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Effect of Infection on Outcome in Acute Pancreatitis

ABSTRACT & COMMENTARY

Synopsis: *Demonstration of pancreatic necrosis by computed tomography identifies a subgroup of patients with the most severe form of acute pancreatitis. Among patients with necrotizing pancreatitis, this study found that the presence of infection in the pancreatic bed increased the overall mortality rate several-fold.*

Source: Buchler MW, et al. Acute necrotizing pancreatitis: Treatment strategy according to the status of infection. *Ann Surg* 2000;232:619-626.

Infection of necrotic pancreatic tissue, likely secondary to bacterial translocation from the colon, is a complication associated with high mortality, and may represent an indication for surgical debridement of the pancreas and retroperitoneal tissues. In a prospective cohort, Buchler and colleagues describe their treatment approach for acute pancreatitis, which relies heavily upon surgical therapy when infected pancreatic necrosis is diagnosed.

Buchler et al describe a series of 204 patients with acute pancreatitis admitted to their hospital in Berne, Switzerland, between January 1994 and June 1999. Of these patients, 86 were found to have acute necrotizing pancreatitis (ANP), based upon CT scan findings. By various indices (Apache II, Ranson's criteria), these 86 patients had more severe systemic disease than the 188 patients with pancreatitis without necrosis. They had a longer hospital stay (44 days vs 13 days) and a higher mortality (10% vs 0%). Twenty-nine (34%) were diagnosed with infected pancreatic necrosis, based upon fine needle aspiration in 28 and post-mortem examination in one patient (despite 3 sterile, fine-needle aspirates in this patient prior to death).

Additional details of Buchler et al's therapeutic strategy are presented in the manuscript, but this summary addresses the role of surgery. The treatment protocol involved surgical decision-making, based primarily upon the results of percutaneous (CT-guided) fine-needle aspiration and culture of the necrotic pancreatic tissue. Growth of organisms mandated surgery, which included resection of necrotic pancreas, followed by post-operative continuous lavage.

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INSIDE

In patients with infected necrosis, the case-fatality rate was 24%, compared to 3.5% for patients with presumed sterile necrosis. One of the patients presumed to have sterile necrosis died and was found to have infected necrosis at autopsy. Therefore, 27 of 28 patients (96%) with infected necrosis were diagnosed on the basis of fine-needle aspiration and culture. One of 16 patients with culture-negative fine-needle aspirates was found to have infected necrosis at autopsy. The remaining 15 patients with culture-negative aspirates survived and did not appear to have pancreatic infection based upon clinical recovery. However, we cannot be certain that infection was not present, and simply responded to conservative (intravenous antibiotic) management. Similarly, the remaining 41 patients considered to have sterile pancreatic necrosis did not undergo fine-needle aspiration, and therefore the true status of the pancreas was unknown in these individuals. One of these patients died from progressive organ failure and was found to have sterile necrosis at autopsy.

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COMMENT BY GRANT E. O'KEEFE, MD

Acute pancreatitis is most often a mild-to-moderate and self-limited disease that requires supportive therapy and subsequent treatment of the underlying cause (cholecystectomy for biliary lithiasis, etc). However, severe inflammation may lead to necrosis of the pancreas and adjacent retroperitoneal tissues, local infection, and the systemic complications of multiple organ dysfunction (MOD). The combination of clinical and radiological (computed tomographic) criteria identifies the majority of patients with severe acute pancreatitis. The demonstration of pancreatic necrosis by CT identifies a subgroup of patients with the severest form (ANP); patients who present a great therapeutic challenge and represent the majority of fatalities. Numerous therapeutic interventions have been tried and various treatment guidelines proposed, but there are few compelling data upon which to base recommendations.

Surgery has been considered an important component in the treatment of ANP, although the indications and timing of operative therapy are controversial. Early surgical intervention, including debridement of necrotic tissue has been considered by some to be an important component of treatment. However, surgery is not without complications, and the benefits are not clear or widely accepted.

