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LETTERS TO THE EDITOR

Inappropriate Use of Meta-Analysis to Estimate Efficacy of Probiotics

TO THE EDITOR: The article by McFarland presents meta-analyses of studies evaluating efficacy of probiotics for antibiotic-associated diarrhea (AAD) and *Clostridium difficile* diarrhea (CDD) (1). While this is a topical article, we believe the analysis is at best contentious, and at worse flawed, and the conclusion potentially misleading. The author combines results from studies that could not possibly have been drawn from the same population, and whose only commonality is the study outcome. The consequence is an artificial narrowing of the overall confidence interval for the efficacy of probiotics.

For example, in the meta-analysis of studies on CDD, results from one study on prevention of CDD are combined with results from five studies on treatment of CDD. Thus an assumption is being made that the magnitude of the benefit of probiotics for prevention or treatment of CDD is the same. This assumption does not seem realistic and no justification is provided. The author defines CDD as diagnosis of diarrhea supported by either a positive *C. difficile* culture test or toxin test. Despite listing "inconsistent outcome measure" as an exclusion criterion, results from studies that did not follow the author's definition of CDD were combined. For example, results from the study by Wullt *et al*. (2) refer to cessation of diarrhea and not the absence of *C. difficile* or its toxin. Other differences among studies include use of different types and doses of probiotic, and different lengths of follow-up, which the author recognizes as sources of heterogeneity in her discussion section. Despite these differences among studies, a fixed-effects meta-analysis, that assumes the true efficacy in each study is identical, was used. The point estimate of the pooled odds ratio is almost entirely determined by the single study that showed a statistically significant beneficial effect (3). However, the overall confidence interval is narrower because of the artificial increase in sample size from 124 to 354 by the addition of information from other studies.

Similarly, the meta-analysis of studies on prevention of AAD combines results from studies of children with those from studies of adults. The author is therefore assuming that the magnitude of the beneficial effect of probiotics is not related to age. This does not seem logical, particularly given that six out of the seven studies that reported a statistically significant beneficial effect were among children.

It would have been more appropriate to carry out a systematic review than a meta-analysis (4).

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Response to the Article: McFarland LV. Meta-Analysis of Probiotics for the Prevention of Antibiotic-Associated Diarrhea and the Treatment of *Clostridium difficile* Disease. Am J Gastroenterol 2006;101:812–22.

TO THE EDITOR: This is the third and most persuasive meta-analysis in recent years suggesting that probiotics reduce antibiotic-associated diarrhea (AAD). Unfortunately, we felt the study had numerous flaws. Different probiotics have different mechanisms of action, with some showing little or no efficacy. The conditions treated varied widely and thus so did the patient characteristics (normal volunteers, children, and adults). An analogy would be doing a meta-analysis on the use of unrelated antibiotics to treat meningitis in any age group, without regard to antibiotic efficacy, causative organism, or antimicrobial sensitivity. Five of the included studies were for treatment of *Helicobacter pylori*, clearly a far cry from the use of broad-spectrum antibiotics in hospital inpatients. Also at least five studies were not analyzed on an intention-to-treat basis (Surawicz, Tankanow, Vanderhoof, Gotz, Adam). We would also suggest that a single-author analysis of this type

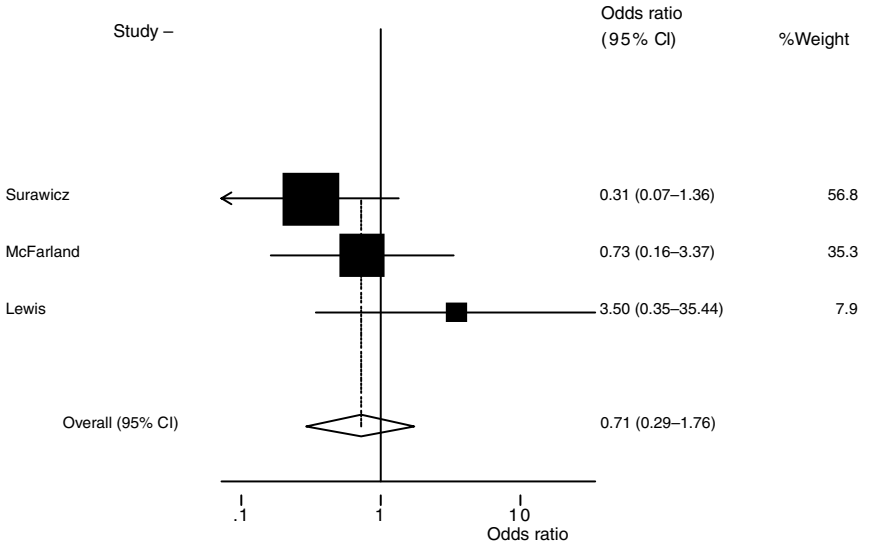

Figure 1. Patients with diarrhea due to *C. difficile* infection.

while thorough did not enable independent data extraction and comparison (she is the author of several of the [better!] included studies), nor did the author advertise her conflicts of interest having received grants from Biocodex, the makers of *Saccharomyces boulardii*.

The author defined the primary outcome, diarrhea, as ≥3 loose stools/day for at least 2 days or ≥5 loose stools/48 h; at least five studies (Lewis, Vanderhoof, Wunderlich, Borgia, Tankanow) did not meet this primary inclusion criteria. The study by Adam *et al.* had one of the biggest impacts on the analysis yet is the most suspect of all the trials with only 19.4% of recruited cases being analyzed, the remainder excluded because of protocol violations!

By far the most important clinical problem is the prevention of diarrhea due to *Clostridium difficile*. Probiotics appear not to offer any protection even when combining the three studies using *S. boulardii* OR 0.71 (95% CI 0.29–1.76).

I would also question the authors' interpretation of the ability of *S. boulardii* to reduce the relapse rate after successful treatment of AAD due to *C. difficile*, as the two studies combined contained different populations of patients, those with their first infection with *C. difficile* where *S. boulardii* is of no proven benefit and those who had previously relapsed after successful treatment of their *C. difficile*.

Considering the limitations as described with regard to a meta-analysis of probiotic studies and also the relatively poor quality of many studies, care should be taken in interpreting the conclusions. Certainly there appears to be little evidence that probiotics given concomitantly with antibiotics can prevent diarrhea due to *C. difficile*. Probiotics are not without risk, with over 11 case reports of *S. boulardii* septicemia in the literature. Uncritical reading of this meta-analysis is misleading and risks injudicious use of possibly ineffective, potentially hazardous therapies and has the potential to distract from proven interventions such as modification of antibiotic policies.

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Response to Drs. Ramnarace and Dendukuri

TO THE EDITOR: These two thoughtful letters point out the advantages and disadvantages of using meta-analyses to review studies. In contrast to review articles, which summarize articles one at a time, meta-analysis allows a global estimate of the efficacy of an investigated treatment across numerous studies. The challenge is to pool studies that are not too heterogeneous, yet to include studies that may have divergent outcome results. My recently published meta-analysis asked the question "Are probiotics effective for the prevention of antibiotic-associated disease (AAD) and the prevention of *Clostridium difficile*-associated disease (CDAD) recurrences?" (1). The following points were raised by the two previous letters:

1. Different probiotics, different conditions, and different patient characteristics were combined. The field of probiotics is diverse and not all probiotics are equally effective. This meta-analysis was a comprehensive examination of the field of probiotics, therefore, different probiotics were included and different study populations were examined. A meta-analysis by Sazawal *et al.* (2) included studies using different probiotics, but also pooled results from different disease outcomes (AAD and traveler's diarrhea and acute diarrhea) into one global risk estimate. I chose to analyze two diseases separately and perform two separate meta-analyses. Of the three other meta-analyses of probiotics and AAD, only Szajewka and Mrukovicz (3) limited their study to one probiotic and the other two meta-analyses included different

probiotics and different age groups (4, 5). Pooling different probiotic studies is needed, as there are a limited number of randomized trials for each type of probiotic. However, it is important to examine the effect of different subgroups (*e.g.*, by separate type of probiotic, pediatric *versus* adult cases, *etc.*), which I did in my meta-analysis. As little significant effect was found for these subgroups, I pooled these studies. Of the five meta-analyses above, most were within the same range of pooled risk estimate (RR 0.43–0.48) for AAD, regardless of which trials were included and excluded. The point is well taken that caution should be exercised when making conclusions about therapy from a pooled risk estimator. Differences in mechanisms of action, age distribution, type of disease, and type of probiotic should be examined (as these were in my paper). AAD is also a "mixed bag" of different etiologies (mostly unknown), different types of inciting antibiotics, and different reasons for prescribing the antibiotics. As the standard definition of AAD is "diarrhea resulting from exposure to at least one antibiotic," I included the studies on *Helicobacter pylori* disease, as these were patients on antibiotics and data on diarrhea were presented in those studies. What ties these different exposures together is the common mechanism of the disruption of the normal colonic flora and loss of colonization resistance. Pooling similar treatments and disease outcomes is not unique to probiotic meta-analyses, as this is seen with other meta-analyses (6, 7).

2. Several included studies were not intent-to-treat (ITT). The meta-analysis followed recommended MOOSE guidelines for meta-analyses, which did not exclude non-ITT studies (8, 9). However, this would have been an informative piece of data to add to the tables.

3. Some studies of AAD did not meet the inclusion criteria of ≥3 *loose stools/day.* Upon re-examination, two studies did not quite meet this criterion, but the authors did use a specific definition of diarrhea (>1–2 loose stools/day); Wunderlich *et al.* (10) did have data for >3 loose stools/day and Lewis *et al.* (11) did use the standard definition of ≥3 loose stools/day. Due to space limitations, a table describing excluded studies was not presented, which would have made it clear what types of outcome were not acceptable (bacterial counts at the end of treatment, duration of diarrhea not in proportion to developing diarrhea, or development of general abdominal symptoms). Excluding the studies with less quantitative definitions of diarrhea did not significantly affect the pooled risk estimate.

