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INSIDE

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Why UTIs Are Different from URIs

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips is a consultant to Cephalon and Ventus and serves on the speakers bureaus of Cephalon and Boehringer Ingelheim.

Synopsis: *For women with suspected urinary tract infection, there is no advantage to routinely sending midstream urine samples for testing; antibiotics based on dipstick tests with a delayed prescription as backup, or empirical delayed prescription, can help to reduce antibiotic use.*

Source: Little P, et al. Effectiveness of five different approaches in management of urinary tract infection: Randomised controlled trial. *BMJ* 2010;340:c199.

THIS STUDY ORIGINATED IN PRIMARY CARE PRACTICES IN SOUTHERN England. The authors were interested in comparing the effectiveness of different management strategies for suspected urinary tract infection (UTI). Specifically, they wanted to compare using dipstick or clinical algorithms with empirical antibiotic treatment, delayed prescribing, and targeted prescribing based on midstream urine culture results. They hypothesized that management strategies that delayed antibiotic prescription (while waiting for the results of midstream urine analysis) would have less favorable outcomes compared with an immediate antibiotic prescription.

To study this issue, general practitioners and nurses recruited women with a suspected uncomplicated urinary tract infection from clinical practices. They excluded those for whom an immediate antibiotic treatment was necessary (e.g., those who were pregnant, had pyelonephritis, nausea, vomiting, or other severe systemic symptoms), those who were older than age 75, had psychosis or dementia, or needed terminal care.

Patients were randomized to one of five basic management groups: immediate antibiotics; delayed antibiotics; symptom score

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(antibiotics offered if two or more of: urine cloudy on examination, urine offensive smell on examination, patient's report of moderately severe dysuria, or patient's report of nocturia); dipstick (antibiotics offered if nitrites or leucocytes and a trace of blood were detected); or midstream urine (symptomatic treatment until microbiology results available and then antibiotics targeted according to results). Self-help advice (regarding fluids, and the use of fruit juices, bicarbonate) was given to those who were not randomized to immediate antibiotics.

This protocol did allow for deviation from randomization based on patient expectations; clinicians were allowed to provide immediate antibiotics or to withhold them pending dipstick or midstream urine in situations where there were strong patient expectations. After analysis, the authors concluded that "subversion of protocol had probably not occurred."

The clinicians recorded clinical information and asked the patients to keep symptom diaries about dysuria, hematuria, frequency, "smelly urine," "tummy pain," generally feeling unwell, and restriction of daily activities. They were asked to grade the severity of symptoms as follows: 0 (no symptoms), 1 (a very slight problem), 2 (a slight problem), 3 (a moderately bad problem), 4 (a bad problem), 5 (a very bad problem), or 6 (as bad as it could be). Patients were also queried about belief in the effectiveness of antibiotics, medically unexplained somatic symptoms, and other medical problems. Patients mailed the questionnaires back when they were complete.

The investigators recruited 309 women between the ages of 18 and 70. The average duration of symptoms rated as moderately bad or worse with immediate antibiotics was 3.5 days.

Those women who delayed antibiotics for 48 hours or more, however, were likely to have 37% longer duration of symptoms rated as moderately bad, although there were no significant differences overall in symptom duration, severity of frequency symptoms, or severity of unwell symptoms between the antibiotic management strategies. Women delayed antibiotics longer in the midstream urine and the delayed groups (the average day starting antibiotics was 1.19 for immediate antibiotics, 2.18 for midstream urine, 1.43 for dipstick testing, 1.40 for symptom score, and 2.21 for delayed antibiotics). There were differences in antibiotic use (immediate antibiotics 97%, midstream urine 81%, dipstick 80%, symptom score 90%, delayed antibiotics 77%).

Of women in the midstream urine group, 66% (36/54) had a confirmed urinary tract infection. Women had similar beliefs in the effectiveness of antibiotics. There was little difference between groups for further contacts recorded in the 4 weeks after consent. Over an average follow-up of 575 days, there was no overall difference in time to reconsultation, but patients who waited for at least 48 hours before using their prescription reconsulted less. No differences in skin rash or thrush were reported. The authors estimate that modest reduction in antibiotic use (20%-25%) was achieved in all groups except the symptom score group.

