98% of the healthy population; **Adequate Intake (AI)**, based on observation and approximations because adequate data are not available, and designed to be at levels at which deficiency has not been observed; and **Tolerable Upper Limits (UL)**, the highest level of daily intake found to pose no risk in healthy people. The commonly cited level for energy (calories) is an EAR and is often referred to as **estimated energy requirement (EER)**; i.e., an average requirement for healthy individuals that will exceed the needs of half the population and be inadequate for the other half. The commonly cited level for protein, and most vitamins and minerals, is the RDA, a level that meets the needs of almost everyone (97-98%) and easily exceeds the needs of the average healthy person.

Physicians and patients often focus excessively on the intake of protein, vitamins and minerals at the expense of adequate attention to caloric intake. In children and in adults trying to heal damaged tissue, positive nitrogen balance is vital, but so are adequate dietary calories, to ensure that protein in the diet can be used to maximum efficiency. All components of nutrition are critical.

The actual impact of disease on nutritional status depends on the location, extent and side effects of the disease and its therapies.

There are five general mechanisms by which nutritional depletion may occur in patients with IBD: (1) reduced or unusual pattern of intake; (2) increased turnover of nutrients; (3) malabsorption; (4) pharmacological interactions with drugs; and (5) inability to utilize nutrients that are present. A great deal has been hypothesized and written about each of these mechanisms, but an understanding of the actual mechanisms may be less important than determining whether a deficiency is likely to occur or already exists, and correcting the problem.

## Altered Pattern of Intake

Reduced or unusual pattern of intake is common. Abdominal pain and diarrhea are inevitably associated with diet; rarely has a patient not attempted to reduce symptoms by altering his or her own diet. In addition to fad diets, we commonly see patients on low fat (low caloric density), low refined sugar (often less appetizing), lactose-free (low calcium), and low residue – "free of irritants" (often associated with low intake). Some patients gain symptomatic relief from some of these diets, but any restrictive diet increases the risk of being nutritionally incomplete. Furthermore, restrictions become cumulative and may exacerbate weight loss, nutrient deficiency, fatigue and general unhappiness of the patient.

## Increased Nutrient Turnover

Hypoalbuminemia is a well-recognized complication of IBD. Decreased serum levels of albumin may reflect decreased synthesis as a result of long-standing protein intake deficiency or excessive loss through the gut. When synthesis decreases, the normal breakdown of albumin adjusts to slow turnover. In addition, albumin in the extravascular space shifts into the vascular compartment. Decreased serum albumin viewed through the context of the body's attempt to compensate may reflect disease activity. To reflect disease activity, however, there must be adequate protein (and calorie) intake to maximize synthesis. Even in patients reporting mild to minimal symptoms, protein loss (as well as minerals, blood and electrolytes) has been consistently found in stools.

## Malabsorption of Fat

Malabsorption is incorrectly incriminated as a frequent cause of malnutrition in IBD. Fat is the most concentrated form of energy (9 kcal/gm versus 4 kcal/gm for carbohydrate and protein). Digestion of fat is generally unaffected by CD or UC. In small bowel disease fat absorption may be altered as a result of loss of surface area due to extensive involvement by inflammatory disease or resection. Bile salt pool

depletion may also result from these causes or from bacterial overgrowth with deconjugation of bile salts. This is especially a problem in areas with poor motility, i.e., stasis loops or stricturous disease.

Nonetheless, studies have consistently confirmed that despite frequent steatorrhea, significant impairment of fat absorption occurs only with extensive disease and most prominently after extensive bowel resection. Filipsson et al[7] report mild steatorrhea in 24% of patients with ileal disease. Ileal and ileocecal valve resection resulted in fat malabsorption in 48%. The extent of the malabsorption was highly correlated with the extent of ileal resection. In general, patients with resections reported to be less than 30 cm had minimal to mild steatorrhea. In the face of decreased intake or with increased demands for healing the "minimal" loss over time could become clinically relevant.

## Specific Nutrients

### Water Soluble Vitamins:

Oxalate, the metabolic breakdown product of Vitamin C (ascorbate), has been linked to renal stones. This relationship between high ascorbate (vitamin C) intake and oxalate stones has been increasingly questioned. In general it is probably prudent to avoid excessive and unnecessary intake of Vitamin C (above 2 grams) especially if there is coexisting fat malabsorption. Except for isolated case reports, water soluble vitamin deficiency is rare in IBD. The exceptions are Vitamin $B_{12}$ and Folate. Both have been associated with anemia in deficient patients. Anemia has been noted in IBD from the earliest descriptions of the disease. The actual pathophysiology is multifactorial and has not always been clear.

### Vitamin B12:

Vitamin B12 is absorbed in the terminal ileum. The body stores the vitamin so that depletion occurs only after a few years of decreased absorption or severe dietary restriction. Bacterial overgrowth may also contribute to depletion and should be monitored in patients with ileal disease and especially ileal resection. Depletion is directly proportional to the length of ileal resection, occurring in 71% of patients with 60-90 cm resection.[8]

### Folic acid:

Folic acid deficiency is common in IBD. The etiology may not be straightforward. Dyer[8] found that among 64% of patients with subnormal folate levels, the depletion was severe in 30%. There was a progressive fall in the RBC folate level as the disease became more active, and there was a positive correlation between serum and RBC folate. There was no correlation with disease location or prior resection. While some studies suggest that folate malabsorption may be significant, direct studies of folate absorption in small bowel CD have failed to show malabsorption.[9] Impaired folate absorption has been found in patients with CD and UC who have been taking 5-ASA compounds. These compounds seem to have a direct effect on folate absorption. Decreased intake of fruits and vegetables, the use of 5-ASA compounds, and a general increase in folate requirement in intestinal mucosal cells undergoing rapid turnover all contribute to risk for folate deficiency. Subacute combined degeneration of the spinal cord after ileal resection and folate supplementation in a Crohn's patient[4] serve as a reminder of the risks of supplementing folic acid while ignoring vitamin B12 requirements.

**...any restrictive diet increases the risk of being nutritionally incomplete.**

## Minerals

### Iron:

Iron deficiency is common in IBD. Dietary intakes are frequently low in CD, and probably also in UC. Blood loss exacerbates the effects of reduced intake. The anemia of CD may be similar to the anemia of chronic illness as manifested by increased levels of inflammatory cytokines, especially IL-6.[10] IL-6 had been associated with poor utilization of ingested iron and is probably an important determinant of iron deficiency in the IBD population.[10] Therefore, in addition to dietary iron supplementation, optimal disease control is very important for preventing iron deficiency.

### Calcium and Vitamin D:

Calcium and vitamin D must always be considered together. Calcium and Vitamin D deficiency are common in patients with CD.[11] The major circulating form of Vitamin D is 25-hydroxy vitamin D (25 OH-D, calcidiol). It is synthesized in the liver from vitamin D-2 (ergocalciferol), the commonly available form in the diet, and vitamin D-3 (cholecaliferol) which results from the action of sunlight on skin. The requirement for dietary vitamin D depends on exposure to sunlight. The actual requirement for vitamin D in the absence of sunlight is unknown. The final, metabolically active form of vitamin D is 1,25 dihydroxy-vitamin D (calcitriol) is responsible for stimulating intestinal absorption of calcium and phosphorous, renal tubular reabsorption of filtered calcium and the mobilization of calcium and phosphorous from bone. Osteoporosis in IBD may result from inadequate dietary calcium and/or vitamin D intake and may be exacerbated by inactivity and the use of corticosteroids. The widespread use of sunblock during the summer may also decrease the synthesis of Vitamin D3.

### Magnesium:

Magnesium deficiency can be associated with any form of chronic diarrhea. If malnutrition coexists, the risk is greater. Some patients with IBD may have received magnesium deficient intravenous fluid for the treatment of dehydration. Intestinal capacity for upregulating magnesium absorption is probably very limited and the use of corticosteroids promotes further loss. Magnesium is primarily an intracellular ion and serum levels may not reflect total body load. Symptomatic and asymptomatic hypomagnesemia have been described[4] in CD and IC.

### Zinc:

In the pediatric literature, zinc deficiency has been associated with growth failure. The techniques used to assess zinc adequacy are highly controversial. Low zinc levels in the serum probably are a reflection of general hypoproteinemia.

## Miscellaneous:

### Polyunsaturated fatty acids (PUFAs):

The omega-3 (w-3) polyunsaturated fatty acids have immunomodulary activities. Those from fish oil,

**eicosapentaenoic acid** (EPA) and **docosahexaenoic acid** (DHA) have been found to decrease levels of some of the pro-inflammatory cytokines. While there is a reasonable theoretical basis for expecting an anti-inflammatory effect from the dietary addition of PUFAs, existing data have failed to establish them as effective therapies.

### Antioxidants:

Antioxidants inhibit lipid peroxidation. There is considerable evidence to support biological effects of these agents. Disappointing results from the use of dietary antioxidants in other diseases (some bioflavinoids have been shown to increase lung cancer in former smokers[12,13]) warrant a careful approach to these agents. There is in general a greatly oversimplified view of these agents' possible benefits.

### Fiber:

All fiber is not the same. Additionally, each individual's bacterial flora may metabolize the fiber to different end-products. The basis for a therapeutic effect of fiber is the belief that the end product of fiber digestion consists of short-chain fatty acids that promote colonocyte health. Apart from the limitation of fiber in patients with stenotic lesions (where it can trigger obstruction, hence the rationale for "low residue diet"), the effects of fiber in IBD patients are unproven. Therefore, as long as fiber does not increase patient symptoms, it should represent the same portion of the diet as it would for any healthy individual. Additionally, some patients with IBD also have symptoms from irritable bowel syndrome. For those patients the fiber may offer significant relief.

### Pre and Probiotics:

Pre-biotics contain carbohydrate substrates that promote the growth of a particular microbial flora. Probiotics actually contain the bacterial flora. Because increasing evidence links the dysregulation of the immune system in IBD to altered response to intraluminal bacterial antigens, the use of flora altering agents is extremely appealing. The role for these agents is yet to be determined.

## Special Nutritional Regimens:

### Enteral Nutrition:

The potential for special defined formula diets to be used as primary therapy has been studied with varied and controversial results.[14,15] In general the use of special diets is reserved for nutritional rehabilitation (and occasionally nutritional maintenance) in an overall pharmacologically centered treatment plan. In general, these "formulas-in-a-can" are administered via a naso-gastric tube that can be placed nightly by the patient for supplementation during sleep. As adjunctive therapy in the well-motivated patient (children, for example, can easily accept this therapy), it removes anxiety about nutritional intake during the day.

## Parenteral Nutrition:

Like enteral nutrition total parenteral nutrition has been proposed as both primary treatment and adjunctive nutritional support. No large prospective studies establish TPN as a primary therapy. It is used in specific situations[15] almost always with other treatments. TPN is frequently employed as pre-surgical therapy to treat malnutrition and improve surgical outcome.

Both enteral and parenteral therapies are primary therapies for malnutrition. When malnutrition accompanies IBD, the choice of nutritional therapy is governed by clinical circumstances. The first goal is to provide therapy via the normal oral route. If this is not possible, then use of the enteral pathway via either a naso-gastric, naso-jejeunal, or gastrostomy device is necessary. Only when it is not possible to use the alimentary canal is TPN the treatment of choice. The focus of nutrition in IBD patient care must be to prevent malnutrition whenever possible.

## Long-term nutrition-Support:

Some patients with CD cannot use their gastrointestinal tracts, often because of severe disease or multiple intestinal resections leading to short-gut syndrome. Options are generally limited to long-term total parenteral nutrition. In lieu of TPN and its complications (most notably hepatic failure secondary to TPN-induced cholestasis), some patients face small bowel or liver-small bowel transplantation. This is becoming a more frequent problem at major multi-visceral transplantation cen-

**Nutritional Assessment of the Patient with Inflammatory Bowel Disease**

| | | |
|---|---|---|
| Subjective Assessment | Past course | Surgery (extent)<br>Medications<br>Special or fad diets<br>Adherence to medications/diet |
| | Current status | Emotional state<br>Psychological co-morbidities<br>Medications<br>Dietary habits |
| | Expected course | |
| Objective Assessment | | |
| Anthropometrics | BMI<br>Height<br>Weight<br>Weight loss<br>Annualized growth velocity*<br>Tanner Stage*<br>Mid arm circ, triceps fatfold | |
| Laboratory | CBC<br>Serum albumin, prealbumin<br>RBC folate, vit B12<br>Serum Fe, TIBC, ferritin<br>Calcium/PO4/magnesium, alkaline phosphatase<br>Cholesterol<br>Bone age*<br>25 hydroxy-vitamin D | |
| Possible | Prothrombin time<br>Vitamin A, E<br>Zinc | |

*Pediatric patients

**Nutrient Mechanisms of Deficiencies and Potential Supplementation**

| Nutrient | Mechanisms | | | Potential Supplements (must be individualized) ** see text |
|---|---|---|---|---|
| Energy (calories) | ↓ intake | ↑ loss with malabsorption | | |
| Iron | ↓ intake | ↑loss (bleeding) | | 60 mg/day (assuming repletion of stores) |
| Calcium | ↓intake,↓activity | ↑bone turnover, ↑ loss,↓absorption ↓ Vit D intake | Steroid meds | 1000mg/day+ Vitamin D |
| Vitamin D | ↓intake,↓sunlight | ↑sun blockers | | Up to 2000 iu with Calcium |
| DHA | ↓ diet | | | 1 gm/day |
| Magnesium | ↓ diet | ↑loss (diarrhea) | | 420 mg/day (elemental) |
| Folic Acid | ↓absorption | ↑loss, ↑cell turnover | ↓interaction with 5-ASA | 800 µgm (assuming adequate Vit $B_{12}$ status) |
| Vitamin B12 | ↓ intake | ↓ absorption (distal ileal rx) | | Requires parenteral (sub q inj or intra nasal route) |
| Probiotics Probiotics Antioxidants Fiber | ? | ? | ? | ??? |

ters. It is hoped that with the newer therapeutic agents, the occurrence of short-gut syndrome will become even rarer.

## Approach to Diet

The best advice is to consume a diet from a variety of sources. The more restricted the diet, the greater the risk of nutritional inadequacy. Protein is important but for most patients it is probably over-emphasized. In order to maximize the efficiency of protein in the diet, the diet must contain adequate calories (otherwise the protein is broken down, the carbon skeletons of the amino acids being burned as fuel and the $NH_3$ component metabolized and excreted as urea.) The energy content must be adequate to maintain weight in adults and provide calories for growth in children. Attention to providing adequate calories simplifies the assessment and provision of all other nutrients. An approach that emphasizes any particular nutrient without adequate attention to energy runs the risk of not meeting either energy requirements or the requirements for the particular nutrient of concern.

Liquid diets are of unproven benefit. There is reason to believe that in those motivated patients who are compliant with liquid supplements, the actual intake over time of other foods is decreased so that there is no net benefit. More importantly, the lack of variety of food consumed poses a real risk of nutrient deficiency.

While particular foods may cause distress for some patients, dietary restriction without clear-cut symptomatic improvement is not beneficial. Restricted diets can be counter productive if they either lead to boring, unappetizing meals that decrease the overall quality of life of the patient, or lead to reduced intake.

When a patient reports symptomatic improvement on a restricted diet of any sort it is imperative to assure that the diet is nutritionally adequate. This requires the professional assistance of a registered dietitian.

Except in specific circumstances, such as high-residue diets leading to excessive colonic bleeding, or symptoms of intestinal obstruction (in the setting of intestinal stricture) a full "normal" diet for age and culture is appropriate.

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# Inflammatory Bowel Disease in Pediatrics

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**Crohn's disease (CD) and ulcerative colitis (UC)** are chronic diseases characterized by unpredictable periods of disease activity and quiescence. Some patients suffer from almost continuous symptoms, others, only rare flares of disease activity. In addition to affecting the daily lives of patients, these diseases can dramatically alter family functioning and the patient's opportunity for becoming a productive adult. As difficult as it may be to manage adults with the disease, the problem of managing childhood disease is made more challenging by children's growth, their emotional and social development, and the knowledge that even after 30 years of complications of the disease and therapies, pediatric patients may just be entering the prime of their productive years. The difficult task of eventually transitioning the adolescent to adult health care providers presents additional challenges.

Current management practices are based on the use of old and new medications neither rigorously tested nor approved for use in children. In an effort to better define the contemporary natural history of IBD in children and augment current management practices, the Pediatric Inflammatory Bowel Disease Research Registry was established in 2002. Initially a collaboration of 21 centers in the US and Canada, this registry has produced several important advances in our understanding of IBD in children. Much of that research is reported in this review. The focus of this paper is to review current advances in pediatric IBD and to emphasize the need for more prospective research.