4. Regarding the meta-analysis for probiotics and Clostridium difficile *disease, Ramnarace and Lewis correctly point out that one study should not be included*. The study by Plummer *et al.* (12) was included to be as comprehensive as possible, as there are only a few randomized trials focused on CDAD. However, if this study is excluded, the pooled RR goes from 0.59 (95% CI 0.41–0.85) to 0.62 (95% CI 0.42–0.91) and the overall conclusion remains the same, that is, probiotics significantly reduce the risk of developing subsequent recurrences of CDAD. It was also criticized that a fixed effects model should not have been used due to the heterogeneity of the trials, but the test for heterogeneity did not allow the rejection of the null hypothesis, so a fixed model was justifiably used. To satisfy curiosity, the pooled estimate using a random effects model for these five studies (RR 0.62, 95% CI 0.40–0.96) did not show a significant difference from the fixed effects model.

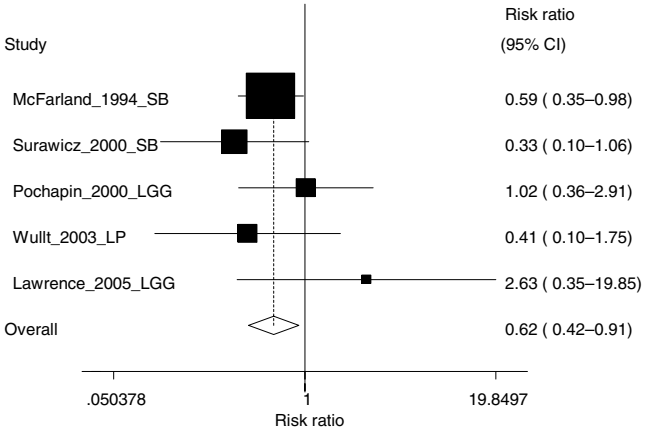

Figure 1. Revised meta-analysis of five randomized controlled trials of probiotics for the prevention of recurrences of *Clostridium difficile* associated disease.

*5. Another valid point was that the study by Wullt et al. (*13*) used a clinical outcome (cessation of diarrhea) and not the absence of* Clostridium difficile *or its toxins*. However, the paper does present data on both clinical and bacteriologic recurrences. When just *Clostridium difficile*-positive recurrences are used the result is slightly different, but not sufficiently to change the overall result of the meta-analysis (see Fig. 1 below).

6. New figure presented by Ramnarace and Lewis. The figure presented in the letter was of three studies using *Saccharomyces boulardii* for the prevention of CDAD recurrences, yet I am unaware of any published study using *Saccharomyces boulardii* for CDAD by Lewis *et al.* and as Dr. Lewis did not present any reference for this study, it remains a mystery. There are two studies by this researcher; one study examines AAD (11) and the other analyzes a prebiotic for CDAD (14), neither is appropriate to be included for a meta-analysis of probiotics and CDAD.

7. Regarding financial conflicts. Typically, financial conflicts no longer active over 5 yr are not disclosed. I was employed by a pharmaceutical company (Biocodex Inc. Seattle, WA), which developed *Saccharomyces boulardii*, but I have not been employed by them since 2001. I have taught several CME courses on probiotics that have been sponsored by this company, but have no stock or equity in this company.

Overall, even with the diversity of probiotics and the differences in study populations, the observation that there is a pooled significant reduction in risk for both AAD and CDAD indicates promise for this treatment strategy. Points brought out by the two letters above and discussed in the previous

meta-analysis should be kept in mind when attempting to apply this general conclusion (or result of any meta-analysis) to the treatment of an individual patient.

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Barrett's Esophagus and Obesity

TO THE EDITOR: Sir, we read with interest the recent article on Barrett's esophagus by Kendall and Whiteman (1). In an Australian health region, they found a greater endoscopic frequency and absolute number of new cases of histologically proven Barrett's esophagus, particularly the short segment disease between 1990 and 2002. They attribute this to a possible increase in the number of endoscopies performed, greater awareness of the condition, and prescribing patterns of proton pump inhibitors. Barrett's esophagus has been suggested to be associated with gastroesophageal reflux disease. Obesity has been associated with a greater risk of gastroesophageal reflux disease symptoms, erosive esophagitis, and esophageal adenocarcinoma, and it has also been linked to greater risk of Barrett's esophagus (2, 3). Furthermore in a recent large study, a strong association has been found between body mass index (BMI) and symptoms of gastroesophageal reflux (4).

Given the above facts and the thought process, we reviewed the Australian database (available online) on the trends of obesity over the last several years. The trend of obesity and the number of people with high BMI have been increasing in the Australian population between 1980 and 2000 (5). We, therefore, think that this factor may also be contributing to the greater incidence of Barrett's esophagus, although in the study population, we do not have data on obesity and BMI. It would have been interesting to know if there is any statistical significance in the greater frequency of Barrett's when correlated to the rising trend in BMI.

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Barrett's Esophagus and Obesity—Response to Drs. Pabla *et al*.

TO THE EDITOR: We thank Dr. Pabla and colleagues for their letter. The aim of our study was to determine temporal changes in the endoscopic frequency of new cases of Barrett's esophagus (1). We showed a significant increase in the endoscopic frequency and absolute numbers of new cases of Barrett's esophagus, particularly short segment disease. Our discussion on number of endoscopies performed, awareness of the condition, and prescribing patterns of proton pump inhibitors was in regard to these factors as potential sources of referral and detection bias. With regard to potential factors linking exposures such as reflux and obesity with the disease, this information was not available on the endoscopic database used for this study. However, we agree with Dr. Pabla and colleagues that obesity may be an important factor in Barrett's esophagus, and our group is currently undertaking research in this area. Indeed, we have recently published the results of a population-based case-control study, in which we observed that the risk of Barrett's esophagus associated with acid reflux was markedly higher in obese people (*i.e.*, BMI $\geq$ 30, adjusted odds ratio [OR] 34.4, 95% confidence interval [CI] 6.3–188) than in people in the healthy weight range (18.5 $\leq$ BMI $<$ 25, OR 9.3, 95% CI 1.4–62.2) (2). Given the population trends for obesity in Australia and other developed nations, the potential role of obesity in causing Barrett's esophagus clearly needs to be further explored.

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Inflammatory Bowel Disease in Young Children

TO THE EDITOR: We read with interest the report by Vind *et al*. (1). This population-based study made several worthwhile observations regarding the changing epidemiology of the inflammatory bowel diseases (IBD). While the authors' finding that there is an increasing incidence of IBD is certainly concerning, the slowed surgical rate and shorter time to diagnosis are certainly welcomed advances in the field.

As pediatric gastroenterologists, we found the authors' conclusion that "patients of young age at diagnosis had more extensive disease, with a significantly higher prevalence of upper gastrointestinal and ileal involvement. . ." to be an unusual observation. A close analysis of the pediatric data in Vind *et al*. provides an explanation that is worth elaboration.

Vind's study is mostly of adult patients. Twenty-four of 562 subjects (4.3%) were below age 18 yr at diagnosis. Some authorities have found that up to 25% of their IBD patients were diagnosed as children and adolescents (2). Population-based studies have demonstrated the prevalence of pediatric IBD to be as high as 7 per 100,000 (3). Therefore, the number of pediatric patients in this cohort seems low and may have skewed the results.

More importantly, the age at diagnosis of the patients in the present study is of note. The youngest patient diagnosed with Crohn's disease was 10-yr old. Rather than serving as the youngest, 10 yr has been found to be the mean age of diagnosis in large pediatric IBD studies (4). When looking at truly young IBD patients, that is those younger than 5–8 yr of age at diagnosis, there are now several large cohort reports showing a colonic predilection for disease distribution (4, 5).

It is interesting that the youngest patients in Vind *et al*. were of 2 yr and 7 yr, and were diagnosed with ulcerative colitis and indeterminate colitis, respectively. This gives strength to the argument that the relatively older age of their pediatric patients affected the authors' conclusions regarding disease location, as their younger patients did have a colonic focus of disease. It is important to bear in mind that, because of the colonic disease distribution, young children can frequently be diagnosed as having ulcerative or indeterminate colitis only to later declare themselves as having Crohn's disease (6).

In summary, it is difficult to draw conclusions about pediatrics from a study of predominately adult patients. Unfortunately, the age at which IBD is diagnosed includes even the youngest of children and, therefore, study of the full pediatric age range is needed to make appropriate conclusions

regarding pediatric IBD. That the disease prefers the colon at the extremes of age is a finding that should spur more investigation.

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Response to Letter by Rosh and Baldassano

TO THE EDITOR: Drs. Rosh and Baldassano raise interesting and important points regarding the pediatric part of our study on the increasing incidences of inflammatory bowel diseases (IBD) in Copenhagen city and county in 2003–2005.

The suggestion that the number of pediatric patients in our cohort may be low, thus possibly skewing the results, cannot be confirmed, since the incidence, and not the prevalence, in the age group 0–15 yr is 7.6/100,000, almost exactly the same as in Wisconsin in 2000 (1). We have been able to survey every single clinical unit that may have been sought by these patients in two geographical areas, and feel certain that none have been missed.

We agree with Drs. Rosh and Baldassano's remarks regarding the difficulty in drawing firm conclusions regarding the pediatric aspects from a study with a predominantly adult population. For instance, only 14 of our 209 patients with Crohn's disease were children. The present study covered only two of Denmark's 16 counties. We look forward to analyzing the Danish Colitis Crohn Database of pediatric patients across the country in forthcoming studies focusing on the pediatric population. An already ongoing inception cohort study on the occurrence, course, and prognosis of IBD in children in East Denmark 1998–2009 will also provide detailed information.

