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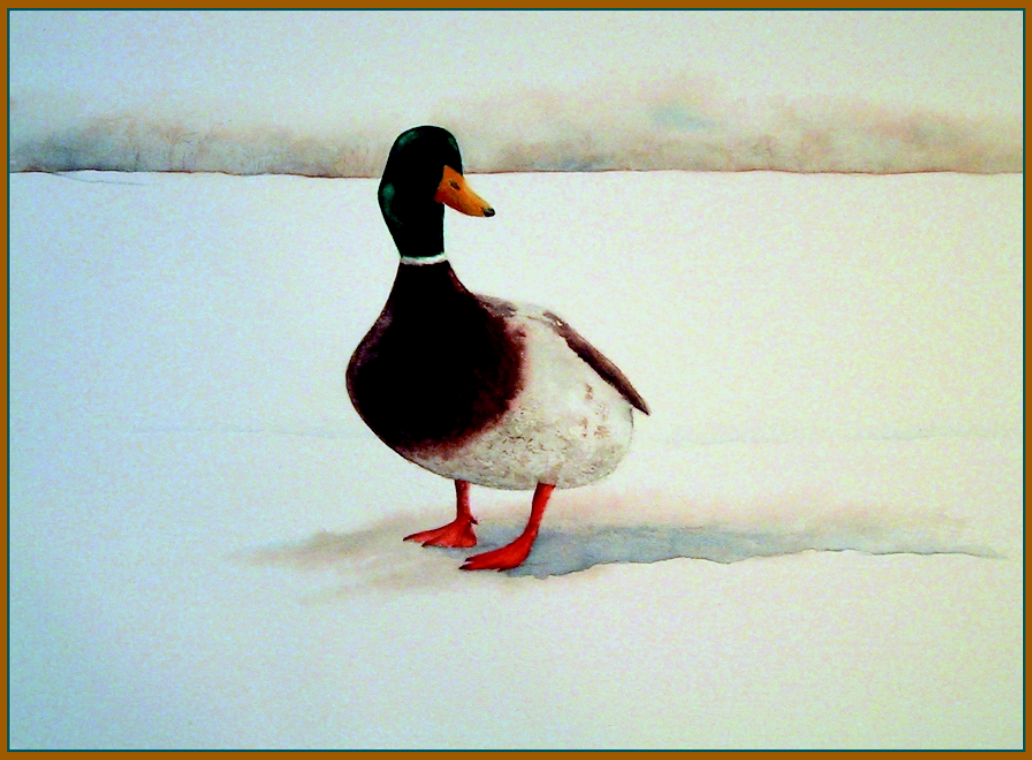

Inflammatory Bowel Disease (Part I)

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COMMENTARIES

CONTRIBUTIONS

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

COLUMNS

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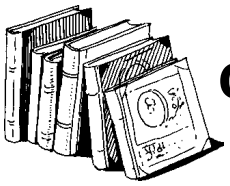

Commentaries

Biased Articles

The *New York Times* recently recounted yet another scandal involving doctors and drug companies. Three prominent psychiatrists, truly "key opinion leaders" in their fields, participated in NIH-funded trials of commercial drugs, ardently advocated reassessments of traditional diagnoses and treatments, even made public documentaries on diagnostic criteria for children with potential psychiatric disorders and gave public talks - without revealing their financial ties to the drug industry. When challenged, the trio made woefully inaccurate responses. We are talking about flagrant disregard in some cases, arguably flagrant in others. This particular column, however, was about articles written by professional writers employed by the drug companies.

Every time I read about a pharmaceutical industry-associated "black eye" for doctors, I assess my own record. The only way to be "squeaky clean' is to avoid contact with industry. I am not so clean. I don't think it's possible to be such, even if so inclined, in the area of clinical research in movement disorders, but I'm sure readers will quibble. I started listing my drug company associations at the end of each column last year, quite belatedly I think; but, on the other hand, no one ever asked during the preceding decade or I would have awakened then.

The *New York Times* article concerns medical articles funded by industry, which seem to fall into a few categories. One is the article written by a ghost writer who gives the paper to the purported lead-writer who then edits it, or accepts it, puts his name as the author, possibly gets paid, although each paper published is an advancement in the academic race so that money may not be the only reimbursement. Other authors may or may not be included, although they may do little but read (or not) the manuscript. These are usually write-ups of multi-center studies and are probably accurate although one is never sure if the authors actually saw the data. It is considered "bad form" in academic medical circles to put your name, at least as first author, on a paper you didn't write. On the Brown main campus it would be a firing offense.

An even more grievous sin was the report of a company writing an opinion piece extolling the company's drug allegedly written by a famous cardiologist. Most likely she agreed with the opinions. Many of us actually do prefer one drug over another for a variety of reasons, even when there's no evidence to base this choice on, and feel that one particular drug works better than its competitors. She may have felt that the article would have looked the same whether she wrote it or not. She should, at least, have said that she got paid by the company to write the piece, as well as give talks for them.

So, here I am, in the middle of a controversy involving a manuscript reporting a multi-center trial of a drug in a study I helped to design. I'm a paid consultant to the company, by the way. Many months after the study ended, the results presented at meetings (all abstracts approved by others plus me, and accurate), I received a manuscript written by Dr X and me according to the title page. I asked if Dr. X had written it, and the answer was no. I hadn't seen it before either. I suggested that the real authors be included as authors and that I'd remain as the last author if I contributed to the manuscript. The paper incidentally was quite good. It was a very honest portrayal of the study results, with the good results presented along with the bad results, the uncertain efficacy of a drug in a study targeted at testing safety.

Then Dr X got hold of the manuscript and decided that these results were spectacular proof of his pet theory on neuropharmacology that he's been trying to establish for several decades. Unfortunately for all of us, Dr X, world famous in his area, was accurately described by a colleague, as being too difficult to debate with because, "I can't yell that loud." And so it was. First of all, the statistics were incorrect, "Everyone knows the two-tailed t-test should have been one-tailed, which would have shown statistical significance in a major outcome that had been insignificant." Of course one can only use one-tailed tests in a treatment that could not possibly have any negative outcome, whereas our drug had never been tested in humans. The idea that the experimental drug could possibly have a negative effect floored him. How could we be so dense? So we rewrote his version of the paper, making it more even-handed, and he rewrote it, again, preparing a claim for the Nobel prize. Revised drafts went back and forth, biased, less biased.

"Dr X, the reviewers are going to see this as biased. I see it as biased. The company sees it as biased. It needs to be more even-handed."

"Let's submit to the *New England Journal* and see what the reviewers say."

At this point the manuscript is still evolving. Dr X is a major consultant to this and other drug companies. I am a minor consultant, easily replaced. The company agrees with me, but will have great trouble disengaging from Dr X because they own the data but his life's purpose lies in the study results. I suggested submitting the paper without my name, since I cannot sign on to its conclusions and biased statistical assessments in its current iteration. I can't imagine any journal publishing it so I'm not worried about making a public fuss.

What attracted me to the topic, however, was the difference in motivations for biased articles. The drug company wants a larger market share, meaning money; and an article at this time is of no commercial value. The bias here was the enormous investment Dr X had in positive results. Anyone can make or steal money, but not everyone can take claim for revolutionary advances in medical understanding. The problem, of course, is in actually making the advance, not the claim.

– Joseph H. Friedman, MD

Disclosure of Financial Interests

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Addendum

Since this was written, a formulation of the manuscript was reached that seemed to be an accurate reflection of the results, suggesting but not claiming a potentially revolutionary advance.

A Brief Inspection of the Navel

The professor of human anatomy addressed his class of first-year medical students. "In what way, " he questioned somewhat authoritatively, "was the body of Adam different from all subsequent male bodies?"

The class remained silent, the students looking timorously at the floor or the ceiling, hoping that they would not be called upon. The professor paused and intoned condescendingly: "Adam had no navel since he was not born of woman." Most students promptly forgot this bit of scriptural arcana since it was not the sort of fact that they were likely to encounter in anatomy examinations. Yet the navel, normally measuring less than an inch in surface diameter and virtually invisible with customary apparel, is central to the fundamental precepts, indeed the core cosmology, of many if not most religions. This inconspicuous belly-button, little more than the residual scar tissue at the site where the umbilical cord had brought oxygen and sustenance to the developing fetus, has evolved into a major cultural icon, ranging in significance from an object of sexual desire to the physical representation of the consecrated center of the universe.

Every language possesses a special word for the navel. The word, *umbilicus*, is the Latin word for navel and appears in a number of medical terms, such as umbilication [pitting] or umbilical hernia.

The ancient Greek word for the navel was *omphalos*. According to myth, Zeus had assigned two eagles, one to the eastern extremity of the world and one to the western edge. He then commanded them to fly toward each other; and where they met was declared to be the center of the world. This locus, called Delphi, was where Apollo, the sun-god, had slain the evil earth-spirit called Python; and so a great dome-like stone was placed on this holy site, a stone called Omphale. A shrine was constructed to protect the world's center in Delphi; and tradition arose that the priests tending the sanctuary sheltering this stone were endowed with gifts of prophecy, the oracles of Delphi. Emperor Theodosius (346? – 395), believing that the Delphic shrine was a temple of heathen practices, finally ordered its destruction.

Divination arising from a sacred stone (an art called geomancy]) was not confined to the rock at Delphi. In Jerusalem, within the Church of the Holy Sepulchre, there is yet another Omphale confirming the ancient belief that Jerusalem was both the spiritual and geographic center of the cosmos.

In Song of Solomon, within the Hebrew Bible, the erotic appeal of the navel manifests itself when Sulaimi is lauded: "Thy navel is like a round goblet, which wanted no liquor." Nowhere else does the anatomical navel appear in the Bible although the word, nave (meaning a convex projection, a dome or the boss of a shield) is found in numerous scriptural Books. And then, of course, there is that existential, non-erotic preoccupation called navel-gazing.

Geocentric stones, denoting the geographic center of things, are found in many sites. In Rome, for example, a small stone, called *Umbilicus urbis Romae* (the navel-center of the City of Rome), represents a specific point from which all Roman roads extending to its far-flung Empire were measured. It is situated in the Roman Forum, protected by a modest stone shelter.

What other characteristics define these sacred stones? Certainly their permanence and immobility. The ancient kings of Ireland, for example, were crowned while sitting upon a specially designated sandstone called the Stone of Destiny. But when Fergus entered Argyll to establish his Scottish kingdom in the year 503, he brought the Stone of Destiny with him and re-established it on the holy island of Iona. For the next four centuries, the stone was integral to each Scottish king's coronation ceremony. In the Tenth Century, the stone was moved to the abbey in the village of Scone where it remained until Edward I of England, in his conquest of Scotland, moved it to Westminster Abbey in 1296 where all subsequent monarchs of England were crowned. On Christmas Day, 1950, four Scottish students stole the stone and secretly returned it to Scotland. The London police retrieved it but British authorities officially returned the Stone to Scotland in 1996, to be briefly returned to Westminster Abbey only when new monarchs are ordained.

Returning to the anatomy lecture hall: Had the professor been more inclined to wander afield, he might have recalled yet another male not precisely of woman born. He might have dimly remembered Shakespeare's drama, Macbeth, wherein Macbeth's anxieties are vastly diminished when he hears that "none of woman born shall harm Macbeth." But Macduff, Macbeth's nemesis, was not of woman, *conventionally,* born: "he had been from his mother's womb untimely ripped" probably a Gaelic form of cesarian section. But presumably he was nurtured during his intra-uterine stay via an umbilical cord from his mother, and hence was duly endowed with a navel. Both the anatomy professor and Shakespeare are otherwise silent on this subject. It must be presumed that Adam is still the sole male born bereft of a navel.

– 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

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

Inflammatory bowel disease (IBD) includes two distinct enigmatic disease entities: (1) **ulcerative colitis (UC)** and (2) **Crohn's disease (CD).** Both are characterized by chronic intestinal inflammation with periodic exacerbations and a variety of local and systemic complications. UC affects the **superficial** mucosa starting with the rectum in a continuous manner and is limited to the colon. Rectal bleeding, diarrhea, tenesmus, and abdominal cramping are the most common symptoms. In contrast, CD can affect any part of the gastrointestinal tract and is characterized by **transmural** inflammation and **granuloma** formation with areas of intervening normal mucosa (hence the term "**skip lesions**"). The transmural inflammation can lead to fibrosis, obstruction, microperforation, fistula and abscess. Symptoms may include crampy abdominal pain, nausea, vomiting, diarrhea, fever, weight loss, and growth retardation/delay of puberty in children/adolescents. While some symptoms of IBD can overlap with **Irritable Bowel Syndrome (IBS)**, the latter notably lacks evidence of mucosal inflammation, bleeding, weight loss, nocturnal symptoms, and lab/endoscopic/radiologic abnormalities. Because IBS is common, it is not unusual to have a patient with both IBS and IBD.

Distinguishing UC from CD is important and usually straightforward. Although standard medical therapy may overlap, the surgical treatment options are distinct. In approximately 10% of patients, it is difficult to distinguish UC from CD based on the histopathology, endoscopic and clinical findings; in these cases, the term indeterminant colitis is used.

These two idiopathic diseases are estimated to affect 1.4 million Americans and result in over 100,000 hospitalizations per year. All ages, ethnic and racial backgrounds, and socioeconomic status are affected. The exact etiology of IBD remains unknown, but is thought to involve a genetic predisposition with an antigenic trigger(s) leading to a dysregulated immune response resulting in chronic intestinal inflammation. In 2001, the first gene linked to CD was identified on chromosome 16 called the CARD 15 (originally named NOD2) gene. Over 32 other candidate genes have recently been identified.

We are excited to have an update on IBD for *Medicine & Health/ Rhode Island* in the next two issues and highlight the **OSCCAR (Ocean State Crohn's and Colitis Area Registry)** study. All the authors for these issues are involved with OSCCAR. OSCCAR is a large, population-based inception cohort enrolling newly diagnosed IBD patients in Rhode Island (see Sands, *et al* in this issue). Despite many advances in IBD, much remains to be done. OSCCAR will hopefully lead to as important epidemiologic and clinical discoveries for IBD as the Framingham Heart study did for coronary artery disease. In this issue, we introduce and describe the ongoing, RI-specific OSCCAR study and present manuscripts reviewing IBD epidemiology, medical treatment, imaging advances as well as separate contributions on surgery for UC, and surgery for CD.

A subsequent issue will highlight IBD

1) Pediatric issues;
2) Nutrition;
3) Bone Disease;
4) Specific Emergencies; and
5) Reproductive issues.

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

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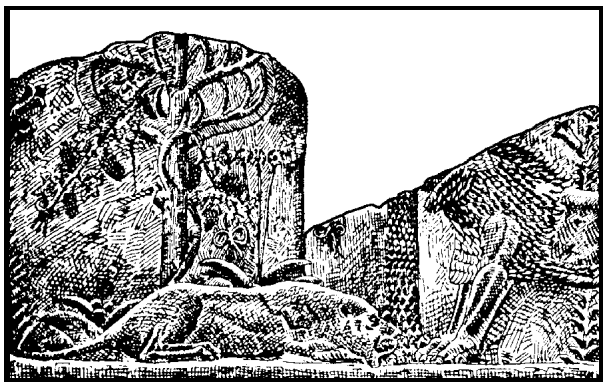

Epidemiology of Inflammatory Bowel Disease and Overview of Pathogenesis

Bruce E. Sands, MD, MS, and Stacey Grabert, PharmD, MS

Crohn's disease (CD) and ulcerative colitis (UC) are believed to affect approximately 1.4 million people in the **United States** (US).[1] In many industrialized and developing parts of the world the incidence is rising. Both genetic and environmental factors are believed to contribute to this rise. However, people of all ages, ethnic, socioeconomic, and racial backgrounds are affected.

Incidence

Incidence is defined as the number of new cases of a disease in a defined population occurring within a specified period of time. Population-based studies conducted in the US and designed to evaluate the incidence rate of IBD have been limited. Between 1990 and 2000 the incidence rate of UC and CD in Olmsted County, MN was estimated to be 8.8 and 7.9 per 100,000 person-years, respectively.[2] In 2003, the population of the US and Canada was approximately 320 million people. Loftus et al. determined that between 7000 and 46,000 residents of the US and Canada are newly diagnosed with UC each year. In addition, 10,000 to 47,000 residents of the US and Canada are diagnosed with CD annually.[1] (Table 1)[2-18]

Prevalence

Prevalence is defined as the total number of cases of a disease in the population at a given time. Similar to incidence, data are limited on the prevalence of IBD. Loftus et al. found 214 cases of UC and 174 cases of CD per 100,000 person-years in Olmsted County, MN, on January 1, 2001.[2] An estimated 780,000 people have UC and 630,000 have CD in North America.[1] (Table 2) [2,6,9-11,13,16-20]

Geographic Characteristics

The highest rates of IBD are found in northern, industrialized countries. North America, United Kingdom and Scandinavia have the highest prevalence of IBD.[21] Historically, IBD has been rare in much of Asia, Latin America and Af-

Table 1: Incidence Rates for studies conducted in North America

Authors	Setting	Case Ascertainment	Incidence Dates	Incidence of UC (cases per 100,000 person years)	Incidence of CD (cases per 100,000 person years)
Garland et al.	15 cities USA	Hospital	1973	3.5	4.5
Nunes et al.	Spokane, WA	Hospital	1981	N/A	8.8
Caulkins et al.	Baltimore, MD	Hospital	1977-1979	2.2	3.1
Pinchbeck et al.	Northern Alberta, Canada	Population	1981	6	10
Hiatt et al.	Northern California	HMO	1980-1981	10.9	7.0
Stowe et al.	Monroe County, NY	Hospital	1980-1989	2.3	3.9
Kurata et al.	Southern California	HMO, Outpatient	1987-1988	N/A	3.6
		HMO, Hospital	1988	N/A	5.4
Loftus et al.	Olmsted County, MN	Population	1984-1993	8.3	6.9
Ogunbi et al.	Georgia	Pediatric African-American Population	1986-1995	5.3	8.8
Bernstein et al.	Manitoba, Canada	Population	1989-1994	14.3	14.6
Blanchard et al.	Manitoba, Canada	Population	1987-1996	15.6	15.6
Kugathasan et al.	Wisconsin	Pediatric Population	2000-2001	2.14	4.5
Bernstein et al.	British Columbia Alberta Saskatchewan Manitoba Nova Scotia	Population	1998-2000	9.9 (BC) 11 (Alb) 10.4 (Sas) 15.4 (Man) 19.5 (NS)	8.8 (BC) 16.5 (Alb) 13.5 (Sas) 15.4 (Man) 20.2 (NS)
Herrington et al.	Northern California	HMO	1996-2002	12	6.3
Loftus et al.	Olmsted County, MN	Population	1940-2000	8.8	7.9
Lowe et al.	Quebec, Canada	Population	1998-2000	N/A	20.2

Adapted from Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease. *Gastroenterol* 2004; 126:1504-17.

rica. However, there are reports of increasing rates of IBD on these continents, highlighting the fact that IBD is a dynamic process.[1, 22-26]

Demographic Characteristics

Gender. CD is marginally more common in females (female to male ratio 1.3).[10,11,16] Studies of UC have found either no gender preference or a slight predilection for males. A higher instance of UC in males is seen after age 40.[10,11,16,27]

Age at Onset. The peak age of onset is between 15 and 30 years old; a smaller peak is seen between the ages of 50 and 70 years old, although IBD can occur at any age. Ten percent of newly diagnosed cases occur among children younger than age 18.[21]

Race. IBD occurs more frequently in Caucasian than African-American, Hispanic and Asian populations; however, racial and ethnic differences seem to be decreasing. Recent studies have reported incidence and prevalence rates in African-Americans and Hispanics similar to those found in Caucasians.[12,19]

Ethnicity. The increased prevalence of IBD among the Jewish population is well established. Ashkenazi Jews (eastern European) were found to have a 5 to 8 fold increased risk of developing IBD when compared to non-Jewish populations. [28] Prevalence of IBD is less among non-Jewish Caucasians, African Americans, Hispanic and Asian populations.