The authors concluded that all five management strategies achieved similar symptom control, and that antibiotics targeted with dipstick tests with a delayed prescription as backup, or empirical delayed prescription, can help to reduce antibiotic use. They concluded that there is no advantage in routinely sending midstream urine samples for testing.

■ COMMENTARY

Urinary tract infections in women are a prevalent problem in primary care, probably affecting about half of women at least once in their lives.[1] Urinary tract infection is distressing, and although antibiotics probably help symptoms, there is debate about whether an immediate antibiotic prescription is necessary. The authors point out that management of UTI is quite different from management of upper respiratory tract infection (URI); few URIs are bacterial whereas most suspected urinary tract infections are.[2]

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This is the first trial comparing the commonly used management strategies of empirical delayed prescribing, targeting by dipstick, targeting by symptom pattern, or waiting for the midstream urine result, and it demonstrates that all management strategies achieve similar symptom control, so there is no advantage to routinely sending midstream urine samples for testing. In addition to expediting treatment of UTI, bypassing this approach could result in reduced use of laboratory resources. ■

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A Persistent Pain in the Chest

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD, MA

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Dr. Wilke reports no financial relationship to this field of study.

Synopsis: *Nonspecific chest pain is a persistent illness and patients with it are subject to overly extensive work-ups.*

Source: Glombiewski JA, et al. The course of nonspecific chest pain in primary care: Symptom persistence and health care usage. *Arch Intern Med* 2010;170:251-255.

PATIENTS PRESENTING WITH CHEST PAIN IN PRIMARY care offices pose a dilemma. If the pain is acute, the course of action is clear: Give the patient an aspirin and a sublingual nitroglycerin and call 911. When it is obviously not an acute myocardial infarction, the decision-making becomes murkier. These investigators from Germany set out to answer three questions: 1) How many patients with nonspecific chest pain, presenting to a primary care physician, will be symptomatic 6 months hence? 2) How many of these patients are "over-investigated"? 3) How many of these patients receive mental health referrals? They went to 209 general practitioners (GPs) to ask if they would participate in the study; 74 agreed. Of 190,000 adults, these GPs recruited 1355, age 35 or older, who had a complaint of chest pain. The age cutoff was chosen to increase the probability that at least some of these cases would eventually be determined to be cardiac in origin. If the pain had resolved more than a month before presentation, if it had previously been investigated, or if the visit was for follow-up of chest pain, the patient was excluded. The patients underwent a standardized history and physical and were followed prospectively. The GPs chose treatment and referral. At 6 weeks and 6 months, the patients were called and asked, "Do you have chest pain at present?" At 6 months, each patient's record was reviewed by a panel made up of a cardiologist, a GP, and one of the investigators to sort the patients into three groups: those who needed immediate hospitalization, those with coronary heart disease (CHD) not requiring hospitalization, and those with a non-CHD diagnosis not requiring hospitalization. This third group included patients with diagnoses such as chest wall syndrome, gastroesophageal reflux disease, benign stomach problems, and neck or shoulder disorders. The third group's diagnoses were further subdivided into psychologically caused nonspecific chest pain (NSCP) and potentially somatically caused NSCP.

After proper exclusion (patients not meeting inclusion criteria, refusal, lack of follow-up, etc.), 1212 patients remained. Four hundred five (405) patients were adjudicated to have unambiguous medical diagnoses, 692 had probably somatically caused NSCP, and 115 had psychologically caused NSCP. The researchers focused on the last two groups (807 patients in total). The average age was 58 years, and there was a female predominance (60%). At 6 months, of the 755 patients who had data available, 419 (55%) still complained of chest pain. Women were more likely to be persistently symptomatic (odds ratio [OR], 1.35; 95% confidence interval [CI], 1.08-1.81). There was no age predilection. Patients with psychologically caused NSCP were more likely to report pain at 6 months than patients with probably somatically caused NSCP (OR, 1.19; 95% CI, 0.79-1.79). This finding was not statistically significant.