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What About Endoscopic Invisible Barrett's Esophagus?

TO THE EDITOR: With interest we read the article by Hanna *et al.* (1) entitled "Detection of Barrett's esophagus after endoscopic healing of erosive esophagitis," which has been published in a recent issue of *The American Journal of Gastroenterology*. The major finding was that erosive esophagitis impairs endoscopic assessment of gastric type mucosa in tubular esophagus in gastroesophageal reflux disease (GERD) patients (1). Therefore, endoscopy in GERD patients is recommended following treatment with a proton pump inhibitor, a consequence of enormous clinical importance for the management of patients with esophagitis and Barrett's esophagus. In addition, the paper points out the morphologic consequences of GERD: inflammation of squamous mucosa (*i.e.*, erosive esophagitis) and columnar-lined esophagus (CLE) resulting from columnar metaplasia of squamous epithelium (2, 3). When compared with esophagitis, CLE harbors a greater risk for malignant transformation (2, 3). In addition to assessment of benign esophageal pathology (esophagitis, ulcer, stricture, CLE), endoscopy aims to identify those with greater risk for malignancy, *i.e.*, Barrett's esophagus (2–5). Going in line with the current view, biopsy sampling includes endoscopic visible segments or tongues of gastric-type mucosa within the tubular esophagus and the level of the rise of the rugal folds, which is considered to be gastric (1, 4, 5). What about endoscopic "invisible" Barrett's esophagus?

The frequency of Barrett's esophagus within biopsies obtained from a normal appearing esophagogastric junction (*i.e.*, squamocolumnar junction coincides with rise of rugal folds) ranges from 11–16% (4, 5). The most fascinating histopathologic investigation of esophagogastrectomy

specimens demonstrated pouch-like dilated esophagus covered by CLE, 0.31–2.05 cm distal to the end of the tubular esophagus (2). We are aware that different criteria for endoscopic and anatomic definition of the beginning of the stomach are used: rise of rugal folds *vs* gut devoid of submucosal glands and covered by peritoneum (3). Using anatomic criteria, squamous mucosa and CLE are esophageal and oxyntic mucosa is gastric (2). CLE and gastric oxyntic mucosa cannot be discriminated by endoscopy (2, 3, 6). Consequently, what is considered to be gastric (*i.e.*, "cardia intestinal metaplasia") during endoscopy is anatomic esophagus (*i.e.*, Barrett's esophagus) (2, 3, 6). The "true" esophagogastric junction cannot be assessed by endoscopy; it is defined by histology (*i.e.*, transition from CLE and or squamous epithelium to gastric oxyntic mucosa) (2, 3).

Taken together, data reported in the study by Hanna *et al.* (1) and recent contributions (2, 3, 6) indicate that in GERD patients endoscopy should be conducted following a course of PPI treatment; biopsy sampling should include (a) visible CLE tongues within squamous mucosa-lined esophagus, (b) the squamocolumnar junction, and (c) the level of the rise of rugal folds, and probably distal to this level for exclusion of endoscopically invisible CLE and *Barrett's* esophagus within a pouch-like esophagus (2, 3). The authors are kindly asked to comment on the suggestions.

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Response to Letter by Riegler *et al.*

TO THE EDITOR: We would like to thank Dr. Riegler and coauthors for their interest in our article that appeared in a recent issue of the *American Journal of Gastroenterology*. At the outset, we would like to clarify that the aim of our study was not to reignite the controversy that surrounds the exact localization of the gastroesophageal junction, but to show that the presence of erosive esophagitis can mask the diagnosis of Barrett's esophagus. If the squamocolumnar junction is displaced proximal to the gastroesophageal junction then Barrett's esophagus is suspected, which should then be confirmed by biopsies that show intestinal metaplasia (1). If the squamocolumnar junction and the gastroesophageal junction coincide then there is no evidence of endoscopic Barrett's and no biopsies are warranted. We thus disagree with the suggestion that biopsy of normal squamocolumnar junction and distal to rugal folds should be done to rule out ultrashort Barrett's or endoscopic invisible Barrett's, because in effect this would entail taking biopsies from the gastric cardia. If these biopsies show intestinal metaplasia, then the diagnosis would be intestinal metaplasia of the gastric cardia rather than Barrett's esophagus. Intestinal metaplasia of the gastric cardia is a clinically distinct entity from Barrett's esophagus with differences in age, ethnicity, and gender of patients (2). More importantly, the prevalence of dysplasia in intestinal metaplasia of the gastric cardia is significantly lower than in Barrett's esophagus, and the current guidelines do not recommend performing surveillance in these patients (3). Misclassifying intestinal metaplasia of the gastric cardia as Barrett's esophagus could lead to unnecessary surveillance for years with huge cost implications.

We, therefore, respectfully disagree with the comments made by some investigators that there is an endoscopically invisible Barrett's esophagus. The initial step in diagnosing Barrett's esophagus is the recognition of an abnormal columnar lining in the distal esophagus; the detection begins with endoscopy rather than histopathology.

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Bugs Be Gone? Prophylaxis of Infection in Acute Pancreatitis

TO THE EDITOR: I read with interest the study by Manes *et al.* about the timing of antibiotic prophylaxis in acute pancreatitis (1). Necrotizing pancreatitis is a potentially life-threatening disorder that warrants the performance of careful studies like the one conducted by Manes *et al.* The study showed that the group who received meropenem as soon as the diagnosis of pancreatitis was made had a reduced rate of pancreatic and extra-pancreatic infections compared with the group who started antibiotics after contrast-enhanced CT scan demonstrated necrotizing pancreatitis. This study was well conceived and addresses a very important issue in the management of severe pancreatitits. I have, however, strong reservations about adopting a policy of early antibiotic administration. My reasons are the following:

1. There was no difference in mortality between the two groups.
2. All four patients with infected necrosis in the early antibiotic group were infected with organisms not susceptible to meropenem. Three of the four patients in the early antibiotic group died whereas only two of nine patients with infected necrosis in the "late" antibiotic group died.
3. All patients received total parenteral nutrition (TPN). TPN may be associated with an increase in septic complications (2, 3). It may also be associated with immune dysfunction. Recently, it has been suggested that jejunal feeds in the setting of acute pancreatitis may reduce the rate of bacterial translocation from the gut, resulting in a reduction in septic complications.
4. The ascension of *Clostridium difficile* is vexing to patients and clinicians alike. More virulent strains (4) have put a strain on our capacity to combat this tenacious bug. In the study by Manes *et al*., 78 patients who were initially started on antibiotics were found to have edematous pancreatitis and (of the authors' own admission) received antibiotics unnecessarily. In this age of cost containment, bacterial resistance, fungal super infections, and surging rates of *Clostridium difficile* colitis, prudence in antibiotic administration is more than justified.

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Response to Dr. Gilman

TO THE EDITOR: We thank Dr. Gilman for his comments on our paper. Most of his reservations were also ours when we designed this study and, afterward, when we analyzed the results.

Cost-effectiveness, emergence of resistant bacterial strains, and super infection with fungi are important topics to be considered when prescribing prophylactic antibiotic therapy in a patient with acute pancreatitis. The results of our study do not suggest treating with antibiotics every patient with acute pancreatitis, but that we have to start the treatment as soon as possible in those patients who are at greater risk of developing septic complications (1).

Presence of pancreatic necrosis is the most important factor conditioning the prognosis in patients with acute pancreatitis, so that antibiotic prophylaxis should be administered only in patients with pancreatic necrosis. The problem is that, according to the results of our study, waiting 48–72 h to start antibiotic therapy, the time needed to recognize and stage pancreatic necrosis by means of computed tomography, could be deleterious and associated with a significantly higher incidence of pancreatic and extrapancreatic necrosis and to a worse clinical course (1). In our study, we suggest that C-reactive protein could be a useful index in recognizing patients with pancreatic necrosis and that only patients with higher C-reactive protein levels (>160 mg/dL) should be treated with antibiotics (1). Other indices could be theoretically suitable for this aim, such as interleukin-6, PMN-elastase, or different scoring systems (2).

Our study failed to demonstrate a significant reduction in mortality between the two groups, but a trend toward a reduction in the occurrence of pancreatic and extrapancreatic sepsis was evident when the antibiotic was started earlier and, accordingly, the clinical course (length of hospitalization and need of surgery) was significantly more favorable. Patients who develop pancreatic sepsis despite an early antibiotic treatment are usually infected with resistant strains and have a worse prognosis and a higher mortality. We speculate that earlier, but not delayed, antibiotic therapy is able to prevent infectious complications with susceptible strains; development of infection notwithstanding a prompt therapy represents a bad prognostic index and a very important problem, because we have, at this time, only a few antibiotics that are effective against meropenem-resistant bacteria.

Infection of pancreatic necrosis is the major cause of death in patients with severe acute pancreatitis. Once pancreatic sepsis and sepsis-related multiorgan failure occur, the mortality rate is up to 50%. Prevention of pancreatic sepsis is, therefore, a fundamental goal to be achieved.

Early jejunal feeding reduces bacterial translocation from the gut in the pancreas, and thus reduces the occurrence of pancreatic sepsis (3). However, jejunal feeding is not always feasible (positioning an enteral tube is not easy in a critical patient with acute pancreatitis) and may be delayed by the presence of ileus. Diffusion of this therapy is thus still limited to a few centers (4). Antibiotic prophylaxis is easy and feasible everywhere. In addition, performing antibiotic prophylaxis does not exclude enteral feeding. Every effort should be made to optimize these two therapies. In the coming future, it is unlikely that new antibiotics with an adequate spectrum of activity will be introduced. It means that we have to learn to use in the best way what is today available. Defining the correct time to start antibiotic therapy is mandatory and was the aim of our study. Definition of the correct doses to be administered according to the extension of the pancreatic necrosis will be probably the next step.