Table 2: Prevalence rates for studies conducted in North America and Puerto Rico

Authors	Setting	Case Ascertainment	Prevalence Date	Prevalence of UC (cases per 100,000 person years)	Prevalence of CD (cases per 100,000 person years)
Pinchbeck et al.	Northern Alberta, Canada	Population	12/31/1981	37.5	44.4
Kurata et al.	Southern California	HMO	1988	N/A	26.0
Loftus et al.	Olmsted County, MN	Population	1/1/1991	229	144.1
Bernstein et al.	Manitoba	Population	12/31/1994	169.7	198.5
Appleyard et al.	Puerto Rico	Hospital	1/1/1996 to 12/31/2000	12.53	5.89
Bernstein et al.	British Columbia Alberta Saskatchewan Manitoba Nova Scotia	Population	7/01/00	162.1 (BC) 185.0 (Alb) 234.3 (Sas) 248.6 (Man) 247.9 (NS)	160.7 (BC) 283.0 (Alb) 263.8 (Sas) 271.4 (Man) 318.5 (NS)
Kappelman et al.	USA	33 States (Health insurance claims)	1/1/2003 to 12/31/2004	< 20 yo: 28 >20 yo: 238	<20 yo: 43 >20 yo: 201
Loftus et al.	Olmsted County, MN	Population	1-1-01	214	174
Herrington et al.	USA	9 Health Plans	1/1/1999 to 6/30/2001	191	129
Lowe et al.	Quebec, Canada	Population	1993-2002	N/A	189.7
Herrington et al.	Northern California	HMO (Health insurance data)	12/31/02	155.8	96.3

Adapted from Loftus, EV Jr. Clinical epidemiology of inflammatory bowel disease. *Gastroenterol* 2004; 126: 1504-17.

Environmental Factors

Despite numerous studies, few environmental risk factors have been established, and these factors do not completely explain the occurrence of IBD and the rising incidence of CD. Environmental and genetic factors in combination play a significant role in the development to IBD.

Smoking. Smoking is regarded as the strongest environmental risk factor for IBD. There is an inverse relationship between smoking and UC. Current smoking is considered protective against the development of UC. The relative risk for developing UC while smoking is 40% that of non-smokers. Ex-smokers are 1.7 times more likely to develop UC and to suffer a worse disease course than those who have never smoked.[1,21,29,30] In contrast, smokers are more susceptible to developing CD than nonsmokers. The relative risk for developing CD while smoking is between 1.15 and 3.9. Smokers with CD have a worse disease course than nonsmokers.[21,29,31]

Appendectomy. Appendectomy has been associated with decreased risk of UC susceptibility.[32,33] In contrast, the relationship between appendectomy and CD is arguable, with conflicting results.[34]

Oral Contraceptives. Studies to determine whether females taking oral contraceptives are at a higher risk of developing IBD have shown a weak association. A meta-analysis demonstrated that after adjusting for smoking the risk of developing IBD while taking oral contraceptives was 1.44 for CD (95% CI: 1.12, 1.86) and 1.29 for UC (95% CI: 0.94, 1.77).[35]

Diet. Diet has been extensively studied as a risk factor for both CD and UC. The most predominant risk factor identified has been intake of refined sugars,[36] although a high fat diet has also been implicated,.[37] A critical review of diet studies in IBD revealed a number of methodological flaws; at this point in time, the link between diet and IBD is inconclusive.

Breastfeeding. A meta-analysis concluded that among individuals who were

Table 3: Summary of IBD Epidemiology

Characteristic		Ulcerative Colitis	Crohn's Disease
Incidence Range (North America)		2.2-19.5	3.1-20.2
Prevalence Rate (North America)		12.53-248.6	5.89-318.5
Gender (female : male)		1.1	1.3
Age at Onset (years)		15-30 50-70	15-30 50-70
Race		Caucasians >African >Americans > Hispanic > Asian	
Ethnicity		Jewish >non-Jewish Caucasian >African American > Hispanic	
Mortality (SMR)		0.8	1.2
Environmental Factors			
	Smoking	Protective	Risk factor
	Appendectomy	Protective	No effect
	Oral Contraceptives	Slight risk	Slight risk
	Breastfeeding	Protective	Protective

Adapted from: Friedman S, Blumberg RS. Chapter 289. Inflammatory Bowel Disease. In Fauci AS, Braunwald E, et al. *Harrison's Principles of Internal Medicine, 17th Edition*.

breastfed (duration unknown) the risk of developing CD was 0.67 (95% CI: 0.52, 0.86) and 0.77 for UC (95% CI: 0.61, 0.96).[38]

Measles Infections. Measles virus has been implicated in the development of IBD; however, the literature does not support a causal association.[39] The preliminary evidence suggesting an association with CD has been strongly refuted.[40,41]

Mortality. In North America, the overall survival rate of patients with IBD is similar to that of the US White population. The standard mortality ratios for UC and CD are 0.8 and 1.2 respectively.[42]

Pathogenesis

The current hypothesis states that overly aggressive acquired (T cell) immune responses to a subset of commensal enteric bacteria develop in genetically susceptible hosts, and environmental factors precipitate the onset or reactivation of disease.[43] The hallmark of IBD is chronic, uncontrolled inflammation of the intestinal mucosa.[21]

Evidence suggests that the dynamic balance between microbes, particularly commensal bacteria, and host defensive responses at the mucosal level plays a pivotal role in the initiation and pathogenesis of IBD.[44] Tolerance to commensal bacteria is lost in IBD. Exposure to luminal microflora initiates an inflammatory response by mucosal immune cells. This leads to a chronic, destructive immune response.[21,45] Possible pathogens for UC may include epithelial antigens or functionally altered aerobes, and for CD the antigens seem to be anaerobic bacteria and cell wall bacterial components. [21]

...at this point in time, the link between diet and IBD is inconclusive.

Overview of Pathology of IBD. Stimulation may occur from the penetration of bacterial products through the mucosal barrier, leading to their direct interaction with immune cells, especially dendritic cells and lymphocyte populations, to promote a classic adaptive immune response.[46] The innate immune system responds first when a pathogen is present in the intestine. Neutrophils infiltrate the intestinal epithelium and release substances that damage surrounding tissues. In addition, neutrophils activate other leukocytes by secreting proinflammatory cytokines TNF-á, IL-â, IL-6 and IL-8..[21,47] Antigen-presenting cells (macrophages) and dendritic cells activate the adaptive immune system. Secretion of cytokines causes the maturation of undifferentialed T cells to effector T cells. These may include TH1, TH2 and, more recently described, T_H17 cell types. [48] Activation of immune-cell populations is accompanied by the production of a wide variety of nonspecific mediators of inflammation (i.e. cytokines, chemokines). These mediators enhance the inflammatory process and tissue destruction, which result in the clinical features of IBD.[46]

Genetic Factors

UC and CD are heterogeneous polygenic disorders sharing some but not all susceptibility loci. [21] However, the presence of a mutated gene does not guarantee that IBD will develop, nor does it predict who will develop IBD .[49] The majority of patients do not have a family history or a known genetic defect,[21,50] yet having an affected family member is the single greatest risk for developing IBD. There is an increased prevalence of IBD in first and second degree relatives, and among these, a higher risk in siblings of affected individuals.[21]

In recent years, much has been learned about the genetic and environmental determinants of disease susceptibility in IBD. Genome wide scanning using linkage mapping has identified over 30 loci in CD.[51] The first susceptibility gene identified was the NOD2/CARD15 gene, located on chromosome 16. Although the pathogenesis of NOD2 mutations in CD patients is incompletely understood, allele variants increase the risk of developing CD. In a meta-analysis of 42 case-control studies the odds ratios of developing CD compared to the general population in homozygotes or compound heterozygotes was 17, while the risk in heterozygotes with the Leu1007fsinsC, Gly908Arg, and Arg702Trp allelic variants were 4, 3, and 2 fold greater, respectively.[52] The association of NOD2 and risk of CD varies by ethnicity and race. Japanese and Asian populations do not report NOD2 mutations, while European countries report ranges between 9% and 14% in Southern Europe and 0% to 9% in Northern Europe.[53] Despite the high relative risk of developing CD with NOD2 mutations, the absolute risk of developing CD among homozygous carriers is only one in twenty-five; thus NOD2 gene mutations alone cannot explain the risk.[53] The most recent genetic studies highlight a few contributing factors to the pathogenesis of IBD; i.e., defects in innate immunity, mucosal barrier function of the gut, regulation of the adaptive immune response and a novel

process called autophagy. The latter process is implicated in recycling of damaged intracellular proteins and organelles, and in dealing with intracellular pathogens, again highlighting the importance of innate immunity in these diseases.[44]

Table 4: Gene Associations with CD and UC

Chromosome	Location (Mb)	Genes of Interest	Associated with CD	Associated with UC
1p31	67	IL23R	Yes	Yes
1q24		EMC1	No	Yes
2q37	231	ATG16L1	Yes	No
3p21	49	Multiple, including MST1	Yes	Yes
5p13	40	Intergenic, PTGER4	Yes	No
5q31	131	Multiple, including SLC22A5	Yes	Unclear
5q33	150	Multiple, including IRGM	Yes	No
5q33	158	IL12B (P40)	Yes	Yes
10q21	64	ZNF365	Yes	Unclear
10q24	101	NKX2-3	Yes	Yes
16q12	49	NOD2	Yes	No
17q21	37	Multiple, including STAT3	Yes	Yes
18p11	12	PTPN2	Yes	Unclear
		BTNL2		Yes
		HLA-DRB1		Yes
1p13	114	PTPN22	Yes	Unclear
1q23	158	ITLN1	Yes	Unclear
1q24	170		Yes	Unclear
1q32	198		Yes	Unclear
5q33	159	IL12B	Yes	Unclear
6p22	21	CDKAL1	Yes	Unclear
6q21	107		Yes	Unclear
6q27	167	CCR6	Yes	Unclear
7p12	50		Yes	Unclear
8q24	127		Yes	Unclear
9p24	5	JAK2	Unclear	Yes
10p11	35		Unclear	Yes
11q13	76	C11orf30	Unclear	Yes
12q12	39	LRRK2,MUC19	Unclear	Yes
13q14	43		Unclear	Yes
17q21	35	ORMDL3	Unclear	Yes
17q21	38	STAT3	Unclear	Yes
21q21	16		Unclear	Yes
21q22	44	ICOSLG	Unclear	Yes

Adapted from Cho JH. The genetics and immunopathogenesis of inflammatory bowel disease. *Nat Rev Immunol* 2008; 8: 458-66; and
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Conclusion

CD and UC are chronic conditions that have a substantial negative impact on patients' quality of life. Several studies have demonstrated that the incidence of UC and CD is rising in North America. Current clinical and subclinical characteristics do not adequately account for or predict the variable rate of disease progression or aggressiveness of IBD. To date, there is a lack of well-defined, prospectively evaluated, population-based studies describing IBD in the US.

The etiology of IBD is unknown. However, IBD is thought to result from a complex interaction between genetics, environmental factors, response to intestinal flora, and alterations in innate and adaptive immunity.[44] Most data support a dysfunctional immune response to normal luminal components, infection, and/or a defective mucosal barrier.[21]

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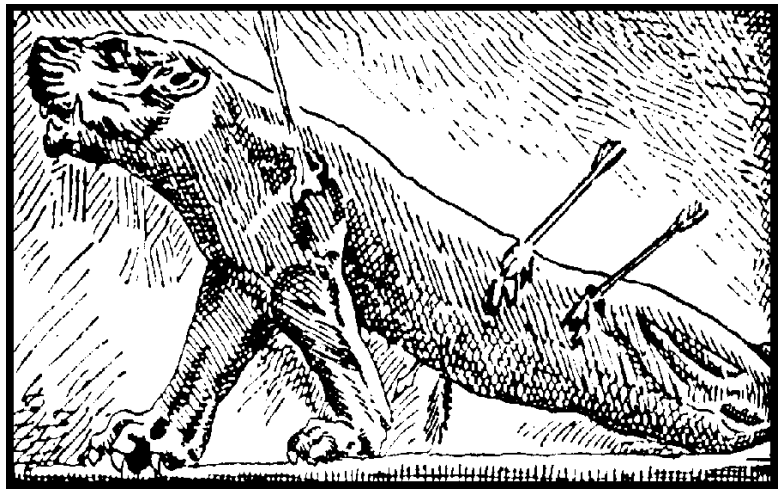


Medical Therapy of IBD in 2009

Adam Harris, MD, Edward R. Feller, MD, FACG, and Samir A. Shah, MD, FACG

Medical therapy for Inflammatory Bowel Disease (IBD) has advanced dramatically in the last decade with the introduction of targeted biologic therapies, optimization of older therapies including immunomodulators and 5-Aminosalicylic acid (5-ASA) drugs, and a better understanding of the mucosal immune system and genetics involved in the pathogenesis of IBD. Here we update the medical management of IBD in 2009.

The goal of IBD therapy is to induce, and then maintain, remission. Since we are unable to predict disease course at diagnosis, the current paradigm of treatment is a step-up approach: moving to aggressive, powerful therapies only when milder therapies with less potential side effects fail or when patients declare themselves to have aggressive disease. If our ability to stratify risk at diagnosis improves, we may see a paradigm shift to top-down therapy with the powerful drugs used first line to change the course of the disease and improve outcomes.[1]

5-ASA

Sulfasalazine and 5-aminosalicylic acid formulations are mainstays of treatment for mild to moderately active ulcerative colitis and mild **Crohn's disease (CD)**.[2]

Ulcerative Colitis

Both topical and oral forms of the 5-ASA medications can be used depending on the distribution of colonic disease. For ulcerative proctitis (rectal involvement up to 20 cm), mesalamine suppositories are effective at inducing and maintaining remission.[3] In patients with left-sided ulcerative colitis (below the splenic flexure), mesalamine enemas can induce and maintain remission. UC extending beyond the splenic flexure, also know as extensive colitis, requires oral therapy. However, rectal mesalamine (either suppository or enema forms) can have an adjunctive role in treating patients with pancolitis, as diarrhea and tenesmus are often due to the left-sided disease. Combining oral and topical therapy leads to faster resolution of rectal bleeding and is also more effective at maintaining remission compared to oral therapy alone. Oral formulations of the drug are differentiated by several factors including the drug delivery system, pH dependence, azo-bonding, and even time-controlled release. All seem to work equally well for mild to moderate UC. Dosing can be adjusted based on the severity of disease. For mild disease, 2.4-3 grams per day is preferred, whereas higher doses (4- 4.8 grams per day) are needed to induce and maintain a remission in moderate UC. Severe disease requires more aggressive therapy (i.e. corticosteroids) to induce remission, and then 5-ASA drugs can be utilized to maintain remission. Finally, a meta-analysis suggested 5-ASA use in UC may decrease colorectal cancer risk by 50%.[4] Adherence to medical therapy is strongly associated with staying in remission compared to nonadherence (see graph below).[6] Cost, pill burden, side effects, inadequate understanding for the rationale for maintenance therapy are some of the factors associated with non-adherence.[6]

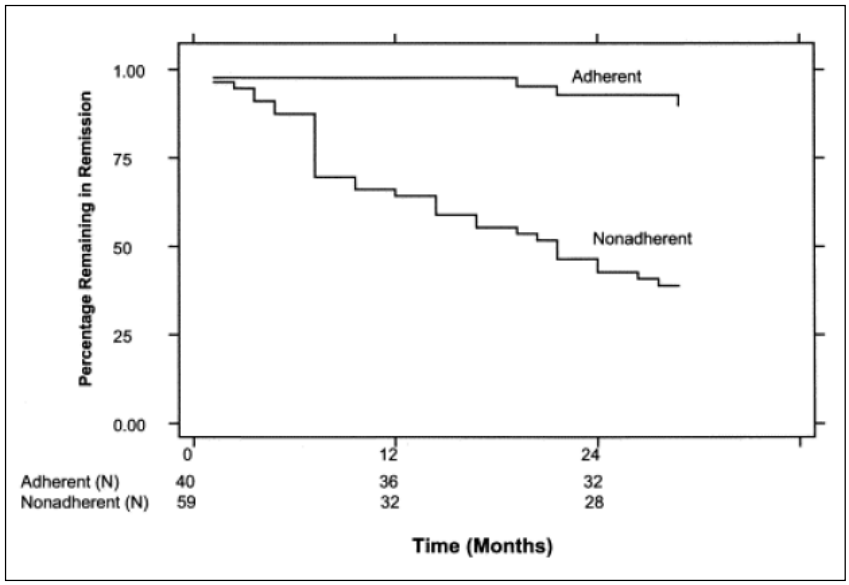
Crohn's Disease (CD)

Mesalamine has some benefit in inducing remission for patients with ileal or colonic CD. However, meta-analyses have shown 5-ASA is no better than placebo in maintaining medically induced remission.[5] Nevertheless, clinical experience favors use of mesalamine in mild CD because of its safety and perceived efficacy in practice. Mesalamine is not effective in patients with moderate or severe CD or in patients requiring steroids to induce remission. The time or pH dependent formulations are most useful for patients with small bowel involvement. 5-ASA drugs have a limited role in preventing/delaying post-operative recurrence.

Overall, 5-ASA drugs are generally tolerated well; but patients and primary care physicians should be aware of potential side effects. Up to 30% of patients taking 4 grams per day of sulfasalazine are intolerant. Side effects include bone marrow suppression, impairment of folic acid absorption, and rash. The newer 5-ASA formulations avoid sulfa related side effects of sulfasalazine. However, both sulfasalazine and 5-ASA formulation can have adverse effects including headache, pancreatitis, GI upset, hair loss, and rarely pulmonary fibrosis, paradoxical worsening of colitis and renal toxicity. The 5-ASA drugs are ineffective in severe disease requiring hospitalization. All patients on 5-ASA therapy should have a baseline creatinine checked prior to starting therapy, several months into therapy, and then annually. Patients with a severe aspirin allergy should not be prescribed 5-ASA.

Antibiotics and Probiotics

Because of the postulated role of bacterial flora in the pathogenesis of IBD, there is great interest in both antibiotics and probiotics. Efficacy of probiotics has not yet been shown in high quality trials;



therefore data do not support use of any probiotic in CD or UC.

Limited data support a role for antibiotics in CD but not in UC except for hospitalized patients with fulminant colitis at risk for sepsis. After colectomy with ileoanal pouch, some patients will develop pouchitis which generally responds to antibiotics (Metronidazole, Ciprofloxacin, or both).

Antibiotics have some benefit in treating CD. Metronidazole is effective in treating mild to moderate CD. There is benefit in perianal disease as well as in delaying recurrence after segmental surgical resection.[7] Ciprofloxacin is also useful in treating CD (both luminal and perianal).