The findings of this study support the concept of a detrimental effect of infected pancreatic necrosis upon outcome, and the potential use of fine-needle aspiration in directing surgical management. However, there are a number of major limitations that physicians and surgeons caring for these patients must consider. We have no knowledge of the infection status of the 41 patients who did not undergo fine-needle aspiration. Therefore, we must consider that at least some of these patients had infections, which responded to antibiotic therapy and resolved without surgery. We also know that one patient died from the ravages of severe, ongoing systemic inflammation and organ failure despite having "only" sterile necrosis.

It is also critical to note that 12 of the 28 patients underwent more than one fine-needle aspiration. Therefore, only 16 (57%) of the initial aspirates were positive, suggesting that the actual sensitivity may be much lower than the reported 96%. Patients with an ultimately positive FNA and with positive intraoperative cultures had a 24% case-fatality rate. As we do not have a comparison group, with known infected necrosis, it is not certain whether surgery effects the course of ANP once infection is established. Conversely, we cannot be certain that waiting for the diagnosis of infected necrosis before

considering operative therapy can be universally applied. Would earlier surgery avert the progression to infection and the systemic complications?

This study raises many of the important issues faced when caring for these complicated, critically ill patients, in whom surgery must be considered in the context of the other supportive therapies. While not definitively answering the questions of: 1) who requires surgery; 2) when should surgery be done; and 3) what procedure should be used, this study provides a rational framework for the consideration of these questions in the management of patients with acute necrotizing pancreatitis. (*Dr. O'Keefe is Assistant Professor of Surgery, University of Texas Southwestern Medical Center, Dallas, Tex.*) ❖

The Skinny on L-carnitine in HIV: Too Skinny for Any Conclusions?

CASE REPORT

Synopsis: *L-carnitine may play a key role in cellular apoptosis and mitochondrial function. Deficiencies of this agent may contribute to muscle and peripheral nerve disorders in HIV, although the data are limited.*

An hiv-infected patient recently presented to my office for initial evaluation. In addition to a lengthy list of vitamins and herbal therapies, he was self-medicating with L-carnitine acquired from a local health food store as part of an "antioxidant regimen," and n-acetylcysteine and grape seed extract. He wanted to know my opinion regarding his use of L-carnitine. But did I have one?

Acetyl-L-carnitine is an ester of the trimethylated amino acid, L-carnitine, which facilitates uptake of acetyl CoA into mitochondria during fatty acid metabolism. It is essential for heart and skeletal muscle function, and it has been proposed as an antidote for everything from depression, dementia, neuropathy, and restoring cognitive function in alcoholics to assisting in the reperfusion of the brain in ischemia. L-carnitine and acetyl-L-carnitine depletion are also believed to be possible factors in the mitochondrial toxicity associated with the long-term administration of the nucleoside analogue agents in HIV infection, leading to the myopathy and neuropathy.[1]

Is L-carnitine just another health food fad, or is this an area of HIV care that requires further attention?

COMMENT BY CAROL A. KEMPER, MD, FACP

We were first required to obtain L-carnitine levels in HIV-infected patients receiving open-label adefovir dipivoxil through expanded access, resulting in the identification of several patients with subnormal levels. While the significance of this finding was not clear, we elected to offer replacement L-carnitine to these patients. Most of these patients had advanced HIV disease, had been heavily treated with antiretroviral therapy, and were generally receiving adefovir dipivoxil in combination with several other agents as part of a salvage regimen. I have since obtained L-carnitine levels in patients with painful peripheral neuropathy, wasting, muscle cramping, myopathy, pancreatitis, and lactic acidosis, and offered L-carnitine to patients with subnormal levels, admittedly without much data to guide this approach.

The possible adverse effects of L-carnitine deficiency in HIV-infection, and the long-term benefits of supplemental use of this agent are not known. Di Marzio and colleagues assessed the effects of acetyl-L-carnitine (3.0 g/d) administered to 11 asymptomatic HIV-infected subjects for five months.[2] L-carnitine administration was associated with a reduction in ceramide generation, a marker of lymphocyte apoptotic cell death, as well as an increase in insulin-like growth factor. Increased levels of IGF-1 may help protect lymphocytes from premature cell death. Earlier work by Moretti and associates suggested that in patients who refused antiretroviral therapy, the administration of L-carnitine 6 g/d for four months resulted in increases in absolute CD4 cell counts at three and five months of therapy.[3] No significant effect on HIV RNA levels was detected.