## IBD in the Pediatric Patient

CD is diagnosed most frequently in patients in their 20s and UC more commonly presents in patients in their 30s. Approximately 10% to 25% of IBD cases are diagnosed before adulthood.[1] Data suggest that presentation in childhood confers a risk of more extensive disease. In a study comparing phenotypic expression of disease, younger children (less than 5) tended to present with isolated colonic disease while those ages 6-17 demonstrated a statistically significant increase in small bowel involvement, predominantly ileocolonic in nature. Furthermore, older children had a more complicated disease course with increased risk for the development of an abscess, fistula, or stricture. While medical management of IBD is preferred, children with extensive disease are at risk for surgical interventions such as intestinal resection. In a retrospective study using data from six IBD centers, Gupta et al. observed surgical rates of 5.7% at one year, 17% at five years and 28.4 % at ten years in pediatric CD.[2] Prospective data from the Pediatric IBD Registry showed a 5% rate of Crohn's related surgery at 1 year and 13% at 4 years.[3] Thus, although treatment of CD primarily is medical, many patients will require surgery at some point.

**Communication with the child's school can be as important an intervention as providing medication.**

## Clinical Presentation

The clinical presentation of IBD typically involves chronic abdominal pain accompanied by some combination of weight loss, diarrhea, or hematochezia. (Table 1) Additionally, some patients may present with (or later develop) extra-intestinal manifestations. (Table 2) In the pediatric population, malnutrition, growth failure, and pubertal delay can be a significant component of disease presentation and morbidity. Between 25-80% of children newly diagnosed with CD will present with some degree of linear growth impairment. This may be attributed to sub-optimal oral intake, chronic inflammation and protein-losing enteropathy. The effects of corticosteroid treatment and chronically elevated inflammatory cytokines may further impair growth. Population trends towards a higher body mass index in children can complicate or delay the diagnosis of IBD in children. Registry data examining BMI in children with newly diagnosed IBD show that 10% of children with newly diagnosed CD and 30% with UC were categorized as overweight.[4]

## Laboratory Assessment

Laboratory evaluation of a patient with suspected IBD tends to focus on signs of chronic disease; e.g., microcytic anemia or hypoalbuminemia, as well as acute phase reactants such as ESR, **C-reactive protein (CRP)**, and thrombocytosis. These tests can establish the presence of an inflammatory illness. Recent IBD consortium data show that among children presenting with mild (more diagnostically challenging) disease, normal laboratory values (hemoglobin, platelet count, albumin,and ESR) were present in 21% of patients with mild CD and 54% with mild UC.[5] This suggests that the diagnosis of IBD should still be pursued in the patient with a clinical presentation consistent with IBD but with normal laboratory values.

## Measurement of Disease Activity

Pediatric gastroenterologists have used the subjective **Physicians Global Assessment (PGA)** for many years. For both clinical application and research purposes, objective quantitative tools to measure disease activity are crucial. Objective assessment of disease activity in children with CD now includes evaluation of pubertal status and the **Pediatric Crohn's Disease Activity Index (PCDAI)**. Assessment of pubertal status is performed clinically by assessing the appearance of secondary sex characteristics. The standard measurement used by pediatricians is the Tanner Stage, based on physical exam findings that focus on gender-specific changes that occur during breast, gonadal, and pubic hair development. A consensus of pediatric IBD experts developed the PCDAI in 1990; it was subsequently validated at 12 North American institutions. In comparison to the (adult) CDAI, the PCDAI decreases the importance given to subjective historical items adding instead height velocity, and adds ESR and albumin to the laboratory measurements. The PCDAI score can range from 0-100: a score

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Lialda tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. Safety and effectiveness of Lialda beyond 8 weeks have not been established.

Lialda is contraindicated in patients with hypersensitivity to salicylates (including mesalamine) or to any of the components of Lialda. Caution should be exercised when treating patients with pyloric stenosis or those allergic to sulfasalazine. Mesalamine has been associated with an acute intolerance syndrome (3% of patients in clinical trials with mesalamine or sulfasalazine) that may be difficult to distinguish from a flare of inflammatory bowel disease. If acute intolerance syndrome is suspected, prompt withdrawal is required. Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported. Reports of renal impairment have been associated with mesalamine medications. In patients with renal impairment, caution should be exercised, and Lialda should be used only if the benefits outweigh the risks. No information is available for patients with hepatic impairment.

Lialda is generally well tolerated. The majority of adverse events in the double-blind, placebo-controlled trials were mild or moderate in severity. In clinical trials (N=535), the most common treatment-related adverse events with Lialda 2.4g/day, 4.8g/day and placebo were headache (5.6%, 3.4% and 0.6%, respectively) and flatulence (4%, 2.8% and 2.8%, respectively). Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with Lialda.

Lialda® is a registered trademark of Shire LLC.
MMX® is a registered trademark owned by Cosmo Technologies Ltd, Ireland, a wholly-owned subsidiary of Cosmo Pharmaceuticals SpA.

**Please see brief summary of Full Prescribing Information on back page.**

**References: 1.** Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology*. 2007;132:66-75. **2.** Lichtenstein GR, Kamm MA, Boddu P, et al. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. *Clin Gastroenterol Hepatol*. 2007;5:95-102. **3.** IMS Health, NPA *Plus*™, Q1 08-Q2 08, TRXs.

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delayed release tablets
*The path to complete remission*

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(mesalamine)1.2g

delayed release tablets

**BRIEF SUMMARY:** Consult the Full Prescribing Information for complete product information.

## LIALDA™ (mesalamine) Delayed Release Tablets **Rx only**

### INDICATIONS AND USAGE

**LIALDA** tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. Safety and effectiveness of **LIALDA** beyond 8 weeks has not been established.

### CONTRAINDICATIONS

**LIALDA** is contraindicated in patients with hypersensitivity to salicylates (including mesalamine) or to any of the components of **LIALDA**.

### PRECAUTIONS

**General:** Patients with pyloric stenosis may have prolonged gastric retention of **LIALDA**, which could delay mesalamine release in the colon.

The majority of patients who are intolerant or hypersensitive to sulfasalazine can take mesalamine medications without risk of similar reactions. However, caution should be exercised when treating patients allergic to sulfasalazine.

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required.

Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported with other mesalamine medications. Caution should be taken in prescribing this medication to patients with conditions predisposing to the development of myocarditis or pericarditis.

**Renal:** Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with mesalamine medications and pro-drugs of mesalamine. For any patient with known renal dysfunction, caution should be exercised and **LIALDA** should be used only if the benefits outweigh the risks. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment. In animal studies with mesalamine, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis.

**Hepatic Impairment:** No information is available on patients with hepatic impairment, and therefore, caution is recommended in these patients.

**Information for Patients:** Patients should be instructed to swallow **LIALDA** tablets whole, taking care not to break the outer coating. The outer coating is designed to remain intact to protect the active ingredient, mesalamine, and ensure its availability throughout the colon.

**Drug Interaction:** No investigations have been performed between **LIALDA** and other drugs. However, the following are reports of interactions between mesalamine medications and other drugs. The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of renal reactions. In patients receiving azathioprine or 6-mercaptopurine, concurrent use of mesalamine can increase the potential for blood disorders.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 104-week dietary carcinogenicity study in CD-1 mice, mesalamine at doses up to 2500 mg/kg/day was not tumorigenic. This dose is 2.2 times the maximum recommended human dose (based on a body surface area comparison) of **LIALDA**. Furthermore, in a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose is 1.4 times the recommended human dose (based on a body surface area comparison) of **LIALDA**.

No evidence of mutagenicity was observed in an *in vitro* Ames test or an *in vivo* mouse micronucleus test.

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.7 times the maximum recommended human dose based on a body surface area comparison). Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with other mesalamine products during controlled clinical trials.

**Pregnancy:**

*Teratogenic Effects: Pregnancy Category B*

Reproduction studies with mesalamine have been performed in rats at doses up to 1000 mg/kg/day (1.8 times the maximum recommended human dose based on a body surface area comparison) and rabbits at doses up to 800 mg/kg/day (2.9 times the maximum recommended human dose based on a body surface area comparison) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Mesalamine is known to cross the placental barrier.

**Nursing Mothers:** Low concentrations of mesalamine and higher concentrations of its N-acetyl metabolite have been detected in human breast milk. While there is limited experience of lactating women using mesalamine, caution should be exercised if **LIALDA** is administered to a nursing mother, and used only if the benefits outweigh the risks.

**Pediatric Use:** Safety and effectiveness of **LIALDA** tablets in pediatric patients who are less than 18 years of age have not been studied.

**Geriatric Use:** Clinical trials of **LIALDA** did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concurrent disease or other drug therapy.

### ADVERSE REACTIONS

**LIALDA** tablets have been evaluated in 655 ulcerative colitis patients in controlled and open-label trials.

In two 8-week placebo-controlled clinical trials involving 535 ulcerative colitis patients, 356 received 2.4g/day or 4.8g/day **LIALDA** tablets and 179 received placebo. More treatment emergent adverse events occurred in the placebo group (119) than in each of the **LIALDA** treatment groups (109 in 2.4g/day, 92 in 4.8g/day). A lower percentage of **LIALDA** patients discontinued therapy due to adverse events compared to placebo (2.2% vs 7.3%). The most frequent adverse event leading to discontinuation from **LIALDA** therapy was exacerbation of ulcerative colitis (0.8%).

The majority of adverse events in the double blind, placebo-controlled trials were mild or moderate in severity. The percentage of patients with severe adverse events was higher in the placebo group (6.1% in placebo; 1.1% in 2.4g/day; 2.2% in 4.8g/day). The most common severe adverse events were gastrointestinal disorders which were mainly symptoms associated with ulcerative colitis. Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with **LIALDA** in patients experiencing this event.

Overall, the percentage of patients who experienced any adverse event was similar across treatment groups. Treatment related adverse events occurring in **LIALDA** or placebo groups at a frequency of at least 1% in two Phase 3, 8-week, double blind, placebo-controlled trials are listed in Table 3. The most common treatment related adverse events with **LIALDA** 2.4g/day and 4.8g/day were headache (5.6% and 3.4%, respectively) and flatulence (4% and 2.8%, respectively).

**Table 3. Treatment Related Adverse Events in Two Phase 3 Trials Experienced by at Least 1% of the LIALDA Group and at a Rate Greater than Placebo**

| Event | LIALDA 2.4g/day (n = 177) | LIALDA 4.8g/day (n = 179) | Placebo (n = 179) |
|---|---|---|---|
| Headache | 10 (5.6%) | 6 (3.4%) | 1 (0.6%) |
| Flatulence | 7 (4%) | 5 (2.8%) | 5 (2.8%) |
| Increased alanine aminotransferase | 1 (0.6%) | 2 (1.1%) | 0 |
| Alopecia | 0 | 2 (1.1%) | 0 |
| Pruritis | 1 (0.6%) | 2 (1.1%) | 0 |

The following treatment-related adverse events, presented by body system, were reported infrequently (less than 1%) by **LIALDA**-treated ulcerative colitis patients in controlled trials.

**Cardiovascular and Vascular:** tachycardia, hypertension, hypotension

**Dermatological:** acne, prurigo, rash, urticaria

**Gastrointestinal Disorders:** abdominal distention, diarrhea, pancreatitis, rectal polyp, vomiting

**Hematologic:** decreased platelet count

**Hepatobiliary Disorders:** elevated total bilirubin

**Musculoskeletal and Connective Tissue Disorders:** arthralgia, back pain

**Nervous System Disorders:** somnolence, tremor

**Respiratory, Thoracic and Mediastinal Disorders:** pharyngolaryngeal pain

**General Disorders and Administrative Site Disorders:** asthenia, face edema, fatigue, pyrexia

**Special Senses:** ear pain

### DRUG ABUSE AND DEPENDENCY

**Abuse:** None reported.

**Dependency:** Drug dependence has not been reported with chronic administration of mesalamine.

### OVERDOSAGE

There have been no reports of overdosage with **LIALDA**. **LIALDA** is an aminosalicylate, and symptoms of salicylate toxicity may include tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting, and diarrhea. Severe intoxication may lead to disruption of electrolyte balance and blood-pH, hyperthermia, and dehydration.

Although there has been no direct experience with **LIALDA**, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. This includes prevention of further gastrointestinal tract absorption by emesis and, if necessary, by gastric lavage. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained.

### DOSAGE AND ADMINISTRATION

The recommended dosage for the induction of remission in adult patients with active, mild to moderate ulcerative colitis is two to four 1.2g tablets to be taken once daily with meal for a total daily dose of 2.4g or 4.8g. Treatment duration in controlled clinical trials was up to 8 weeks.

Store at room temperature 15˚C to 25˚C (59˚F to 77˚F); excursions permitted to 30˚C (86˚F). See USP Controlled Room Temperature.

Manufactured for **Shire US Inc.**, 725 Chesterbrook Blvd., Wayne, PA 19087, USA.  U.S. Patent No. 6,773,720. by license of Giuliani S.p.A., Milan, Italy. Made in Italy. 476 1207 002B

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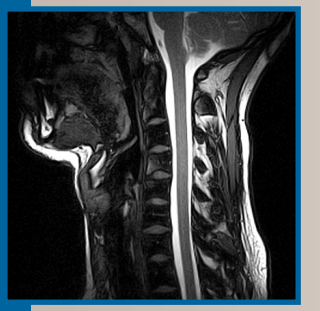

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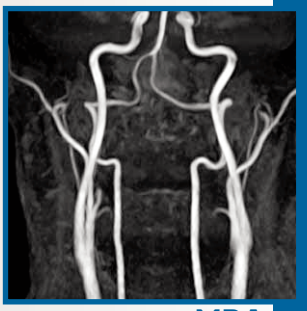

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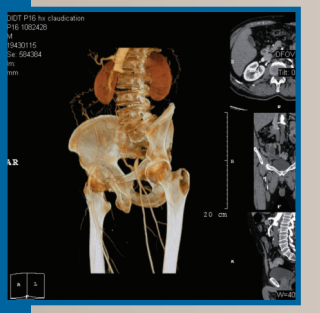

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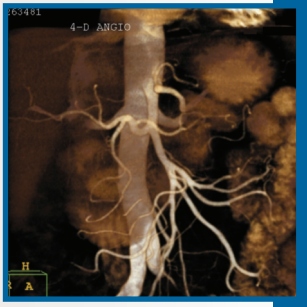
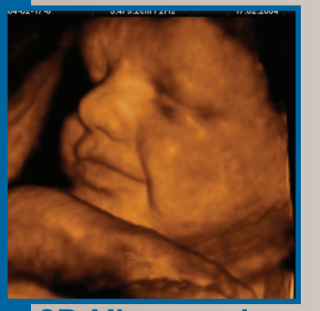
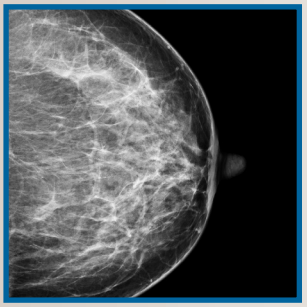


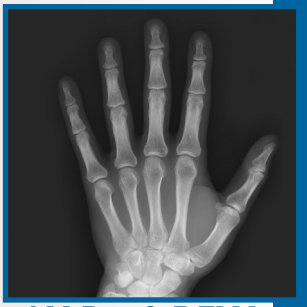

CTA



3D Ultrasound



Digital Mammography



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- **Proven** long-term remission
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- **Proven** fistula closure in Crohn's

## Unmatched Experience

- **More than one million patients** treated worldwide across all uses[1*]
- **Over 400,000 IBD patients** treated worldwide[1†]
- **Over 16 years of safety data** collected in 37 clinical trials[1]

**Please see Important Safety Information contained in this advertisement.**

REMICADE® is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

REMICADE® is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

REMICADE® is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

*As of August 2008. Uses include rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, and plaque psoriasis. **See full indication statements in Full Prescribing Information.**

†As of August 2008. Uses include Crohn's disease and ulcerative colitis.

