Advanced Modeling Techniques

Assignment: Non-linear Models

Assignment date: February 23, 2017

Due date: At oral exam

1 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) commonly refers to ulcerative colitis (UC) and Crohn disease (CD), which are chronic inflammatory diseases of the GI tract of unknown etiology. Crohn disease is also referred to as regional enteritis, terminal ileitis, or granulomatous ileocolitis.

Pathophysiology: In UC, inflammation always begins in the rectum, extends proximally a certain distance, and then abruptly stops. A clear demarcation exists between involved and uninvolved mucosa. The rectum is always involved in UC, and no "skip areas" are present. UC primarily involves the mucosa and the submucosa, with formation of crypt abscesses and mucosal ulceration. The mucosa typically appears granular and friable. In more severe cases, pseudopolyps form, consisting of areas of hyperplastic growth with swollen mucosa surrounded by inflamed mucosa with shallow ulcers. In severe UC, inflammation and necrosis can extend below the lamina propria to involve the submucosa and the circular and longitudinal muscles, although this is unusual.

UC remains confined to the rectum in approximately 25% of cases. In the remainder of cases, UC spreads proximally and contiguously. Pancolitis occurs in 10% of patients. The small intestine is never involved, except when the distal terminal ileum is inflamed in a superficial manner, referred to as backwash ileitis. Even with less than total colonic involvement, the disease is strikingly and uniformly continuous. As the disease becomes chronic, the colon becomes a rigid foreshortened tube that lacks its usual haustral markings, leading to the lead pipe appearance observed on barium enema. The skip areas (ie, normal areas of the bowel interspersed with diseased areas) observed in CD of the colon do not occur in UC.

CD, on the other hand, consists of segmental involvement by a nonspecific granulomatous inflammatory process. The most important pathologic feature is involvement of all layers of the bowel, not just the mucosa and the submucosa, as is characteristic of UC.

Furthermore, CD is discontinuous, with skip areas interspersed between one or more involved areas. Late in the disease, the mucosa develops a cobblestone appearance, which results from deep longitudinal ulcerations interlaced with intervening normal mucosa. The 3 major patterns of involvement in CD are (1) disease in the ileum and cecum, occurring in 40% of patients; (2) disease confined to the small intestine, occurring in 30% of patients; and (3) disease confined to the colon, occurring in 25

UC and CD are generally diagnosed using clinical, endoscopic, and histologic criteria. However, no single

finding is absolutely diagnostic for one disease or the other. Furthermore, approximately 20% of patients have a clinical picture that falls between CD and UC; they are said to have indeterminate colitis.

The incidence of gallstones and kidney stones is increased in CD because of malabsorption of fat and bile salts. Gallstones are formed because of increased cholesterol concentration in the bile, caused by a reduced bile salt pool. Patients who have CD with ileal disease or resection also are likely to form calcium oxalate kidney stones. With the fat malabsorption, unabsorbed long-chain fatty acids bind calcium in the lumen. Oxalate in the lumen normally is bound to calcium. Calcium oxalate is poorly soluble and poorly absorbed; however, if calcium is bound to malabsorbed fatty acids, oxalate combines with sodium to form sodium oxalate, which is soluble and is absorbed in the colon (enteric hyperoxaluria). The development of calcium oxalate stones in CD requires an intact colon to absorb oxalate. Patients with ileostomies do not develop calcium oxalate stones.

Extraintestinal manifestations of IBD include iritis, episcleritis, arthritis, and skin involvement, as well as pericholangitis and sclerosing cholangitis.

We have a clinical trial with 291 subjects, divided over four treatment arms: 0: placebo; 1: 1000 mg; 2: 2000 mg; 3: 4000 mg. Subjects are measured during a 7 week period. The outcome of interest is an IBD activity score. The same score is measured at baseline as well.

2 Data Set

The data can be found in `IBD.SAS7BDAT`.

The following variables are present:

PATIENT: 291 subjects
WEEK: measured at weeks 1 through 7
TREAT: Treatment indicator: 0, 1, 2, 3
IBDSC: IBD score
IBDSC0: IBD score at baseline

3 Assignment

1. Construct a dose-response relationship with IBDSC as the outcome variable, as a function of time. You can consider linear and non-linear models.
2. Construct a binary outcome variable:

$$\text{IBDSCbin} = \begin{cases} 1 & \text{IBDSC} >= 100, \\ 0 & \text{otherwise} \end{cases}$$

   Construct a non-linear dose-response relationship with IBDSCbin as the outcome variable.

Properly take the missingness into account. It is up to you to decide what best to do with the baseline score. In all cases, carefully describe the choices made.