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Osteoporosis and Inflammatory Bowel Disease

TO THE EDITOR: We read with interest the article of Kornbluth *et al.* (1). In their discussion, the authors concluded that fracture risk is directly related to bone mineral density (BMD) in inflammatory bowel diseases (IBD). We do not agree with their conclusion. In a study performed in 293 Crohn's disease (CD) patients, subjects with BMD T scores <-1 ($N = 156$) underwent thoracolumbar spine X-rays with combined visual and quantitative vertebral morphometry to identify compression fractures (2). Among them, 34 (22%) had 63 osteoporotic vertebral fractures, the vast majority of which (88%) were asymptomatic. Only 38% of the patients with vertebral fracture had spine BMD that was in the osteoporotic range (*i.e.*, T score < -2.5).

These data are consistent with a large prospective cohort study of postmenopausal women followed for 8.5 yr after baseline BMD measurements (3). In this study, only 25–39% and 21–28% of spine and hip fractures, respectively, were as a result of osteoporosis. In two large prospective population-based studies (4, 5), the authors demonstrated that homocysteinemia is a predictive factor for hip fracture independently of BMD. The mechanism underlying the association between homocysteinemia and fracture risk may involve homocysteine interference with collagen cross-linking (6). These data are of interest because hyperhomocysteinemia is very frequent in IBD patients. Indeed, we recently reported that hyperhomocysteinemia (>15 μmol/L) was observed in 59.7% of CD patients (7) and was a risk factor for osteoporosis (OR 61.4, 95% CI 23–250, $P < 0.001$) (8).

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Response to Dr. Roblin

TO THE EDITOR: We appreciate the comments regarding homocysteine and its possible role in bone loss in inflammatory bowel disease (IBD) made by Dr. Roblin and Bonaz.

However, they are mistaken in their reading of our Discussion section (1). We do not conclude that "fracture risk is directly related to bone mineral density in IBD." We state several times in our discussion that bone mineral density (BMD) is likely only one of several factors that contribute to fracture risk, and that other factors are likely involved, including, but not limited to, inflammatory cytokines. Clearly, additional research is required to determine risk factors for fracture in patients with IBD.

Asher Kornbluth, M.D.

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Palmar Lipid Deposits and Profound Hypercholesterolemia that Resolved After Orthotopic Liver Transplantation for Primary Biliary Cirrhosis

The report by Kóuletaki *et al.* was of considerable interest to us (1) because we have encountered two women with primary biliary cirrhosis (PBC) who demonstrated palmar lipid deposits associated with profound hypercholesterolemia. In both cases, these features resolved following orthotopic liver transplantation (OLT).

The first woman was diagnosed with PBC at age 44, and was referred to this center for consideration of liver transplantation the following month, October 1995. Her principal complaints were of fatigue, weight loss, and generalized pruritus. She had treated hypothyroidism. In addition to thyroxine, she took ursodeoxycholic acid (UDCA) in a daily dose of 15 mg/kg body weight and simvastatin 10 mg/day. Examination revealed jaundice, widespread scratch marks, and numerous lipid deposits on both palms, notably the palmar creases and adjacent digital web spaces. However, she did not have periorbital xanthelasmata, tendon xanthomata, or eruptive xanthomata. The median total serum cholesterol and low-density lipoprotein cholesterol (LDL-C) concentrations prior to OLT were 1,945 mg/dL (range 1,342–1,970) (normal <200) and 1,526 mg/dL (range 1,302–1,915) (normal <130). Her thyroid stimulating hormone (TSH) concentration was 4.73 IU/L (range 0.5–5.6). There was no proteinuria. She underwent OLT in October 1996; almost 10 years later, she has good graft function, but histological evidence consistent with recurrent PBC. Since OLT, the median total serum cholesterol concentration has been 213 mg/dL (range 174–787) (normal <200); however, the clinical manifestations of hypercholesterolemia have resolved completely.

The second patient was 42 yr old at the time of referral for liver transplant evaluation (August 2004) and had been diagnosed with PBC 8 yr previously. She also had Sjogren's syndrome, and the caloinosis, Raynand's phenomenon, esophageal involvement, sclerodactyly, telangectasiae variant of scleroderma. UDCA had been taken since diagnosis at a dose of 13 mg/kg body weight daily, but was suspended during a pregnancy (2000) and only restarted shortly before we met her. Physical examination revealed jaundice and scratch marks on the abdominal wall, but no hepatosplenomegaly or ascites. Multiple small, palpable lipid deposits were distributed widely on the palmar surfaces of her hands, the palmar creases, finger pulps, and in the web spaces. She had been given to understand these findings were a manifestation of CREST syndrome. No periorbital xanthelasmata, tendon, or eruptive xanthomata were evident. The total serum cholesterol concentration was 1,637 mg/dL (normal <200), the fasting triglyceride concentration was 359 (normal <150), and her LDL-C level was too great as to be estimated. Her TSH concentration was 1.48 IU/L (normal 0.5–5.6). There was no proteinuria. Treatment with atorvastatin, 20 mg/day, had no impact on her serum cholesterol concentration: 4 months later it was 2,084 mg/dL (normal <200). In May 2005, she underwent OLT and within 4 wk her total serum cholesterol concentration was 177 mg/dL (normal <200). It has remained normal since (median value 158 mg/dL, range 135–177), and exactly 12 months after OLT the deposits in her hands have resolved completely.

Both women had profound hypercholesterolemia presumed secondary to PBC, which resolved successfully after OLT. The clinical demonstration of hypercholesterolemia in their hands was neither typical (2) nor among the cutaneous manifestations of PBC documented by the authors (1). However, other investigators have described similar findings recently (xanthoma striatum palmare) (3, 4). It would have been interesting to know the median serum cholesterol concentration of those patients described by Kóuletaki and colleagues, especially those with dermatological manifestations of hyperlipidemia.

The predominant lipid component in PBC patients with profound hypercholesterolemia is lipoprotein-X, whose density falls within LDL-C range. (Neither of our patients had lipoprotein-X levels estimated.) By contrast, patients with familial hypercholesterolemia (FH) lack lipoprotein-X even though they have elevated LDL-C concentrations. This difference may account for the varying clinical patterns of lipid deposition and the different risk profiles for cardiovascular disease between patients with PBC (5) and FH, respectively (2).

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Response to Smith *et al*.

TO THE EDITOR: We very much appreciated the interest of Smith *et al*. to our paper. Within the spectrum of the dermatological lesions described in our primary biliary cirrhosis (PBC) patients, we found two with eruptive xanthomas and seven with xanthelasmas. None of the described PBC patients had any signs of palmar lipid deposits. As the authors of this letter mention, this type of xanthoma (xanthoma striatum palmare) has been previously described in PBC patients, but always associated with profound hypercholesterolemia. On the other hand, eruptive xanthomas and especially xanthelasmas occur in cholestasis even without associated lipoprotein elevations (1). Indeed, the median level of cholesterol in our patients without xanthomas or xanthelasmas was 222 mg/dL (range 107–299, normal <200) and low-density lipoprotein (LDL) was 130 mg/dL (range 57–207, normal <130), not significantly different from the nine patients with the xanthomatosis (cholesterol 237 mg/dL, range 136–382; LDL 169 mg/dL, range 87–316 mg/dL).

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Smoking and DNA Mismatch Repair Polymorphisms in Colorectal Polyps and Cancer

TO THE EDITOR: We read with interest the article by Yu *et al*., on mismatch repair (MMR) polymorphisms and colorectal polyps (1). It is not surprising that the authors failed to find significant association between MLH1 and MSH6 allele frequency and presence of adenomas. Mutation rates in MMR-defective colorectal cancer (CRC) are reported to be 100–1,000 times that seen in normal cells even in the absence of carcinogens (2). This leads to a greatly accelerated adenoma–carcinoma sequence, explaining the paucity of adenomas in such patients.

Although MMR status or high microsatellite instability (MSI-H) status is not currently used to direct therapy, as chemotherapy agents and prognostic data become more refined, they will become more significant in patients with CRC. This is because sporadic colorectal carcinomas with MSI-H are reported to have better prognosis and may not respond to 5-FU-based chemotherapies (3). The revised Bethesda guidelines is one tool currently used to select patients to test for MSI/MMR status (4). The guidelines include clinical and pathologic criteria, with sensitivity for detection of MSI-H of approximately 96%.

Smoking is reported to be associated with DNA MMR in patients with CRC and the authors report a specific genotype (hMLH1-93G > A) that may increase susceptibility to such damage. Further studies are recommended to ascertain if heavy smoking history should be used as a criterion to screen for MSI-H/MMR in individuals with CRC.

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Urinary Sodium/Potassium Ratio on Random Sample as a Useful Tool to Assess Diuretic-Induced Natriuresis on Chronic Liver Disease-Associated Ascitis

TO THE EDITOR: Ascites is associated with worse prognosis in cirrhotic patients, with a 50% mortality at 2 yr after initial diagnosis. With worsening sodium retention, refractory ascites appears (1), affecting up to 10% of inpatients and with a 50% mortality at 1 yr (2). Splanhnic arterial vasodilation reduces the glomerular filtration rate and increases sodium tubular retention (3–5). If all glomerular sodium is retained at the proximal tubule, ascites becomes refractory to diuretic therapy (6), thus explaining why urinary sodium excretion is a predictive factor assessing diuretic treatment response (7) and useful in the early diagnosis of refractory ascites (8). Thus urinary sodium is important to assess diuretic compliance and efficacy. Under a low sodium diet (88 mmol/d), a 24-h urinary sodium excretion above 78 mmol translates into a negative sodium balance.

We conducted a small prospective study to evaluate the accuracy of random sample urinary sodium/potassium ratio assessing diuretic-induced natriuresis.