Antibiotic therapy in CD is limited by the side effect profile of the drugs. Metronidazole can lead to peripheral neuropathy and can cause a disulfiram-like reaction with concurrent alcohol use. Ciprofloxacin is contraindicated in children and can cause tendonopathy in all patients using the medication. Use of antibiotics is a risk factor for *Clostridium difficile* infection, an increasingly common problem for many patients, including those with IBD.

Steroids

Corticosteroids, used for over 50 years to treat IBD, are used to treat moderate to severe UC. Steroids have no role/efficacy in maintenance of remission. Steroid enemas have been beneficial in distal UC; systemic absorption can lead to steroid related side effects. For patients who do not tolerate 5-ASA enemas, cortenemas and particularly cortifoam may be better tolerated initially.

Corticosteroids in CD have been studied extensively. Two large trials validated their use for inducing remission (NCCDS and ECCDS).[8] However, concern exists over patient outcomes once they are started on a prolonged course of steroids. A Minnesota cohort of Crohn's patients [9] was followed after steroid treatment. Of those who responded, only 32% had a prolonged response to steroids (at one year), 28% had become steroid dependent, and 38% had undergone surgery. Increasingly, clinicians appreciate that the need for steroids in IBD defines a subgroup of patients with aggressive disease. In this subgroup, immunomodulator therapy or a biologic will likely be needed in CD and may be needed in UC to achieve steroid-free remission. Steroids are neither effective nor recommended as maintenance therapy or for post-operative prevention of recurrence.

Dosing of corticosteroids for IBD is different than that used for pulmonary and rheumatologic disorders. Prednisone can be given orally at a dose up to 60 mg per day with a slow taper over months. Higher doses have no additional benefit and are associated with worse side effects. Too rapid a taper can lead to relapse. Intravenous steroids are preferred for hospitalized patients who are generally sicker and may have impaired absorption.

Budesonide, a steroid with less systemic side effects than oral prednisone, is designed to release in the distal ileum / proximal colon and hence is ideal for inducing and prolonging remission in mild to moderate CD involving those areas. Budesonide has fewer side effects than prednisone, but still has the potential for adverse effects and can suppress the hypothalamic-pituitary axis.[10]

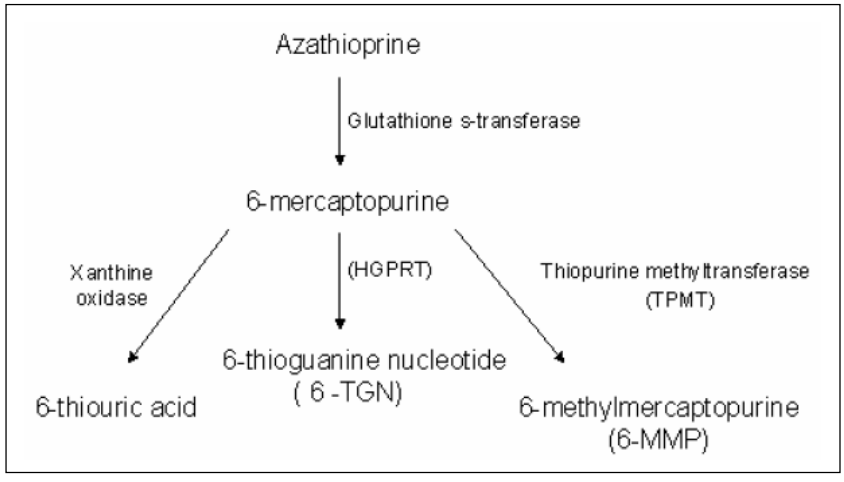
Numerous steroid side effects include acne, striae, "moon facies", edema, mood/sleep disturbance, as well as glucose intolerance. Prolonged use of steroids can lead to myopathy, osteoporosis, cataracts, and avascular necrosis of the femoral head. Another important concern for those on prolonged steroids is an increased susceptibility to infection. An analysis of the TREAT registry concluded that steroid and narcotic use were both independently associated with increased risk of infection and mortality in CD.[11] Finally, tapering steroids is not easy, as abrupt withdrawal can lead to acute adrenal insufficiency.

Immunomodulators

Immunomodulators, in particular **azathioprine (AZA)** and **6-mercaptopurine (6MP)**, have long been used for treatment of UC and CD. **Methotrexate (MTX)** also has immune-modifying and anti-inflammatory properties, leading to its use in rheumatoid arthritis, psoriasis, as well as CD (but not UC). Cyclosporine, a powerful immunosuppressant, has been used for severe IBD.

AZA (2-2.5mg/kg qd) and 6-MP (1-1.5 mg/kg qd) are used in UC patients who are steroid dependent or unresponsive to corticosteroid or mesalamine therapy. These oral medicines are effective long-term steroid-sparing agents for UC and are useful in maintaining remission. However, these drugs do not reach maximal effect until 2-4 months of administration. Therefore, these drugs are usually initiated in concert with another form of therapy until they have reach steady-state levels. Cyclosporine has been used in steroid-refractory severe colitis in a last attempt to prevent colectomy.[12] Cyclosporine, if effective, is used as a bridge to AZA or 6-MP long term therapy. Therefore, cyclosporine should not be considered if a patient has already failed or is unable to take AZA/6-MP because of intolerance or side effects.

Immunomodulators are also used in the treatment of CD. Present et al [13] established the efficacy of 6-MP with a 70% response rate in patients with steroid- refractory CD. The mean time of treatment required for response was 3.1 months. In addition to decreasing disease activity, 6-MP had other beneficial effects, including healing and closure of fistulas and maintenance of remission in



both CD and UC. Methotrexate is a second-line therapy used for steroid-dependent or refractory CD. Studies have shown efficacy at inducing and maintaining remission with the intramuscular administration at a 25mg per week dose and 15 mg/week dose respectively. Oral MTX does not work as well in CD.[7]

AZA/6-MP can cause pancreatitis as well as hepatotoxicity and pancytopenia. Both agents are metabolized by **thiopurine methyltransferase (TPMT).** Individuals who are heterozygous for TPMT need a reduced dosage of the medication in order to avoid excessive myelosuppression. The rare patient (1 in 300) who has absent TPMT activity (recessive for 2 mutant copies of TPMT) will develop profound myelosuppression if given AZA/6-MP; hence their use is contraindicated in this rare situation. Complete blood count and hepatic function panels should be monitored. A CBC should initially be checked weekly, then every 2-3 months, along with liver enzymes, once on a steady dose. Allopurinol will increase the serum levels of AZA/6-MP metabolites which could lead to significant myelosuppression. Also, AZA/6-MP decrease serum levels of warfarin.

MTX must be administered in conjunction with folic acid. A majority of the side effects are gastrointestinal, including nausea and vomiting. MTX also has potential hepatotoxic, myelosuppressive, and pulmonary side effects. A baseline chest x-ray prior to MTX and subsequent monitoring of CBC and LFTs is advised. Patients have had adverse reactions with concomitant use of NSAIDS and penicillin while using MTX.

Cyclosporine has a host of serious side effects including potentially fatal opportunistic infections. **Pneumocystis carnii pneumonia (PCP)** prophylaxis should be given if cyclosporine is started. Cyclosporine can also lead to renal impairment, hepatotoxicity and seizures. Given its significant toxicity, including a mortality rate of 1 in 200, we suggest only experienced centers/clinicians use this therapy.

Biologics

The biologic medications have efficacy in moderate to severe UC and CD.[14] These medications include infliximab, adalimumab, and certolizumab pegol which all inhibit TNF-alpha. Infliximab is a chimeric anti-TNF alpha monoclonal antibody given intravenously. Adalimumab is a recombinant human monoclonal antibody which is administered subcutaneously and can be self-injected. Certolizumab pegol is a humanized anti-TNF alpha antibody FAB fragment that has been pegylated and is administered subcutaneously. All three are approved for use in CD; currently, only infliximab is approved for use in UC.

Infliximab was tested in UC patients who were refractory or intolerant to steroids and/or Azathioprine/6-MP and 5-ASA.[15] These studies showed that Infliximab was superior to placebo in establishing and maintaining remission, mucosal healing, discontinuation of steroids, and avoiding colectomy.

The biologic medications have efficacy in moderate to severe UC and CD.

Extensive data exist for use of biologics in CD. Infliximab was studied in a group of patients with moderate to severe CD who were refractory to steroids, ASA, and/or immunomodulators.[16] Patients who responded to an initial infusion had a statistically significant achievement of remission compared to placebo. Infliximab was later tested in patients with fistulizing CD.[17] This placebo-controlled study illustrated that infliximab was successful in treating patients with active fistulas with greater evidence of healing than placebo.

Adalimumab is effective in clinical studies in inducing and maintaining remission in moderate to severe CD..[18,19] Placebo-controlled studies demonstrated that patients naive to anti-TNF therapy had significant improvements in initiating and maintaining remission. Patients on adalimumab also had more steroid discontinuation and healing of fistulae compared to placebo. Concomitant use of immunomodulator therapy did not cause significant improvements in these studies. Therefore, monotherapy with a biologic is considered the preferred strategy in patients who have previously been on immunomodulators. Both adalimumab and infliximab have shown increases in quality of life, fewer hospitalizations and surgeries with maintenance use. Therefore, although these medicines are expensive, they may result in overall savings.

Certolizumab, the newest anti-TNF drug approved for use in CD,[20] has not yet been studied in fistulizing CD or as a steroid sparring agent.

Without head-to-head trials comparing the anti-TNF agents, there is no basis to recommend one over another. If one compares the trials (realizing different patient populations, different definitions of response and time points of assessment), the initial efficacy for inducing remission and maintaining remission for the first 6 months appear similar. Further experience will determine if a particular anti-TNF has an efficacy, safety or cost advantage. For those patients who lose response or have side effects, an alternate anti-TNF agent can be tried with some, although reduced, efficacy compared to a patient naive to anti-TNF therapy.

Safety of Biologics

Adverse reactions range from infusion or injection site reactions,[21] minor upper respiratory tract infections to serious infections and malignancies. Reactivated TB and fungal infections (particularly histoplasmosis) are a significant concern and should be considered in any patient with fever, and other symptoms suggesting infection.[22]

Non-Hodgkin's lymphoma has been reported in patients taking anti-TNF medications; however, it is not clear whether these lymphomas are related to anti-TNF agents, other agents, or underlying disease. Studies have yielded conflicting results on lymphoma risk with anti-TNF therapy ranging from no increased risk to a 3 fold increase in relative risk.

Hepatosplenic T cell lymphoma (HSTLC) is a rare, fatal disease that has been described in 16 IBD patients[23] between 2002 and 2008 (age range 12-58, 15 males, 1 female) who were using combination therapy with an anti-TNF and either AZA or 6-MP. Therefore, the current recommendation is to avoid combining an immunomodulator with an anti-TNF in younger males and in patients who have previously failed immunomodulators. Anti-TNF medications should be avoided in

patients with severe heart failure, demyelinating disorders, and active HBV. All patients should be assessed for TB and HBV prior to initiating anti-TNF agents; furthermore, patients should be prompted to remind all caregivers that they are on a powerful drug that can increase the risk of dangerous opportunistic infections.

Top Down Therapy in CD

One recent study compared early aggressive treatment with infliximab plus azathioprine versus a traditional step up approach. Patients randomized to early aggressive treatment had faster time to remission, less steroid use and higher rates of complete mucosal healing.[24] Whether this approach improves long term outcome without the potential side effects of these aggressive therapies is still under investigation.

A new landmark study, **SONIC (Study Of Biologic and Immunomodulator Naïve Patients In Crohn's Disease)**, investigated CD patients who had not responded to 5-ASA, antibiotics, or steroids or were steroid dependent.[26] These patients were naive to immunomodulatory agents and biologics and had CD for a shorter time compared to patients enrolled in previous trials with anti-TNF agents. Patients were randomized to AZA, Infliximab, or combination AZA + Infliximab. Infliximab monotherapy was superior to AZA monotherapy at 6 months. However, combination therapy was superior to both monotherapy arms. This study is the first to show that combining therapy has increased efficacy in CD. Previous studies did not document benefit with combination therapy. The earlier studies enrolled patients who had failed immunomodulators whereas the SONIC trial enrolled patients who were naive to both immunomodulators and anti-TNF agents. Longer term follow-up of patient outcome in this study is eagerly awaited to help clinicians guide therapy and balance benefits versus risks.[26]

Natalizumab

Natalizumab is a recombinant humanized antibody that targets alpha-4 integrin and thereby prevents inflammatory cells from getting to the gut and central nervous system and is effective in both **multiple sclerosis (MS)** and CD. **Progressive multifocal leukoencephalopathy (PML)** has been reported in 6 patients. Therefore, its use in CD patients is restricted to those have failed other therapies including at least one anti-TNF drug. Other drugs blocking cell trafficking and other aspects of intestinal inflammation are in clinical trials.

Surgery

Surgery has an important role in treating IBD and sometimes is the preferred alternative. It should not be seen as a last resort but an important option to consider depending on the clinical situation and the patient's preference. For example, a patient with 20 years of CD and symptomatic short fibrotic stricture with proximal dilation will not respond to any medical therapy and is best served by a surgical approach. The indications and options for surgery in both CD and UC are discussed in separate articles in this issue.

A team approach with the patient, gastroenterologist, surgeon and primary care physician can optimize outcome.

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Discussion of off-label usage and any productsor services

6-MP, AZA, MTX, Cyclosporine, Ciprofloxacin, Metronidazole

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OSCCAR: Ocean State Crohn's and Colitis Area Registry

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Epidemiology studies describe population characteristics of disease states. The results are important for determining the allocation of healthcare resources, developing preventative measures, identifying risk factors for disease and predicting outcomes of disease. The **Ocean State Crohn's and Colitis Area Registry** (**OSCCAR**) is a population-based cohort of newly diagnosed patients to be followed prospectively to determine the epidemiologic characteristics of **Crohn's disease** (**CD**) and **ulcerative colitis** (**UC**). This study has used the population of Rhode Island as a defined base.

Much of what we know about IBD in the US population comes from studies conducted in Canada and Olmsted County, MN.[1-6] Data from these studies may not be applicable to the more diverse population of the **United States** (**US**). In addition to a homogenous population, residents of Olmsted County are 3 times more likely to be employed in health care services and 1.5 times more likely to have completed college compared to the general population.[4] The Olmsted results may also be limited by misclassification bias due to retrospective data acquisition.[3]

Several population-based studies have used hospital admission data,[7-11] but because the majority of patients with IBD are treated as outpatients, the incidence and prevalence rates may be underestimated. Sonnenberg et al. reviewed admission data for patients with the Veterans Administration to determine the incidence and prevalence of IBD,[12] but the VA has a very specific, largely male, patient population. The resulting data may not be generalizable to the US population.

More recent studies have used HMO and insurance claims data to determine incidence and prevalence of IBD.[11,13-16] These studies have several limitations. The populations sampled are not random. Health plans do not represent all age groups or uninsured patients. Most plans do not collect detailed demographic patient information, such as ethnicity or race. There may also be misclassification or coding inconsistencies. Claims data lack sufficient clinical evidence to confirm diagnosis.

Due to the fragmented nature of the health care system, epidemiologic studies of the general population of the US are costly and difficult. Studies of patients seen at referral centers likely reflect the outcomes of the most severely affected individuals, who may not reflect the broad population of individuals with these diseases. These differences are critical to understanding why the course of these diseases is so highly variable and, at the present time, unpredictable. The ability to identify otherwise unselected Americans with new diagnoses of IBD, and to track their outcomes over time would greatly enhance our understanding of these diseases and their effect.

The lack of a well-defined, prospectively evaluated, population-based inception cohort in the US is a critical impediment to developing generalizable prognostic markers and models of disease progression in IBD. OSCCAR is necessary for several reasons: (1) To date, population-based studies designed to evaluate IBD have been limited to small relatively homogeneous populations; (2) Incidence rates of IBD continue to rise – an increase not completely attributable to increased awareness and advances in disease diagnosis; (3) The natural history of IBD is incompletely described. While studies have helped to define the natural history of IBD in aggregate, they do not allow prediction of the individual course of disease or prognosis. None reflect treatment practices in the US, with increasing use of immunomodulators and anti-TNF antibodies;(4) Determinants of prognosis are poorly understood. Little is known about the clinical implications of genetic

Table 1: Census Bureau Data for Rhode Island for the Year 2006 [24]

Population	1,067,610
Females	51.6%
Males	48.4%
Age Distribution	
< 5 years old	5.8%
5-17	22.2%
18-64	58.1%
≥ 65	13.9%
Caucasian	79.6%
Hispanic	11%
African-American	6%
Asian or Pacific Islander	2.8%
Native American	0.6%

Table 2: Diagnosis of IBD According to The NIDDK IBD Genetics Consortium Phenotype Operating Manual [21]

A Symptoms including one or more of: diarrhea, rectal bleeding, abdominal pain, fever, complicated perianal disease, extraintestinal manifestations, weight loss or failure to thrive; and

B Symptoms on two or more occasions separated by at least 8 weeks or ongoing symptoms of at least 6 weeks duration. When there has been a single episode of colitis (in some instances less then 6 weeks duration) resulting in colectomy and resolution of disease symptoms, pathology on the colectomy specimen should be consistent with idiopathic IBD and microbiology studies should be negative; and

C One or more of the following providing *objective* evidence of inflammation:

1.C Endoscopic: Mucosal edema, erythema, loss of normal submucosal vasculature, friability, ulceration, stricture formation, pseudopolyps. *Where there are only minor changes (mucosal edema, erythema, loss of normal submucosal vasculature, friability) mucosal biopsies should have been done to confirm the presence of IBD; and/or*

2.C Radiologic: Mucosal thickening and/or nodularity, ulceration, stricture, pseudopolyps, fistula formation, pseudosacculation. Minor changes alone (mucosal thickening and/or nodularity) should not be sufficient to make a diagnosis of IBD; and/or

3.C Histologic: Mucosal erosion or ulceration, architectural changes of crypts, Paneth cell metaplasia (in colon), transmural inflammatory infiltrate*, fibrosis of muscularis propria*, noncaseating granuloma*. (*Crohn's disease only)

profiles on prognosis, with regard to the correlation of genotype and phenotypic presentation of disease.[17-19] Few environmental risk factors have been established, and these risk factors do not completely explain the occurrence of IBD and the rising incidence rates of CD.

Rhode Island, with a diverse population of over 1 million, provides an ideal base for a prospective inception cohort of IBD patients, limiting referral bias in estimates of prognosis, and enhancing generalizability of predictive models. (Table 1) Based on American estimates of incidence rates of CD (7-8 cases per 100,000 person-years) and UC (8-9 cases per 100,000 person-years),[20] approximately 70 and 80 cases of CD and UC will be diagnosed annually, respectively.

Description

OSCCAR is a population-based study designed to capture each new case of inflammatory bowel disease diagnosed in Rhode Island. This is the first of its kind and one of very few such cohorts in the world. The goals of the study include: 1) describing the incidence rates of CD and UC; 2) describing disease outcomes; and 3) identifying factors that predict disease outcomes. In the coming years, we anticipate enrolling between 150 and 250 newly diagnosed individuals annually. As we track the diversity of backgrounds and exposures, we expect to describe the outcomes of these diseases with great detail and precision. More important, we expect to begin to unravel the reasons for these diverse outcomes, and eventually to predict the course of the disease with increasing accuracy.