To these researchers, "over-investigation" of NSCP meant 1 visit to a cardiologist or 2 cardiac diagnostic investigations (ECG, angiography, echocardiography, chest X-ray, etc.) in the 6 months after the initial visit. Sixty (14%) of the 419 patients saw a cardiologist at least once and 161 (38%) had at least one cardiac test. Forty-five (11%) patients met their definition for over-investigation. These patients were more likely to receive

a diagnosis of psychologically caused NSCP than patients appropriately referred to cardiac and imaging services (OR, 2.2; 95% CI, 1.07-4.53).

Of course, cardiologists are not the only specialists to whom a GP could refer a NSCP patient. In this study, 219 of 419 (52%) patients were referred to a medical specialist. Referrals were counted even if the patients did not make the appointments. Only 6 visits were to a psychiatrist or a psychologist. Cardiologists were visited twice as often by patients with psychologically caused NSCP than were patients with potentially somatically caused NSCP (OR, 2.15; 95% CI, 1.01-4.15). This was just barely statistically significant.

■ COMMENTARY

This study has several strengths. The numbers were large and there was little dropout. It studied patients in primary care settings that are probably similar to the ones that we practice in, and it followed them long enough for any cardiac disease to manifest. It has some limitations. Were these German patients demographically similar to ours? Were the patients in the practices that declined to participate different than the ones here? Are patients who do not present to GP offices with chest pain different from the ones that do? (The authors point out that there is far less use of emergency departments in Germany than in the United States.) Was the chest pain that the patients reported at 6 months the same they presented with? The article did not contain all of the data in tables, so the odds ratios could not be confirmed.

One interpretation of the over-investigation of patients with psychologically caused NSCP is that they needed a more thorough investigation before the physicians could make that diagnosis. Perhaps the patients themselves were not accepting of a psychological diagnosis and demanded these investigations. The "elephant in the middle of the room" is the question of why there was such an imbalance between "medical" referrals and "mental health" referrals. The study recorded referrals whether the patients showed or not. Did the GPs not recognize that the NSCP could have a psychological basis? Did they doubt that their patients would benefit from a psychological evaluation/intervention? The evidence for the effectiveness of psychological intervention in NSCP is mixed at best,[1-4] but because of the prolonged nature of the problem, for our patients' sake, we should give it the benefit of the doubt. Unlike in the United States, it was not out of concern that their patients couldn't afford the visit: Germany has universal health care. ■

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There Really Is No Safe Level of Smoke Exposure

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips is a consultant to Cephalon and Ventus and serves on the speakers bureaus of Cephalon and Boehringer Ingelheim.

Synopsis: *Even in people who had never smoked cigarettes, pipe and cigar smoking was associated with decreased lung function and increased odds of airflow obstruction.*

Source: Rodriguez J, et al. The association of pipe and cigar use with cotinine levels, lung function, and airflow obstruction: A cross-sectional study. *Ann Intern Med* 2010;152:201-210.

As cigarette smoking has decreased (from a prevalence of 33% in 1983 to 19.8% in 2007), pipe and cigar smoking have substantially increased in the United States in recent years. These authors set out to determine whether pipe and cigar smoking results in biological absorption of tobacco smoke, and to test the hypotheses that pipe smoking or cigar smoking is associated with impaired pulmonary function. To accomplish this, they did a secondary analysis of the MESA (Multi-Ethnic Study of Atherosclerosis) cohort.

In brief, MESA is a longitudinal study of more than 6000 men and women aged 45-84 years from 6 U.S. communities.[1] People excluded from participation in MESA included those with clinical cardiovascular dis-

ease, body weight > 300 lbs, pregnancy, or impediment to long-term participation.

MESA participants underwent extensive assessment of a variety of lifestyle and medical factors, including age, sex, race or ethnicity, educational attainment, medical history, occupational exposure to dust, fumes, or smoke, environmental tobacco smoke exposure, and family history of emphysema. They also underwent extensive baseline testing of cardiovascular risk factors. Along the way, they had pulmonary function testing, had urinary cotinine measured, and were queried about smoking behaviors. Smoking was assessed by means of the American Thoracic Society questionnaire.[2] Pack-years of cigarette smoking were calculated in a standard way. For pipe smoking, participants were first asked, "Have you smoked at least 20 pipe-bowls in your lifetime?" If they answered "yes," additional questions included, "How old were you when you first started smoking pipes?" "On average, about how many pipe-bowls a day do/did you smoke?" "Have you smoked a pipe within the last 30 days?" and, if relevant, "How old were you when you quit smoking?" "Cigar-years" were calculated as the self-reported age of starting to the age of quitting (or current age if participants still smoked) multiplied by the number of cigars per day.