Eighteen patients with chronic liver disease (CLD) admitted for ascites were selected. All gave written informed consent and the study was approved by the hospital ethic commission. CLD diagnosis was established based on clinical, imaging, or histology criteria. Patients with: a) diuretic contraindications (hepatic encephalopathy, serum Na <120 meq/L, serum creatinine >1.5 mg/dL), b) sediment urine abnormalities or proteinuria, and c) potential increase in extrarenal sodium losses (diarrhea or diaphoresis) were excluded. After at least 2 days on a low sodium diet and diuretic treatment (furosemide and spironolactone), urinary sodium and potassium were assessed on a random sample and a 24-h urine collection. Data are expressed as median and interquartile range. Spearman correlation was applied when appropriate. A P value of 0.05 was considered statistically significant.

Table 1. Study Population

N = 18		
Age (yr)	57.0 (45.0–71.3)	
CLD etiology	Alcohol	11
	HCV	4
	HCV + alcohol	1
	HCV + HBV + alcohol	1
	AIH	1
CTP score	10.0 (8.8–12.0)	
Na_{u24h} (mmol)	83.6 (31.3–180.2)	
Na_u/K_u (random sample)	2.1 (0.6–3.6)	

HCV = hepatitis C virus; HBV = hepatitis B virus; AIH = autoimmune hepatitis; CTP = Child-Turcotte Pugh; CLD = chronic liver disease.

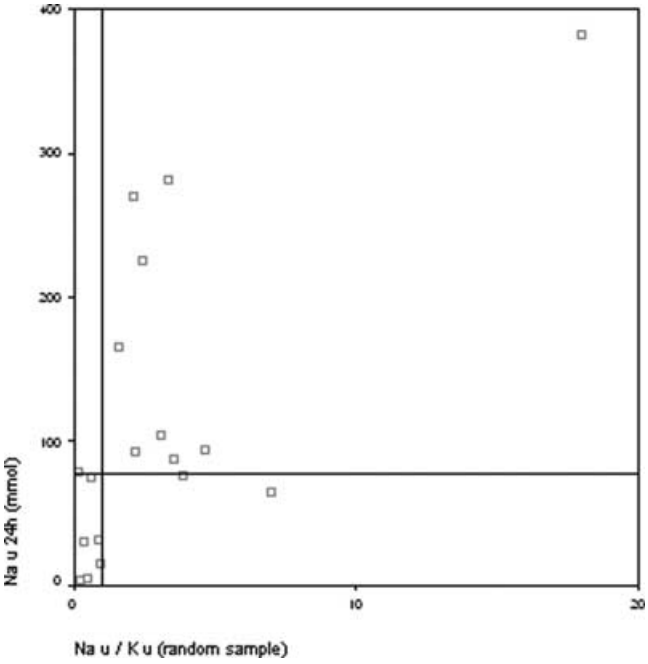

Figure 1. Correlation between 24-h urinary sodium (Na_{u24h}) and urinary sodium/potassium ratio (Na_u/K_u) on random sample.

The study population results are summarized in Table 1. For five patients, it was the first admission for ascites. On an outpatient basis, 10 patients were already compliant with a low sodium diet and 13 were under diuretic therapy. Overall, 10 patients (56%) had a 24-h urinary sodium (Na_{u24h}) $\geq$78 mmol. Na_{u24h} correlated with Na_u/K_u ratio on random urinary sample (r_s 0.58, $P = 0.013$; Fig. 1). Selecting patients with $Na_{u24h} \geq 78$ mmol, the ratio $Na_u/K_u \geq 1$ showed: sensitivity 0.9, specificity 0.75, likelihood ratio 3.6, positive predictive value 0.82, negative predictive value 0.86.

In this study, outpatient compliance to diuretic treatment was superior when compared to a low sodium diet. The Na_u/K_u ratio on random sample correlated well with the 24-h natriuresis, showing a good sensitivity to identify a negative sodium balance. We underline that, in one patient, a $Na_u/K_u > 1$ corresponded to an Na_{u24h} of 77 mmol (Fig. 1), decreasing the specificity and positive predictive value from 0.86 to 0.75 and 0.91 to 0.82, respectively. These values are similar to the only published study (abstract form), to the best of our knowledge, where $Na_u/K_u > 1$ had a positive predictive value of 0.95 to detect an $Na_{u24h} \geq 78$ mmol (9).

We conclude that measuring sodium and potassium on random urine samples is a useful tool assessing diuretic response in CLD-associated ascitic patients, being less cumbersome, faster, and less expensive when compared with a 24-h urine collection.

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Pitfalls of Cyst Fluid Findings Obtained by Endoscopic Ultrasonography Fine-Needle Aspiration on a Pancreatic Lymphoepithelial Cyst

TO THE EDITOR: Lymphoepithelial cysts (LEC) occurring in the pancreas are rare, true, and benign cysts, which are characterized histologically by a keratinizing squamous epithelium surrounded by lymphoid tissue and the presence of keratinous material in the cyst lumen. The lesion is separated from the pancreatic parenchyma by a thin capsule of fibrotic tissue. Although LEC is mostly diagnosed histologically by examining the pancreatic mass postoperatively, some cases can be diagnosed preoperatively by performing fine-needle aspiration (FNA). Computed tomographic (CT) scan- and endoscopic ultrasonography (EUS)-guided FNA can therefore be used as the first step in the diagnosis of pancreatic LEC (1–3). The most accurate approach available so far for the differential diagnosis of cystic lesions of the pancreas seems to consist of combining cyst fluid tumor marker levels and cytologic analysis (4, 5). However, the use of FNA has several limitations, which make it unsuitable for differentiating between the biological and cytological features of LEC and mucinous cystic neoplasms, in particular.

A 45-yr-old Caucasian woman was referred to our hospital for chronic hepatitis C evaluation. Physical examination was normal. Abdominal ultrasonography carried out before a liver biopsy showed the presence of a homogeneous hypoechoic mass in the pancreatic head without any septas, cyst wall irregularity, or intracystic solid regions. CT scan confirmed the ultrasonographic findings and showed the existence of a unilocular 3-cm thin-walled cyst in the head of the pancreas and a normal adjacent pancreas. EUS showed the presence of a hypoechoic macrocyst abutting the portal vein without any encasement or invasion, as well as a fine sludge-like hyperechoic material recalling a "starry sky" (Fig. 1). Analysis of cytologic cyst material on conventional smears obtained by EUS-FNA showed the presence of inflammatory cells consisting mainly of histiocytes and some columnar epithelial cells. Normal amylase and lipase levels were found in serum and cyst fluid, whereas high carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels were detected in the cyst fluid (413 ng/mL, 39,612 U/mL, respectively) but not in the serum. A laparotomy was subsequently performed owing to the existence of preoperative cytological and biochemical features of mucinous cystadenomas. A bisubcostal incision brought to light a well-circumscribed encapsulated cyst measuring 3 cm in diameter localized on the superior side of the pancreatic head. The decision to perform a simple cyst enucleation was made due to the location of the cyst. The postoperative course was uneventful. The enucleated cyst was single and well circumscribed. Histopathologic findings showed a cyst lined by a nonkeratinizing squamous epithelium, with the lumen containing an acellular substance and cholesterol clefts. A subepithelial rim of lymphoid tissue with some lymphoid follicles and no teratomatous elements strongly confirmed the diagnosis of LEC.

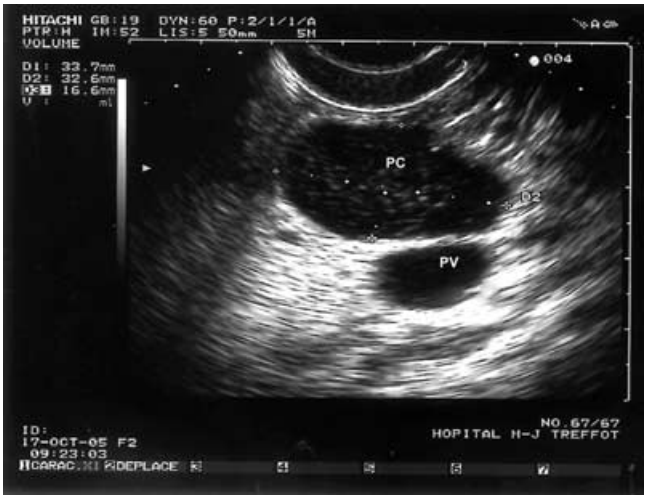

Figure 1. EUS: hypoechoic macrocyst with numerous granular hyperechoic areas above the portal vein. PC = pancreatic cyst; PV = portal vein.

LEC mainly affects middle-aged men, whereas mucinous cystadenomas are diagnosed almost exclusively in women during their 5th to 6th decade of life. Contrary to previous reports, this case confirms that LEC does not occur only in men. The usual location of LEC in the pancreas is equally distributed from head to tail (6). LEC are as often asymptomatic

and incidentally detected during US or CT imaging of the abdomen as symptomatic, in which case they frequently involve abdominal pain alone, of the pancreatic type or not (6). The lesion can be easily identified by performing US, CT, or MRI of the abdomen. However, there are no specific radiologic characteristics that can be used to strictly differentiate LEC from other cystic lesions of the pancreas such as mucinous cystic neoplasms, in particular (6). This is the main issue in the diagnosis of this lesion, because the prognosis and the treatment of these entities are different. Linear EUS-FNA can play an important preoperative role as a means of diagnosing the different kinds of pancreatic cysts by assessing cytologic features and tumor markers in the cyst fluid, and thus helps to decide whether surgery is required. However, preoperative diagnosis of LEC differentiating it from mucinous neoplastic cysts of the pancreas can be problematic for at least three reasons: (a) cytopathologic proof of LEC appears hard to achieve, because mucinous cystic neoplasms contain areas of denuded epithelium with sporadically distributed lining cells; (b) cytopathologic diagnosis often poses a dilemma, because the cytopathologic characteristics of LEC, especially the presence of squamous epithelial cells and/or keratinized material, can be absent from the cyst fluid; (c) material from the cystic lesion can be mistaken for mucinous glandular-type epithelium, because there is a risk of the aspirated fluid being contaminated by the needle when it crosses the gastric or upper duodenal wall. Nevertheless, the diagnosis o f LEC has sometimes been confirmed by EUS-FNA, as in two recent cases reported by Lui *et al*. and Zou *et al*., where cytological examination of cyst fluid showed the presence of keratinizing squamous epithelial cells and lymphocytes (2, 3). In one of these two cases, the cyst was not removed because of the presence of LEC cytological characteristics and the patient was doing well at the time the paper in question was written (3).