Remicade®
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# IMPORTANT SAFETY INFORMATION FOR REMICADE®

## RISK OF INFECTIONS

**Patients treated with REMICADE® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue REMICADE® if a patient develops a serious infection or sepsis.**

**Reported infections include:**

- **Active tuberculosis (TB), including reactivation of latent TB. Patients frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before REMICADE® use and during therapy.[2,3] Treatment for latent infection should be initiated prior to REMICADE® use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, and pneumocystosis. Patients may present with disseminated, rather than localized, disease. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

**The risks and benefits of treatment with REMICADE® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with REMICADE®, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.**

## MALIGNANCIES

**HEPATOSPLENIC T-CELL LYMPHOMAS**

**Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with REMICADE®. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of these hepatosplenic T-cell lymphomas with REMICADE® have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine.**

In clinical trials of all TNF inhibitors, more cases of lymphoma were observed compared with controls and the expected rate in the general population. However, patients with Crohn's disease, rheumatoid arthritis, or plaque psoriasis may be at higher risk for developing lymphoma. In clinical trials of some TNF inhibitors, including REMICADE®, more cases of other malignancies were observed compared with controls. The rate of these malignancies among REMICADE®-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected. As the potential role of TNF inhibitors in the development of malignancies is not known, caution should be exercised when considering treatment of patients with a current or a past history of malignancy or other risk factors such as chronic obstructive pulmonary disease (COPD).

## CONTRAINDICATIONS

REMICADE® is contraindicated in patients with moderate to severe (NYHA Class III/IV) congestive heart failure (CHF) at doses greater than 5 mg/kg. Higher mortality rates at the 10 mg/kg dose and higher rates of cardiovascular events at the 5 mg/kg dose have been observed in these patients. REMICADE® should be used with caution and only after consideration of other treatment options. Patients should be monitored closely. Discontinue REMICADE® if new or worsening CHF symptoms appear. REMICADE® should not be (re)administered to patients who have experienced a severe hypersensitivity reaction or to patients with hypersensitivity to murine proteins or other components of the product.

## HEPATITIS B REACTIVATION

TNF inhibitors, including REMICADE®, have been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases were fatal. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating REMICADE®. Exercise caution when prescribing REMICADE® for patients identified as carriers of HBV and monitor closely for active HBV infection during and following termination of therapy with REMICADE®. Discontinue REMICADE® in patients who develop HBV reactivation and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of REMICADE® and monitor patients closely.

## HEPATOTOXICITY

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported rarely in patients receiving REMICADE® postmarketing. Some cases were fatal or required liver transplant. Aminotransferase elevations were not noted prior to discovery of liver injury in many cases. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develop, REMICADE® should be discontinued, and a thorough investigation of the abnormality should be undertaken.

## HEMATOLOGIC EVENTS

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some fatal, have been reported. The causal relationship to REMICADE® therapy remains unclear. Exercise caution in patients who have ongoing or a history of significant hematologic abnormalities. Advise patients to seek immediate medical attention if they develop signs and symptoms of blood dyscrasias or infection. Consider discontinuation of REMICADE® in patients who develop significant hematologic abnormalities.

## HYPERSENSITIVITY

REMICADE® has been associated with hypersensitivity reactions that differ in their time of onset. Acute urticaria, dyspnea, and hypotension have occurred in association with REMICADE® infusions. Serious infusion reactions including anaphylaxis were infrequent. Medications for the treatment of hypersensitivity reactions should be available.

## NEUROLOGIC EVENTS

TNF inhibitors, including REMICADE®, have been associated with rare cases of new or exacerbated symptoms of demyelinating disorders including multiple sclerosis, optic neuritis, and Guillain–Barré syndrome, seizure, and CNS manifestations of systemic vasculitis. Exercise caution when considering REMICADE® in all patients with these disorders. Consider discontinuation for significant CNS adverse reactions.

25IN08522

**Please see Brief Summary of Full Prescribing Information accompanying this advertisement.**

**References: 1.** Data on file. Centocor Ortho Biotech Inc. **2.** American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med.* 2000;161:S221–S247. **3.** See latest Centers for Disease Control guidelines and recommendations for tuberculosis testing in immunocompromised patients.

**REMICADE® (infliximab) for IV Injection Brief Summary** See package insert for Full Prescribing Information.

**WARNINGS**

**RISK OF SERIOUS INFECTIONS**

**Patients treated with REMICADE are at increased risk for developing serious infections that may lead to hospitalization or death (see WARNINGS and ADVERSE REACTIONS). Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.**

**REMICADE should be discontinued if a patient develops a serious infection or sepsis.**

**Reported infections include:**

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before REMICADE use and during therapy.[1,2] Treatment for latent infection should be initiated prior to REMICADE use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

**The risks and benefits of treatment with REMICADE should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.**

**HEPATOSPLENIC T-CELL LYMPHOMAS**

**Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with REMICADE. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of these hepatosplenic T-cell lymphomas with REMICADE have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine.**

**CONTRAINDICATIONS:** REMICADE at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), REMICADE treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure (see *WARNINGS* and *ADVERSE REACTIONS, Patients with Heart Failure*). REMICADE should not be re-administered to patients who have experienced a severe hypersensitivity reaction to REMICADE. Additionally, REMICADE should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins. **WARNINGS: RISK OF SERIOUS INFECTIONS (See *Boxed WARNINGS*) Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving TNF-blocking agents. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported. Patients have frequently presented with disseminated rather than localized disease, and are often taking concomitant immunosuppressants such as methotrexate or corticosteroids with REMICADE. Treatment with REMICADE should not be initiated in patients with an active infection, including clinically important localized infections. The risks and benefits of treatment should be considered prior to initiating therapy in patients: • with chronic or recurrent infection; • who have been exposed to tuberculosis; • who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or • with underlying conditions that may predispose them to infection. Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving REMICADE, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating REMICADE and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating REMICADE, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG). Anti-tuberculosis therapy should also be considered prior to initiation of REMICADE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection.[3] Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Tuberculosis should be strongly considered in patients who develop a new infection during REMICADE treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with REMICADE. REMICADE should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with REMICADE should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated. For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. Serious infections were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of REMICADE and anakinra is not recommended. HEPATOSPLENIC T-CELL LYMPHOMAS (See *Boxed WARNINGS*) Rare postmarketing cases of hepatosplenic T-cell lymphomas have been reported in adolescent and young adult patients with Crohn's disease treated with REMICADE. All of these reports have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine. The clinical course of this disease is very aggressive with a fatal outcome in most patients within 2 years of diagnosis.[4] The causal relationship of hepatosplenic T-cell lymphoma to REMICADE therapy remains unclear. Hepatitis B Virus Reactivation** Use of TNF blockers, including REMICADE has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers, including REMICADE, for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely. **Hepatotoxicity** Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury (see *ADVERSE REACTIONS, Hepatotoxicity*). **Patients with Heart Failure** REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear. (See *CONTRAINDICATIONS* and *ADVERSE REACTIONS, Patients with Heart Failure*.) **Hematologic Events** Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities. **Hypersensitivity** REMICADE has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE infusion. However, in some cases, serum sickness-like reactions have been observed in patients after initial REMICADE therapy (i.e., as early as after the second dose), and when REMICADE therapy was reinstituted following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema, and/or dysphagia. These reactions were associated with marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE should be discontinued for severe hypersensitivity reactions (see also *CONTRAINDICATIONS*). Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids, and/or epinephrine) should be available for immediate use in the event of a reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*). **Neurologic Events** REMICADE and other agents that inhibit TNF have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and CNS manifestation of systemic vasculitis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of demyelinating or seizure disorders. Discontinuation of REMICADE should be considered in patients who develop significant CNS adverse reactions. **Malignancies** In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis (RA), Crohn's disease (CD), psoriatic arthritis (PsA), ankylosing spondylitis (AS), ulcerative colitis (UC), and plaque psoriasis (PsO), 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected. In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients developed lymphomas among 5707 patients treated with REMICADE (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In RA patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for RA, CD, PsA, AS, UC, and PsO, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately 4-fold higher than expected in the general population. Patients with CD, RA or PsO, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking (see *ADVERSE REACTIONS*; *Malignancies*). Prescribers should exercise caution when considering the use of REMICADE in patients with moderate to severe COPD. Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for REMICADE, NMSCs were more common in patients with previous phototherapy (see *ADVERSE REACTIONS*; *Adverse Reactions in Psoriasis Studies*). The potential role of TNF-blocking therapy in the development of malignancies is not known (see *ADVERSE REACTIONS*; *Malignancies*). Rates in clinical trials for REMICADE cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving REMICADE. **PRECAUTIONS: Autoimmunity** Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE, treatment should be discontinued (see *ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome*). **Vaccinations** No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently. It is recommended that all pediatric CD patients be brought up to date with all vaccinations prior to initiating REMICADE therapy. The interval between vaccination and initiation of REMICADE therapy should be in accordance with current vaccination guidelines. **Information for Patients: Patients developing signs and symptoms of infection should seek medical evaluation immediately**. Patients or their caregivers should be provided the REMICADE Medication Guide and provided an opportunity to read it and ask questions prior to each treatment infusion session. Because caution should be exercised in administering REMICADE to patients with clinically important active infections, it is important that the patient's overall health be assessed at each treatment visit and any questions resulting from the patient's or caregiver's reading of the Medication Guide be discussed. **Drug Interactions** Concurrent administration of etanercept (another TNFα-blocking agent) and anakinra (an interleukin-1 receptor antagonist) has been associated with an increased risk of serious infections, and increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Other TNFα-blocking agents (including REMICADE) used in combination with anakinra may also result in similar toxicities (see *WARNINGS, RISK OF SERIOUS INFECTIONS*). Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in RA or CD clinical studies received one or more concomitant medications. In RA concomitant medications besides MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids, and/or narcotics. Concomitant CD medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA, and aminosalicylates. In PsA clinical trials, concomitant medications included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory agents, folic acid and corticosteroids. Patients with CD who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants (see *ADVERSE REACTIONS, Immunogenicity* and *Infusion-related Reactions*). Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of CD including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates. **Carcinogenesis, Mutagenesis and Impairment of Fertility** A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. cV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg, or 40 mg/kg cV1q given weekly for

6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for CD. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. The significance of these findings for human risk is unknown. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study. **Pregnancy Category B** Since infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed. **Nursing Mothers** It is not known whether REMICADE is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from REMICADE, women should not breast-feed their infants while taking REMICADE. 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** REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active CD who have had an inadequate response to conventional therapy (see *Boxed WARNINGS, WARNINGS, INDICATIONS AND USAGE, PRECAUTIONS, Vaccinations, DOSAGE AND ADMINISTRATION, CLINICAL STUDIES, Active Crohn's Disease in Pediatric Patients* and *ADVERSE REACTIONS, Adverse Reactions in Pediatric Crohn's Disease*). REMICADE has not been studied in children with CD <6 years of age. The longer term (greater than one year) safety and effectiveness of REMICADE in pediatric CD patients have not been established in clinical trials. Safety and effectiveness of REMICADE in pediatric patients with UC and PsO have not been established. The safety and efficacy of REMICADE in patients with juvenile rheumatoid arthritis (JRA) were evaluated in a multicenter, randomized, placebo-controlled, double-blind study for 14 weeks, followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. Patients with active JRA between the ages of 4 and 17 years who had been treated with MTX for at least 3 months were enrolled. Concurrent use of folic acid, oral corticosteroids (≤0.2 mg/kg/day of prednisone or equivalent), NSAIDs, and/or DMARDS was permitted. Doses of 3 mg/kg REMICADE or placebo were administered intravenously at Weeks 0, 2 and 6. Patients randomized to placebo crossed-over to receive 6 mg/kg REMICADE at Weeks 14, 16, and 20, and then every 8 weeks through Week 44. Patients who completed the study continued to receive open-label treatment with REMICADE for up to 2 years in a companion extension study. The study failed to establish the efficacy of REMICADE in the treatment of JRA. Key observations in the study included a high placebo response rate and a higher rate of immunogenicity than what has been observed in adults. Additionally, a higher rate of clearance of infliximab was observed than had been observed in adults (see *CLINICAL PHARMACOLOGY, Pharmacokinetics*). A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg REMICADE was 35% (21/60) over 52 weeks compared with 18% (10/57) in patients who received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting, fever, headache, and hypotension. In the 3 mg/kg REMICADE group, 4 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg REMICADE group, 2 patients had a serious infusion reaction, one of whom had a possible anaphylactic reaction. Two of the 6 patients who experienced serious infusion reactions received REMICADE by rapid infusion (duration of less than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3 mg/kg REMICADE compared with 12% (6/49) of patients who received 6 mg/kg. A total of 68% (41/60) of patients who received 3 mg/kg REMICADE in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg REMICADE in combination with MTX over 38 weeks. The most commonly reported infections were upper respiratory tract infection and pharyngitis and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient. **Geriatric Use** In RA and PsO clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with RA and 75 patients with PsO, aged 65 or older who received REMICADE, compared to younger patients although the incidence of serious adverse events in patients aged 65 or older was higher in both REMICADE and control groups compared to younger patients. In CD, UC, AS, and PsA studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (see *ADVERSE REACTIONS, Infections*). **ADVERSE REACTIONS:** The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients with RA, 1106 patients with CD, 202 with AS, 293 with PsA, 484 with UC, 1373 with PsO, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond one year. (For information on adverse reactions in pediatric patients see *ADVERSE REACTIONS, Adverse Reactions in Pediatric Crohn's Disease*.) One of the most common reasons for discontinuation of treatment was infusion-related reactions (e.g. dyspnea, flushing, headache and rash). Adverse events have been reported in a higher proportion of RA patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in patients with CD. **Infusion-related Reactions** *Infusion reactions*. An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated patients in all clinical studies experienced an infusion reaction compared to approximately 10% of placebo-treated patients. Among all REMICADE infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infusion reaction rates remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion reactions (i.e., an adverse event occurring within 1 to 2 hours) was 7% in the 3 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group. Patients who became positive for antibodies to infliximab were more likely (approximately 2- to 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and infusion reactions (see *ADVERSE REACTIONS, Immunogenicity* and *PRECAUTIONS, Drug Interactions*). In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with REMICADE administration. *Delayed Reactions/Reactions following readministration. Plaque Psoriasis* In psoriasis studies, approximately 1% of REMICADE-treated patients experienced a possible delayed hypersensitivity reaction, generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within two weeks after repeat infusion. *Crohn's disease* In a study where 37 of 41 patients with CD were retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year. **Infections** In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE and may reflect recrudescence of latent disease (see *WARNINGS, RISK OF SERIOUS INFECTIONS*). In the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54 weeks Crohn's II Study, 15% of patients with fistulizing CD developed a new fistula-related abscess. In REMICADE clinical studies in patients with UC, infections treated with antimicrobials were reported in 27% of REMICADE-treated patients (average of 41 weeks of follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of infections, including serious infections, reported in patients with UC were similar to those reported in other clinical studies. In post-marketing experience in the various indications, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving REMICADE alone or in combination with immunosuppressive agents. The onset of serious infections may be preceded by constitutional symptoms such as fever, chills, weight loss, and fatigue. The majority of serious infections, however, may also be preceded by signs or symptoms localized to the site of the infection. **Autoantibodies/Lupus-like Syndrome** Approximately half of REMICADE-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately one-fifth of REMICADE-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon. **Malignancies** In controlled trials, more REMICADE-treated patients developed malignancies than placebo-treated patients (see *WARNINGS, Malignancies*). In a randomized controlled clinical trial exploring the use of REMICADE in patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were treated with REMICADE at doses similar to those used in RA and CD. Nine of these REMICADE-treated patients developed a malignancy, including 1 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 3.51-14.56). There was one reported malignancy among 77 control patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04-9.10). The majority of the malignancies developed in the lung or head and neck. Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving REMICADE during post-approval use. **Patients with Heart Failure** In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. There were trends towards increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II) (see *CONTRAINDICATIONS* and *WARNINGS, Patients with Heart Failure)*. **Immunogenicity** Treatment with REMICADE can be associated with the development of antibodies to infliximab. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in CD patients receiving REMICADE after drug free intervals >16 weeks. In a study of PsA, where 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*) than were patients who were antibody negative. Antibody development was lower among RA and CD patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients treated with 5 mg/kg induction (Weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for one year and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in psoriasis patients as compared to patients with other diseases treated with REMICADE over the long term is not known. The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading. **Hepatotoxicity** Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving REMICADE (see *WARNINGS*, *Hepatotoxicity*). Reactivation of hepatitis B virus has occurred in patients receiving TNF-blocking agents, including REMICADE who are chronic carriers of this virus (see *WARNINGS*, *Hepatitis B Virus Reactivation*). In clinical trials in RA, CD, UC, AS, PsO and PsA, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls, both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications. In RA clinical trials (median follow-up 58 weeks), 34% of patients who received REMICADE + MTX experienced elevations in ALT at >1 to <3 times the upper limit of normal (ULN) compared to 24% of patients treated with placebo + MTX. ALT elevations ≥3 times ULN were observed in 4% of patients who received REMICADE + MTX compared with 3% of patients who received MTX alone. ALT elevations ≥5 times ULN were observed in <1% of patients in both REMICADE + MTX and MTX alone groups. In CD clinical trials (median follow up 54 weeks), 39% of patients receiving REMICADE-maintenance experienced elevations in ALT at >1 to <3 times the ULN compared to 34% of patients treated with placebo-maintenance. ALT elevations ≥3 times the ULN were observed in 5% of patients who received REMICADE-maintenance compared with 4% of patients who received placebo-maintenance. ALT elevations ≥5 times ULN were observed in 2% of patients who received REMICADE-maintenance compared to none in patients treated with placebo-maintenance. In UC clinical trials (median follow up 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for REMICADE.), 17% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 12% of patients treated with placebo. ALT elevations ≥3 times the ULN were observed in 2% of patients who received REMICADE compared with 1% of patients who received placebo. ALT elevations ≥5 times ULN were observed in <1% of patients in both REMICADE and placebo groups. In an AS clinical trial (median follow up 24 weeks for placebo group and 102 weeks for REMICADE goup) 51% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 15% of patients treated with placebo. ALT elevations ≥3 times the ULN were observed in 10% of patients who received