After elimination of data from those who had exclusion criteria or who had restrictive lung disease, the authors had 3528 participants whose data could be used to perform the analysis. Their mean age was 66 years, 49% were male, 35% were non-Hispanic white, 26% were African American, 22% were Hispanic, and 17% were Chinese American. Nine percent reported ever smoking pipes, but most of these had quit. Eleven percent reported ever smoking cigars, and about one-fifth of these was still smoking cigars at the time of analysis. Fifty-two percent reported ever smoking cigarettes, and 9% were current cigarette smokers. Of 484 participants with a history of pipe or cigar smoking, 88% also reported a history of cigarette smoking. Participants with a history of pipe or cigar smoking were more likely to be male, to be white or African American, and to have higher educational attainment.

The odds ratio for airflow obstruction was approximately doubled among participants who smoked pipes or cigars only compared with never-smokers, but was even greater among participants who smoked pipes or cigars in addition to cigarettes. The reduction in pulmonary function was modest and not statistically significant in the 56 participants who smoked pipes or cigars only, but (as expected) was greater and statistically significant in the much larger group who smoked cigarettes only, and was greatest of all in those who smoked pipes or cigars in addition to cigarettes.

In the entire sample, the number of pipe-years of smoking was inversely associated with FEV1. When the analysis was restricted to those who had smoked pipes but who had never smoked cigarettes, effect estimates were of larger magnitude, but were no longer statistically significant. The decrease in lung function from pipe smoking was much larger in pipe smokers who smoked heavily (most of whom were white and male). The mean FEV1 in the 64 participants with 50 or more pipe-years was 154 mL lower than that of participants who had never smoked pipes, and the mean FEV1:FVC ratio was 2.1 percentage points lower ($P = 0.039$). With regard to cigar smoking, more cigar-years were associated with greater decreases in FEV1 and FEV1:FVC ratio, and increased odds ratio for airflow obstruction. As expected, the number of cigarette pack-years was inversely associated with FEV1 in the entire sample in fully adjusted models. Cotinine levels were less than 10 ng/mL in never-smokers, 43 ng/mL in current cigar smokers, 1324 ng/mL in current pipe smokers, and 4304 ng/mL in current cigarette smokers.

The authors concluded, "Pipe and cigar smoking increased urine cotinine levels and was associated with decreased lung function and increased odds of airflow obstruction, even in participants who had never smoked cigarettes."

■ COMMENTARY

Significant progress has been made in reduction of cigarette smoking in the United States. This change has been the result of much effort by many people, and has resulted from a combination of education, fiscal policy (e.g., increased excise taxes), and advocacy. Unfortunately, other kinds of tobacco use have actually increased during the same time period. Smoking of all types of cigars increased by nearly 50% from 1993 to 1997, and pipe and cigar tobacco smoking increased by 28% and 8%, respectively, from 2002 to 2006. In 2006, the prevalence of pipe and cigar smoking in the United States was 1% and 6%, respectively.[3,4]

The health effects of both active and passive cigarette smoking are well known. Cigarette smoking is the main cause of COPD and lung cancer, and is the fourth leading cause of death in the United States.[5] Much less is known about the health effects of pipe and cigar smoking. Two large cohort studies have suggested that pipe and cigar smoking are associated with an increased risk of hospitalization and death,[6,7] but these studies had methodologic problems. The current report is the first U.S. study to investigate the possible effects of cumulative pipe and cigar smoking on lung function. And the

new isn't good. The evidence presented here indicates that the use of these forms of tobacco increases the risk of obstructive airway disease, and there is measurable absorption of nicotine in pipe and cigar smokers. Smoking is just not good for you. ■

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Pharmacology Update

Dalfampridine Extended Release Tables (Ampyra™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

THE FDA HAS APPROVED A POTASSIUM CHANNEL BLOCKER to improve walking in adults with multiple sclerosis. Dalfampridine was originally used as a bird poison and was previously known as fampridine. It has been used in a compounded formulation since the 1980s. It is marketed by Acorda Therapeutics as Ampyra™.