Because the diagnostic accuracy of EUS-FNA cytology has been variable in the case of pancreatic cystic lesions, many groups have attempted to look for tumoral markers in the aspirated cyst fluid. An increasing number of tumor markers are available, such as CEA, CA 19-9, carbohydrate antigen 72-4 (CA 72-4), and carbohydrate antigen 15-3 (CA 15-3) (5). Among these markers, the CEA level appears to have the greatest diagnostic value and may be the most useful means of discriminating between nonmucinous and mucinous lesions. A CEA level >400 ng/mL provides reasonably certain evidence that a lesion is mucinous (4, 5, 7), and the specificity of this test as a means of distinguishing mucinous cystic neoplasms from other pancreatic cystic lesions was found by Hammel *et al*. to be 100% (7). To the best of our knowledge, this is the first case of LEC in which both high CEA and CA 19-9 levels have been detected in material aspirated from a cystic pancreatic lesion by performing EUS-FNA. These results confirm those of previous studies, where only high CEA levels were recorded in aspirate from the cystic lesion (CEA value = ND) (8) or more commonly, where both high CEA (5,000 ng/mL (9), 26,880 ng/mL (1), 2,700 ng/mL, and 9,900 ng/mL (10)) and CA 19-9 levels were detected in the cyst aspirate obtained under radiological guidance (1, 9) or in resected specimens (10). As in this case, significant increases in the CEA and CA 19-9 values can both be misinterpreted, leading to a false diagnosis of mucinous tumor. We found no cases in the literature where normal cyst fluid CEA from LEC patients was detected.

In view of the benign evolution of this entity, the excellent outcome after a simple enucleation of the cyst, and the usefulness and pitfalls of the cyst fluid findings obtained after performing EUS-FNA, the following recommendations can be made: (a) when FNA firmly establishes the diagnosis of LEC based on cytological examination of the cyst fluid in an asymptomatic patient, surgery can be avoided and the patient can be followed u; (b) however, as reported in this case, the absence of LEC cytological proof does not rule out definitely an LEC diagnosis, even if high CEA and CA 19-9 levels are recorded in the cyst fluid.

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Pulmonary Aspiration of a Capsule Endoscope

Capsule endoscopy (CE) has become a significant tool in evaluating patients with obscure gastrointestinal bleeding, Crohn's disease, and other diseases of the gastrointestinal tract, such as the polyposis syndromes. We describe a patient who had a temporary aspiration of a video capsule into a bronchus and we discuss methods to prevent capsule aspiration and suggest ways to make an early diagnosis.

A 75-yr-old man with progressive anemia had normal upper intestinal endoscopy and colonoscopy and was referred for video capsule examination of the small intestine. He did not have any history of esophageal symptoms and the previously performed upper gastrointestinal endoscopy was performed without difficulty or complication. Because the patient did not have any symptoms of small bowel obstructive symptoms, upper gastrointestinal barium studies were not performed.

The patient was initially unable to swallow the Pillcam capsule (Given Imaging, Yoqneam, Israel), which was administered with water. He eventually "swallowed" the capsule but he developed a severe coughing episode and expectorated the capsule. Because of these difficulties, a gastroenterologist then placed the capsule into the small bowel at the time of an upper gastrointestinal endoscopy. When the capsule study was read, in addition to views of the GI tract, the images also revealed the right lower lobe bronchus confirming temporary aspiration of the capsule (Fig. 1).

CE is considered to be safe, but there have been reports of esophageal complications, such as a videocapsule impaction at the cricopharyngeus (1) or capsule aspiratation into the lung, with either spontaneous coughing up of the capsule without complication or (2, 3), in another case, where the capsule had to be removed at the time of bronchoscopy (4).

The patient we described is the only one in more than a thousand of our patients who have undergone CE where the capsule was aspirated into a bronchus. This low incidence of aspiration and esophageal complications may be attributed to our policy of placing the capsule into the duodenum at the time of an upper GI endoscopy in patients with esophageal dysmotility or strictures of the esophagus.

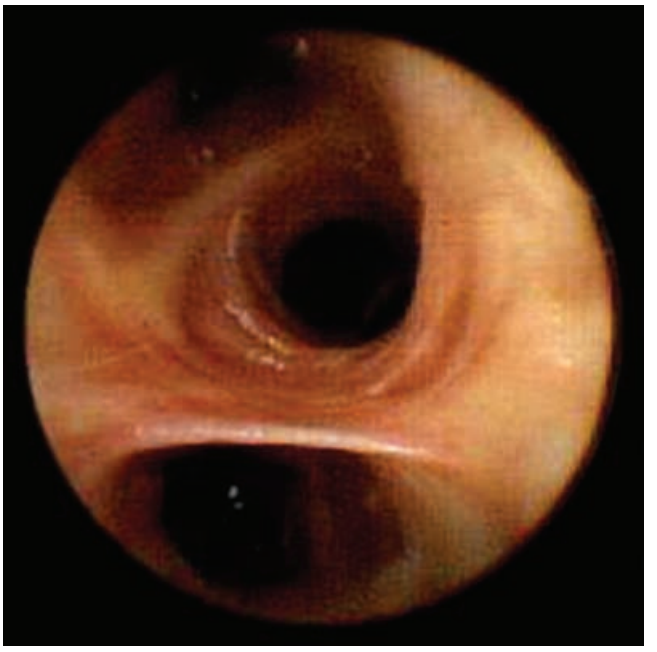

Figure 1. This image demonstrates that the capsule has been aspirated into the right lower lobe bronchus.

Leighton *et al*. (5, 6) have demonstrated that the video capsule studies appear to be safe in patients with pacemakers and defibrillators. However, if there is pulmonary aspiration of the capsule, there is some concern that a capsule lodged in the lung might have prolonged proximity to a pacemaker/defibrillator that might interfere with pacemaker or capsule function (7).

As more patients with pacemakers undergo video capsule studies, it is important that physicians become aware of the inherent risks of aspiration and its sequelae.

Our recommendations to help prevent capsule aspiration and to make an early diagnosis of this complication are as follows:

1. Patients with swallowing disorders should have the capsule placed into the duodenum at the time of upper endoscopy. The capsule should never be placed in the stomach because of prolonged emptying times following endoscopy and IV sedation.
2. If a patient appears to have difficulty swallowing the capsule after two or three attempts, the capsule should be placed endoscopically.
3. When real-time capsule location is more readily available, the abdomen can be scanned after the initial ingestion to be sure that capsule reached the stomach.

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HBsAg-Negative HBV Mutant Transfusion-Related Acute Hepatitis B

TO THE EDITOR: A 59-yr old man was referred from the hematology department for evaluation of recently elevated aminotransferases (AST = 416 IU/L, ALT = 758 IU/L). He was diagnosed to have a severe myelodysplastic syndrome of unspecified type according to WHO classification 1 yr ago and had been treated with erythropoietin 10,000 IU thrice weekly and cyclosporine 150 mg twice daily since then. He was also transfused regularly with a mean of two units of packed red blood cells per month. His past medical history included allergic rhinitis, bronchial asthma treated with inhaled bronchodilators, and arterial hypertension treated with atenolol. Physical examination was unremarkable except for palor. Laboratory tests showed: HBsAg negative, anti-HBs positive (33 IU/L), anti-HBc positive, IgM anti-HBc positive, anti-HDV negative, anti-HCV negative, anti-$HIV_{1,2}$ negative, total anti-HAV positive, IgM anti-HAV negative, IgM anti-CMV negative, IgM anti-EBV negative, IgM anti-HSV negative, autoantibodies negative, and thyroid hormones within normal range. Serum HBV DNA was detectable (34,700 copies/mL) by real-time polymerase chain reaction (PCR) assay (sensitivity: 250 copies/mL), while serum HCV RNA was undetectable by qualitative PCR (Cobas Amplicor, Roche Diagnostics, Basel, Switzerland sensitivity 50 IU/L). According to these findings, our differential diagnosis included HBsAg-negative acute hepatitis B or exacerbation of HBsAg-negative chronic hepatitis B in a patient under immunosuppression. The patient was then advised to discontinue the cyclosporine and start treatment with lamivudine (100 mg daily) remaining under close follow-up. His laboratory data during the following 4 months are shown in Figure 1.

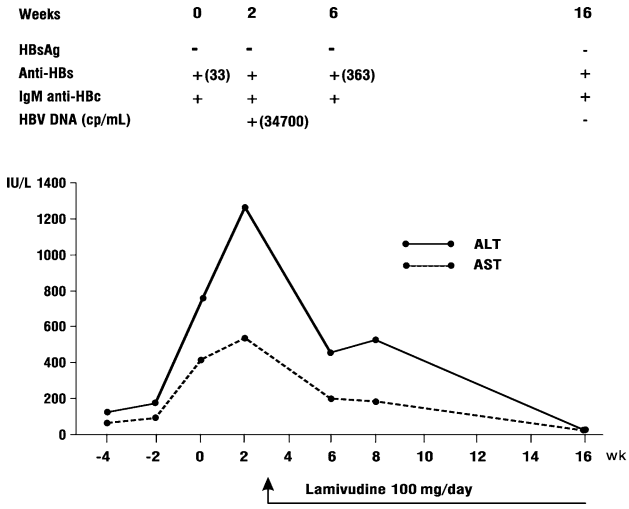

Figure 1. Changes of aminotransferases values (ALT: alanine, AST: aspartate aminotransferase), serological markers and serum HBV DNA levels (cp/mL:copies/milliliter) in a patient with acute hepatitis B caused by an HBsAg mutant hepatitis B virus strain.