REMICADE compared to none in patients who received placebo. ALT elevations ≥5 times ULN were observed in 4% of patients who received REMICADE compared to none in patients treated with placebo. In a PsA clinical trial (median follow up 39 weeks for REMICADE group and 18 weeks in placebo group) 50% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 16% of patients treated with placebo. ALT elevations ≥3 times the ULN were observed in 7% of patients who received REMICADE compared to none in patients who received placebo. ALT elevations ≥5 times ULN were observed in 2% of patients who received REMICADE compared to none in patients treated with placebo. In PsO clinical trials, (ALT values are obtained in 2 phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and 16 weeks for placebo). 49% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 24% of patients treated with placebo. ALT ≥3 x ULN were observed in 8% of patients who received REMICADE compared to <1% who received placebo. ALT elevations ≥5 x ULN were observed in 3% of patients who received REMICADE compared to none in patients treated with placebo. **Adverse Reactions in Pediatric Crohn's Disease** There were some differences in the adverse reactions observed in the pediatric patients receiving REMICADE compared to those observed in adults with CD. The following adverse events were reported more commonly in 103 randomized pediatric CD patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult CD patients receiving a similar treatment regimen: anemia (11%), blood in stool (10%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%). Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more frequently for patients who received every 8 week as opposed to every 12 week infusions (74% and 38%, respectively), while serious infections were reported for 3 patients in the every 8 week and 4 patients in the every 12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8 week and 1 in the every 12 week maintenance treatment groups). Herpes zoster was reported for 2 patients in the every 8 week maintenance treatment group. In Study Peds Crohn's, 18% of randomized patients experienced one or more infusion reactions, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's, there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions. Antibodies to REMICADE developed in 3% of pediatric patients in Study Peds Crohn's. Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in CD clinical trials; 4% had ALT elevations ≥3 x ULN, and 1% had elevations ≥5 x ULN. (Median follow-up was 53 weeks.) **Adverse Reactions in Psoriasis Studies** During the placebo-controlled portion across the three clinical trials up to Week 16, the proportion of patients who experienced at least 1 SAE (defined as resulting in death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 1.7% in the 3 mg/kg REMICADE group, 3.2% in the placebo group, and 3.9% in the 5 mg/kg REMICADE group. Among patients in the 2 Phase 3 studies, 12.4% of patients receiving REMICADE 5 mg/kg every 8 weeks through one year of maintenance treatment experienced at least 1 SAE in Study I. In Study II, 4.1% and 4.7% of patients receiving REMICADE 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through one year of maintenance treatment experienced at least 1 SAE. One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg REMICADE. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving REMICADE 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1 serious infection. The most common serious infections (requiring hospitalization) were abscesses (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg REMICADE group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting REMICADE. In placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received REMICADE at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients who received placebo. In the psoriasis studies, 1% (15/1373) of patients experienced serum sickness or a combination of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints, and immobility. **Other Adverse Reactions** Safety data are available from 4779 REMICADE-treated adult patients, including 1304 with RA, 1106 with CD, 484 with UC, 202 with AS, 293 with PsA, 1373 with PsO and 17 with other conditions. (For information on other adverse reactions in pediatric patients, see *ADVERSE REACTIONS, Adverse Reactions in Pediatric Crohn's Disease*.) Adverse events reported in ≥5% of all patients with RA receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated RA, AS, PsA, PsO and CD patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with CD. In the CD studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons. The percentages of adverse events for placebo-treated patients (n=350; average weeks of follow-up 59) and REMICADE-treated patients (n=1129; average weeks of follow-up 66), respectively, are: *Gastrointestinal:* Nausea: 20, 21; Abdominal pain: 8, 12; Diarrhea: 12, 12; Dyspepsia: 7, 10; *Respiratory:* Upper respiratory tract infection: 25, 32; Sinusitis: 8, 14; Pharyngitis: 8, 12; Coughing: 8, 12; Bronchitis: 9, 10; Rhinitis: 5, 8; *Skin and appendages disorders:* Rash: 5, 10; Pruritis: 2, 7; *Body as a whole—general disorders:* Fatigue: 7, 9; Pain: 7, 8; *Resistance mechanism disorders:* Fever: 4, 7; Moniliasis: 3, 5; *Central and peripheral nervous system disorders:* Headache: 14, 18; *Musculoskeletal system disorders:* Back pain: 5, 8; Arthralgia: 7, 8; *Urinary system disorders:* Urinary tract infection: 6, 8; *Cardiovascular disorders, general:* Hypertension: 5, 7. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice. The most common serious adverse events observed in clinical trials were infections (see *ADVERSE REACTIONS, Infections*). Other serious, medically relevant adverse events ≥0.2% or clinically significant adverse events by body system were as follows: *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela; *Blood:* pancytopenia; *Cardiovascular:* circulatory failure, hypotension, syncope; *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia; *Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness; *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia; *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis; *Metabolic and Nutritional:* dehydration; *Musculoskeletal:* intervertebral disk herniation, tendon disorder; *Myo-, Endo-, Pericardial, and Coronary Valve:* myocardial infarction; *Platelet, Bleeding, and Clotting:* thrombocytopenia; *Neoplasms:* basal cell, breast, lymphoma; *Psychiatric:* confusion, suicide attempt; *Red Blood Cell:* anemia, hemolytic anemia; *Reproductive:* menstrual irregularity; *Resistance Mechanism:* cellulitis, sepsis, serum sickness; *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency; *Skin and Appendages:* increased sweating, ulceration; *Urinary:* renal calculus, renal failure; *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis; *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy. **Post-marketing Adverse Events** The following adverse events, some with fatal outcome, have been reported during post-approval use of REMICADE: neutropenia (see *WARNINGS, Hematologic Events*), interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and very rare rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), psoriasis (including new onset and pustular, primarily palmar/plantar), transverse myelitis, and neuropathies (additional neurologic events have also been observed, see *WARNINGS, Neurologic Events*) and acute liver failure, jaundice, hepatitis, and cholestasis (see *WARNINGS, Hepatotoxicity*). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure. The following serious adverse events have been reported in the post-marketing experience in children: infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions, and hypersensitivity reactions. Serious adverse events in the post-marketing experience with REMICADE in the pediatric population have also included malignancies, including hepatosplenic T-cell lymphomas (see *Boxed WARNINGS* and *WARNINGS*), transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies. **OVERDOSAGE:** Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. **Administration Instructions Regarding Infusion Reactions** Adverse effects during administration of REMICADE have included flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin rashes. Anaphylaxis might occur at any time during REMICADE infusion. Approximately 20% of REMICADE-treated patients in all clinical trials experienced an infusion reaction compared with 10% of placebo-treated patients (see *ADVERSE REACTIONS, Infusion-related Reactions*). Prior to infusion with REMICADE, premedication may be administered at the physician's discretion. Premedication could include antihistamines (anti-H1 +/- anti-H2), acetaminophen and/or corticosteroids. During infusion, mild to moderate infusion reactions may improve following slowing or suspension of the infusion, and upon resolution of the reaction, reinitiation at a lower infusion rate and/or therapeutic administration of antihistamines, acetaminophen, and/or corticosteroids. For patients that do not tolerate the infusion following these interventions, REMICADE should be discontinued. During or following infusion, patients that have severe infusion-related hypersensitivity reactions should be discontinued from further REMICADE treatment. The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs.

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**Table 1 Symptoms at the time of diagnosis of IBD in Children < 18**

| Sign/Symptom | Crohn's Disease | Ulcerative Colitis |
|---|---|---|
| Abdominal Pain | 72-86% | ~60% |
| Diarrhea | 56-80% | ~87% |
| Rectal Bleeding | 22-49% | ~92% |
| Growth failure* | 25-88% | 15-25% |
| Weight Loss | 22-59% | ~46% |
| Fever | ~44% | ~30% |
| Perianal skin tags[17] | 5% | N/A |
| Perianal disease (fistula, fissures)[17] | 10% | N/A |
| Arthralgia | 8-17% | ~8% |
| Skin or eye complaints | 1-8%% | ~4% |

(adapted from numerous sources)

of <10 distinguishes inactive vs. active disease; 10-30 = mild disease; > 30 = moderate-severe disease. A decrease of 12.5 points is taken as evidence of improvement.

The PCDAI has been further validated along with the **physician global assessment (PGA)** in multi-center trials.[6] The study concluded that the PCDAI accurately reflects disease activity and is an appropriate tool for intervention trials in CD in children. The PCDAI is able to show short term (3 month) changes in patient condition, even though the growth velocity is unlikely to change over 3 months. In long-term trials, changes in growth parameters would be reflected in the PCDAI rather than the CDAI. The PCDAI has become the standard for quantifying pediatric CD activity.

The recently validated **Pediatric Ulcerative Colitis Activity Index (PUCAI)** is used to quantify changes in disease activity in children with UC.[7] The PUCAI assesses bowel frequency, consistency, presence of blood, nighttime diarrhea and limitation of normal activities. It does not rely on any laboratory findings

## Psychosocial Aspects of Disease

Symptomatic disease can result in frequent, sometimes prolonged hospitalizations requiring school absence. Some children face frequency and urgency to move their bowels, an embarrassing situation if they are unable to access a private restroom at school. Communication with the child's school can be as important an intervention as providing medication.

Furthermore, recent data suggest that adolescents may have less than 50% adherence to IBD drug regimens.[8] While the younger child may focus on symptomatic complaints, teenagers often struggle with regimented medication schedules and the social implications of chronic steroid exposure (i.e. cushingoid features and facial acne). A diagnosis of IBD in the pediatric patient has the potential to have devastating effects on quality of life.

In evaluating **health-related quality of life (HRQOL)** in the first year after diagnosis, the pediatric IBD registry administered a validated questionnaire (IMPACT II) to 218 patients over the age of nine. Initial assessment demonstrated expected significant differences between those presenting with mild, moderate and severe disease phenotypes. However, re-evaluation at 6 months and again at 1 year demonstrated statistically significant improvements in HRQOL overall.[9] These data stressed the importance of successful induction and maintenance of remission. The challenge is finding the balance between aggressive disease management and acceptable risk to the patient.

## IBD Management in the Pediatric Patient

While generally the goals of managing IBD in children and adults are similar, there are important differences, based on the developmental stages of the patient. Therapeutic goals focus on achieving symptomatic control and mucosal healing; however, the ultimate challenge and underlying responsibility of the pediatric practitioner is ensuring that the child live as normal a life as possible and eventually become a productive member of adult society. Medications used for medical management are summarized in Table 3 (medications discussed in detail in previous issue by Harris et al).

Mild disease is generally treated with 5-aminosalicylate compounds. Antibiotics may also be employed. While these medications are considered less potent and often well tolerated, they are not without side effects. Clearly the child on chronic antibiotics is at risk for development of resistant organisms and infection with toxigenic strains of *Clostridium difficile* as well as fungal infections. For distal disease (proctitis) topical therapy is available in the form of steroid enemas and mesalamine enemas, foams and suppositories. Despite effectiveness in some

**Table 2 Extraintestinal Manifestations of Inflammatory Bowel Disease**

| Site | Manifestation |
|---|---|
| Skin | Erythema nodosum, pyoderma gangrenosum, metastatic Crohn's disease (especially around mucous membranes) |
| Liver | Steatosis, nonspecific transaminitis, chronic hepatitis, sclerosing cholangitis, cholelithiasis, acalculous cholecystitis, Budd-Chiari syndrome |
| Bone | Osteopenia, aseptic necrosis |
| Joint | Arthralgias, arthritis, ankylosing spondylitis, sacroiliitis |
| Eye | Uveitis, episcleritis, keratitis,glaucoma (2° to steroids) |
| Uro-gynecologic | Nephrolithiasis, obstructive hydronephrosis, enterovesical fistula, recto-vaginal fistula, nephritis, amyloidosis |
| Hematologic | Anemia (iron, folate, B12, autoimmune hemolytic), thrombocytosis, thrombocytopenia |
| Vascular | Hypercoagulability (thrombosis, thrombophlebitis, portal vein thrombosis, sinus vein thrombosis) |
| Pancreas | Pancreatitis |
| Other | Growth delay/failure, pubertal delay, menstrual irregularities, increased risk of colonic malignancy with chronic inflammation,(lymphoma 2° to meds) |

**Table 3 Commonly used Pharmacologic Therapy of Inflammatory Bowel Disease in Children (note * denotes not an approved use for children)**

| Medications | Indications | Complications |
|---|---|---|
| Aminosalicylates (*mesalamine) | Mild-to-moderate UC, mild Crohn's colitis, or mild distal small bowel disease | Rash, headache, vomiting, dyspepsia, bloody stools, pancreatitis, alopecia |
| Corticosteroids (*prednisone, *budesonide) | Budesonide: Mild-to-moderate distal small bowel and proximal colon (CD); Prednisone: moderate-to-severe UC or CD | Cushingoid facies, growth suppression, osteopenia, hypertension, acne, potential adrenal crisis if not appropriately weaned |
| Antibiotics (*metronidazole, *ciprofloxacin, *cephalexin) | Perirectal fistula, abscess pouchitis (CD), bacterial overgrowth | Diarrhea, c. difficile, development of resistant organisms |
| Immunomodulators (*6-mercaptopurine, *azathioprine, *methotrexate) | Severe small or large bowel disease, steroid-dependent or refractory disease, severe fistula, growth failure (CD or UC) | Bone marrow suppression, pancreatitis, hepatitis, infection |
| Biologic therapy (*infliximab, *adalumimab *certolizumab pegol) | Steroid-dependent or refractory CD, perirectal fistulae, maintenance of remission | Hypersensitivity reactions, infection, autoimmune disease |

*= FDA approved for children > 6

situations, young children and teens may resist rectally instilled medications.

The next line of therapy typically involves systemic steroids. Pediatric IBD Registry data show that in children with CD 84% have a complete or partial response to steroids, but even with the addition of immunomodulators, at one year 31% were corticosteroid-dependent and 8% had required surgery.[10] In children with UC treated with corticosteroids, disease activity at three months was inactive or mild-moderate in 87%. At one year 50% were considered steroid-responsive; however, 45% were corticosteroid dependent and 5% had colectomies.[11]

Prolonged exposure to steroids is unacceptable in children. Use of immunomodulators such as 6-MP are well studied and effective as maintenance therapy, but also present a set of risks and disadvantages. As the onset of action is typically 4-6 months, the patient with moderate-to-severe disease often requires additional therapies while awaiting clinical response. In addition, monitoring is required as 6-MP metabolites can result in hepatoxicity, pancreatitis and bone marrow suppression. Prior to initiating therapy, TPMT (Thiopurine s-methyltransferase) genetic profiles are obtained to assess the activity of the enzyme responsible for 6-MP metabolism. A study in 2000 demonstrated a statistically significant response to early introduction of 6-mercaptopurine versus placebo in 55 pediatric patients recently diagnosed with CD. Specifically, researchers concluded that early introduction of 6-MP therapy achieved and maintained a much higher rate of steroid-free remission.[12] A recent follow-up study from the Pediatric IBD registry demonstrated a decrease in both steroid use and number of hospitalizations in patients with moderate to severe CD started on immunomodulators within the first year of diagnosis.[13]

**Prolonged exposure to steroids is unacceptable in children.**

The "biological" therapies represent the next level of medical management of IBD. The principle biological agents are monoclonal antibodies against the inflammatory cytokine tumor necrosis factor alpha (TNF-alpha). These medications offer much potential benefit to the steroid-dependent or refractory patient.[14] The major concern is immunosuppression and risk of secondary infections. The appropriate role of biological agents (infliximab, adalimumab as well as newer agents) is the subject of active and ongoing study. Of concern, however, are reports of lymphoproliferative disease such as the highly fatal hepatosplenic T-cell lymphoma associated with infliximab exposure. The majority of the reported cases involved patients who were receiving concomitant therapy with immunomodulators such as 6-MP or systemic steroids. Thus, the true long-term risks of lymphoma and other malignancies in children receiving TNF inhibitors are unknown (but are generally estimated at about 1:1000 medication recipients).