Funding Source

The **Centers for Disease Control and Prevention (CDC)** has granted funds to the **Crohn's & Colitis Foundation of America (CCFA)** to support OSCCAR (Project # 1 UO1 DP000340-03). In addition, the **National Institutes of Health (NIH)** has granted funds to subsidize OSCCAR (NIH grant # 5R21DK078555-02). This study is being conducted jointly by investigators at the Harvard Medical School and the Warren Alpert Medical School of Brown University.

Objectives

The initial study objectives include: (1) establishing study procedures to develop and maintain a population based, prospective inception cohort of IBD patients in the state of Rhode Island; (2) determining the incidence rates of CD and UC in Rhode Island and extrapolating these rates to the general US population; (3) defining the natural history of IBD in the setting of contemporary treatment practices in the US, and obtaining preliminary data to identify clinical and subclinical factors associated with disease progression in CD and UC; and (4) identifying clinical and subclinical (including genetic) risk factors for steroid resistance in IBD.

Subject Selection

All adults and children living in Rhode Island, and newly diagnosed with CD, UC, or indeterminate colitis, will be invited to join the study. As there are no gold standard tests for diagnosing Crohn's disease and ulcerative colitis, new diagnoses of IBD depend upon signs and symptoms consistent with the diagnosis and confirmed on endoscopy, pathology, or imaging. Histopathologic confirma-

Table 3: Categorization of IBD into Subtypes According to The NIDDK IBD Genetics Consortium Phenotype Operating Manual [21]

Crohn's Disease (CD)	
1	Evidence of small intestinal inflammation with endoscopically, radiologically or histologically demonstrated ulcerations, fistulization, mucosal fissuring, nodularity or cobblestoning, stricture formation or histologically demonstrated transmural inflammation with or without granuloma formation.
2	Isolated esophageal, gastric or duodenal inflammation with the finding of noncaseating granuloma.
3	Colonic inflammation which is patchy (normal segments separating areas of inflammation, as described above) or associated with one or more of the following features: complete rectal sparing, multiple (>10) aphthoid ulcers, deep ulceration (into the muscularis propria), transmural inflammation, extensive fibrosis and wall thickening, fistulization, non-caseating granuloma.
4	The presence of complex suppurative perianal disease (i.e. more than a superficial fistula or uncomplicated superficial abscess).
5	If there are fewer than 10 aphthoid ulcers in the cecum (and the rest of the colon appears normal) in a patient with small bowel disease then this should be called small bowel disease only. Similarly, if the colon is normal except for the presence of a fistula extending from inflamed small bowel, the patient should be said to have small bowel disease alone. If the cecum is involved with ulcers larger than aphthoid ulcers or ulcers that are deep or if the involvement has resulted in deformity of the cecum this would be considered to be colonic involvement.
Ulcerative Colitis (UC)	
1	Superficial inflammation and/or ulceration (involving only the mucosa and submucosa) of the colon which is continuous from the rectum extending proximally without skip lesions or complete rectal sparing (N.B. Relative rectal sparing is allowed for patients receiving topical rectal therapy).
2	No inflammation of the small intestine ("backwash ileitis" is allowed - nonstenosing superficial inflammation of the terminal ileal mucosa associated with severe pancolitis which resolves following medical or surgical treatment of the colitis).
3	No features of Crohn's disease listed above.
Indeterminate Colitis (IC)	
1	Confirmed IBD by A, B and C above (Table 2).
2	Physician unable to classify individual into either CD or UC based on above criteria and/or patient has features of both CD and UC with none of the features diagnostic of one or the other.

tion is usually possible-based on review of endoscopic biopsies. For this study, a diagnosis of IBD is made according to the NIDDK IBD genetics consortium criteria as described in their phenotype operating manual (May 10, 2006).[21] (Tables 2 and 3)

Individuals diagnosed with CD, UC, or indeterminate colitis prior to the study start date (i.e., prevalent cases), those unwilling to provide informed consent, those who are prisoners at the time of diagnosis and pregnant women will not be permitted to enroll.

Subject Enrollment

We believe that the majority of patients suspected of having IBD are evaluated by a gastroenterologist or colorectal surgeon to establish a diagnosis. The clinician will present OSCCAR to the patient at anytime up to 6 months from diagnosis. Patients who agree to be contacted will complete a referral form, which is available in pamphlets distributed to all gastroenterology and colorectal surgery practices in the state, and in practices in Southeastern Massachusetts along the eastern border of Rhode Island. The referral forms are faxed to the study office. Alternatively, online referrals can be made through the study website at http://www.osccar.org.

Table 4: Summary of Data Being Collected

1. General subject information (date of birth, place of residency, contact information)
2. Demographic data (age, gender, race, ethnicity, occupation, marital status, education level)
3. Symptoms at diagnosis
4. Tobacco history
5. Family history of IBD
6. History of immune-related conditions and cancer (patient and family history)
7. Pediatric growth and development
8. Laboratory and serology results at diagnosis
9. Endoscopy findings
10. Surgical findings and procedures
11. Pathology findings
12. Radiology findings
13. Past and present medication use for the treatment of IBD
14. Interval history at 3, 6 and 9 months, and annually, including development of extraintestinal manifestations, medication use, hospitalizations, endoscopic procedures, imaging studies, and/or surgery
15. Disease activity indices: Harvey Bradshaw Index (CD) or Simple Clinical Colitis Activity Index (UC or IC) [25,26], Pediatric Crohn's Disease Activity Index (PCDAI) or Pediatric Ulcerative Colitis Activity Index [27,28]
16. Dietary history using the Food Frequency Questionnaire [29,30]

Study Procedures

Once a referral is received, study personnel will contact the patient to schedule an intake visit, in either the patient's home or in a place of their choosing. In the case of children, the intake visit takes place at the Hasbro Children's Hospital. During that visit, lasting approximately 2 hours, personnel obtain informed consent (available in English, Spanish, and Portuguese) and provide detailed education regarding the diagnosis of IBD. Personnel record demographic data, past medical history and disease-related information, administer quality of life and disease activity questionnaires (Tables 4 and 5), and collect blood, urine and stool samples. Later, study personnel obtain additional data elements by standardized chart review of the subject's medical record.

Study personnel will contact subjects by telephone at months 3, 6 and 9 for a brief follow up interview. Patients (or their parents, in the case of children under age 18) are queried about their disease activity, the medical and surgical treatments or procedures they have received since their most recent interview, and reasons for discontinuing any medical therapies. In addition, personnel will administer the **Short Inflammatory Bowel Disease Questionnaire (SIBDQ)** , a measure of disease activity for adults, or the **IBD Quality of Life Survey (IMPACT-35 Questionnaire)**, for children. [21,22]

One year from diagnosis, study personnel will arrange a return visit. Personnel will re-obtain the initial data elements (except for demographic data), will abstract interval data from the medical record, and will collect blood, urine, and stool samples. Personnel will schedule return visits annually.

Subjects will be compensated: Each subject will receive a one-hundred dollar stipend upon enrollment, and a fifty dollar stipend for each annual visit completed.

Procedure for Missed Cases

Initial experience since the start of the study suggests that the capture rate of newly diagnosed patients by initial referral by a gastroenterologist or colorectal surgeon has been good; but to improve the capture rate, we have asked each prac-

Table 5: Quality of Life Questionnaires	*Acronym*	*Description*
Inflammatory Bowel Disease Questionnaire[31] and Short Inflammatory Bowel Disease Questionnaire[23]	IBDQ SIBDQ	Health-related quality of life questionnaire specific for adults with IBD
IBD quality of Life Interview (IMPACT-35)[22]	IMPACT-35	Health-related quality of life questionnaire specific for pediatric population with IBD
SF-36[32]	SF-36	Generic quality of life questionnaire
EuroQol [33,34]	EQ-5D	Generic quality of life questionnaire for adults
Work Productivity and Activity Impairment Questionnaire[35]	WPAI:SHP	Generic questionnaire assessing the effects of a condition on ability to work or perform regular activities (adults)
Functional Assessment of Chronic Illness Therapy[36]	FACIT	Generic questionnaire assessing patent fatigue level related to a health condition (adults)

Patient self referral form

Enrollment Contact Form

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

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

Health care professional 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:

_____

Completed by: _____

The Ocean State Crohn's & Colitis Area Registry

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

Table 6: Enrollment Table as of January 15, 2009

	Adult		Pediatric		Total
	Male	Female	Male	Female	
Enrolled	21	34	9	8	72
Pending	4	0	0	1	5
Ineligible	5	5	0	0	10
Unresponsive/ Declined	3	2	0	1	6

tice to search billing data for a defined period of time by ICD-9 codes mapping to IBD. Any patients discovered during this process and not previously referred to the study may be contacted by their gastroenterologist and referred at that time with the patient's permission. Each practice will undergo a diagnostic review every 4 months. Diagnostic review has resulted in an increased overall capture rate.

Use of Specimens

Blood samples are collected during the intake and annual study visits. Peripheral blood is collected for isolation of messenger RNA (mRNA) for gene expression arrays. Plasma is collected for proteomics studies, and serum for serologic studies. DNA is being isolated for studies of genetic susceptibility and genetic determinants of phenotype and prognosis.

Urine is collected and stored for future metabolomics studies.

Stool samples are collected for speciation of fecal flora by non-classical bacteriologic methods, such as 16S ribosomal RNA speciation or multiplex PCR of IS900 integration loci. Ultimately we intend to apply high-throughput novel technologies to elucidate factors and/or profiles associated with phenotype of disease and prognosis. Steroid dependence remains an increasing problem in IBD and this will be the first focus of the laboratory effort.

Current Status of OSCCAR

OSCCAR has been open to enrollment since January 1, 2008. Ninety-seven gastroenterologists/colorectal surgeons from 22 practices have agreed to refer patients. Study staff and the principal investigators visited each practice prior to initiation and the study was gradually rolled out to each practice. Brochures describing OSCCAR and IBD educational booklets have been distributed to each practice. (Table 6)

Contribution of OSCCAR

Initially, each subject will benefit from individual and private education about their new diagnosis of IBD. It is hoped that OSCCAR will provide an accurate incidence rate applicable to the US population. In addition, the results will provide information regarding determinants of steroid resistance, describe disease outcomes and identify predictors of disease, such as environmental and genetics risk factors. The knowledge gained from OSCCAR will assist with the creation of treatment algorithms for IBD and provide insight into areas of future research.

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What's New In Surgical Treatment for Crohn's Disease

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Crohn's disease (**CD**) has no cure. Surgery is reserved for 3 specific categories of complications: 1) urgent/ emergent, 2) chronic type conditions and 3) refractoriness to medical therapy. Approximately 70% of patients with CD will require at least one surgery during their lifetime.

The type of surgery required depends upon the clinical and anatomic presentation. CD can manifest anywhere from the mouth to the anus; unfortunately, for most patients, disease tends to eventually recur at the anastomotic site. The goal of treatment is similar in all cases: to resolve the symptoms, improve quality of life and reduce the risk of disease complications. The three anatomic areas that most commonly need surgical treatment are the distal small bowel, the large bowel and the ano-rectal area. Surgical treatment of the large bowel or colon will sometimes require a total colectomy or segmental resection which may require a temporary or permanent ostomy. The small bowel and the ano-rectal area present more difficult challenges. Anorectal disease can be quite debilitating, but can usually be palliated with drainage of abscesses and temporary indwelling drains. A team approach with medical and surgical therapy is associated with better outcome.[1] Severe ano-rectal disease may require a permanent ostomy in rare cases. There are some new techniques for ano-rectal surgery to palliate the disease.

For the small bowel, overall treatment goals are to preserve bowel length and thus prevent a short gut syndrome, while at the same time providing palliation and resolution of the problem with as little resection as possible by the least invasive techniques. Long-term studies have reported that on average a Crohn's patient will have 2.5 operations in a lifetime. For these reasons the use of laparoscopy, a less invasive technique thought to produce less scarring and trauma to the tissues, is an excellent way to reduce morbidity.

Laparoscopy in Crohn's Disease

The technique of laparoscopy has revolutionized abdominal surgery, allowing smaller incisions, better visibility, and less post-operative pain after procedures as diverse as cholecystectomy, appendectomy, hernia repair, and even surgery for morbid obesity. This technique is performed by using several small incisions (5 to 10 mm each) to gain access to the peritoneal cavity and employing small instruments to dissect under direct visualization provided by a camera (laparoscope.) When used for larger procedures including colonic surgery, one larger incision is often made for specimen extraction or for the insertion of a hand-assist port. This incision is almost always smaller than one that would have to be made for a conventional open operation.

Compared to conventional open surgery, improvements include decreased post-operative pain, shorter hospital stay, better cosmetic result and shorter recovery period.[2] When applied specifically to CD, the important issues are whether or not recurrence rates, morbidity and quality of life are equivalent to open surgery, therefore justifying its use to gain the above advantages. The next section reviews recent evidence regarding minimally invasive surgical treatment of CD.

Since 2005, three separate meta-analyses have evaluated laparoscopy in CD. The predominant operation by far was ileocolic resection, with a minority of studies reporting on Hartmann's procedures or abdominoperineal resections. All three studies demonstrated a statistically significant shorter length of hospitalization and earlier return of bowel function with the laparoscopic approach.[2,3,4] Additionally, Tan *et al* reported a lower overall cost in the laparoscopic group, likely related to earlier discharge.[2] Rosman and co-workers showed a lower rate of recurrent CD requiring surgery. No difference was observed in operative blood loss, rate of reoperation for complications, or mortality in any of these analyses. Overall morbidity was also found to be lower in the laparoscopic group, but there was no difference when individual complications were analyzed.[3] Conventional open surgery provided significantly shorter operative times than the laparoscopic approach. These studies concluded that the results justified the use of laparoscopy as a safe and viable option in the surgical treatment of CD.[2,3,4]

Additional data support the position that laparoscopic surgery has the lowest recurrence rate, fewest complications, and highest patient satisfaction. A comparative study of the two methods by Eshuis et al. showed similar rates of recurrence and quality of life after resection. The open surgery group had a higher rate of hernia formation and laparoscopy was associated with better cosmetic result; these results however did not reach statistical significance.[5] A prospective randomized trial by Stocchi et al confirmed similar recurrence rates and a trend toward higher rate of hernia formation, as well as a significantly greater rate of multiple operations in the open surgery group.[6] These studies did not demonstrate a superiority for the laparoscopic approach, but provided further evidence that its use in CD is acceptable with better cosmetic results and potentially decreased morbidity.

Other operative technologies are evolving, and some may be of assistance in the surgical management of RD. Robotically assisted laparoscopic surgery is used in abdominal surgery, and there

Complications:	Urgent/Emergent	Chronic/Long-term
Indications for operation	Bowel perforation/ obstruction toxic colitis	Stricture / recurrent partial obstruction
	Massive hemorrhage	Cancer
	Abscess	Abscess/ Fistula
	Refractory disease	Refractory disease

has been speculation that the ability to perform intracorporeal suturing may make it advantageous in the performance of strictureplasty. **Natural Orifice Transluminal Endoscopic Surgery (NOTES)** has gained attention recently, although its application in CD is as yet unclear. There are no reports of these techniques applied specifically to the treatment of inflammatory bowel disease, but as comfort and experience grow with the technology, there may be a role for each of these approaches.

Minimally invasive surgery has become an important element of the colorectal surgeon's arsenal. Patients often request laparoscopy, as they are aware of the potential advantages, including a faster recovery. While it may not be appropriate for every patient, it is an acceptable initial approach under the correct circumstances. Regardless of an open or laparoscopic approach, the ultimate goal is to achieve effective treatment of the diseased intestine and preserve as much bowel length as possible given the high likelihood for disease recurrence and need for reoperation.

Bowel Preservation and Strictureplasty

An area of surgery that is unique to CD is strictureplasty, which is the opening of a fibrotic narrowing (stricture) of the bowel lumen and suturing it back in a different orientation to allow more normal flow of intestinal contents without needing resection. Because CD has no cure, patients are prone to multiple operations with multiple bowel resections, and thus are at high risk of getting "short gut" syndrome, which can lead to death or lifelong dependence on total parenteral nutrition. For this reason the surgical approach to CD has become more and more conservative, focusing on techniques such as strictureplasty to preserve bowel length whenever possible. In CD a large inflammatory component can make resection the only possibility.

The strictures in CD come in various types and lengths, and there are different techniques to manage different types. If the stricture has a large inflammatory component refractory to medical treatment, a resection is indicated.

Indications for strictureplasty include:

1. Multiple strictures in a diffusely affected bowel
2. High risk for "short gut" because of previous resection and small amount of remaining bowel.
3. Fibrotic stricture without inflammation.

To justify surgical intervention, the stricture must also be symptomatic, usually manifesting as intermittent obstruction, restriction of food intake, weight loss, and/or inability to tolerate certain foods (particularly high residue); malnutrition can occur. Even in a patient who meets these criteria there are reasons that a strictureplasty should not be done. The following is a list of contraindications:

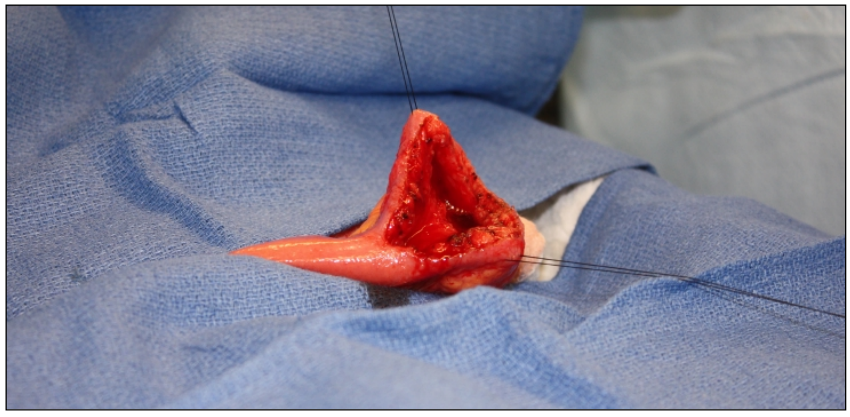

Image 1. Incision is made along the anti-mesenteric border of the stricture.

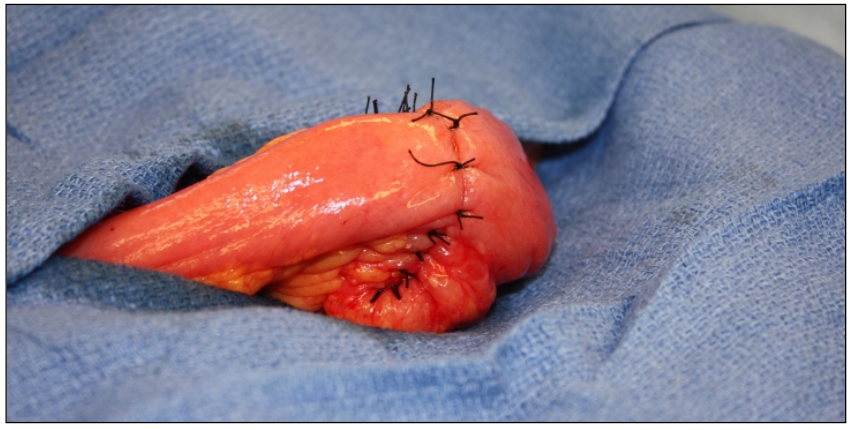

Image 2. Then sutured back together transversely.