Analysis of a serum sample stored at the diagnosis of myelodysplastic syndrome showed that the patient was negative for all HBV serological markers (HBsAg, anti-HBc, anti-HBs) and serum HBV DNA by PCR.

Thus, acute hepatitis B with negative HBsAg at diagnosis due to early clearance of HBsAg or due to infection with HBsAg-negative HBV mutant was considered to be the most plausible diagnosis. We therefore performed DNA sequencing in a sample during the acute hepatitis phase. Analysis of the surface antigen region (codons 1–226) revealed an amino acid replacement from Gly to Arg at codon 145 (G145R). Phylogenetic analysis showed that the sequence of the S region classified as genotype D.

Thus, our patient had acute hepatitis B caused by an HBsAg mutant HBV strain most probably transmitted from one of his multiple red blood cells transfusions. Since he was mostly transfused at a local transfusion center where samples from blood units are not usually stored, the confirmation of posttransfusion hepatitis was impossible. It should be noted, however, that undetectability of HBsAg is associated with presence of mutations within the "a" determinant affecting conformational epitope recognition or HBsAg secretion or expression, since immunoassays used for HBsAg serological detection employ capture antibodies with specificity for the epitopes of the antigenic "a" determinant of HBsAg (1). The most frequently identified mutation associated with serum HBsAg undetectability and immune escape is the G145R located at the second loop of the "a" determinant of HBsAg (2). Despite the loss of anti-HBs antibody recognition, the mutant epitope is still immunogenic and it seems to affect

secretion as well as stability of HBsAg leading to low levels of circulating virus (3). In Europe and North America, HBsAg escape mutations have been identified in small numbers of children born from HBV-infected mothers following postnatal HBV vaccination and hepatitis B immune globulin (HBIG) prophylaxis and in liver transplant recipients who develop HBV reinfection despite HBIG prophylaxis (4). The G145R escape mutant is a stable and transmissible strain that can cause chronic liver disease (5, 6) and could present a risk to blood safety. This case further supports the need for routine HBV nucleic acid testing on all blood products or the implementation of new generation assays capable of detecting additional HBsAg antigenic epitopes.

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Transient Type III Atrioventricular Block After Infliximab Infusion in a Fistulizing Perianal Crohn's Disease Patient

TO THE EDITOR: The safety and efficacy of infliximab, a chimeric monoclonal immunoglobulin antibody to tumor necrosis factor (TNF-α), has been established in a number of controlled trials for the treatment of moderate to severe active and fistulizing Crohn's disease (1), and more recently for active ulcerative colitis (2). The safety profile of infliximab is a timely issue because its use and indications are rapidly growing. Infliximab is generally well tolerated and adverse events are categorized as either acute or delayed. An adverse event that occurs during or within 24 h of an infliximab infusion is considered as an acute infusion reaction. These infliximab infusion acute reactions are observed in approximately 5% of infusions and most commonly include hypotension/hypertension, dyspnea, fever, chest pain, or urticarial rash (3–5). Infusion rate adjustments and treatment with antihistamines, steroids, acetaminophen, and/or epinephrine are usually of some efficacy (3).

We report the case of a transient atrioventricular block type III that occurred within 1 h of an infliximab infusion in a perianal fistulizing Crohn's disease patient.

A nonsmoking 25-yr-old woman with fistulizing perianal Crohn's disease presented for her sixth perfusion of infliximab (Remicade®, Schering Plough, Levallois-Perret, France) indicated as maintenance therapy. Her medical past was dominated by fistulizing perianal Crohn's disease considered as refractory due to iterative *fistula-in-ano* recurrence following surgical drainage with seton placement and immunosuppressive drug administration (azathioprine at a 2.5 mg/kg daily dosage). Except for an acute edematous pancreatitis related to 5-ASA intake, she had no other medical or surgical history, and especially no symptoms of dizziness or previous syncope and no family history of chronic cardiovascular disease. Her current medications included infliximab as maintenance therapy every 8 wk, azathioprine at a daily dosage of 125 mg/day, and ferrous sulphate 80 mg/day. The clinical exam on the day of her perfusion was normal with normal heart rate (72/min) and blood pressure (120/60 mmHg). The patient was considered as in remission with a Crohn's Disease Activity Index (CDAI) of 95 and no sign of recurrent perianal fistula. Prior to infliximab infusion, an acute reaction prophylaxis treatment was administered that included rapid IV administration of 5 mg dexchlorpheniramine followed by IV 200 mg hydrocortisone administered in a 100 mL glucose 5% vehicle over 1 h. The infliximab was then infused at a standard 5 mg/kg dosage over a 2-h period at an initially slow rate gradually increased. An emergency kit was readily available and the patient's signs and symptoms were monitored every 15 min throughout the infusion and every 30 min for 2 h after the end of infusion. Thirty minutes after the end of infusion, the patient developed dizziness and syncope, a heart rate of 38/min with a blood pressure of 100/70 mmHg was noticed. The ECG showed a third degree atrioventricular block (Fig. 1A). A rapid spontaneous recovery was observed a few minutes later with no pharmacological intervention. Figure 1B shows the postcritical ECG with normal sinusal pace. Cardiac enzymes as well as serum electrolyte levels were normal. The patient was discharged after a 12-h hospital rest and was evaluated by a cardiologist a few days later.

No clinical or baseline ECG abnormality was found and a 24-h rhythmic Holter monitor demonstrated no sign of rhythmic dysfunction.

Our patient was successfully reinfused at the regular dose without occurrence of infusion reaction. The first reinfusion was made with first an infliximab test dose (10 mL/h) given for 15 min. The rate was then increased and the infusion continued over 3 h (3). The infliximab treatment was continued and patient is doing well at follow-up without any other secondary side effects.

Various adverse effects have been reported with infliximab (4). The commonly reported cardiac side effects being exacerbation of congestive heart failure, hypotension, and syncope. Symptomatic disorders of cardiac rhythm associated with its use have been reported only rarely (6, 7). In these observations, the cardiac conduction block was considered as severe enough to interrupt definitely the infliximab infusion. Interactions between infliximab and heart function have been known for long and Kwon *et al*. examined spontaneous adverse reports to the U.S. Food and Drug Administration's (FDA) MedWatch system for evidence of TNF-α antagonist-related heart failure (8). Half of the patients with new onset heart failure had no identifiable heart failure risk factors. Withdrawal of TNF antagonists and administration of heart failure treatment indicated a causal connection. The reason why this TNF-α antagonism adversely affects the clinical status in heart failure is not clear (9). However, caution is required in heart failure patients before infliximab therapy induction (9). In our observation, no clinical sign to suspect cardiac dysfunction was observed and we can speculate that the transient heart block may have been related to a transient vagal hypertonia common after infliximab infusion (3).

Extragastrointestinal features of inflammatory bowel disease (IBD) are well recognized and affect many systems. Cardiac involvement has been described only rarely. If pericarditis is the most common manifestation, reports on heart block related to IBD are very uncommon and all have occurred in patients with ulcerative colitis (10). To our knowledge, no cases related to Crohn's disease are described, and subsequently, this may support the hypothesis of a disease-related event rather than a treatment side effect.

In conclusion, infliximab infusion may be associated with the development of heart block. In a patient with no pre-existing cardiac disability, even a transient complete heart block does not constitute an absolute indication for discontinuing infliximab therapy. However, we recommend caution in patients with concomitant heart disease, particularly those with a history of conduction abnormalities and advanced age.

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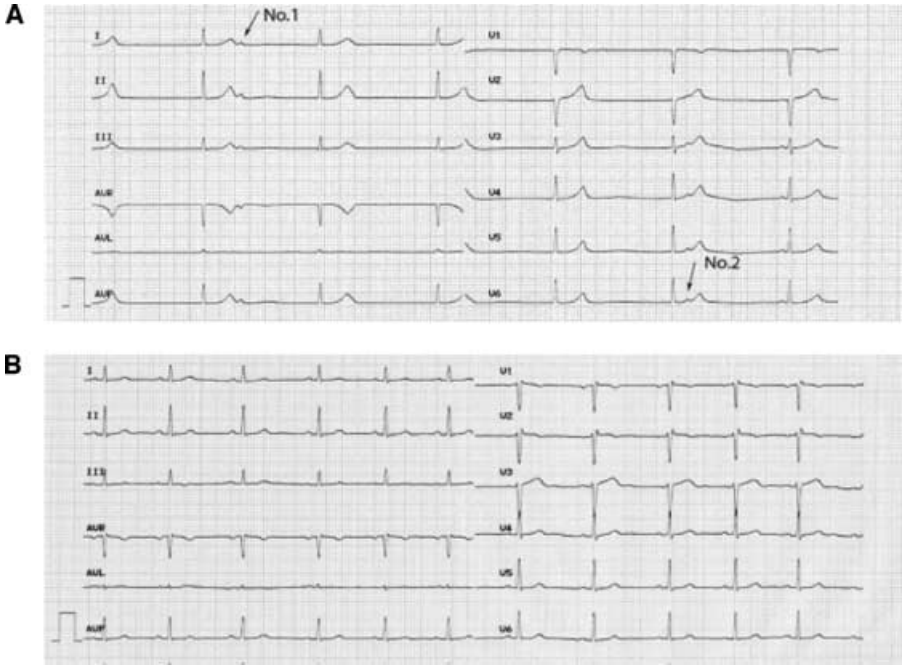

Figure 1. *(A)* ECG exhibiting complete atriventricular block. Arrows show dissociated P waves. *(B)* ECG after rhythm normalization.