With no definitive way to manage the child with IBD, there is marked variability among centers. Kappelman et al. demonstrated statistically significant inter-center variation in utilization of the five classes of medications most commonly used to manage pediatric CD (immunomodulators, steroids, antibiotics, 5-ASA compounds, and biologics such as infliximab).[15] An underlying theme in these management strategies is minimizing exposure to corticosteroids. While treatment must be individualized, so far differences in outcome have not been associated with the different approaches.

## Ongoing Research

Today, optimal care for children with IBD requires a multi-disciplinary team of physicians, nurses, clinical nutritionists, social workers, and child psychologists. Current research efforts are trying to address the lack of understanding of the natural history of IBD in the child as well as the role of the newest therapies (as well as many of the old standby therapies). This can be especially challenging since most therapies have never been specifically approved for use in the pediatric age group. The pediatric IBD registry follows over 1000 children with IBD. In the first 5 years since its inception in 2002, this consortium has been responsible for several major research papers[3-5, 9-11, 13, 15-17] describing aspects of the natural history of IBD. The division of Pediatric Gastroenterology at Hasbro Children's Hospital has enrolled over 90 patients and is the second largest contributor to the registry. Most recently the Ocean State Crohn's

and Colitis Area Registry study has been launched in Rhode Island (OSCCAR). OSCCAR is a prospective study of an inception cohort of newly diagnosed adult and pediatric patients in Rhode Island (see previous issue, "introduction to OSCCAR"). OSCCAR promises to provide a wealth of new and exciting information into the natural history of IBD. Taken together, OSCCAR and the Pediatric Collaborative Research Consortium will provide new insights into IBD epidemiology, genomics, metabolomics, microbiology, pathophysiology and environmental determinants of disease susceptibility.

## Future Directions

A consortium of pediatric IBD centers, including members of the IBD registry, recently reported that the rate of complicated CD increases in children as the number and magnitude of immune reactivity assays increase. Disease progression is significantly faster in children expressing immune reactivity.[16] Whether these results will have practical consequences remains to be seen. However, this could be a powerful indicator of one's future clinical course. As can be appreciated from this review, much of the newest data emphasize the role of studies such as the Pediatric IBD registry and OSCCAR. While both these studies are based on the biological determinants of disease, they lack focus on the equally important psychological components. Establishment of a prospective behavioral health registry that will provide knowledge from an integrated biopsychosocial model perspective is anticipated in the near future. Thus, the ongoing analysis of prospectively acquired data promises to provide much insight into the natural history of IBD and inform us about the most effective therapeutic strategies.

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# Reproductive Issues In Inflammatory Bowel Disease

*Sumona Saha, MD, and Silvia Degli Esposti, MD*

**Inflammatory bowel disease (IBD)** is predominantly a disease of young people with a peak incidence between ages 20 and 40 years.[1] Indeed, for an adolescent or young adult this diagnosis can be devastating. Patients suddenly face a chronic incurable illness that may require lifelong treatment. Medication toxicity, the ability to lead a productive life, and life expectancy are common concerns for patients. In addition, given the age of affected individuals, reproductive issues are important concerns.

Patients may worry about their ability to conceive, the effect of their disease on pregnancy and the effect of pregnancy on their disease. They may also worry about the likelihood of passing IBD onto their children. "Am I going to be able to have a family? Will I find an understanding life partner? Will my children be healthy?" Patients with IBD frequently ask these questions of their physicians. It is therefore important that physicians understand the reproductive issues associated with IBD and manage them appropriately.

## Fertility

Initial epidemiologic data suggested higher infertility rates and smaller family size in individuals with **Crohn's disease (CD)**.[2] These studies, however, did not take into account higher voluntary childlessness rates in patients with IBD. Voluntary childlessness, likely the result of fear of pregnancy and sexual avoidance, may be able to be reduced with sound medical advice along with psychological and psychosocial support.[3]

More recent studies have found infertility rates for men and women with IBD range from 5-14%, which is no higher than in the general population.[4] However, notable subgroups of patients do have compromised fertility. This includes patients who have undergone colectomy with ileal pouch construction[5] and potentially other IBD surgeries.[6] Infertility after surgery is likely due to adhesions in the pelvis and impaired tubal function. Laparoscopy, anti-adhesion gels, and "pexing" of the ovaries may prove helpful in preserving fertility, however, at this time it is very important that women who are considering surgery should be aware of this risk. Some may want to defer surgery until after childbearing.

**Pregnancy does not significantly alter the course of pre-existing IBD or increase the risk of future complications.**

Women with active inflammation may also have impaired fertility. Transmural inflammation in CD can create fistulas from the bowel to the vagina, uterus and ovaries. This may decrease fertility by causing painful intercourse or by impairing ovulation and implantation. CD may also invade the fallopian tubes and ovaries and impair ovulation or cause tubal occlusion. Weight loss and nutritional deficiencies may decrease fertility by causing dysmennorrhea or amenorrhea. Finally, feelings of disfigurement (e.g., from having an ostomy) or embarrassment (e.g. from excessive flatulence, fecal incontinence, perianal fistulas) may lower body image and sexual confidence in patients with IBD and thereby lower fertility.[7,8]

Male fertilty is affected by sulfasalazine use which reversibly decreases sperm count, impairs motility and alters morphology.[9] Low sperm counts are also caused by methotrexate.[10] Impaired fertility has also been described in some men who have undergone pouch surgery due to retrograde ejaculation and erectile dysfunction;[11] however, overall pouch creation has been found to improve male sexual function.[12]

## IBD Inheritance

Many parents are concerned about the risk of passing IBD onto their children. This may influence their reproductive choices and behaviors. While the risk of IBD is higher in family members, heritability is still poorly understood.

The relative risk of IBD in first-degree relatives is 5 to 35 for CD and 10 to 20 for **ulcerative colitis (UC)**.[13] Ethnicity plays an important role in heritability with patients of Jewish origin having a higher age-adjusted IBD risk compared with non-Jews. This translates into a lifetime risk of approximately 5% for non-Jews and 8% for Jews for developing IBD if a parent has CD. Likewise for children of a parent with UC, the lifetime risk is approximately 2% for non-Jews and 5% for Jews.[13] Children with a parent with IBD are at highest risk of developing the same disease as their parent but they are also at increased risk for developing an alternate version of IBD.

There is no commercially available genetic test for IBD. Parents who are concerned about disease transmission should be aware that their children carry a higher risk of developing IBD than the general

Table 1. Food and Drug Administration Categories for the Use of Medications in Pregnancy

| FDA Category | Definition |
|---|---|
| A | Controlled studies in animals and women have shown no risk in the first trimester and possible fetal harm is remote |
| B | Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester. |
| C | No controlled studies in humans have been performed, and animal studies have shown adverse events, or studies in humans and animals are not available; give if potential benefit outweighs the risk |
| D | Positive evidence of fetal risk is available, but the benefits may outweigh the risk if life-threatening or serious disease. |
| X | Studies in animal or humans show fetal abnormalities; drug contraindicated |

population; however, due to environmental factors and other non-genetic factors accurately predicting a person's risk of developing IBD is difficult.

## Pregnancy

Pregnancy does not significantly alter the course of pre-existing IBD or increase the risk of future complications.[14] It may even be protective.[15] Thus, pregnancy is not contraindicated in women with IBD.

Disease remission at the time of conception is very important. Women with inactive disease at conception have the same rate of relapse as non-pregnant women.[16,17] In contrast, women with active disease have a 70% chance of continued or worsening disease activity during pregnancy.[18]

While pregnancy doesn't affect the overall course of the disease, just having previous diagnosis of IBD, independent of disease activity, creates a high-risk pregnancy[19] with poorer pregnancy outcome than previously thought. Thus disease flares should be managed aggressively since IBD may lead to complications in both mother and baby. Maternal complications include bowel obstruction, hemorrhage, perforation, and sepsis. Risks to the baby include premature birth, low birth weight, small for gestational age and delivery by cesarean section (C-section).[20]

Treatment of flares in pregnancy follows the same guidelines as for non-pregnant patients with the added goal of inducing a rapid remission to maintain a healthy pregnancy. Budesonide, intravenous steroids, antibiotics, cyclosporine and anti-TNF agents have all been used to control disease activity in pregnancy. Women with medically refractory disease, toxic megacolon, or a high-grade stricture may require surgical intervention despite the risk inherent to surgery in pregnancy of miscarriages and premature birth.[21]

The mode of delivery in women with IBD is dictated by obstetric considerations. One exception is women with active perianal disease in whom C-section is advised. Vaginal delivery in these patients may further disrupt the perineum and injure the anal sphincter.[22] Notably, healed perianal disease and presence of an ileal pouch are not contraindications to vaginal delivery although some experts may advocate for C-section in the setting of an ileal pouch in order to preserve sphincter function.

Pregnant women with IBD should see their physicians regularly to allow for monitoring of disease activity, nutritional status and medication adherence. A successful pregnancy requires team effort with regular communication among the treating gastroenterologist, obstetric medicine specialist, obstetrician and/or maternal fetal medicine specialist. Rhode Island is unique in being able to offer this service. The "team approach" is being piloted at Women & Infant's Hospital for IBD and other serious illnesses in pregnancy in the High Risk Pregnancy Clinic.

Table 2. Safety of IBD Medications During Pregnancy and Lactation

| DRUG | FDA Category | Recommendations for pregnancy | Recommendations for breast feeding |
|---|---|---|---|
| Adalimumab | B | Limited human data: low risk | No human data: Probably compatible |
| Amoxicillin/Clavulinic Acid | B | Low risk | Probably compatible |
| Azathioprine/ 6-mercaptopurine | D | Data in IBD, transplant literature suggest low risk | Limited human data: potential toxicity |
| Balsalazide | B | Low risk | No human data: potential diarrhea |
| Certolizumab pegol | B | No human data | No human data |
| Ciprofloxacin | C | Avoid: Potential toxicity to cartilage | Limited human data: probably compatible |
| Corticosteroids | C | Low risk: possible increased risk of cleft palate, adrenal insufficiency, premature rupture of membranes | Compatible |
| Cyclosporine | C | Low risk | Limited human data: potential toxicity |
| Fish Oil Supplements | -- | Safe. Possibly beneficial | No human data |
| Infliximab | B | Low risk | Limited human data: probably compatible |
| Loperamide | B | Low risk | Limited human data: probably compatible |
| Mesalamine | B | Low risk | Limited human data: potential diarrhea |
| Methotrexate | X | Contraindicated: Teratogenic | Contraindicated |
| Metronidazole | B | Given limited efficacy in IBD, risk of cleft palate, would avoid. | Limited human data: potential Toxicity |
| Natalizumab | C | No human data | No human data |
| Olsalazine | C | Low risk | Limited human data: potential diarrhea |
| Rifaximin | C | Animal teratogen. No human data | No human data-probably compatible |
| Sulfasalazine | B | Considered safe. Give folate 2 mg daily | Limited human data: potential Diarrhea |
| Tacrolimus | C | Use if mothers health mandates | Limited human data: potential toxicity |
| Thalidomide | X | Contraindicated: Teratogenic | No human data: potential Toxicity |

Adapted from Kane S. Caring for women with inflammatory bowel disease. *J Gender Specific Med* 2001;4:54-9.

## IBD Medications in Pregnancy

Most patients with IBD require pharmacologic therapy to maintain disease remission. Since controlled disease at conception is key to maintaining remission through pregnancy, medication discontinuation before attempting to conceive is not advised. With few exceptions, medications should be continued during the pre-conception period and pregnancy. However, since definitive data on the safety of the drugs used to treat IBD are largely unavailable, it is important to carefully evaluate the risks and benefit of each medication with patients.

While the **US Food and Drug Administration (FDA)** categories provide some guidelines for medication use in pregnancy (Table 1) , the discussion regarding the drug use in pregnancy should extend beyond the FDA classifications to include post-marketing data and expert opinion. A comprehensive study evaluating long term effect of IBD and its medical therapy in pregnancy is underway nationwide, with two sites enrolling patients in Rhode Island.

The **5-aminosalicylates (5-ASAs)** are all FDA pregnancy category B except olsalazine, which is category C. They are generally considered safe for the treatment of mild IBD in pregnancy.

Corticosteroids (FDA category C) have been used extensively for the treatment of various inflammatory conditions in pregnancy. Early reports suggested an increased risk of oral clefts, especially when used during the first trimester.[23] However, subsequent studies as well as decades of clinical experience suggest minimal teratogenicity due to steroids.[24] Maternal hyperglycemia, macrosomia, and fetal adrenal suppression are potential complications of prolonged steroid use in pregnancy for which vigilant monitoring is required.[25]

The thiopurines (FDA category D), azathioprine and 6-mercaptopurine (6-MP) are used as maintenance therapy in patients with moderate IBD. Although animal studies have demonstrated teratogenicity, studies on their use in pregnancy in the transplant setting have not confirmed an increased risk of fetal malformations.[26] In addition, a study of pregnant women with IBD on thiopurines did not find any increase in preterm delivery, spontaneous abortion, congenital abnormalities or childhood cancer.[27] As a result most experts agree that the benefits of continuing these drugs in pregnancy outweigh their potential risks.[28]

Methotrexate and thalidomide are used for moderate or refractory IBD. Both are known teratogens and therefore FDA category X.[29] Furthermore, methotrexate is an abortifacient. These drugs should be used with extreme caution in young patients and discontinued for at least 3 to 6 months before conception.[28]

Cyclosporine (FDA Category C) is occasionally used in the treatment of fulminant UC. Studies in transplant recipients have not found it to be a significant teratogen. Its safety and efficacy has been described in a few case reports for steroid-refractory UC in pregnancy; but definitive safety data are lacking.

Prolonged antibiotics for the primary treatment of IBD are generally avoided during pregnancy. Patients with abdominal abscesses, phlegmons impending perforation, or fulminant colitis may however require them. The antibiotics used most commonly in IBD, ciprofloxacin (FDA category C) and metronidazole (FDA category B), should be used with caution. Animal studies have shown a potential risk for the quinolones to cause cartilage defects[29]and metronidazole has been shown to cause fetal malformations when given during the first trimester.[30]

Recently several monoclonal antibodies have been introduced for the treatment of IBD. Three anti-TNF agents and one anti-cellular adhesion molecules are approved by the FDA: infliximab (FDA category B), adalimumab (FDA category B), certolizumab pegol (FDA category B) and natalizumab (FDA category C). Infliximab and adalimumab have not been found to be teratogenic or associated with miscarriage;[31,32] but long-term safety data are lacking. Given that these drugs are relatively new and safety data are limited, patients may fear their use in pregnancy. While this is understandable, at this time women are not advised to abruptly stop treatment with an anti-TNF agent given the risk of precipitating a disease flare during pregnancy. Frank discussion of the benefits and potential risks of these drugs are needed.

## Breastfeeding

Breastfeeding is unlikely to influence disease activity and may in fact be protective for the development of IBD.[33] However, many women with IBD choose not to breastfeed. Physician recommendations, the fear of medication transmission, and personal preferences are the most common reasons cited,[34] Physicians must therefore be aware of the actual risks so they can educate their patients.

Sulfasalazine, mesalamine and corticosteroids are considered compatible with breastfeeding[35]. There are no definite recommendations on lactation and azathioprine, 6-MP and anti-TNF use.

## Conclusions

Reproductive issues are important for most young people with IBD. Preconception counseling is important and physicians should be prepared to initiate a frank discussion with their patients of reproductive age and answer questions about fertility and pregnancy. The association of IBD with maternal and fetal complications necessitates an aggressive approach in the management and treatment of these patients. The well known principle "healthy mother, healthy baby" certainly applies to the care of our pregnant IBD patients.