Indications

Dalfampridine is indicated for improving the walking ability (increase in walking speed) in patients with multiple sclerosis.[1]

Dosage

The recommended dose is 10 mg twice daily (roughly 12 hours apart). It may be taken with or without food.[1]

Dalfampridine is available as 10 mg tablets.

Potential Advantages

Dalfampridine produced a 25% improvement in walking speed compared to 5% for placebo.[1,2]

Potential Disadvantages

Dalfampridine can cause seizures and this effect is dose-dependent.[1] The drug is contraindicated in patients with moderate-to-severe renal impairment. The most common adverse events are urinary tract infection, insomnia, dizziness, headache, nausea, back pain, and balance disorder.

Comments

Dalfampridine is a potassium channel blocker and is reported to restore conduction of action potential in some demyelinated nerve fibers.[3] Its effectiveness was evaluated in two randomized, placebo-controlled trials in multiple sclerosis patients with a mean duration of disease of 13 years and a mean Kurtzke Expanded Disability Status Scale (EDSS) score of 6.1 Potential subjects with a history of seizures or EEG evidence of epileptiform activity were excluded. The study designs differed slightly. Study 1 (n = 296) was a 14-week, double-blind protocol with a 4-week no-treatment follow-up after single-blind placebo run-in.[2] Study 2 (n = 237) had 9 weeks of double-blind treatment and 2 weeks of no-treatment follow-up. Study participants were randomized to dalfampridine (10 mg twice daily) or placebo. The primary endpoint was walking speed as measured by the Timed 25-foot Walk (T25W). A responder was defined as a patient with a faster walking speed for at least 3 of the 4 visits during the double-blind treatment period than the maximum speed for any of the first 5 off-drug visits (4 before the treatment and one 2 weeks into the follow-up period). Response rates were 34.8% for dalfampridine vs 3% for placebo in study 1 and 42.9% vs 9.3% in study 2. The average improvement in walk-

ing speed was about 25% vs 4.7% (or 0.51 feet/sec vs 0.1 feet/sec) and was maintained during the 14-week treatment period.[2] Timed walk responders showed a reduced self-assessed ambulation-related disability compared to non-responders independent of whether they were randomized to dalfampridine or placebo.[2] The most frequent adverse events were insomnia, fatigue, back pain, and balance disorders. The discontinuation rate was 5% for dalfampridine and 4% for placebo.[2]

Clinical Implications

Dalfampridine is the first drug of its kind for patients with multiple sclerosis. A large proportion of patients with multiple sclerosis has difficulty walking. However, the benefit of the drug is modest (additional 0.4 feet/sec over a 25-foot walk compared to placebo) and only about one-third of patients are considered responders. There is no evidence that dalfampridine affects the progression of multiple sclerosis. Only some MS patients would be expected to benefit from the mechanism of dalfampridine.[2] ■

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CME Questions

11. Which of the following is *true* concerning management of urinary tract infections (UTIs)?
a. Unlike respiratory tract infections, UTIs are rarely bacterial.
b. Use of antibiotics based on symptom score results in increased reconsultation.
c. Symptom duration is longer if antibiotic treatment is delayed.
d. This is an uncommon clinical problem.

12. In the study of nonspecific chest pain, which of the following was *not* true?
a. Women were more likely than men to have pain at 6 months.
b. Younger women have less persistent nonspecific chest pain than older women.
c. More than half of the patients had chest pain at 6 months.
d. Patients with nonspecific chest pain were rarely referred to mental health specialists.

13. With regard to pipe and cigar smoking and pulmonary function:
a. Pipe smoking affects the risk of airflow obstruction, but cigar smoking does not.
b. Urinary cotinine levels are not elevated in pipe and cigar smokers, indicating that these smoking techniques do not result in much nicotine absorption.
c. Pipe and cigar smoking increase the odds of measurable airflow obstruction.
d. Most pipe and cigar smokers do not also smoke cigarettes.