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Bedside Examination of the Stomach Through PEG Catheters Using a Superthin, Battery-Powered Endoscope

TO THE EDITOR: There are many instances where a simple, quick, and safe examination of the stomach would be clinically useful. We show that a portable battery-powered fiberscope can be passed through the lumen of a percutaneous endoscopic gastrostomy (PEG) catheter and used to visualize the stomach. The instrument is a "superthin," battery-powered fiberoptic (nonvideo) endoscope (LF-DP, Olympus, Tokyo, Japan) initially designed to assist in endotracheal intubation. It is entirely self-contained and does not require an external light, air, or water source or a video processor (1). The field of view is 90 degrees. The outer diameter is 3.1 mm and the working length is 60 cm. The tip of the endoscope can be deflected 120 degrees up and down with right/left deflection being obtained by torquing the shaft. There is a 1.2 mm single channel through which air and water can be injected manually. No biopsy capability is currently available, but video capability is available. The light source consists of a halogen lamp located in a holder attached to the proximal end of the fiberoptic endoscope and powered by a lithium battery with a life span of approximately 60 minutes.

Case Report

An 86-yr-old woman with dysphagia due to cerebral infarction underwent PEG initial placement 7 months earlier. Because of catheter deterioration, PEG replacement was performed at her home using a PEG Ponsky replacement kit (20 F; Medicon, Osaka, Japan). After the replacement, the battery-powered endoscope was inserted into the stomach through the PEG catheter and air was insufflated using a hand-held air pump device, similar to those used with a sphygmomanometer. The bumper was seen to be properly placed (Fig. 1). Of interest, a gastric ulcer was also seen at the angulus of the stomach. The presence of the ulcer was subsequently confirmed by upper endoscopy.

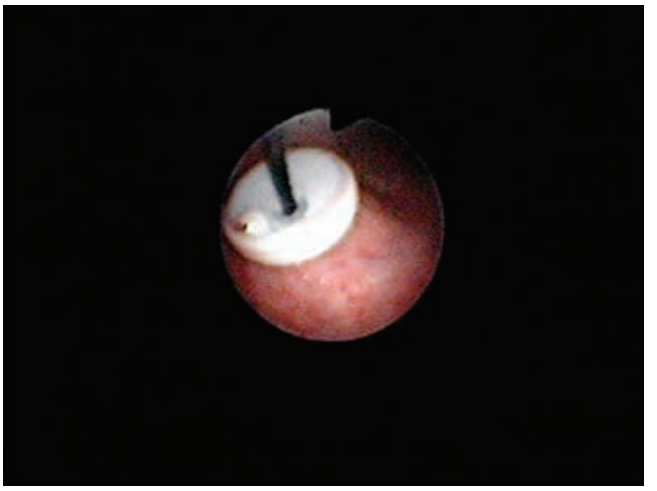

Figure 1. The endoscope used is a 3.1 mm diameter, 60 cm long, battery-powered fiberoptic endoscope (LF-DP, Olympus). The bumper was seen to be properly placed using the battery-powered endoscope through the PEG catheter.

Battery-powered endoscopy small diameter endoscopes have many potential uses. For example, they have been used for unsedated esophagoscopy (1). The fact that the instrument is portable and battery powered allows it to be potentially used whenever examination of the lumen of the gut is indicated and particularly when access is limited to a small diameter opening or when access to traditional fiberoptic equipment is limited. We explored a possible application (*i.e.*, bedside confirmation of proper PEG replacement). We also examined the stomach and discovered a gastric ulcer. We found that examination of the stomach following entry of the stomach through the lumen of a PEG tube was both possible and practical. The 60 cm length of the device would also allow examination of the distal esophagus and proximal duodenum if clinically indicated. We predict that this superslim portable endoscope will be very useful for solving clinical problems as it allows quick access to heretofore inaccessible sites. Its usefulness will only be limited by the imagination of endoscopists.

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Effective Steroid Pulse Therapy for the Biliary Stenosis Caused by Autoimmune Pancreatitis

TO THE EDITOR: Autoimmune pancreatitis (AIP) is a recently described unique form of chronic pancreatitis, characterized by sausage-like diffuse swelling of the pancreas, diffusely irregular narrowing of the main pancreatic duct, and a high serum IgG4 concentration (1–4). In addition, the presence of autoantibodies, increased levels of serum γ-globulin, lymphoplasmacytic infiltration with fibrosis, association with other autoimmune diseases, and effective oral steroid therapy support the notion that an autoimmune mechanism plays a major role in its pathogenesis (4, 5). Because oral steroid therapy requires a long period for the drug tapering (3–6), the biliary stenosis suspected to be caused by AIP but cannot be distinguished from malignancy is not indicated for the therapy. We report a case of bilioenteric anastomotic stenosis caused by AIP that was dramatically improved with steroid pulse therapy for a short period.

A 68-yr-old woman presented with general itching and jaundice. The diagnosis of hypothyroidism and retroperitoneal fibrosis had been made 10 yr earlier. She had also undergone biliojejunostomy for biliary stenosis caused by so-called mass-forming pancreatitis 6 yr earlier. Although serum γ-globulin and IgG levels were within normal limits, hepatobiliary enzymes and IgG4 (235 mg/dL) levels were elevated. Rheumatoid factor, antinuclear antibody, and anti-Sjögren's syndrome A and B antibodies were all negative. We re-evaluated imaging studies performed 6 yr ago, which disclosed swelling of the pancreas head, irregular narrowing of the main pancreatic duct, and smooth stenosis of the lower bile duct. Biopsy specimens of the pancreas at previous surgery also disclosed marked fibrosis with marked infiltration of lymphocytes and IgG4-positive plasma cells around the pancreatic duct branches. On imaging studies at the present admission, irregular narrowing of the main pancreatic duct and smooth stenosis of the lower bile duct remained, and the bilioenteric anastomotic stenosis accompanied by marked dilatation of the intrahepatic bile duct (Fig. 1) was disclosed.

Because of a high serum IgG4 level and previous and/or present imaging and histologic studies, the anastomotic stenosis was suspected to be caused by AIP, but could not be distinguished from malignancy. We also planned surgical treatment for the jaundice patient, and oral steroid therapy is not indicated because of requirement of a long period for the drug tapering. We therefore treated her with weekly 2 courses of steroid pulse therapy (500 mg/day methyl-prednisolone for 3 days). Because she had a weak constitution (154 cm, 47 kg), the drug dosage was reduced. Two weeks later, the intrahepatic bile duct dilatation improved dramatically, and serum hepatobiliary enzyme levels were normalized. Oral prednisolone was prescribed at 20 mg/day as a maintenance treatment, and was gradually reduced. She has remained asymptomatic without elevations of hepatobiliary enzymes or biliary stenosis.

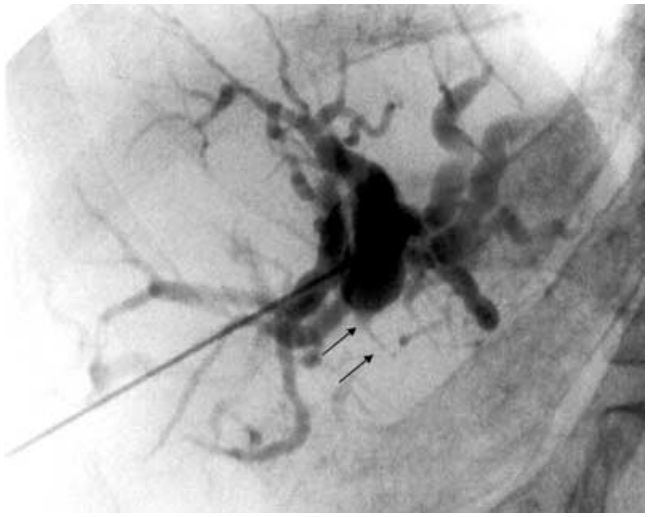

Figure 1. Percutaneous transhepatic cholangiography shows the tapered smooth stenosis of the bilioenteric anastomosis (*arrows*) and marked dilatation of the intrahepatic bile duct. The jejunum is not visualized through the stenosis.

The dramatic response to oral steroid therapy is a well-known phenomenon in AIP. Prednisolone is usually initiated at 30–40 mg/day for 2–4 wk, and tapered by 5 mg every 2–4 wk. Some recommend a maintenance dose of 2.5–5.0 mg/day of prednisolone to prevent relapses without complete discontinuation of steroid (4, 6–9). Obstructive jaundice and/or cholestatic liver dysfunction are sometimes associated with AIP caused by an external biliary stenosis in the swollen pancreas (9). Biliary stents are usually inserted in addition to oral steroid therapy (7). In most patients with AIP, oral steroid therapy is effective for the biliary stenosis as well as the diffuse pancreas swelling and irregular pancreatic duct narrowing (2–4, 6–10). In unresponsive patients with biliary stenosis, surgery is often necessary not only for the relief of symptoms but also for differentiation from malignancy (4, 6, 11).

In our patient, the biliary stenosis was suspected to be caused by AIP, but could not be distinguished from malignancy. Oral steroid therapy was not indicated because of the requirement of a long period for the drug tapering. In case of malignant stenosis, delayed surgery after the drug tapering indicates disease advancement. Steroid pulse therapy is a well-recognized alternative for refractory autoimmune disorders without steroid tapering (12). We therefore applied steroid pulse therapy in the patient, resulting in dramatic resolution

of the stenosis for a short period. When oral steroid therapy is not indicated because of the requirement of a long period for the drug tapering, steroid pulse therapy should be considered, and thereby may prevent unnecessary surgery.

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