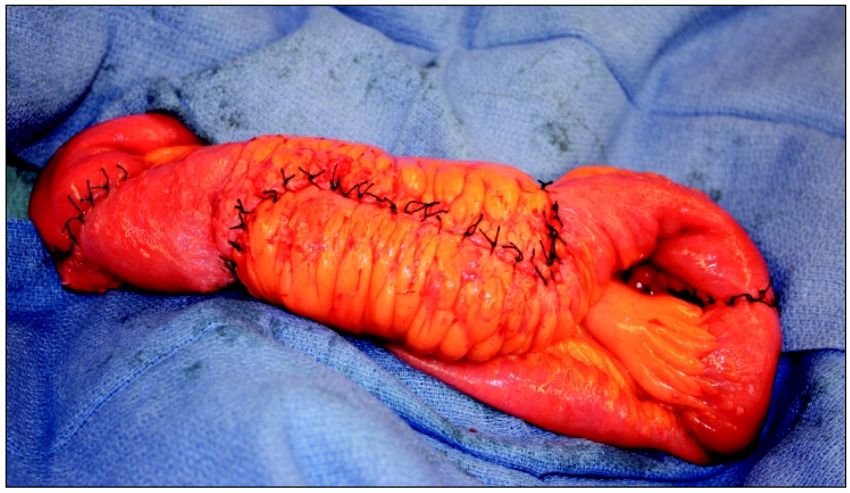

Image 3.

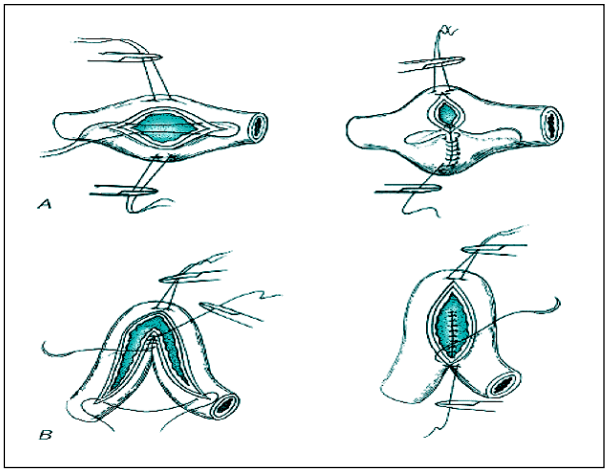

Diagram 1.

1. Perforated bowel
2. Severely inflamed loops of bowel forming a mass with or without a fistula to other bowel or skin.
3. Multiple strictures close together that would be better to resect.
4. Albumin < 2.0g/dl
5. Colonic strictures or a stricture close to a site that is being resected.

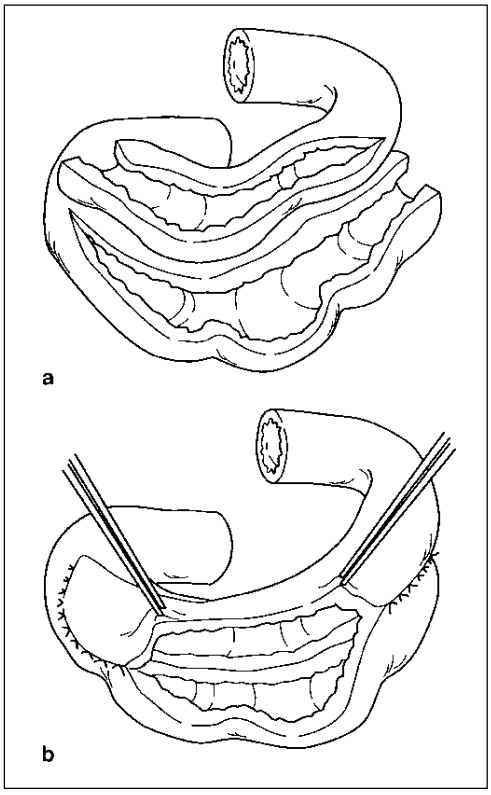

Diagram 2. Side to Side Iso-Peristaltic strictureplasty with two simple short segment strictureplasties one on either side.

There are several techniques of strictureplasty depending on the size and location of the lesions and the history of the patient. The size of the strictures are general broken down into 3 categories, <10cm, 10-20cm, and >20cm, each with increasing difficulty. If the tissue is not amenable to extensive suturing, the simplest, safest procedure is always resection; but this must be balanced with the amount of remaining bowel length and the patient's nutritional absorption. The smaller the stricture the easier the strictureplasty; the basic idea is to incise the wall of the bowel along the direction of the stricture and sew it back together in a way so as to create a new lumen and allow passage of intestinal contents without removing any bowel.

For the short segments strictures this can be accomplished by a longitudinal incision along the anti mesenteric side of the bowel followed by suturing it closed in the opposite and transverse direction. (Diagram 1(A) and Images 1 and 2)

For the medium length strictures the bowel is folded back onto itself and after incising along the anti-mesenteric side of the stricture the opening is closed by sewing to the opposite side and creating a lumen into which the intestinal contents can flow into and back out easily. (Diagram 1(B))

The longer segment strictures are the most difficult and often will be resected, but strictureplasty is important for the patient who is not able to tolerate a resection. One technique for the long strictures is to do a very long folded side to side anastamosis. This however will result in a large lumen or cavity that is not in continuity with the flow of the bowel and can lead to stasis and bacterial overgrowth. The technique that was developed more recently and seems to provide a more physiologic function is a side to side iso-peristaltic anastamosis. This is done by transecting the bowel in the middle of the stricture and placing the two portions of bowel side by side. By transecting and not folding it is possible to suture it together in a way that the lumen remains in continuity and thus prevent stasis of the intestinal contents. See Diagram 2 and Image 3.

Strictureplasty of all types can be done with good results. A systematic review with meta-analysis, done in 2007, examined these three types of strictureplasty in 3,259 patients. The morbidity was low with a septic (abscess/fistula/leak) complication rate of 4%. The recurrence rate overall was 28% after strictureplasty. Ninety percent of these were at non-strictureplasty sites. Two patients developed adenocarcinoma at the site of previous strictureplasty. The risk of cancer in the area of the stricture must always be kept in mind during a strictureplasty. Any suspicious lesions must be biopsied and evaluated.

Ano-rectal Abscess and Fistula

Infection of the ano-rectal area is seen in approximately 20-25% of patients. It is often in conjunction with other areas of disease as well. Only about 3-5% of patients will have the ano-rectal area as their only site of disease. Anal abscess/fistula in CD can be debilitating. The abscess can be drained but often there is a connecting fistula and this is difficult to treat because of the poor wound healing related to the CD. Typically a drain or "seton" would be placed to allow for resolution of the sepsis associated with a fistula. Some patients retain that drain on an intermittent or permanent basis. The use of either Infliximab or Adalimumab has reduced the need for surgical treatment. A careful evaluation for perianal abscesses prior to medical treatment includes either pelvic MRI or ano-rectal ultrasound depending on local expertise combined with exam under anesthesia. This approach has 100% sensitivity in detecting abscesses that should be drained prior to treating with a biologic[12,13]. Infliximab is very effective in healing anal fistulas, or at least decreasing drainage where the

symptoms are not as troublesome.

One new surgical technique for anal fistulas from all causes is the collagen plug. The plug is a piece of porcine collagen that has been formulated into a cone shape with a small tip that is brought through the fistula tract from the inside to out and the large end is sutured in place to obliterate the internal opening and thus help the fistula to heal. Initial results showed success rates as high as 80%, but as experience has grown, success is falling to 50-65% in current series. The success with CD is even less with rates as low as 26%.[8] The best success seems to be in long fistulas without significant inflammation or abscess, thus treatment with an anal seton or drain prior to the plug is often beneficial. However, in these Crohn's patients even if 25-30% of people benefit, it may be worthwhile because this less invasive procedure, with minimal cutting, has less chance for complications related to poor wound healing.

Conclusion

CD poses difficult medical and surgical dilemmas. The ultimate goal is to give patients the best quality of life possible for their situation. Someday there may be a cure, but currently the surgical perspective is to palliate symptoms with as minimally invasive techniques as possible; these advances include laparoscopy, strictureplasty and anal fistula plugs. Refinements in other techniques, such as Robotics and **Natural Orifice Transluminal Endoscopic Surgery** (**NOTES**), are likely in the future.

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The authors have no financial interests to disclose.

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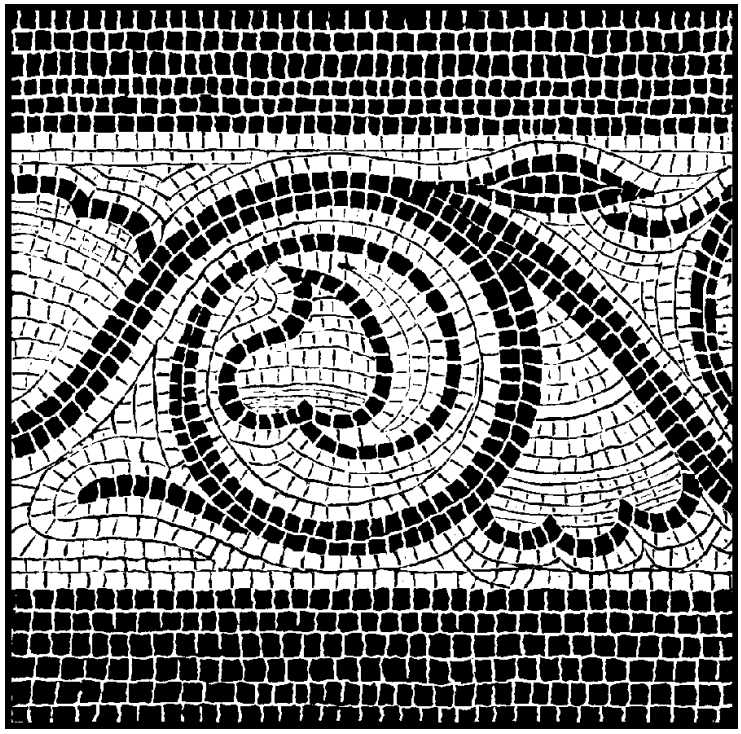

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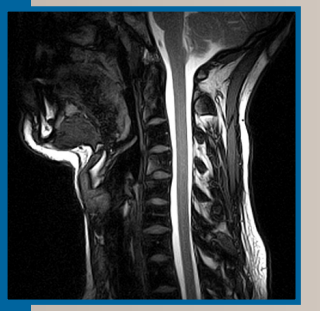

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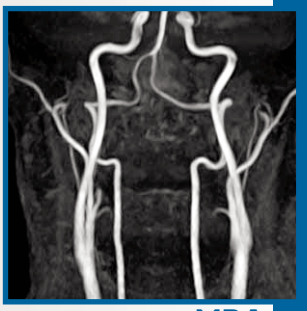

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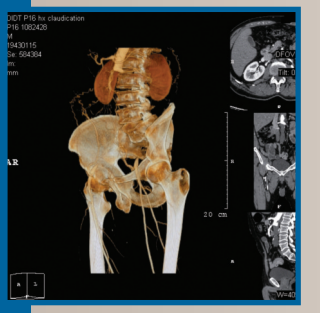

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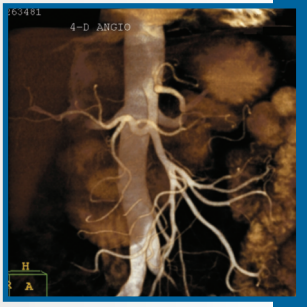

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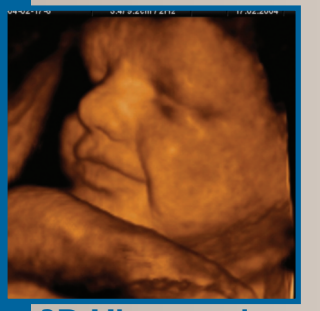

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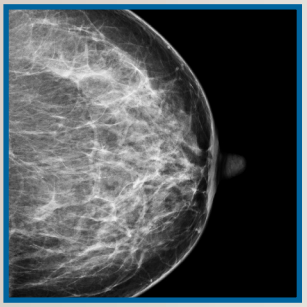

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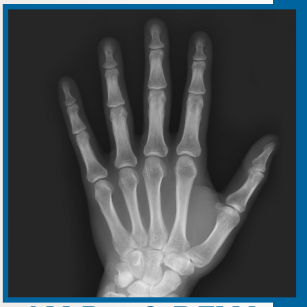

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Please see Important Safety Information contained in this advertisement.

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.

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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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Ileal Pouch-anal Anastomosis for Ulcerative Colitis – The Rhode Island Experience

Victor E. Pricolo, MD

Indications and Rationale for Surgery in Ulcerative Colitis

Despite significant progress in the medical management **of ulcerative colitis** (**UC**), over 20% of patients affected by this chronic and medically incurable disease still require surgical intervention. There are three main groups of indications for an operation in UC: **acute** life-threatening complications, medical intractability or side effects, and cancer risk. [1]

Severe complications include massive hemorrhage, obstructing stricture, toxic colitis or megacolon, and perforation with sepsis. UC patients often require emergency surgical care while debilitated by anemia, malnutrition and immunocompromised from their chronic disease or from medications (e.g. azathioprine, 6-mercaptopurine, corticosteroids, infliximab, etc.). Timing of surgery in patients hospitalized for severe UC is best determined by a coordinated effort between gastroenterology and colorectal surgery staff.

Patients may become unresponsive to medications, or dependent on them, or develop severe side-effects from chronic use. Particular care and precautions have to be considered in these patients who are at higher risk of surgical infections, poor wound healing and venous thrombo-embolic events from their hypercoagulable state. Growth failure in children is also a recognized indication for colectomy.[2]

In patients with early onset and long-standing (> 10 years), extensive disease (pancolitis), there is also a progressive increase in the dysplasia-carcinoma sequence over time. The cumulative cancer risk has been estimated at 2% at 10 years, 8% at 20 years, and 18% after 25 years of colitis. [3] Such risk is quadrupled in patients with primary sclerosing cholangitis as one of the extra-intestinal manifestations associated with UC.

Since UC is limited to the large intestine, removal of the target organ will achieve definitive cure. The colon and rectum are not essential for nutrition and/or survival and their removal does not require any nutritional supplementation. Small bowel adaptation over several months allows it to assume some colon-like absorptive functions, a startling example of the adaptability of our gastrointestinal tract to anatomical and environmental changes (e.g. stasis, pH, bacterial flora).

History of Surgical Options for Ulcerative Colitis

Until about thirty years ago, surgery for UC patients essentially meant accepting the need for a permanent ileostomy, after removal of the whole colon, the rectum as well as the anus. Understandably, the prospect of a permanent ileostomy bag remains a powerful deterrent to patients who may be surgical candidates.

IPAA...is now the most commonly performed procedure for the definitive treatment of UC.

Ideally an operation for ulcerative colitis should satisfy four major criteria: 1) ability to cure by completely eliminating the disease; 2) safety in its acceptable complication rate; 3) applicability to most affected patients; 4) effectiveness in restoring quality of life and preserving enteric continence. [4] The operation that comes closest to this "ideal" is the **ileal pouch-anal anastomosis** (**IPAA**) or restorative proctocolectomy. It involves complete removal of the colon and rectum, but it preserves the anal mucosa and sphincteric complex, to which an ileal reservoir is attached, thereby maintaining continence. Sir Alan Parks et al in 1980 in England first reported experience with ileal pouch-anal anastomosis in humans, and the operation bore his name for several years thereafter as "Parks' procedure." [5] However, as is often the case, such accomplishment was the culmination of decades of efforts on the part of multiple scientists and investigators.

Nils Kock in Sweden in 1969 had described an ileal reservoir that was attached to the skin of the lower abdomen after complete removal of anus, colon and rectum. [6] This "continent ileostomy" still did not obviate the need for a stoma, required significant patient compliance and education in emptying it several times a day, and was associated with a high complication and revision rate. [7] A more recent modification, the **Barnett continent ileal reservoir** (**BCIR**), larger than the "Kock pouch", has a different valve mechanism; presently this operation is rarely indicated and performed.

The idea to reestablish enteric continuity by attaching the ileum to the anus was first suggested in 1933 and later the United States in the late 1940s. [8] Therefore, the ileal pouch-anal anastomosis can be seen as a merger of the two concepts of anal preservation and fashioning of a reservoir, in order to maintain continence and improve quality of life after proctocolectomy for UC and other conditions. IPAA is generally contraindicated in patients with Crohn's disease, given the high risk of recurrent disease and complications leading to pouch failure.

In acute life-threatening emergency situations, the preferred surgical procedure is a **total or sub-total colectomy** with temporary ileostomy. At a later date, a completion proctectomy can be associated with an IPAA.

In patients with very poor anal sphincter function, anal preservation in not warranted, in view of expected poor functional outcome. Such patients are best served by a **proctocolectomy with permanent ileostomy**, when surgery is necessary.

In most patients undergoing IPAA in the elective or urgent setting (not emergency), an IPAA is generally accompanied by a temporary ileostomy that can be reversed eight to twelve weeks later. In selected patients who come to surgery in very good overall health, a temporary ileostomy may be omitted and the whole procedure may be performed in one stage.

IPAA has gained progressive acceptance over the past two decades and is now

the most commonly performed procedure for the definitive treatment of UC.

Patient Outcome after Restorative Proctocolectomy

Proctocolectomy with IPAA is safe, durable and applicable to most patients with UC.[9] Although its overall complication rate can be in the 20-30% range, its mortality is generally below 1% in large series from very experienced surgeons.[10, 11] Complications of IPAA can occur in the immediate postoperative period or months and years later.

Early surgical complications include bleeding, small bowel obstruction, pelvic sepsis and anastomotic leak. In some situations, reoperation may be required to preserve pouch function, but often percutaneous interventional techniques may suffice.

Late complications may include incisional hernia, anastomotic stricture, pouch-cutaneous or pouch-vaginal fistulas, and pouchitis. Some fistulas may be managed medically, especially if Crohn's disease is suspected, but most eventually require surgical correction. Pouchitis is the most common long-term complication and its incidence increases with time. However, in most cases this pouch mucosal inflammation is transient; it responds to antibiotic therapy and may be controlled with probiotics as well. Pouch failure requiring excision and conversion to a permanent ileostomy is rare and generally occurs in less than 3% of patients. Pelvic cysts may occur as a result of adhesions and fertility problems in women are more frequent after IPAA than in the general population.[12] (See "Reproductive Issues in Inflammatory Bowel Disease" by Sumona Saha, MD, and Silvia Delgi Esposti, MD in April 2009 *Medicine & Health/Rhode Island*.) The safest delivery method for a pregnant woman after IPAA remains controversial. Cesarian section prevents anal sphincteric and pudendal nerve injury from forceps delivery, vaginal tears or episiotomies. Vaginal delivery has been reported as safe in the short term follow-up, but may lead to higher rates of incontinence with advancing age. Although sexual dysfunction in men after proctectomy from injury to the hypogastric plexuses and pelvic autonomic nerves may occur, most men describe an improvement in sexual function after IPAA, likely as a result of their improved overall health.

The functional results have yielded quality of life standards that approach those of the healthy population and demonstrate consistently improvement over pre-surgical performance status for patients that are not doing well with medical management.[13] The average number of daily bowel evacuations is higher than normal controls at 2-8 (average 4-5) during daytime and 0-1 at nighttime. Nonetheless, in terms of quality of life, a more important element is the ability to defer defecation, which is greatly improved to 30-60 minutes with a healthy ileal reservoir and a good anal sphincter. In fact, some of the most aggravating symptoms in UC patients are the urgency and tenesmus secondary to the inflammation and lack of distensibility of the rectum, with consequent loss of its reservoir volume and compliance. Over a period of ten to twelve months, the pelvic ileal pouch undergoes progressive dilatation and mucosal adaptation to colonic metaplasia, flattening of its villi and increase in goblet cells. Such adaptive changes, likely secondary to stasis and increased bacterial anaerobic counts in the pouch, enhance its storage capacity, absorptive function, ability to thicken stool and decrease frequency. It is important to follow patients with dietary advice and stool retardant medications as needed, to optimize functional outcome. Medications used to treat UC before surgery can be discontinued postoperatively and corticosteroids can be tapered off gradually.