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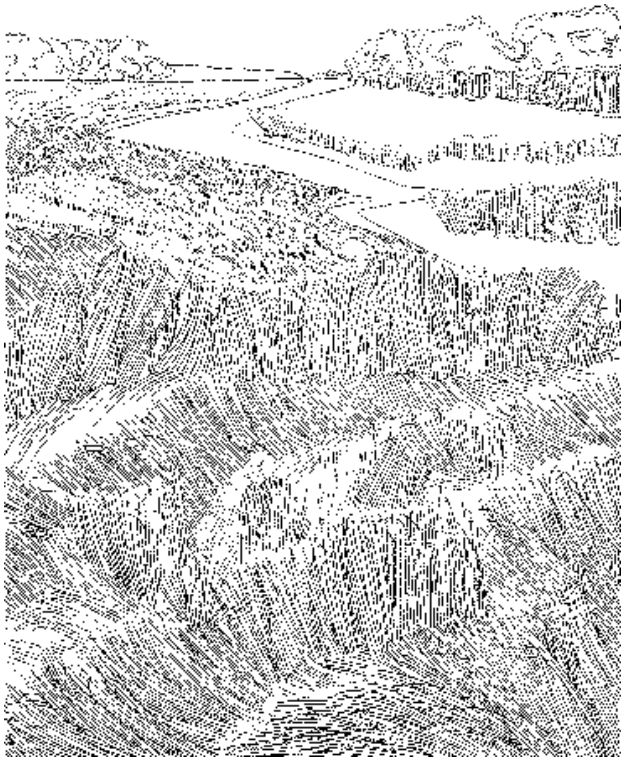


# Anticoagulation In the Octogenarian With Atrial Fibrillation

*Mahim Kapoor, MD, and Lynn McNicoll, MD*

**BI, an 82 year old woman, presents to the hospital with a mixed** expressive and conductive aphasia after waking up. She has a history of well controlled Type II diabetes mellitus, hypertension, hypercholesterolemia, chronic stable angina, osteoarthritis, osteoporosis, and a recently repaired hip fracture. Medications included metformin, lisinopril, atorvastatin, aspirin, ibuprofen, calcium and Vitamin D supplements, and alendronate. An MRI of her brain showed multiple, small infarcts suggestive of embolic disease in the left middle cerebral artery territory consistent with her aphasia, and MRA of her neck showed minimal carotid and posterior circulation atherosclerotic disease. Review of telemetry revealed multiple bouts of **atrial fibrillation (AF)** with ventricular rate in the 100s, with spontaneous conversion to sinus rhythm. Echocardiogram showed a low-normal ejection fraction, with no focal wall-motion abnormalities, nor obvious sources of thrombus or vegetation. She was managed conservatively with aspirin, a statin, blood pressure control, and the question of anticoagulation with warfarin was addressed on discharge, given her diagnosis of paroxysmal AF.

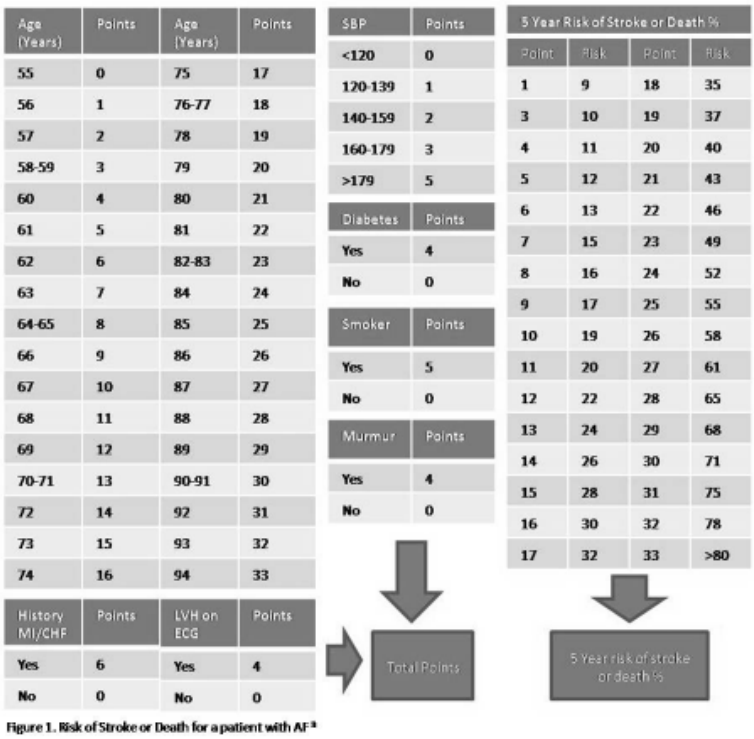
## Risks of Atrial Fibrillation without Anticoagulation

The annual rate of ischemic stroke in patients aged 75 and older with AF and at least one other risk factor (previous stroke, diabetes, hypertension, or heart failure) who are not on warfarin can be as high as 8.1% .[1] The decision to anticoagulate older adults with AF with warfarin is encountered in inpatient and outpatient settings. AF is the most common dysrhythmia in the older patient, with 75 years the mean age of AF patients. The prevalence of AF in this population is expected to increase significantly.[2] At present, 15% of all strokes occur in individuals with AF, resulting in 25% 30-day mortality and significantly more morbidity than in non-cardioembolic strokes[2] Warfarin is highly effective in primary and secondary prevention of ischemic stroke, with a relative risk reduction of 62% when compared to placebo. [3] Warfarin is also known to lead to a reduction in devastating outcomes when ischemic strokes do occur in patientswith AF.[4]

Nevertheless, warfarin remains underutilized, especially in patients older than age 80, due primarily to fears of bleeding.[5] In addition, the alternatives to warfarin, such as low molecular weight heparin, aspirin, and clopidogrel, can be expensive, and their additional benefits compared to warfarin remain to be proven.[2]

## Risks of Anticoagulation with Warfarin in Older Persons

Pooled data from the primary stroke prevention trials showed the annual rate of major hemorrhage (intracranial and extracranial) among AF patients treated with warfarin was 2.3%. The annual rate of intracranial hemorrhage, specifically (a more clinically important end-point given the greater morbidity and mortality), was 0.3%.[6,7] Meta-analysis of six randomized controlled trials showed warfarin to be associated with an absolute risk increase for intracranial hemorrhage of *only* 0.2% per year, when compared with placebo.[3] Despite the data elaborating the proven benefit of warfarin with the relatively low rate of hemorrhage, concerns abound regarding the generalizability of such results, especially in elder patients, for whom advanced age confers an independent risk factor for major bleeding on warfarin.[2] This lack of generalizability stems from a paucity of participants over 80 years old in primary prevention trials, placebo controlled studies and observational studies. Additionally, there is a selection bias in the literature as only patients who were initially deemed suitable candidates for long term warfarin therapy were included in the published studies, and major bleeding events from the early phase of warfarin therapy (where the risk of bleeding is the greatest) were often excluded. [2] Thus, these data may underestimate the risk of bleeding in elderly patients on warfarin.



| Age (Years) | Points | Age (Years) | Points |
|---|---|---|---|
| 55 | 0 | 75 | 17 |
| 56 | 1 | 76-77 | 18 |
| 57 | 2 | 78 | 19 |
| 58-59 | 3 | 79 | 20 |
| 60 | 4 | 80 | 21 |
| 61 | 5 | 81 | 22 |
| 62 | 6 | 82-83 | 23 |
| 63 | 7 | 84 | 24 |
| 64-65 | 8 | 85 | 25 |
| 66 | 9 | 86 | 26 |
| 67 | 10 | 87 | 27 |
| 68 | 11 | 88 | 28 |
| 69 | 12 | 89 | 29 |
| 70-71 | 13 | 90-91 | 30 |
| 72 | 14 | 92 | 31 |
| 73 | 15 | 93 | 32 |
| 74 | 16 | 94 | 33 |

| History MI/CHF | Points | LVH on ECG | Points |
|---|---|---|---|
| Yes | 6 | Yes | 4 |
| No | 0 | No | 0 |

| SBP | Points |
|---|---|
| <120 | 0 |
| 120-139 | 1 |
| 140-159 | 2 |
| 160-179 | 3 |
| >179 | 5 |

| Diabetes | Points |
|---|---|
| Yes | 4 |
| No | 0 |

| Smoker | Points |
|---|---|
| Yes | 5 |
| No | 0 |

| Murmur | Points |
|---|---|
| Yes | 4 |
| No | 0 |

| 5 Year Risk of Stroke or Death % | | | |
|---|---|---|---|
| Point | Risk | Point | Risk |
| 1 | 9 | 18 | 35 |
| 3 | 10 | 19 | 37 |
| 4 | 11 | 20 | 40 |
| 5 | 12 | 21 | 43 |
| 6 | 13 | 22 | 46 |
| 7 | 15 | 23 | 49 |
| 8 | 16 | 24 | 52 |
| 9 | 17 | 25 | 55 |
| 10 | 19 | 26 | 58 |
| 11 | 20 | 27 | 61 |
| 12 | 22 | 28 | 65 |
| 13 | 24 | 29 | 68 |
| 14 | 26 | 30 | 71 |
| 15 | 28 | 31 | 75 |
| 16 | 30 | 32 | 78 |
| 17 | 32 | 33 | >80 |



Figure 1. Risk of Stroke or Death for a patient with AF [8]

| Condition | Points |
|---|---|
| CHF (C) | 1 |
| HTN (H) | 1 |
| Age (A) > 75 Yrs | 1 |
| DM (D) | 1 |
| Stroke (S)/TIA | 2 |

| CHADS2 Score | 1 Year Stroke Risk (%) |
|---|---|
| 0 | 1.9 |
| 1 | 2.8 |
| 2 | 4.0 |
| 3 | 5.9 |
| 4 | 8.5 |
| 5 | 12.5 |
| 6 | 18.2 |

**Figure 2. CHADS2 Score.[11]**

Ultimately, more evidence is needed to reconcile the risks and benefits of warfarin in patients over 80 years old, and the choice to anticoagulate these patients requires careful assessment of risk factors and circumstances for each patient. Such factors include baseline risk for stroke, inherent risk of bleeding, fall risk, and personal preferences regarding warfarin and the associated frequent blood monitoring required. [2]

## Models to Predict Risk of Stroke with AF

Many models, derived from different populations, are available to guide clinicians in assessing baseline risk for stroke. Advancing age, history of prior stroke/transient ischemic attack, hypertension, heart failure, diabetes, and female sex are consistently mentioned in these models; e.g., one developed from the Framingham Heart Study http://www.framinghamheartstudy.org/risk/death.html[8] and the CHADS2 scoring system. CHADS2 may be less accurate in estimating risk of stroke because it dichotomizes age and hypertension (i.e. age greater than 75 years or not, and hypertensive or not hypertensive) and fails to consider smoking, LVH, and presence of heart murmurs. The Framingham tool, in contrast, accounts for these factors and attributes different point totals for ages and systolic blood pressures.[2] These tools, though commonly used in clinical settings and generally viewed as accurate in predicting risk for ischemic stroke, notably fail to take into account risk of bleeding, a significant concern in older adults in whom warfarin is being considered.

## Models to Predict Risk of Bleeding with Warfarin

There have been attempts at developing models to assess bleeding risks in elderly patients on warfarin anticoagulation for their AF. In 2007, Wess et al attempted to combine assessment of stroke and bleeding risk in a decision support tool for determining which patients with AF ought to receive warfarin.[4] While their tool systematically evaluated for history of prior gastrointestinal bleeding, anemia, and renal insufficiency in addition to known risk factors for stroke, it omitted fall risk factors and prior intracranial hemorrhage. In addition, it did not include warfarin-associated extracranial hemorrhage, which actually occurs with greater frequency.[7] Finally, it did not address warfarin use

| Factors Associated with Increased Bleeding Risk in Warfarin Recipients | |
|---|---|
| Age > 70 years | Male gender |
| History of remote bleeding | Alcohol/drug abuse |
| Diabetes mellitus | Anemia |
| Antiplatelet Use | Fall Risk |
| NSAID/Acetaminophen use | Dietary changes |
| Infrequent INR monitoring | Medication changes |

Figure 3. Factors Associated with Increased Bleeding Risk in Warfarin Recipients.[2,5]

in patients older than 80. Shireman et al. additionally identified that age greater than 70 years, female gender, remote bleeding, bleeding during most recent hospitalization, alcohol and drug abuse, diabetes, anemia, and antiplatelet use were significant predictors of major bleeding risk in patients receiving warfarin for AF.[5] However, despite knowledge about the multiple risk factors for ischemic stroke and intracerebral hemorrhage, no official guidelines or models account for both baseline stroke risk and bleeding risk conferred by warfarin in patients with AF.

## Other Factors Guiding the Decision to Use Warfarin

Finally, patient preference, medical comorbidities, and ability to comply with frequent INR monitoring are important. Guidelines mandate an INR of 2.0 to 3.0 for stroke prevention in patients with AF. Numerous studies have documented increased risk of bleeding for INR values greater than 4 and increased risk of stroke causing disability or death with INR values less than 2. Furthermore, older patients warrant more vigilant INR testing, as they are more sensitive to changes in diet and medications, and are on more medications that can modify their INR. Changes in diet and antibiotic prescription should be done judiciously to maintain consistent levels of Vitamin K. A thorough review of a patient's medicines should take place to avoid potential interactions with warfarin. In particular, analgesics such as nonsteroidal antiinflammatories and acetaminophen, and antibiotics like quinolones should be used with caution as there have been reports of both drugs augmenting warfarin's anticoagulant effect. For patients who require aspirin, such as patients with coronary disease who could benefit from an antiplatelet agent, it has been suggested that doses less than 100 mg daily minimize risk of bleeding when taken concomitantly with warfarin.[9] Finally, while fall risk should not automatically disqualify a patient from treatment with warfarin, individual fall risk assessments should be done, and efforts should be made to minimize both extrinsic and intrinsic factors that may cause falls and subsequent hemorrhage on warfarin.[10]

## Summary

BI's baseline annual risk of stroke was 12.5% by CHADS2 score; her 5-year stroke risk by the Framingham tool was 59%. Risk factors for bleeding included diabetes, aspirin use and ibuprofen use, and a moderate fall risk by physical therapy assessment due to her osteoarthritis and deconditioned state. Given her fall risk, she and her family decided against anticoagulation with warfarin. She was discharged to an acute rehabilitation facility on aspirin alone.

The decision to utilize warfarin for anticoagulation in the elderly patient with AF remains an art, involving judicious use of tools to evaluate baseline risk of stroke, careful evaluation for risk factors for bleeding, and diligent consideration of the patient, and his or her comorbidities, medications and ability to comply with treatment and monitoring.

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# *Letter to the Editor*

## To the Editor:

(Inspired by Dr. Joseph Friedman's, "Acronyms: What's In A Name?" in the February 2009 issue), I am submitting "Acronymic Adventures of an Octogenarian."

Having had to learn new terminology when I entered the New York University School of Medicine in 1942, I am now, 67 years later, able to express myself with symbolic brevity.

After symptoms of BPH for many years, I fortunately avoided episodes of UTI and have not had a C & R. I've gone about my ADL quite well. The Heberden's Nodes in my distal IPJs have not interfered with my IADL. Having had some annoying episodes of SVT, I was pleased to learn that my PMI was in the 5th ICS in the MCL, and my BP was normal. My ECG was normal, without BBB. I have never had JVD, PND, other signs of CHF, or PVD. My SVT never evolved into paroxysmal AF or AFL. My ECHO showed no signs of MI, MS, AI or AS. I signed out of the ER, AMA and AOR. I did have an elevated LDL and low HDL. I am taking a statin QD; those values are now WNL.

After cataract extractions OU, my post-op vision is better OS than OD; my EOMs are fine. After I had an unexplained brief episode of blurred lateral field vision in OD, my ophthalmologist assured me I was not having a CVA.

A few years ago I fell and injured my right knee. An MRI showed a slight tear in my MCL and a normal ACL. With rest and PT, I recovered fully.

A reluctant dental patient since childhood, I have had many BWXs while struggling, without success, to retain most of my teeth. I have had better luck after my annual winter attacks of acute bronchitis, which never deteriorated into BOOP and have not left me, a cigarette smoker from ages 15-26, with COPD.

As the son of an otorhinolaryngologist, I have had no serious ENT problems, except for one episode of BPPV, which resolved spontaneously. My lifelong allergies have resulted in annual episodes of SAR, particularly when June grasses and August ragweed are in bloom.