Answers: 11. c, 12. b, 13. c.

CME Objectives

Upon completion of this educational activity, participants should be able to:
- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
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Kidney function, proteinuria, and adverse outcomes

Source: Hemmelgarn BR, et al. Relations between kidney function, proteinuria, and adverse outcomes. *JAMA* 2010;303:423-429.

STAGING OF CHRONIC KIDNEY DISEASE (CKD) is based primarily upon estimated GFR. Proteinuria (PRO) is a strong marker for kidney disease, yet its severity is not included in current risk stratification schemes, which are instead driven by GFR. Indeed, the majority (75%) of proteinuric patients do not have a GFR < 60 mg/min. Intuitively, since either PRO or stage of CKD predicts risk, the combination of the two might be an even better risk predictor.

To study the relationship of CKD, PRO, or the combination with outcomes, data from 920,985 Canadian adults were analyzed. Persons with end-stage renal disease at study inception were excluded.

Over 35 months of follow-up, for each decrement in GFR, all-cause mortality, MI, and end-stage renal disease increased. Within each quartile of GFR, progressively increasing levels of proteinuria (normal, mild, heavy) were associated with increased risk. Persons with the very lowest GFR (i.e., most advanced kidney disease), however, experienced less relative impact per degree of proteinuria; in other words, adverse outcomes are more compounded by proteinuria in CKD 2-4 than by CKD 5.

The recent adoption of a standardized staging system for CKD is a major step forward. These data suggest that future stratification methods would benefit from inclusion of proteinuria as well as GFR. ■

Inhaled corticosteroids and COPD exacerbations

Source: Agarwal R, et al. Inhaled corticosteroids vs placebo for preventing COPD exacerbations: A systematic review and metaregression of randomized controlled trials. *Chest* 2010; 137:318-325.

ACUTE EXACERBATIONS OF COPD (AE-COPD) are costly to patients. Not only is the symptomatic deterioration and commonplace requirement for hospitalization burdensome, but an AE-COPD is typically followed by loss of pulmonary function that does not return. Additionally, mortality from hospitalized AE-COPD has been reported to be as high as 10%.

We have no known disease-modifying pharmacotherapy for COPD. Although symptom improvement is considerable from bronchodilators and inhaled corticosteroids (ICS), they do not change disease progression. Short of that outcome, reduction in AE-COPD is a worthy goal to seek.

Agarwal et al reviewed data from 11 placebo-controlled COPD trials (n = 8164) employing ICS to examine the impact upon AE-COPD. Overall, ICS use was associated with an 18% relative risk reduction in AE-COPD; this beneficial effect was driven primarily by persons with an FEV1 < 50%.

Recent meta-analyses have shown an increased risk of pneumonia in COPD patients receiving ICS. Because the risk reduction for AE-COPD is modest, careful consideration to the risk-benefit balance of ICS use is appropriate. ■

Non-alcoholic fatty liver disease in Japanese patients

Source: Hamaguchi E, et al. Histological course of nonalcoholic fatty liver disease in Japanese patients. Tight glycemic control, rather than weight reduction, ameliorates liver fibrosis. *Diabetes Care* 2010;33:284-286.

IN THE UNITED STATES, DIABETES AND metabolic syndrome are the disorders most commonly associated with nonalcoholic fatty liver diseases (NAFLD). Because obesity, dyslipidemia, hypertension, and insulin resistance are typical operative components of these disorders, it is difficult to make a clear attribution about which is the primary culprit leading to NAFLD.

Japanese subjects do not demonstrate the same degree of obesity as Americans. Study of NAFLD in this population might provide insight about the primary drivers of pathology.

Serial liver biopsies on two occasions were obtained from 39 Japanese NAFLD patients over a mean follow-up of 2.4 years. During this interval, NAFLD improved in 30.7%, worsened in 28.2%, and was unchanged in 41%.

Improvement in glycemic control, as measured by A1C, was the best predictor of NAFLD improvement. Transforming growth factor-beta and plasminogen activator inhibitor type 1 are known regulators of hepatic fibrosis, both of which are stimulated by high glucose levels. ■

In Future Issues: **BMI or Metabolic Syndrome — Which Is More Important?**