The Rhode Island Experience

Since the author performed the first IPAA procedure in Rhode Island, at Rhode Island Hospital in April 1991, the collaboration and dedication of gastroenterologists and surgeons, combined with enterostomal therapists, nutrition and other support services has allowed the growth of a very successful and comprehensive program. The proximity of Women and Infants' Hospital on the same campus has also facilitated collaboration of care in pregnant women with exacerbation of inflammatory bowel disease and toxic colitis. Since the late 1990s, pediatric surgeons at Hasbro Children's Hospital have performed IPAA procedures in children. More recently, the contribution of additional colorectal surgeons in the state has broadened the availability of these procedures to other hospitals.

Over the past eighteen years, the author's personal experience includes 312 patients,

166 males and 146 females, ranging in age from 9 to 75 years old (mean = 36 years old).

The indications for surgery were UC in the vast majority of cases (287), familial polyposis in 23 patients and colorectal inertia in 2 cases. Six of the UC patients had a carcinoma at the time of surgical resection. Although ileal pouches can be S-shaped, W-shaped , T-shaped or J-shaped, all patients in this series had the J-shape for its ease of construction and equivalent storage ability after adaptation. Another area of controversy involved the choice of transanal mucosal excision and hand-sewn anastomosis versus the double-stapled technique. We have used both options depending on patient's variables, after conducting a trial to individualize operative choices on the basis of age, anal sphincter baseline function, as well as cancer risk. [14] To date, 275 pouches were double-stapled and 37 were hand-sewn.

Most patients (n = 222, 71%) underwent a two-stage procedure, while 26 (8%) required a three-stage IPAA as a result of life-threatening indications. The remaining 64 patients (21%) could be done in a single stage, by virtue of their overall good preoperative health. An increasing number of IPAAs have been done with the laparoscopic minimally invasive techniques in recent years. This technical advance has decreased postoperative convalescence time more than hospital length of stay for this particular operation in our experience. The use of bioresorbable membrane application to reduce peritoneal adhesion formation during surgery and other technical innovations have contributed to a low rate of small bowel obstruction, pelvic cyst formation and preservation of fertility in both female and male patients.

Major short-term complications in our series included two pouch anastomotic leaks (0.6%), one ileostomy closure leak (0.3%), one pouch necrosis (0.3%), five deep venous thromboses (1.6%) and one death secondary to pulmonary embolism (0.3%).

Major long-term complications have included pouch-vaginal fistula in 5 patients (3 with unsuspected Crohn' s disease)

(1.6%), one anal cuff carcinoma twelve years post-IPAA (0.3%), and chronic idiopathic pouchitis requiring treatment in 34 patients with a diagnosis of UC (11%). Eventually, 11 patients (3.5%) had their diagnosis changed to Crohn's disease.

Overall, only 5 patients (1.6%) have required conversion to permanent ileostomy, one for anal cuff cancer, one for pouch necrosis, and three for intractable complicated pouch and perineal Crohn's disease.

Our patient support network allows patients considering having IPAA surgery to talk to individuals who have undergone the procedure. Given our large case series, we match patients by age and gender, so they are more comfortable in discussing issues of recovery, lifestyle, and quality of life.

In addition to our clinical efforts, our program has collaborated with basic scientists in the Division of Gastroenterology at Brown University. This fruitful interaction has led to several publications that have expanded knowledge and deepened understanding of UC, especially as it relates to alterations in smooth muscle contractility as a result of mucosal inflammation.[15] Until we discover the etiology and can better elucidate the pathogenesis of this complex disease, surgery is likely to remain the only option able to provide definitive cure.

In summary, Rhode Island can offer state-of-the-art expertise in management of ulcerative colitis, including surgical expertise with a track record of outcome results that exceed national standards.

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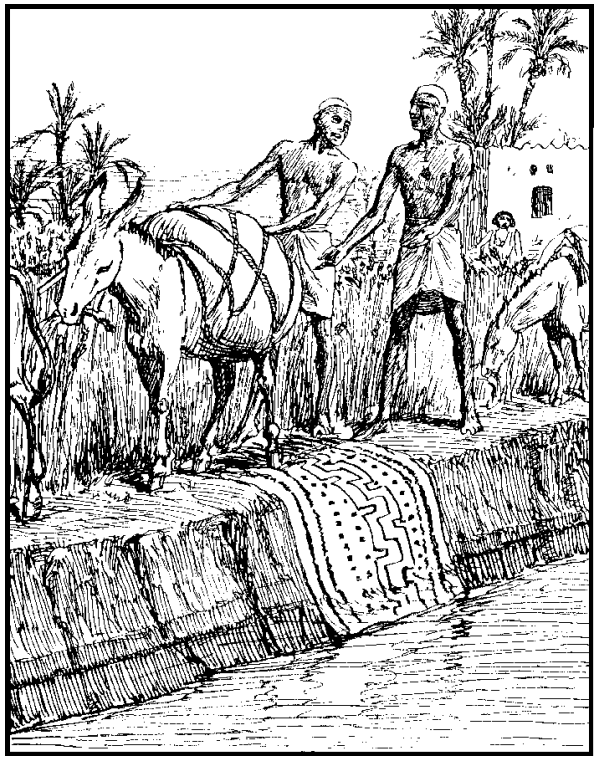


Advances In Imaging In Crohn's Disease

David J. Grand, MD

Radiologic evaluation plays a critical role in the assessment of patients with inflammatory bowel disease, particularly **Crohn's disease (CD).** In UC, colonic mucosa is readily accessible for endoscopic evaluation; thus radiologic techniques are less useful. Traditionally, fluoroscopic studies including the small bowel series and barium enema, along with CT, were the mainstays of imaging. These modalities were used to diagnose disease, document its extent, identify complications including fistula, stricture, abscess and obstruction.

CT enterography (CTe) and, more recently, **MR enterography** (MRe), which provide a comprehensive assessment of both luminal and extraluminal disease, have supplanted fluoroscopic studies. MRe is particularly exciting because it provides all of the information of CTe as well as additional information regarding disease activity without exposing patients to ionizing radiation.

The small bowel series and barium enema are essentially historic examinations for the detection and evaluation of inflammatory bowel disease. These studies, while effective at detecting mucosal abnormalities, are poorly tolerated by sick patients, provide assessment only of the bowel lumen (particularly the mucosa) and are physician dependent, limiting their reproducibility. A properly performed and interpreted SBFT or BE is unfortunately a lost art and available only in select centers. Additionally, of course, these studies may involve significant doses of radiation. Colonoscopy remains an essential diagnostic tool to visualize and biopsy the mucosa of the large bowel and distal ileum in **inflammatory bowel disease (IBD).**

CTe is currently the gold-standard imaging study for the evaluation of Crohn's disease, especially non-mucosal. The fundamental difference between a traditional CT and a CTe examination is the use of "negative" or low-attenuation oral contrast (which is dark on CT) as opposed to the more commonly used "positive" or high-attenuation contrast such as barium (white on CT). Negative oral contrast yields distension of the small bowel with low-attenuation, dark, fluid. After administering IV contrast, the mucosa enhances, which is striking against the dark bowel lumen. The degree of mucosal enhancement has been correlated with disease activity in patients with Crohn's disease.

CTe also provides fast, well-tolerated and comprehensive evaluation of all bowel segments as well as evidence of extraluminal complications such as abscess formation. However, there are drawbacks and limitations inherent to this technique.

MRe is superior to other imaging modality in its ability to distinguish active from chronic fibrotic disease.

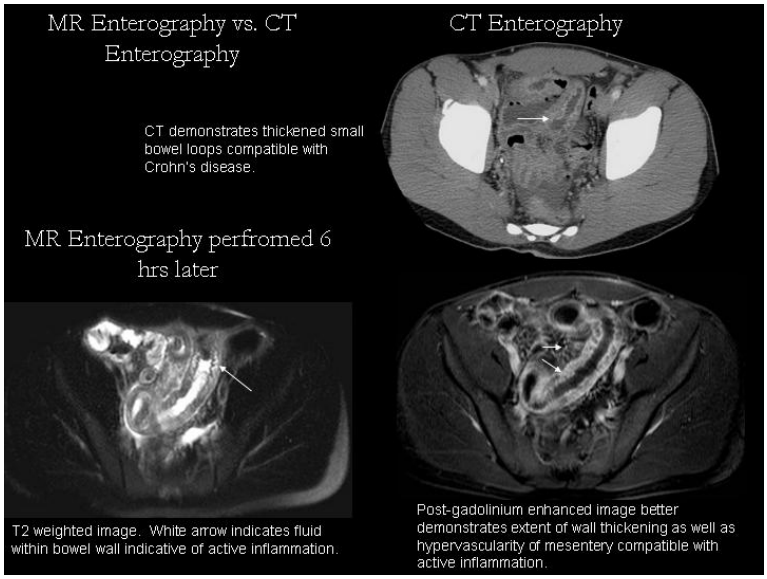
The potential dangers of ionizing radiation exposure have been increasingly recognized in recent years as more people undergo CT examinations, but also as more people undergo multiple CT examinations. This reality is of particular concern in Crohn's disease as patients are often diagnosed when young and will often require multiple imaging evaluations during their lives. This repeated radiation exposure may lead to an increased lifetime risk of developing cancer, particularly lymphoma. Because negative contrast is used for CTe, small abscesses may be difficult to distinguish from loops of bowel and regular CT or MRe should be employed if abscess is suspected or in the immediate post operative state.

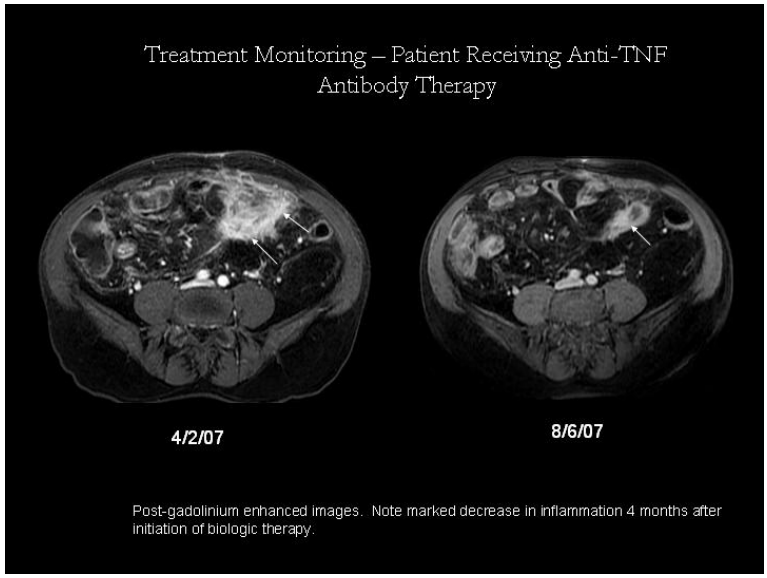
MRI evaluation of the small bowel is a fairly new application. MRe refers to comprehensive examination of the small bowel using the same oral contrast material as used in CTe. Previously, MRe could not adequately assess the small bowel because of small bowel motion as well as the presence of air within bowel loops, which created extensive imaging artifacts. Additionally, traditional MR coils were designed to cover the abdomen or pelvis, but did not provide a large enough field of view to cover both the abdomen and pelvis simultaneously. These problems have recently been overcome with faster sequences, including the adaptation of sequences originally intended for cardiac imaging, oral contrast regimens which minimize small bowel air, and new coils which enable much larger fields of view.

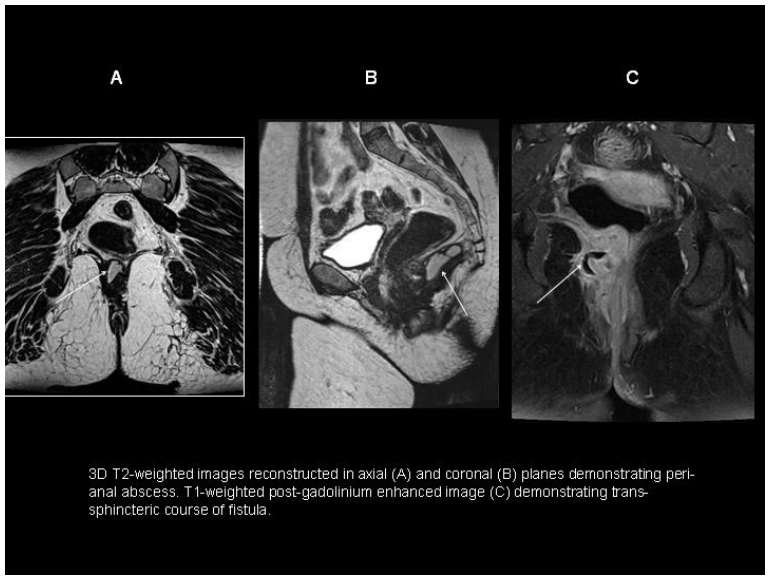
MRe, however, has many potential advantages over CTe. The ability to assess disease activity is probably the most important advantage of MRe over CTe. Clinically, it is often difficult to distinguish between active and chronic changes of inflammatory bowel disease in symptomatic patients. This distinction has become increasingly important with the advent of new, biologic therapies for active inflammatory disease which, while extremely effective, are expensive and may also be potentially toxic. Although beneficial for patients with active inflammatory disease, these agents do not benefit patients whose symptoms are secondary to a fibrotic stricture. Rather, these latter patients will require surgery for symptomatic relief.

MRe is superior to other imaging modality in its ability to distinguish active from chronic fibrotic disease. This unique ability is multifactorial. First, MRI, particularly, T2-weighted images, is exquisitely sensitive to the presence of fluid which has been shown to indicate the presence of active inflammation rather than chronic disease. Fluid is detected easily as it is very bright on MRI images against the black background of fat. These fluid-sensitive and fat-suppressed images are a critical portion of MRe examinations.

Second, the contrast resolution of MRI is far superior to that of CT (see Images of the month). Contrast resolution refers to the ability to detect subtle differences in signal or attenuation of normal versus abnormal tissues. Thus, the abnormal enhancement of the small bowel mucosa on MR imaging is significantly more dramatic than the same







change demonstrated on CT, allowing both for more accurate diagnosis and grading of disease activity.

Third, MRe provides assessment of each bowel segment at multiple time points and allows for real-time cine bowel imaging. This is of critical importance. Because CTe provides only a single snapshot of the bowel, it may not be possible to distinguish a collapsed loop, which may simply be the result of normal peristalsis, from a strictured bowel loop. During a small bowel series, the radiologist would further evaluate such loops with real-time fluoroscopic imaging. This is simply not possible with CT imaging due to what would be a prohibitive radiation dose.

Because MRe does not involve exposure to ionizing radiation, imaging of each bowel segment is performed at multiple time points to allow collapsed bowel segments to reopen with normal peristalsis. Additionally, cardiac real-time cine imaging sequences have been adapted to allow imaging of concerning segments as a "movie" loop in real time.

Finally, MRe is also more accurate than CT to image some extraluminal complications of Crohn's disease, specifically fistulae. Fistulae, particularly peri-anal, can be difficult if not impossible to detect on CT examinations. Because of the exquisite sensitivity of MRI to detect fluid as well as its superior soft tissue contrast, MRe easily depicts entero-entero, enterovesicular, enterocutaneous, peri-anal fistulae and perianal abscesses. Not only is sensitivity improved with excellent depiction of the anatomic relationship of fistulae to sphincter musculature. This anatomic "road-map" is critical for accurate surgical planning. Another advantage of MRe is that it can detect Primary Sclerosing Cholangitis, an extraintestinal complication seen in some patients with IBD.

Of course, MRe has drawbacks compared to CT. It is more time-consuming, requiring 20-25 minutes and multiple episodes of breath holding. According to the 2009 Medicare reimbursement schedule, it is 1.5 X more expensive. Nephrogenic sclerosis rarely complicates gadolinium administration in patients with significant renal dysfunction. Therefore, this agent should be avoided in patients with known renal failure/insufficiency.

These factors must be considered

when choosing an examination for each individual patient. As a general rule, patients who cannot hold their breath for 15 seconds should not undergo MRe as the examination will likely be limited by respiratory motion. Additionally, in this era of rising health-care costs it is critical to utilize limited resources appropriately. The added value of MRe is particularly significant in young patients, female patients, and patients with chronic disease who will likely require multiple imaging examinations throughout their lives. MRe is worthwhile and appropriate in this population to minimize lifetime radiation dose and its consequences. Finally, MRe may be cost-effective in patients considering biologic therapies, which are very promising for active inflammatory disease but ineffective for symptoms related to fibrotic strictures.

Research on the efficacy of MRe and its role in imaging patients with CD is ongoing at Rhode Island Hospital and its affiliates. Data from our ongoing trials highlighting the spectrum of CD as demonstrated by our first 100 exams with MRe have been presented at the 2008 Annual Meeting of the American College of Gastroenterology and will be presented at the Annual Roentgen Ray Society Meeting. This study has shown that MRe nicely demonstrates the entire spectrum of CD including active and chronic disease, skip lesions, colonic lesions, abscesses and fistulae. Additionally, our data have shown that MRe is well tolerated by patients and significantly impacts patient management as evaluated by a survey of the ordering clinicians who unanimously responded that MRe positively impacted patient management and that they will use it to benefit future patients. Therefore, we speculate that MRe will be the preferred method of imaging for CD in the near future.

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Family Caregiver Health: What To Do When a Spouse or Child Needs Help

Gary Epstein-Lubow, MD

Scenario; Scene One: You are finishing the office visit, suggesting to your patient's wife that she schedule the next visit in four to six weeks. By then, the new memantine starter pack will be finishing. While walking near your patient toward the door, she says softly so only you can hear, "I don't know how much longer I can do all this." You know she's been stressed, you have heard about this from their daughter, but the only person in the family who is truly your patient just walked nonchalantly out of the room, unaware of his wife's distress.

Family caregiving is common in the United States. A caregiver is a person who provides unpaid assistance with daily activities to another adult. The specific assistance must be beyond the "normative" or "usual" responsibilities that one would undertake in a marriage or as a parent, grandparent, offspring or friend. There are about 44 million American caregivers,[1] 22% of whom care for a person who has **Alzheimer's disease (AD)** or "mental confusion".[2] Compared to family caregivers for patients with other diseases, those who care for a person with AD are twice as likely to be providing the highest level of home care (more than 40 hours of direct care each week), and are also more likely to be living with the person.[2]

Caregiving is a public health priority. Determining the cost of family caregiving is made difficult by methodological challenges; however, a recent study estimated household costs between $5,500 - $12,350/year and reduced work hours or job loss due to caregiving responsibilities for 34% of caregivers.[3] Caregiving can be more cumbersome for women, who serve as 50% of the workforce and also provide most home-based caregiving. Now, with the aging of the baby boomers, family caregiving will soon emerge into the public health spotlight. Population-based studies at the state level are being called for in order to identify the most-vulnerable caregivers and the interventions with the greatest evidence base of benefit.[4] This public health directive is in part driven by concerns about depression and other illnesses in caregivers.