In 1946, as commanding officer of the medical detachment of the 27th Infantry Regiment in Occupied Japan, one of my major missions was mosquito control. I dispatched teams of NCOs and enlisted men with DDT equipment to designated areas. At that time, DEET was not available for cutaneous prophylaxis.

A few years ago I had an episode of bilateral low back pain. Xrays of my hips and lumbo-sacral spine showed no evidence of DISH, but I had extensive DJD, surely now worse though I remain free of pain or disability (another unexplained medical mystery).

I hope to join both the Nonagenarian and Centenarian Clubs in the near and distant future. By then, Acronyms won't matter.


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# The RI Board of Medical Licensure and Discipline: 2008 Year in Review

*Robert S. Crausman, MD, MMS, Mary E. Salerno, MAT, Linda Julian, Lauren Dixon, and Bruce McIntyre, JD*

**In 2008, despite a State budget crisis the Board of Medical** Licensure and Discipline continued its functions unabated. We completed our second electronic biennial renewal of physician licenses, issued one position statement clarifying the requirements for completing death certificates when cross-covering a colleague, amended the licensing regulations to allow for provisional licensure by endorsement in certain circumstances, and continued to investigate and adjudicate complaints regarding unprofessional conduct in the practice of medicine.

## THE RHODE ISLAND BOARD OF MEDICAL LICENSURE AND DISCIPLINE

As noted in last year's update,[1] The Board is an agency of state government established, by law, to protect the public and to assure high practice and professional standards in the nearly 5000-member physician community. The Board discharges these responsibilities primarily through the licensing process, receiving and investigating complaints, and serving as a disciplinary body as authorized by Chapter 5-37 of the RI General Laws [www.rilin.state.ri.us/Statutes/TITLE5/5-37/INDEX.HTM].[2]

## BOARD ACTIVITIES

### Licensing

In 2008 Rhode Island physicians completed biennial electronic license renewal for the second time. Of 4704 physician renewals, 4480 [95%] were processed electronically.

Effective January 2009, the Department will no longer issue wallet license cards to licensees at the time of renewal. Upon initial licensure the individual will receive written notification from the Department that a license was issued that will provide the license number, expiration date, and instructions on how to verify the license using our license verification website.

The Department of Health certifies that it maintains the information for the license verification function of its website, performs daily updates to the website, and considers the website to be a secure, primary source for licensure verification. Employers, licensees, and the public can access the verification website at www.health.ri.gov and clicking onto "Verify the License of a Health Professional." In 2008, the Board processed 764 license verifications.

In 2008 a total of 295 initial completed applications were processed. There were 279 MD and 14 DO licenses granted with 2 rejections. This compares to 332 applications, 320 MD, 11 DO and 1 rejection in 2007.[1] There were 266 new limited [training] licenses issued and a total of 717 active limited licenses. There was one limited academic faculty license.

The Board also streamlined the licensure process and encouraged "license portability." Rhode Island, along with the other New England States and certain western states, are taking part in a "License Portability Demonstration Project" that is funded, in part, by the United States Department of Health and Human Services. The Board may now grant an expedited provisional license to applicants with a verified full and unrestricted license in another state with administrative approval from the Chief Administrative Officer provided that the candidate shall:
(1) have no formal disciplinary actions or active or pending investigations; past, pending, public or confidential restrictions or sanctions, by the board of medicine, licensing authority, medical society, professional society, hospital, medical school or institution staff sanctions in any state, country or jurisdiction. (2) hold unrestricted licenses in every jurisdiction that the candidate holds a license, (3) meet minimum requirements for a license in the state of Rhode Island, (4) have submitted a completed application. [www.health.state.ri.us/hsr/bmld/regulations.php]

Another phase of the License Portability Project is the **Common Licensure Application [CLAF]**. It is hoped that this application will become the template for licensure nationwide. Rhode Island is the 4th state to transition to this system effective December 18, 2008. Ohio, New Hampshire, and Kentucky have also switched to CLAF. The CLAF was developed in partnership with the **Federation of State Medical Boards [FSMB]** and the **United States Medical Licensing Examiners [USMLE]**. The CLAF is supported by the FSMB and therefore data fields related to the USMLE, ECFMG and FCVS [Federation Credentials Verification Service] will be populated directly and considered verified. Adoption of the CLAF by other states will clearly facilitate the process for physicians seeking subsequent licensure. Initially a secondary paper-based RI addendum will be required. Complete electronic submission is anticipated by January 2010.

## COMPLAINTS AND DISCIPLINE

In 2008, the Board received and reviewed 263 new complaints. It opened 152 (58%) for investigation: 133 investigations closed, with an average time-to-close of 171 days; 69 were both opened and closed in 2008 with an average time-to-close of 63 days. In 2007, the Board received and reviewed 279 new complaints. It opened 182 for investigation: 126 closed with an average time-to-close of 117 days.[1]

In recent years the Board has developed close relationships with professional boards for nursing, pharmacy and physician assistants. Joint investigations of complaints and consistent application of professional standards have become the norm. The Board continues to work with law enforcement for cases involving criminal conduct.

In many cases the Board makes a determination in favor of the physician; i.e., a finding of no unprofessional conduct, but still finds "areas of concern" relating to that physician's prac-

tice. Common examples include poor documentation, suboptimal prescribing, or ineffective communication with patients and families. In these cases the Board's first approach is with remediation, often requiring the submission of a corrective action plan or the completion of Board-directed continuing medical education (CME).

The Board continues to work closely with the Physicians Health Committee and play a supportive role in physician health while maintaining appropriate safeguards for patient care.

### In 2008 the Board issued 13 public orders regarding physicians:*

- A physician received a reciprocal suspension relating to suspension in a neighboring state for medical negligence involving several patients.
- A physician who previously voluntarily surrendered his/her medical license while under investigation for inappropriately purchasing approximately 50,000 Vicodin tablets, not for patient use, was reinstated. This physician was prohibited from prescribing or otherwise purchasing narcotics.
- A physician was summarily suspended for insurance fraud and gross medical negligence. The physician was indicted by the Federal government for, amongst other things, billing of third-party payers for services that exceeded the number of hours in a day and for gross medical negligence relating to the care of patients with cancer, rheumatoid arthritis and Hepatitis C. This physician has fled the country.
- A physician was placed on probation for accepting payment for scheduled services that were not performed; without providing patient refunds.
- A physician received a 30-day suspension and 1 year probation for a relapse during a previous monitoring agreement with the Board and Physician's Health Committee.
- A physician received a reprimand for failure to report a hospital disciplinary action as required on his/her medical license renewal application.
- A physician previously summarily suspended agreed to license revocation for a felony conviction for open and gross lewdness.
- A physician voluntarily surrendered his/her license after writing fraudulent narcotics prescriptions for nonexistent patients, taking narcotics from certain patients for personal use and two felony counts of possession of controlled substances.
- A physician was licensed with a voluntary restriction to activities relating to post-graduate training program. This physician had required 8 attempts to pass part 1 of the USMLE and 5 to pass part 2. This physician will be eligible to reapply for an unrestricted license after successful completion of the fellowship program.
- A physician received a suspension for engaging in a sexual relationship with a patient.
- A physician received a reprimand for failing to adhere to the terms of a prior monitoring and treatment agreement with the Board and Physician's Health Committee.
- A physician received a reprimand for his/her role as attending surgeon in a wrong-site knee surgery.
- A physician received a reciprocal reprimand for prescribing controlled substances for self and family members without a legitimate physician-patient relationship in a neighboring state.

*These orders are public documents.[http://www.health.state.ri.us/hsr/bmld/disciplinary.php].

Orders are presented as gender neutral.

## Policy Statements

The Board disseminates policy statements, which interpret or clarify the standard of care. [http://www.health.state.ri.us/hsr/bmld/positions.php] RI licensed physicians are required to review these statements at least biannually with their license renewal.

In 2008 the Board articulated only one new statement.

### Death Certificate Registration for Cross-Covering Attending Physicians

A cross-covering Attending Physician assumes applicable responsibility of the Attending Physician enumerated under RIGL 23-3-16 Section 2-C and "...shall immediately furnish for registration a completed standard certificate of death to a funeral director..." When appropriately required, allowance will be made for a reasonable opportunity for a patient record review.

## Conclusion

The Board of Medical Licensure and Discipline continues to play a vital role in the regulation of the practice of medicine.

## References


1. Crausman RS, Salerno ME, et al. The RI Board of Medical Licensure and Discipline, 2007 year summary. Med Health RI 2008;7:232-4.
2. Crausman RS. Protecting the public and assuring high practice and professional standards in the physician community. Med Health RI 2003:279-81.



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### Disclosure of Financial Interests

The authors have no financial interests to disclose.

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# *Point of View*

## Military Pediatricians Join Reach Out and Read at Naval Health Clinic New England

*by Anthony Amaio, MD*

**To help military children succeed in the classroom and cope** with anxieties about their parent's deployments, pediatricians at 30 US military bases send their patients home with free books and important advice for parents: "Read to your child every day." Naval Health Clinic New England in Newport, RI, was selected as one of the initiative's pilot sites.

Since February, Naval Health Clinic New England has participated in **Reach Out and Read's** (**ROR**) Military Initiative, which was launched last fall to extend the 20-year-old early literacy program to American military families.

At every checkup from age 6 months to 5 years, healthcare providers give each child a free new book, starting with board books for babies followed by picture books for preschoolers. Along with the free book, providers dispense advice to parents about the importance of reading aloud with their children. Each child who participates in ROR starts kindergarten with a home library of up to 10 books.

Naval Health Clinic New England, like all military bases participating in ROR, has created a literacy-rich waiting room, with child-size furniture and bookcases, where ROR-trained volunteers read with the children while their families wait for appointments.

This year alone, doctors and nurses at Naval Health Clinic New England will distribute more than 1,000 books to the 534 preschool children they serve.

ROR has one of the strongest records of research support of any primary care intervention. More than a dozen peer-reviewed studies indicate that parents who get books and literacy counseling from their health care provider are more likely to read to their children, read to them more often, and provide more books in the home. Children who participate in ROR score significantly higher on vocabulary tests and show improved language development—the single strongest predictor of school success.

According to ROR founder Barry Zuckerman, MD, more than one-third of American children arrive at school without the basic literacy skills they need to learn to read.

Reach Out and Read in the Military serves more than 90,000 children of soldiers, sailors, airmen, and Marines at military installations across the globe. That represents more than 25% percent of the children in U.S. military families ages 0-5 years worldwide.

In addition to the program's selection of "doctor-recommended" children's books, children will receive books designed specifically to calm anxieties about deployment and military service, such as *While You Were Away*, by Eileen Spinelli.

Pediatricians recognize the benefits of this program for children whose parents are deployed. When children and parents share books that deal with deployment, it provides an opportunity to determine how well the child is dealing with her parent's absence. Reading books together that deal with deployment opens up dialogue and lets the child know that she is not alone in going through this.

In addition, the children reap the same rewards enjoyed by all infants, toddlers, and preschoolers whose parents read to them. Anything that increases parents reading to their children is beneficial on so many levels – their cognitive learning, their speech development – but also the bonding that takes place between parents and children when they read together.

ROR's Military Initiative is funded by the Department of Defense and jointly administered with Strategic Resources Inc. ROR is endorsed by the American Academy of Pediatrics and was one of five organizations worldwide to be awarded a 2007 UNESCO literacy award.

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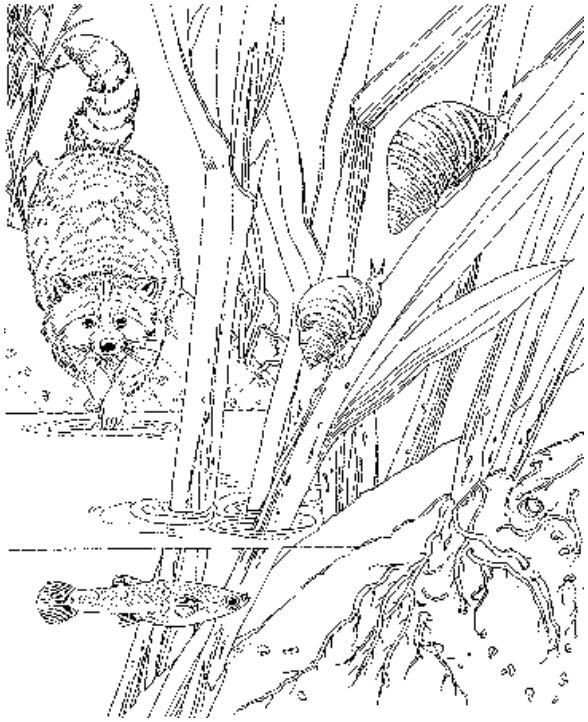


# Images In Medicine

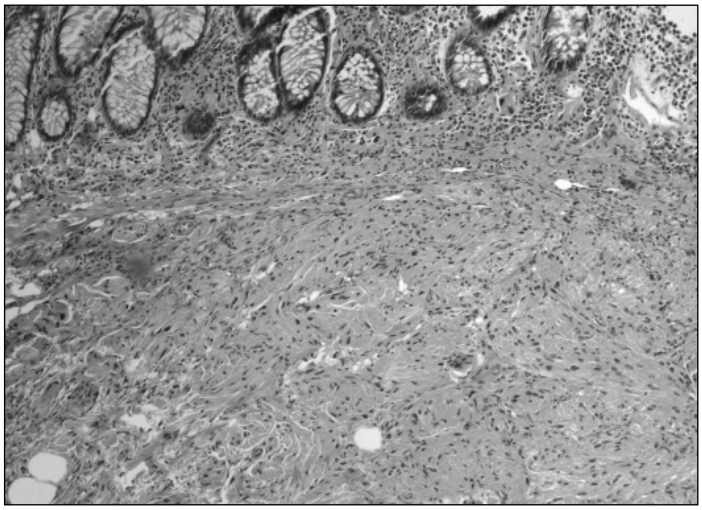
## Granular Cell Tumor of Ileocecal Valve

*Robert Bagdasaryan, MD, and Ramakrishna Nayak, MD*

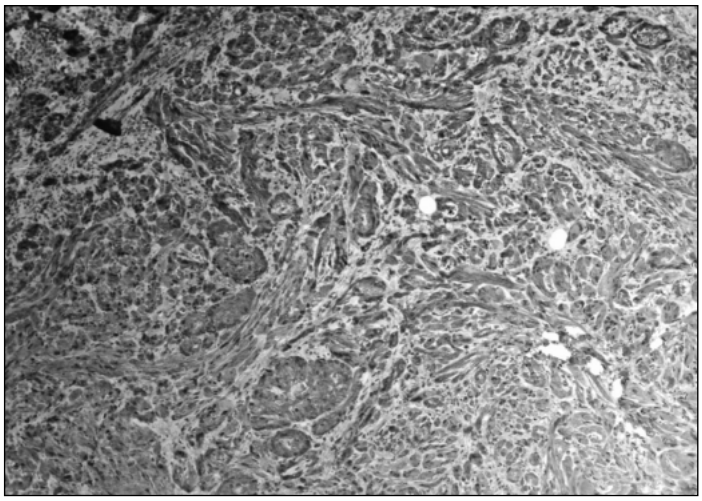
**A 51 year-old man underwent colonoscopy, and a 0.7 cm** sessile polyp was snared from the ileocecal valve. On microscopic examination, a submucosal unencapsulated tumor composed of plump, rounded and polygonal cells with variable nuclear size and abundant granular eosinophilic cytoplasm was found.

Immunohistochemical analysis revealed that the tumor expressed S-100 (nerve sheath tumor marker) protein as well as CD68 (marker of macrophages). All other markers, such as CD117 and CD34 (**GIST**) (**Gastrointestinal Stromal Tumor**) markers, cytokeratins (epithelial cell markers), and markers for muscle differentiation, were negative. All these findings were supportive of granular cell tumor.