Caregiver burden and depression are serious concerns. The typical dementia caregiver experiences a variety of mild to moderate depressive and anxious symptoms.[5] These symptoms may be described as "burden," a specific type of stress experienced by caregivers. Few longitudinal studies have been conducted regarding burden; however, it is likely that chronic burden increases the risk for subsequent depression.[6] Self-report, structured interview and longitudinal data show dementia caregivers to be at significantly increased risk for depressive and anxious symptoms. In the general population, the estimated lifetime prevalence of major depression is 10-25% for women and 5-12% for men, and the rate of major or minor depression in late life is 11%; in contrast, the risk for depression in caregivers is about two to three times these rates. Ultimately, one-third of all dementia caregivers will experience a major depressive episode, and at least half of these caregivers will struggle with chronic symptoms. Symptoms may persist without clinical intervention because few caregivers seek treatment for themselves.[7]

Caregivers are at risk for medical illness and death. In 1999, Schulz and Beach reported a 63% higher risk in 4-year, all-cause mortality for stressed spousal elderly caregivers.[8] Those caregivers who reported "some" or "a lot" of strain were at increased risk of death, compared to non-caregiving controls. Additional studies have shown that caregivers report worse health than non-caregivers, and engage in fewer health-promoting behaviors. They get less rest, sleep and exercise, and have worse medication compliance compared to non-caregivers. In a recent review, caregiver depression and care-recipient behavior problems were the factors most consistently related to worse caregiver health, and this correlation was the strongest for dementia caregivers, the elderly, and men.[9] To add emphasis to these results, Christakis recently published data showing an increased death rate for spouses of hospitalized patients; spouses of individuals with dementia were the most at risk.[10]

Psychosocial interventions produce improvements for dementia caregivers. The literature regarding family caregiving began over 40 years ago. Educational programs, a variety of psychotherapies and social support decrease depression[11] and other psychological distress. The most successful programs are intensive, involve family members, are modified to caregivers' specific needs[12] and include a social support or combined social support and problem solving approach.[13] To determine the best manner for individualizing effective treatments for caregivers, Schulz and colleagues developed "Resources for Enhancing Alzheimer's Caregiver Health (REACH)" and REACH II. REACH introduced multiple interventions across several sites, and produced small to moderate effects in depressive symptoms and burden.[5] REACH II investigated the effects of a multi-component intervention tailored to individual caregivers in response to an interview-based risk assessment; results at six months showed significant improvement in quality of life and reduced prevalence of clinical depression.[14]

Scenario; Scene Two: You ask the wife of your patient if she has another minute to talk, as you look toward the chair where she had been sitting. While she returns to her seat, you escort your patient to the waiting room and invite your assistant: "See if he would like a drink of water, I'm chatting with his wife for a few minutes." You begin the next five minutes by telling the caregiver that you would like her to schedule a longer visit when her husband returns. Then, in the brief time you have, try to sort out: does she need a referral for depression, more information about what to expect with her husband's illnesses, increased help at home, a support group, or simply reassurance that even though things may seem quite wrong, she is doing everything just right?

What resources are available for caregivers in Rhode Island? Helping caregivers manage and find additional resources is oftentimes the bread-and-butter of what office staff, social work and nursing are doing on both ends of the 15-minute office visit. It can be helpful to have one key staff person in your office who keeps track of local agencies and can take time to call a caregiver at home as an established part of her/his office responsibilities. You will want this person to inform you if the caregiver seems excessively stressed, confused or depressed, so that you may consider making direct contact with one of the caregiver's clinicians, who then might pursue a mental health referral. If your practice only occasionally requires caregiving resources, you could begin by calling a friendly geriatrician's practice, a local memory clinic or a private neuropsychologist. The Rhode Island Chapter of the Alzheimer's Association is an excellent resource for caregivers regarding both urgent concerns and routine matters related to dementia care; they offer educational programs and individualized referrals, and they maintain databases of support groups and counseling resources. For critical situations, it may be reasonable to recommend an in-home assessment or treatment plan that can be developed by a visiting nurse agency or a private geriatric care manager. For eligible patients, caregivers may benefit greatly from comprehensive services available through Hospice and the **Program for All-Inclusive Care of the Elderly** (**PACE**). Finally, several ongoing caregiver research studies may provide telephone-based or other support; regarding dementia, the Alzheimer's Association provides a quarterly post of active studies.

Where to Find Assistance for Caregivers

- Office Staff
- Social Worker
- Primary Care Clinician
- Individual Counselor and/or Psychiatry
- Support Group
- Education and the Alzheimer's Association
- Home Health Services and VNA
- Geriatric Care Manager
- PACE
- Hospice
- Research Studies

Scenario; Scene Three: You receive a thank you note from your patient's daughter. She writes to tell you that her father is about the same but her mother seems much better. They don't know how much longer Dad will be able to stay at home; but for now, with the increased help and services, things are okay. She signs it, "Thanks, for your time, and your compassion."

Resources:

Alzheimer's Association, Rhode Island Chapter (401) 421-0008 or (800) 272-3900, http://www.alz-ri.org/caregiver.htm

National Alliance for Caregiving, http://www.caregiving.org/

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The author has no financial interests to disclose.

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Information for Contributors

Medicine & Health/Rhode Island

Medicine & Health/Rhode Island is a peer-reviewed publication, listed in the *Index Medicus*. We welcome submissions in the following categories.

Contributions

Contributions report on an issue of interest to clinicians in Rhode Island: new research, treatment options, collaborative interventions, review of controversies. Maximum length: 2500 words. Maximum number of references: 15. Tables, charts and figures should be camera-ready, or as separate files (jpg, tif, pdf). Photographs should be saved as separate files. Powerpoint files and slides are not accepted.

Creative Clinician

Clinicians are invited to describe cases that defy textbook analysis. Maximum length: 1200 words. Maximum number of references: 6. Photographs, charts and figures may accompany the case.

Point of View

Readers share their perspective on any issue facing clinicians (e.g., ethics, health care policy, relationships with patients). Maximum length: 1200 words.

Advances in Pharmacology

Authors discuss new treatments. Maximum length: 1200 words.

Medical Myths

Authors present an iconoclastic, research-based analysis of long-held tenets. Maximum length: 1200 words.

For the above articles: Please submit 4 hard copies and an electronic version (Microsoft Word or Text) with the author's name, mailing address, phone, fax, e-mail address, and clinical and/or academic positions to the managing editor, Joan Retsinas, PhD, 344 Taber Avenue, Providence, RI 02906. phone: (401) 272-0422; fax: (401) 272-4946; e-mail: retsinas@verizon.net

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We encourage submissions from all medical disciplines. Image(s) should capture the essence of how a diagnosis is established, and include a brief discussion of the disease process. Maximum length: 250 words. The submission should include one reference. Please submit the manuscript and one or two clearly labelled cropped files with the author's name, degree, institution and e-mail address to: John Pezzullo, MD, Department of Radiology, Rhode Island Hospital, 593 Eddy St., Providence, RI 02903. Please send an electronic version of the text and image to: JPezzullo@lifespan.org.

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Health By Numbers
Rhode Island Department of Health • David Gifford, MD, MPH, Director of Health
Edited by Samara Viner-Brown, MS

Traumatic Brain Injury In Rhode Island

Hyun (Hanna) Kim, PhD, Kate McCarthy-Barnett, EdD, and Deborah Garneau, MA

Traumatic Brain Injury (TBI) is a blow or jolt to the head or a penetrating head injury that disrupts the function of the brain.[1] In the United States, 1.4 million individuals sustain a TBI per year. Of those, 235,000 are hospitalized, 1.1 million are treated and released from an emergency department and 50,000 die.[2] The Centers for Disease Control and Prevention (CDC) estimate that 5.3 million people who sustained a TBI need assistance with daily living activities and incur direct and indirect medical costs totaling an estimated $60 billion.[3]

On July 1, 2007, the Rules and Regulations Pertaining to the Rhode Island Traumatic Brain Injury Registry of the General Laws of Rhode Island became effective. The Regulations mandate hospitals within the State to report to the Department of Health within fourteen days of diagnosis all cases of TBI diagnosed through inpatient and emergency departments. As part of this notification, hospitals were required to send the following data: principal diagnosis, cause of injury, place of incident, type of discharge, dates of admission/discharge and patient demographics including name, address, social security number, date of birth, gender, ethnicity and race.

This report describes the incidence, principal diagnosis and the leading cause of TBI in Rhode Island using the first full year of the TBI registry data.

Methods

All cases of TBI occurred in RI and reported to the RI Department of Health during July 1, 2007-June 30, 2008 were analyzed for this report (N=5,301 cases).

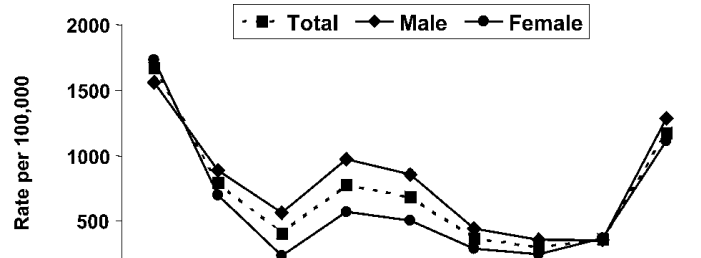
The principal diagnosis of TBI (ICD-9-CM External Cause of Injuries Codes) reported was categorized according to the Barell Injury Diagnosis Matrix, Classification by Body Region and Nature of the Injury as Type 1 TBI, Type 2 TBI, Type 3 TBI, Other Head and Late Effects TBI.[4] (Definitions of Type 1, 2 and 3 TBI are described in the Matrix.[4]) The causes of TBI, categorized using the ICD-9 CM External Cause Codes (E800.0-E999.9), included unintentional falls (E880-E886.9, E888), motor vehicle traffic accidents (E810-E819.9), striking against / struck accidentally (E916-E917.9), assaults (E960-E969), other (all other E codes), and unknown (no E codes).[5] Incidence rates were calculated per 100,000 population using the 2007 RI population estimates from the US Bureau of the Census. Although data were analyzed by age and gender, race/ethnicity data were not included due to the high incompleteness of those data.

Results

During July 1, 2007-June 30, 2008, 5,301 TBI cases were reported to the Rhode Island Department of Health. Of those cases, 12% (654 cases) were classified as the most severe Type 1 TBI; 46% (2,434 cases) were classified as severe Type 2 TBI; 40% (2,133 cases) were classified as Other Head Injury; and 2% (80 cases) were classified as Late Effects TBI. The overall incidence rate for TBI in Rhode Island was lower than the national rate (501.1 per 100,000 for RI in 2007 vs. 538.2 per 100,000 for US in 2003).[6]

Incidence of TBI

The incidence rate varied substantially by age and gender. (Figure 1) Overall, infants had the highest rate of TBI (1,672 per 100,000), followed by adults aged 80 and older (1,174 per 100,000). Adults aged 46-59 years had the lowest rate (299 per 100,000). Among those aged 6-79 years, teens (13-18) and young adults (19-25) had higher rates of TBI compared to the rest of the age groups.



	< 1	1-5	6-12	13-18	19-25	26-45	46-59	60-79	>= 80
Total	1672	793	404	778	684	364	299	362	1174
Male	1557	884	564	975	858	440	357	355	1286
Female	1728	697	235	571	503	290	242	367	1111

Figure 1. Incidence Rate of Traumatic Brain Injury by Age and Gender, Rhode Island, July 1, 2007-June 30, 2008

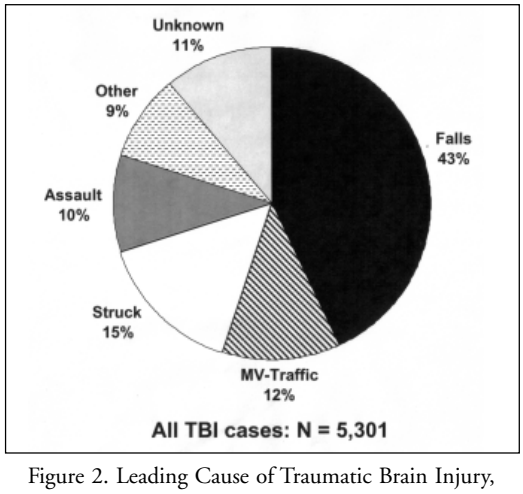


Figure 2. Leading Cause of Traumatic Brain Injury, Rhode Island, July 1, 2007-June 30, 2008

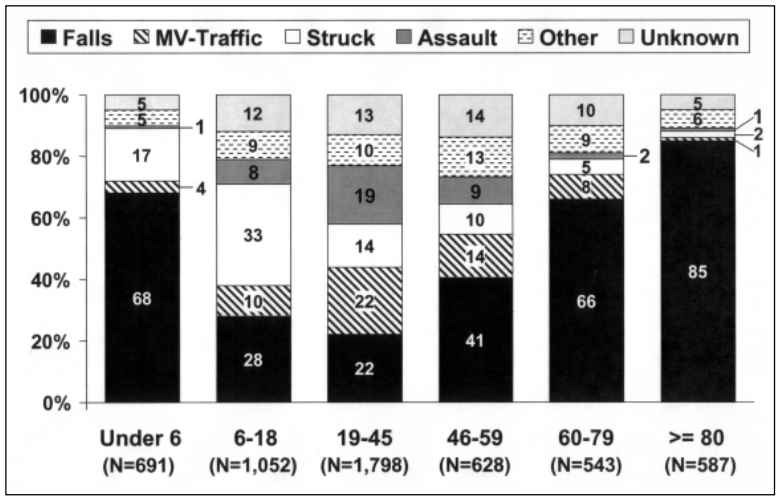


Figure 3. Leading Cause of Traumatic Brain Injury by Age, Rhode Island, July 1, 2007-June 30, 2008

In general, males had higher rates of TBI (584.3 per 100,000) than females (420.2 per 100,000) in RI. Except for infants and adults aged 60-79 years where females had higher rate of TBI than males, all other age groups showed males had higher rates. The male-female differences in the rates were larger for children through young adults (6-25 years of age groups) than the rest of the groups.

Causes of TBI

Overall, falls (unintentional) were the leading cause of TBI in RI (2,278 cases or 43%), followed by striking against / struck accidentally (810 cases or 15%), motor vehicle traffic accidents (653 cases or 12%), and assaults (505 cases or 10%). (Figure 2) Rhode Island had a higher percentage of unintentional falls than the US (43.0% for RI in 2007 vs. 32.1% for the US in 2003).[6] Although unintentional falls were the leading cause of TBI for all age groups except for those 6-18 years of age, the proportion of falls varied significantly by age group, ranging from 22% for those 19-45 years of age to 85% for adults 80 years and older. (Figure 3) The highest percentage of striking against / struck accidentally occurred among adolescents 6-18 years of age (33%), followed by children under 6 years of age (17%). Adults aged 19-45 had the highest percentage of motor vehicle traffic accidents (22%) and assaults (19%) compared to other age groups.

Specifically, the most frequent cause of TBI for infants was "falls from bed" (24%); for children aged 6-18 years, "striking against or struck by objects in sports" (18%); for adults aged 19-45 years, "motor vehicle traffic accident involving collision motor vehicle" (16%) and "unarmed fight/brawl" (10%); and for those aged 80 and older, "falls from other slipping, tripping or stumbling" (32%).

Discussion

The data in this report are based on the first full year of hospital emergency and inpatient reporting of TBI to the RI Department of Health. With the passage of requirements, the reporting rate increased by 3600% (from 147 cases in 2006 to 5,301 cases in 2007) resulting in increased insight into the demographics of TBI in RI including the incidence, diagnosis and cause of injury. Although there are limitations in the data, e.g., large missing data in race and ethnicity, this report demonstrates some interesting findings. While RI had a slightly lower rate of TBI than the US overall, the proportion of falls as a cause of TBI was much higher in RI than the US. This report also identifies high-risk populations for TBI such as the elderly, infants, teens and males. The leading causes of TBI were found to be different for each age group, indicating that different intervention programs are needed for different age groups.

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Pain and Prejudice:
The Use of Chronic Narcotic Therapy In Medical Practice

Robert S. Crausman, MD, and Bruce McIntyre, JD

"Pain is such an uncomfortable feeling that even a tiny amount of it is enough to ruin every enjoyment."

– Will Rogers

The Board of Medical Licensure and Discipline receives complaints and questions relating to narcotic therapy almost daily. In one common scenario, a patient asserts that a physician has violated the patient's rights by not prescribing narcotics as requested. In another scenario, a physician's office inquires whether it is recommended to discharge a patient because he/she requires chronic narcotic therapy for the treatment of pain. Clearly this is an area of confusion.

Fortunately for both patients and physicians there is guidance from the State legislature, the Board, national organizations such as the **Federation of State Medical Boards** [FSMB], and the literature. Patients should expect that their pain will be assessed and addressed appropriately by their physician. Physicians can expect that their clinical judgment will prevail with regard to prescribing.

CASE

In 2008 the Board received complaints from several pharmacists alleging inappropriate prescription of narcotics by a specific community-based physician for a particular patient. This particular patient's case was noteworthy for his young age, having received rapidly escalating dosages of schedule 2 narcotics, and for frequent early refills.

This young adult man had presented with low back pain 3 years prior that he loosely related to his work as a laborer. He had initially been treated with non-narcotic medications but was shortly thereafter transitioned to narcotics and titrated up to achieve adequate analgesia. At the time of the Board review he was receiving OxyContin 200 mg twice daily.

The well-documented medical record detailed all prescriptions. There was notation of phone calls from family members expressing concern that the patient was abusing his medication, and another during which the patient called to confess that he was "hooked on narcotics and buying significant amounts on the street to prevent withdrawal", and the physician's own suspicion of narcotic abuse.

The medical record was also remarkable for its total lack of any imaging studies, sub-specialty consultation, use of a narcotics contract, or even a specific diagnosis beyond "back pain". The physician had recommended medical imaging on numerous occasions, but the patient had always declined, citing the expense and his lack of insurance coverage. He did, however, pay for his medications out of pocket; The average retail price for #20, 80mg OxyContin tablets was $242 at the time.

The physician voiced his frustration to the Board at having to balance the competing needs to both treat legitimate pain and to not prescribe inappropriately for patients who may be attempting to divert or abuse narcotics. He articulated difficulty assessing a subjective symptom like pain, appropriately weighting collateral information such as phone calls from family, balancing trust and suspicion in the patient-physician relationship, and in meeting the requirements of Rhode Island's pain statute.

Although an extreme example, this case echoes many of the concerns expressed by physicians on numerous prior cases reviewed by the Board. It also provides an opportunity to review Rhode Island's rules and regulations related to pain assessment[1] and the standard of care that the Board applies when investigating an allegation of inappropriate prescription of chronic narcotics.

RULES AND REGULATIONS RELATED TO PAIN ASSESSMENT

In May of 2003 the Department of Health promulgated regulations related to pain assessment. The Rhode Island General Assembly had previously declared "…pain affects quality-of-life, job performance and security; nearly 30% of nursing home resident with daily pain were receiving no pain medication of any form; pain untreated or under-treated adversely impacts the quality-of-life for patients; up to 95% terminally ill patients pain can be relieved with adequate pain management; and too many in Rhode Island are as are suffering and dying in needless pain…"

The regulations, written to apply to both healthcare facilities and healthcare providers, required that all patients be assessed for pain upon initial evaluation, using a combination of patient's self report, a healthcare provider's assessment and/or a pain intensity tool. The care must include ongoing reassessment, to be documented in the clinical record.

Of note, the regulations are mute regarding specific treatment of pain and defer entirely to the judgment of the healthcare provider and community practice standards. Many clinicians and patients have misconstrued these regulations. They are not a mandate to treat pain in a fashion inappropriate to the clinical context.

CHRONIC NARCOTIC THERAPY

The model policy for the use of controlled substances promulgated by the Federation of State Medical Boards underscores that "physicians should not fear disciplinary action... for ordering, prescribing, dispensing or administering controlled substances... for a legitimate medical purpose and in the course of professional practice. The board will consider prescribing…

controlled substances for pain to be for a legitimate medical purpose if based on sound clinical judgment… ."[2]

Allegations of inappropriate prescribing are evaluated individually in a clinical practice context. When reviewing the medical record of a patient on chronic narcotic therapy, the Board first determines whether there is a legitimate physician-patient relationship. Without a legitimate physician-patient relationship documented by a clinical record, narcotic prescription is always inappropriate. This acknowledges that a genuine physician-patient relationship also exists for physicians participating in a cross coverage or group practice.

Patients receiving chronic narcotic therapy must have an adequate clinical evaluation that should include a history and physical examination, relevant radiographic/imaging and laboratory studies, and subspecialty consultation. Chronic therapy is defined as at least 6 months in duration. There should be a specific diagnosis or at least a considered attempt to make one. There must be a documented treatment plan. Patient follow-up should include assessment and reassessment of pain as well as reevaluation for intercurrent illness and disease progression.

In recent years there has been a movement towards the use of a "narcotics contract" which provides informed consent with review of the possible adverse outcomes including addiction and abuse.[2,3] Such agreements may also require that all narcotics prescriptions be provided by one provider and be filled at a specific pharmacy. The Board advises that such contracts be employed as a general "best practice."

Concerning History

Although trust is central to the physician-patient relationship, the safe and appropriate prescription of narcotics requires a judicious level of suspicion. The prudent clinician should consider whether the subjective complaint of pain is proportionate to the underlying biomedical condition. Concerning factors would include excessive quantities of controlled substances required to control symptoms, frequent or early refills, use of multiple pharmacies, prescriptions from multiple providers, use of street slang in referring to medications e.g. "Percs", "Vics", or "Oxys" and failure to follow-up on recommended tests or consultations.[5]

A positive urine toxicology screen for illicit substances, criminal proceedings such as DUI, or apparent intoxication at the time of evaluation are also of grave concern. Phone calls and letters from family members or anonymous sources should also prompt further investigation or discussion with the patient. Finally, drug utilization reports issued by third party insurers or regulatory agencies to alert providers to poly-pharmacy and doctor shopping must be addressed and should be included in the medical record.

Punishment

The FSMB and the American Academy of Pain Medicine co-sponsored a study of physician discipline relating to narcotics between 1998 and 2006.[6] During this time there were actions against 725 out of the 700,000 US physicians, or a rate of 0.1%. Reasons included drug trafficking, distributing, racketeering, fraud, money laundering, murder/manslaughter, falsification of records, and inappropriate relationships with patients.

The RI experience mirrors the national one. In recent years the Board has issued sanctions for prescribing with inadequate, nonexistent or falsified medical records, prescribing in exchange for sex or money, drug diversion, and drug abuse. There have been no adverse actions simply for prescribing high doses of narcotics where a legitimate medical record documented a genuine need and treatment plan. Finally, as in the case example, the Board tends to emphasize education and mentorship whenever reasonable.

Conclusion

A physician has the paramount ethical obligation to treat pain and to alleviate suffering. RI law mandates pain assessment and continuing reevaluation. At the same time physicians are expected to take reasonable precautions to avoid contributing to abuse and diversion. The Board expects that all narcotics prescribing occur in the context of a bona fide physician-patient relationship, and that patients undergo proper medical evaluation and ongoing reassessment. Subspecialty consultation from pain or addiction specialists can often be helpful.

There is little evidence to substantiate a general concern that physicians are at risk to be sanctioned simply for prescribing high doses of narcotics.

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Point of View

A Time for Real "Change" In Primary Care

N.S. Damle, MD, FACP

The election of a new President brings with it an expectation of verdant approaches to many societal issues including health care. For "Change" to be more than a political sound bite, the new administration will need vision and courage to provide a better health care system for this country. Part of that vision will need to be a vibrant primary care workforce.

The United States has one of the most advanced systems for clean water and toxic waste disposal, food and medication quality and safety requirements, availability of vaccines and advanced medical/surgical expertise and technology in the world. Yet this country also ranks among the lowest for developed countries in primary care functions (prevention of infant mortality, obesity, vaccination rates, chronic disease management and others), lowest in health care outcomes and highest in cost.[1]

Paradoxically, our system of medical education attracts some of the best and brightest to medicine, educates them well in its medical schools and provides unparalleled training in its post graduate programs. Our research institutions, private industry and universities have given us exciting new therapies and technologies.

Despite these advances, we still have forty-five million people without health insurance, a crumbling access and supply of primary care and a system we cannot afford. Health insurance premiums increased 114% between 1999 and 2007, while workers' earnings increased by 27%. Health care spending in the United States is 16% of the Gross Domestic Product and increasing yearly - 6% higher than any other developed country.[2]

The path to high quality and affordable health care can only be forged with a vibrant primary care workforce. Countries with strong primary care have higher quality with lower costs to society (New Zealand, Australia, Great Britain, Canada, Sweden, Germany, Japan and others).[2] National studies demonstrate decreased death from cancer, heart disease and stroke in states with higher ratios of primary care physicians to population. One example of the power in preventive/primary care is the reduced rate of hospitalization (avoidance of 5 million admissions to hospitals in a year) with a cost savings of 26.5 billion dollars per year.[10]

Various factors have contributed to the dearth of primary care.

The Problem

A widening gap between supply and demand for primary care:

As the population ages, statisticians project a 20-27% (35,000-44,000 physicians) shortfall in primary care within the next fifteen years—a deficit exacerbated by an uneven geographic distribution.

Census estimates are that the US population will grow to 349 million by 2025 and the population above age 65 years will increase by 73%. Primary care physicians provide 52% percent of all office visits. This segment of the population also uses a majority of health care services resulting in a 29 percent increase in workload for adult care.[3]

The decline in interest in primary care:

The peak in interest in primary care occurred in 1998, when 9,348 residents entered practice. Since then, there has been a decrease to 1995 levels of new primary care physicians. During this period the US population has grown by 12%.

Today's status is the end result of a process which began with the priorities of medical schools and students entering the profession. In the 1980s and 90s there was an appreciable shift by medical schools to support primary care and recruit interested student. The result was a short-lived increase in students entering these residency programs. Since 1998 there has been a steady decrease in interest, with only 2% of medical students now thinking about a career in general internal medicine.[15] Some of the decline is attributable to an increasing desire for sub-specialization with 62% of general internal medicine graduates entering specialties.[4,5,6]

The culture of physician training and preferences

The cultural training ground for future physicians, a priori, does not foster an interest in primary care. The clinical curriculum is primarily tertiary care-centered for third and fourth year medical students. This environment is also the setting for post graduate education. Though this institutional structure has been in place for close to 100 years, the allure of the subspecialties has developed over the past twenty five years. Many of the mentors during training are sub-specialists, the cases are often complex and require sub-specialty care with procedural and surgical solutions to medical problems that seem on the surface to lend more professional satisfaction.

Further, studies have shown a trend in medical students of prioritizing a balance between work, leisure time and a controllable lifestyle. Primary care is viewed as less able to satisfy these preferences.[7]

Income disparities

Income disparities and levels of educational debt are partially responsible for the decline in primary care. Numerous studies demonstrate a two-to-threefold difference in compensation between primary care and any procedural medical subspecialty or non-internal medicine-based specialty. Further, the income gap is widening. In the past decade there has been a 20% change in net income in primary care and a 30 to 75% increase in net income in non primary care medicine.[8,9]

The Solution

Recognition by the general public, legislators and policy makers of the value of a strong primary care workforce. Primary care can be a powerful driver for controlling costs and maintaining a high quality health care system through the following measures:

a) Provide health prevention strategies, combat obesity, manage diabetes and heart disease and other chronic illnesses that account for 75% of health care costs.[10]

b) Provide care coordination utilizing a team approach (Patient Centered Medical Home) and health information technology in the form of the electronic medical records, electronic prescribing and a health information exchange.

c) Primary care can reduce the rate of hospitalization and control the rate of technology use that accounts for one half to two thirds of health spending growth.

Create a hybrid system of reimbursement for primary care, consisting of a global fee for care management and fee for service for each patient. Provide additional payment for meeting standardized and proven quality measure targets, that improve health outcomes in patients.

The genesis for some of these changes will need to come from the **Medicare Physician Advisory Committee (MedPAC)**.This committee advises the **Centers for Medicare/ Medicaid Services (CMS)** on reimbursement structure and payment. Health plans often seek guidance from CMS on payment models.

Similarly, the **Relative Value Scale Update Committee (RUC),** developed by the American Medical Association and other organizations, will need to substantially increase primary care membership and change the elements of the scale to reflect the importance of evaluation and management services and change or eliminate the **sustainable growth rate (SGR)** formula.

The improved reimbursement model would bring primary care income in parity with procedural sub-specialists in internal medicine.

There should be concurrent changes in the training environment for medical students and internal medicine residents. Providing role models in the community as well as the academic medical centers will foster an appreciation for the role of primary care in health care delivery. Loan forgiveness programs and scholarships for entering primary care and practicing in underserved areas, while helpful, will not solve the problem without changes in reimbursement.

The source of funding is the "sixty-four thousand dollar" question. The answer has several elements:

- Studies reveal that there is already enough money in the health care system to fund these changes. At present, the money is not spent wisely and is offering poor quality at high costs.
- Examine the "for profit" health plans and the pharmaceutical industry for their contribution to rising health care costs.
- To some degree, funding will need to shift from procedural and imaging services to cognitive services.
- Technology costs will have to be substantially decreased through judicious use and proven benefits. As an example, MRI and CAT scans account for 100 million dollars annual cost, with estimates of a 20% per year increase in these services. Fifteen percent of these may be "unnecessary testing."
- Savings will accrue from decreased rates of hospitalization, health prevention through early screening, promoting healthy lifestyles and management of chronic illness to prevent secondary complications.
- Establish an institute that evaluates comparative effectiveness of therapies (procedural, medical and surgical), addressing costs and safety. According to the Congressional Budget Office: "as much as 30% of medical spending ($700 billion per year) does nothing to improve care."

Health care reform is a complex issue with multiple stakeholders. Visionary and "Real Change" will have to start with a strong and vibrant primary care workforce in an affordable health care system.

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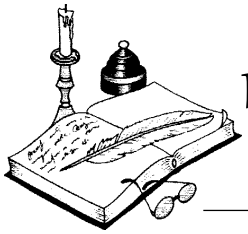

Physician's Lexicon

A Frantic Assemblage of Words

Truly, English is the most versatile, most expressive of languages, particularly in conveying nuanced meanings, subtle shades of difference and emotional moods. Consider the many word-choices in expressing the feelings, perhaps tinged with anger, experienced by an anxiety-ridden, manic individual.

The word frenzy comes to mind. This noun is usually defined as someone exhibiting wild excitement, visible agitation, even excessive spiritual enthusiasm. The word stems directly from the Latin, *phrenesis* which comes from a Greek word, *phreniticos,* meaning inflammation of the brain. The English terms, frenetic and frantic, are both derived, via the French [*frenetique*], from the same source. Medical terms such as phrenitis [an obsolete word for encephalitis], phrenology and schizophrenia also descend from this word. The phrenic nerve is from a more primitive and less defined Greek root [*phren-*] variously meaning mind, heart or diaphragm. On the other hand, the English word, fervent, meaning warmth or intensity of spirit, comes from the Latin, *fervere*, meaning to seethe or boil. Analogous words include fervency, effervescent and ferment.

Amok, sometimes spelled amuck, is a Malaysian word describing overwhelming agitation allegedly leading to homicide. W. Somerset Maugham wrote a short tale about the emotional state of amok, describing it as though it were a tropical pestilence, a jungle madness and, much like malaria, capable of affecting anyone. Stefan Zweig authored a novella called *Amok*.

Berserk is defined as one who is a homicidal maniac, violently frenzied in behavior. The word is of Scandinavian origin and was likely the name of an ancient, legendary Norse warrior. *Berserk!* is also the name of a Joan Crawford 1968 movie of eminently forgettable content.

Delirium, an acute pathologic state of febrile excitement sometimes associated with delusions. It stems from the Latin, *delirare*, meaning to turn aside from the furrow. From this agronomic meaning eventually came the metaphoric sense of being cast to one side, of being deviant, eccentric, even deranged.

Deranged, a hybrid word from the Latin, *dis-,* meaning apart or asunder, and the French verb, *ranger*, meaning to put into line thus yielding a word now meaning to push away from conventional sanity, to make insane.

Manic [and mania as well as words ending with –mancy such as necromancy] are taken from the Greek *manichos* meaning from the mind or insane.

Enthusiasm, meaning filled with zeal and fervor, is derived from the Greek, *theos* [meaning god] and thus had yielded an earlier meaning of being divinely inspired.

– Stanley M. Aronson, MD

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

Vital Statistics

Edited by Colleen Fontana, State Registrar

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

Underlying Cause of Death	Reporting Period			
	March 2008	12 Months Ending with March 2008		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	289	2,731	258.2	3,265.0
Malignant Neoplasms	199	2,328	220.1	6,442.5
Cerebrovascular Diseases	33	393	37.2	650.0
Injuries (Accidents/Suicide/Homicde)	43	527	49.8	8,564.0
COPD	52	476	45.0	347.5

Vital Events	Reporting Period		
	September 2008	12 Months Ending with September 2008	
	Number	Number	Rates
Live Births	1,046	12,566	11.9*
Deaths	724	10,037	9.5*
Infant Deaths	(8)	(82)	6.5#
Neonatal Deaths	(7)	(65)	5.2#
Marriages	397	5,452	5.2*
Divorces	194	2,778	2.6*
Induced Terminations	not available	not available	not available
Spontaneous Fetal Deaths	49	790	62.9#
Under 20 weeks gestation	(41)	(718)	57.1#
20+ weeks gestation	(8)	(72)	5.7#

(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 1,057,832 (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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March 1919, Ninety Years Ago

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

March 1959, Fifty Years Ago

O.M.Jankeoson, MD, Assistant Physician Tufts Medical Services), delivered the following talk at the Teaching Program on Cancer at Rhode Island Hospital: "Some Errors in the Diagnosis of Gastrointestinal Neoplasms." He pointed specifically to errors of omission, cautioning the audience to mark the clues to gastrointestinal neoplasms; e.g., unexplained changes in digestive patterns or bowel habits, intestinal obstruction, fever.

James Wattt, MD, Director, National Heart Institute at NIH, contributed "Pharmacological Revolution," a talk presented at the 112th annual meeting of the Providence Medical Association. He traced the "real revolution" to antimalarial programs of World War II, which led to "the synthesis of more than 29,000 compounds."

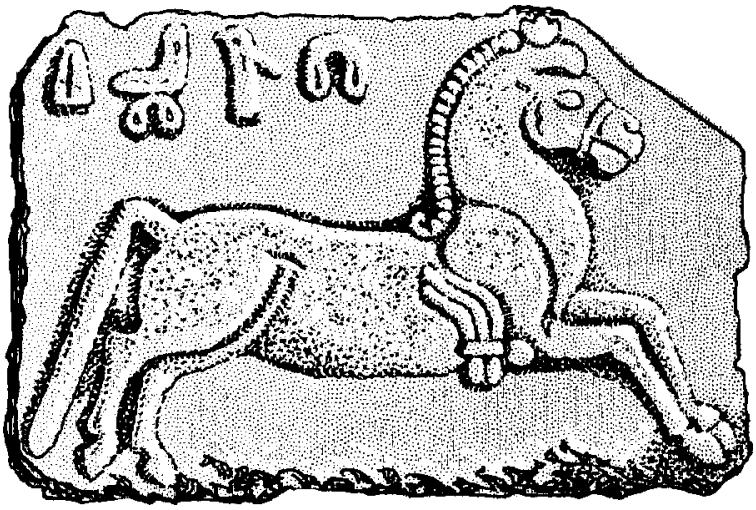
Peter L. Mathieu, MD, Sui Yen Wang, MD, Alfred Toselli, MD, and Betty Burkhardt Mathieu, MD, contributed "Glucosamine-Potentated Tetracycline in Pediatrics." The authors discussed the results of treating 150 children, ages 1 month to 14 years, including 15 children from the RI State Infirmary for Chronic Mentally Ill Children, 31 inpatients at St. Joseph's and 104 seen in the office or on house calls. Eighty patients showed an "excellent response." The authors commented, "No patient failed to respond to the therapy and no patient developed side effects."

An Editorial, "New Standards for Foreign Doctors," discussed the 7600 Foreign Medical Graduates in the United States on exchange or student visas, and the more than 1000 FMGs who had immigrated permanently to the US.

March 1984, Twenty-Five Years Ago

Amerinco A. Savastano, MD, in "Clinical Experiences with Dimethyl Sulfoxide (DMS) in Human Subjects," cautioned: "Approval must be withheld until safety in extended use is established." The author, on behalf of the Squibb Institute of Medical Research, had conducted a double-blind clinical trial on 90% solutions of DMS, with and without sterioids. After the author had treated 35 cases, the Food and Drug Administration ordered Squibb to halt the study "as there was evidence linking the drug to cataracts in laboratory animals."

The Case Record from Rhode Island Hospital's Clinical pathological conference discussed a 41 year-old woman admitted for cardiac catheterization because of post-infarction angina. The subsequent autopsy found: "'incidental' cardiac involvement and a malignant lymphoma. Discussants were Maurice M. Albala, MD, Tom J. Wachtel, MD, George F. Mesissner, MD, and Mark Fagan, MD.



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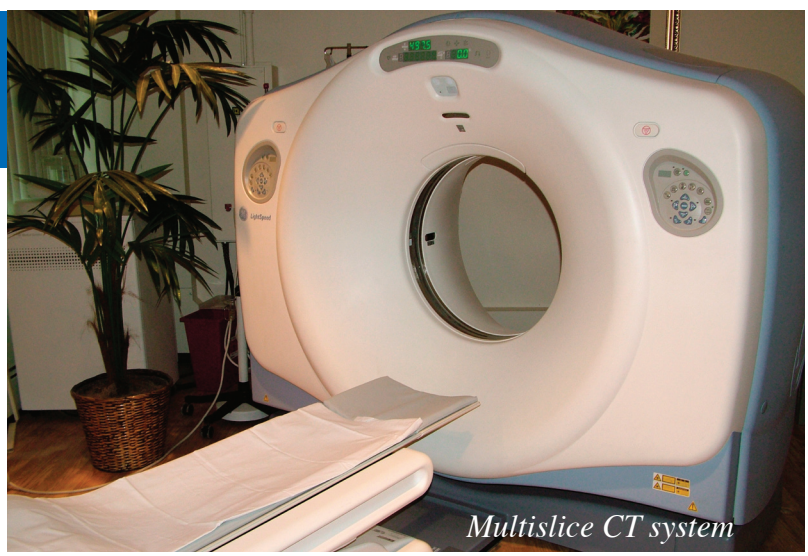
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