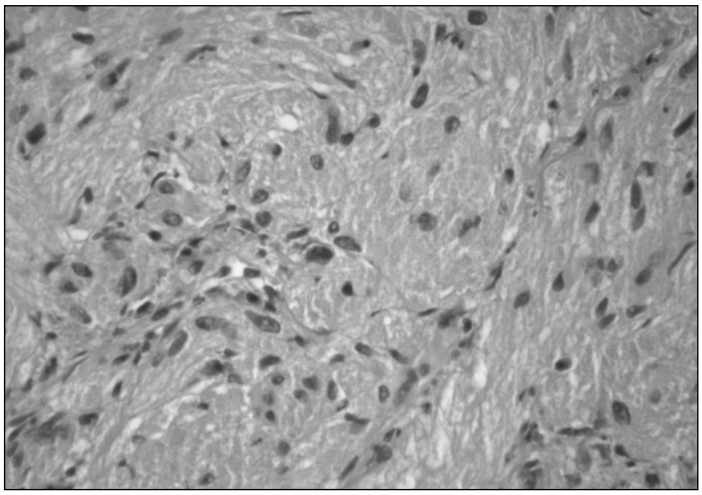
**Granular cell tumors** (**GCT**)s usually arise in the tongue or dermis but can occur in virtually any anatomic site. Within the gastrointestinal tract, GCTs are most common in the esophagus. The colon is the second most common gastrointestinal site for a primary, followed in descending order by the perianal region, stomach, appendix, and small bowel. Colonic GCTs have a predilection for the right colon and rectum, and are in most cases an incidental finding. Endoscopically, they typically appear as smooth, sessile submucosal polyps, ranging in size from a few millimeters to 2 to 3 cm; they are usually covered by an intact colonic mucosa. Endoscopic polypectomy is the treatment of choice. Only 1% to 2% of granular cell tumors in extraintestinal sites behave in a malignant fashion. In the largest published series of gastrointestinal granular cell tumors, none of 75 tumors recurred or metastasized.[1]



Granular cell tumor in the submucosa



Granular cell tumor. S-100 protein expression



Granular cell tumor. High power view.

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1. Johnston J, Helwig EB. Granular cell tumors of gastrointestinal tract and perianal region. *Dig Dis Sci* 1981;26:807-16.
2. Enzinger FM, Weiss SW. *Soft tissue tumors, 3rd ed*. St. Louis, Mosby, 1995: 821-88.

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Robert Bagdasaryan and Ramakrishna Nayak have no financial interests to disclose.

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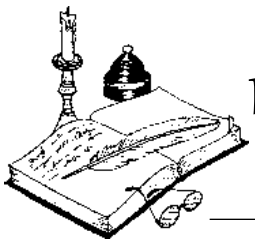


# Physician's Lexicon

## Behold, the Ambiguous Root

***Homo sapiens*** **[Latin, *sapere,* to be wise] is** the Linnaean designation given to the human species, with the genus name for primates, *Homo*, also from the Latin, meaning man. In both medical and theological texts, Homo has been, unambiguously, a name for human or humanoid creatures. In a fateful declarative in the Scriptures, for example, Pontius Pilate, the sixth Procurator of the Roman province of Judea, points to Jesus and declares: *"Ecce Homo"*, [Behold, the man.]

Yet four virtually identical roots in English terminology, especially medical vocabulary, result in much misinterpretation of words incorporating the root, *homo-* [*homi-* or *homeo-*].

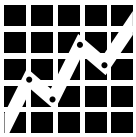
Words such as homicide and homunculus [meaning little man, from the Latin diminutive of *Homo*] both clearly descend from the Latin root meaning man.

But then there are words such as homosexual, homogamous, homeopathic and homophony where the *homo-* [or *homeo-*] root stems not from the Latin, *homo-* but from the Greek, *omo-* meaning resembling, similar to or identical. Therefore homosexual means having sexual desire for one of the same gender. And a homophone is a word identical in sound to another word but differing in meaning [eg, sale, sail or bear, bare]. Still other terms derived from the Greek *omo*—there is no letter 'h' in Greek—include homodont [teeth of similar form], homogenize [to blend, to make similar], homologous [agreeing, of being of one mind], homoplastic [of being of the same form], all conveying the sense of two or more things resembling or identical to each other in one or more characteristics.

But then we have a cluster of words such as homiletic [pertaining to sermons or the art of preaching] and homily [a sermon]. These are based upon the Greek word *omilos*, meaning to be together, to converse with, to assemble for conversation and are related, indirectly, to the Greek *omo*.

Finally, there are words based upon the English word, home, all of Old Germanic origin and spelled variously as *hem, ham* [as in hamlet], *heim* [as in Blenheim or Mannheim], or *hjem*. The *hem-* root also crops up in the geographic term, Bohemia [*Boii-heim*], meaning the home of the Boi tribes of Celtic ethnicity.

– Stanley M. Aronson, MD



Rhode Island Department of Health
David Gifford, MD, MPH
Director of Health

# Vital Statistics

Edited by Colleen Fontana, State Registrar

The Rhode Island Department of Health Office of Vital Statistics regrets that this will be *the last month this information will be published* for an indefinite period of time. Staff shortages have created a backlog of tasks, including data entry and data coding. We encourage anyone who has need of this information to call us at 401-222-7822. Some of the data may become available but at irregular intervals.

## Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

| Underlying Cause of Death | Reporting Period | | | |
|---|---|---|---|---|
| | April 2008 | 12 Months Ending with April 2008 | | |
| | Number (a) | Number (a) | Rates (b) | YPLL (c) |
| Diseases of the Heart | 226 | 2,762 | 261.1 | 3,417.5 |
| Malignant Neoplasms | 197 | 2,377 | 224.7 | 6,650.0 |
| Cerebrovascular Diseases | 35 | 389 | 36.8 | 632.5 |
| Injuries (Accidents/Suicide/Homicde) | 44 | 539 | 51.0 | 8,451.5 |
| COPD | 36 | 488 | 46.1 | 422.5 |

| Vital Events | Reporting Period | | |
|---|---|---|---|
| | October 2008 | 12 Months Ending with October 2008 | |
| | Number | Number | Rates |
| Live Births | 1,102 | 12,554 | 11.9* |
| Deaths | 841 | 10,050 | 9.5* |
| *Infant Deaths* | (8) | (85) | 6.8# |
| *Neonatal Deaths* | (7) | (68) | 5.4# |
| Marriages | 722 | 5,435 | 5.1* |
| Divorces | 318 | 2,783 | 2.6* |
| Induced Terminations | not available | not available | not available |
| Spontaneous Fetal Deaths | not available | not available | not available |
| *Under 20 weeks gestation* | -- | -- | -- |
| *20+ weeks gestation* | -- | -- | -- |

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,067,610 (US Census: July 1, 2007)

(c) Years of Potential Life Lost (YPLL)

***Notes:*** *Estimated total population for Rhode Island has been updated in this month's rates.*

*Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.*

* Rates per 1,000 estimated population
\# Rates per 1,000 live births

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Issued Monthly under the direction of the Publications Committee
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## Ninety Years Ago, April 1919

Because key Medical Society members staff were serving in World War I, the Society suspended publication of the Journal through 1919.

## Fifty Years Ago, April 1959

Samuel D. Clark, MD, Medical Officer, Radioactivity Center, Massachusetts Institute of Technology, spoke at the Providence Medical Society. The Journal reprinted his talk, "The Watches That Won't Run Down: Results of Investigations of Victims of Radium Poisoning After an Interval of 30 Years." In 1924, a New York dentist, Theodore Blum, had written one of the first articles on the indications of the toxicity of radium, in the *Journal of the American Dental Association*. In 1933 Robly D. Evans discussed 6 laboratory tests for determining radium poisoning in the *American Journal of Public Health*. In 1925 Dr. Harrison Martland, the medical examiner of Newark, linked radium to the deaths of painters of luminous dials. Decades later, scientists were searching for former dial painters and their co-workers. The author noted, "There may be surprisingly marked x-ray changes without any symptoms whatsoever." The author requested help from physicians in locating "laboratory case-material."

Lt. Saverio Caputi, JR, MC, USNR, Chief, Department of Dermatology, US Naval Hospital, Newport, submitted "Histopathological Changes Induced by the Nitrogen Mustards in the Lymphomas: A Brief Review of the Literature."

William B. O'Brien, MD, William V. Vindzberg, MD, and Gladys Longo, in "Alcohol and Tuberculosis: A Story of 200 Patients Admitted to the Dr. U.E.Zambarano Memorial Hospital, Wallum Lake," discussed the patients admitted between August 1954 through September 1955. Most (185) had tuberculosis. The authors concluded: "…the quantity of alcohol consumed does not have much effect on the treatment of TB; but alcohol consumers do suffer from malnutrition, poor general health, bad hygiene, disability…The only important effect is…that alcohol does interfere with the normal course of treatment of the patients, and furthermore such a patient becomes a real health menace when he is turned loose into the community."

Jose M. Ramos, MD, in "The Value of Phenylbutazone in generalized Osteoarthritis," discussed 150 cases, given 300 mgm daily for 5 days, then 200 mgm for 3 days. "In no instance were toxic reactions noted…" The author called it "one of the most useful and important anti-rheumatic drugs."

Milton Hodosh, DMD, in "A New Concept in Implant Dentistry," discussed "third teeth," "artificially placed, and cosmetically as well as physiologically functional."

## Twenty-Five Years, April 1984

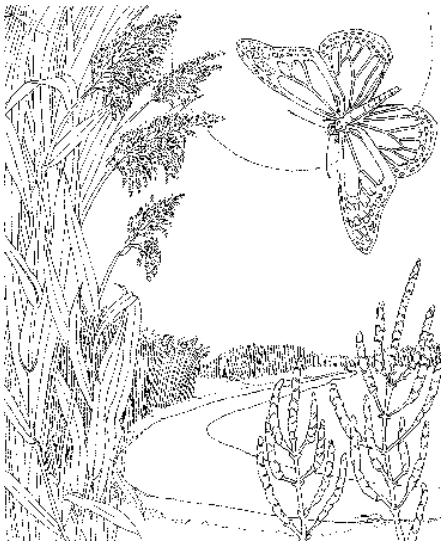
An Editorial, "Take Care of Yourself," recounted statistics from a CDC study; e.g., 60% of respondents didn't use seat belts, 31% smoked cigarettes, 20% were acute drinkers; 13% led sedentary lifestyles. A 1980 survey conducted by SEARCH and the RI Department of Health echoed the findings: 82% of Rhode Islanders didn't use seat belts, 35% smoked, 59% of men and 47% of women led sedentary lives.

On the President's Page, Charles P. Shoemaker, Jr, MD, discussed "Non-Physician Health Care Professionals: A More Systematic Approach is Needed." In 1984 Rhode Island optometrists were seeking the General Assembly's permission to prescribe drugs. In 37 states, including RI, optometrists could use "diagnostic agents" in their practices. Chiropractors and physician assistants were also attempting "to extend their practice privileges by legislative fiat." Dr. Shoemaker urged the legislature to establish a commission to study these professionals, rather than review each bill piecemeal.

In "Depression Following Cranial Radiation for Brain Tumor," Richard J. Goldberg, MD, Alan D. Steinfeld, MD, and Robert M. Tull, PhD, discussed the case of a 40 year-old man. The authors concluded: "Impaired function appeared to be due to tumor, irradiation therapy or both."

As part of a Brown University honors program at Brown University, Kemi Nakabayashi, Sarah C. Aronson, Michael Siegel, William Q. Sturner, MD, and Stanley M. Aronson, MD, analyzed "Traffic Fatalities in RI. Part II. The Timing of Accidents and the Role of Marital Status, Alcohol and Psychoactive Drugs." Most accidents occurred on Fridays, Saturdays, Sundays; the fewest, on Tuesdays. The worst months were March, April, and May.

Srecko Pogacar, MD, and Roger S. Williams, MD, in "Alzheimer's Disease Presenting as Slowly Progressive Aphasia," discussed a 56 year-old man whose aphasia had progressed for a year, with no cognitive symptoms. "This may be the first recorded case of this sequence."



# The Name of Choice in MRI

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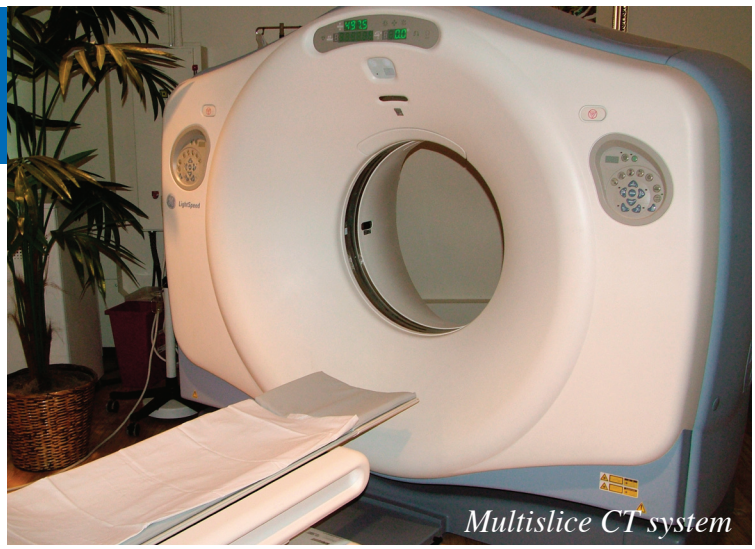
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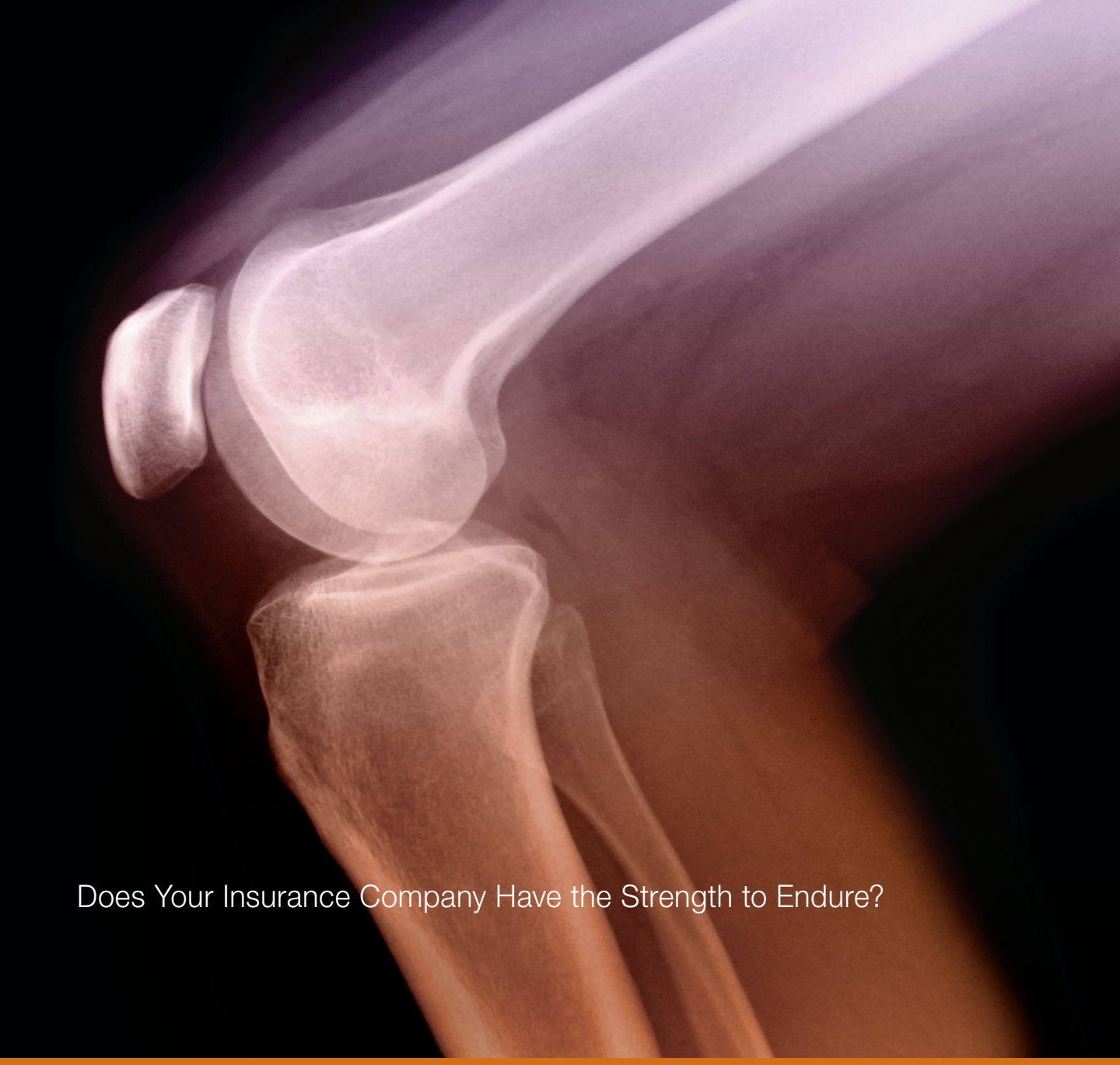

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