In addition to the effects on lymphocyte apoptosis, deficiencies of L-carnitine have been implicated by some as contributing to the mitochondrial toxicity associated with the long-term administration of nucleoside reverse transcriptase inhibitors. Progressive hearing loss in some patients with HIV infection who are receiving long-term nucleoside analog agents may be related to the irreversible loss of mitochondria in cochlear cells.[4] Mitochondrial damage may also be a factor in the development of painful peripheral neuropathy (PPN) associated with the long-term administration of these agents, leading to suggestions that L-carnitine may play a role in the treatment of this disorder.[5,6] An open-label assessment of 16 HIV-infected patients with PPN who received acetyl-L-carnitine (0.5-1.0 g/d) resulted in improvement of symptoms, using an analog scale, in 63% of patients and no change in 31%.[5] The small number of patients enrolled

in this study and the open-label design unfortunately limit the usefulness of these data.

Mitochondrial toxicity has also been implicated in a recently described life-threatening syndrome of myopathy, hepatic steatosis, and severe lactic acidosis in HIV-infected patients, possibly as the result of the long-term administration of zidovudine, didanosine, or stavudine.[7,8] A similar toxic reaction was associated with the administration of fialuridine (FIAU), another nucleoside analogue previously under investigation in the treatment of hepatitis B, resulting in severe hepatic failure requiring transplantation in two people and five deaths.[9] Widespread hepatocellular mitochondrial damage was observed using electron microscopy. In such cases, the emergent administration of L-carnitine, in addition to fluids and bicarbonate, has been recommended.[10]

L-carnitine may be important in other disease states. Substantially reduced serum concentrations can be found in many patients on chronic hemodialysis because of dialytic loss. This has led to suggestions that L-carnitine should be given as chronic replacement therapy to patients on long-term hemodialysis. In one study of 12 patients undergoing dialysis three times weekly, repeated administration of L-carnitine restored serum concentrations to normal within eight weeks.[11] A recent randomized, double-blind, crossover study evaluated the effects of parenterally administered L-carnitine (20 mg/kg) or placebo for 12 weeks, followed by a six-week washout, and then crossover to the alternate therapy for 12 weeks in 16 chronic hemodialysis patients.[12] The study enrollment was limited to patients with symptomatic myopathy, cardiomyopathy, low energy levels, or a lack of response to erythropoetin (EPO). No statistically significant association was found between the administration of daily L-carnitine and improvement in quality of life or other secondary symptoms such as muscle cramping, anemia, or EPO requirements. Other data suggest that red blood cell (RBC) carnitine is essential for RBC function in renal anemia. A statistically significant increase in hematocrit was observed in 14 hemodialysis patients, who had previously responded poorly to EPO, following 12 weeks of orally administered L-carnitine 500 mg daily.[13]

No significant adverse effects from the administration of L-carnitine have been reported, although it has been my observation that L-carnitine at higher dosages (≥ 1.0 g/d) can result in diarrhea. The use of L-carnitine and acetyl-L-carnitine in the treatment of HIV-related conditions, such as myopathy, painful peripheral neuropathy, and lactic acidosis, requires further study, hopefully in the context of good controlled, randomized clinical trials. Based on these limited data, it is hard to advocate the supplemental use of this agent as "prophylaxis," although it seems reasonable to offer replacement therapy to patients with evidence of low serum levels. On the other hand, L-carnitine appears to be well tolerated, is relatively inexpensive, and there appears to be no good basis for dissuading an individual keen on taking it as supplemental therapy. ❖

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Sodium Lauryl Sulfate—Washing Away the HIV Virus

ABSTRACT & COMMENTARY

Source: Poster presentations at the 40th Interscience Conference on Antimicrobials and Chemotherapy (ICAAC) and interviews with Jocelyne Piret, PhD, and Robert P. Rapp, PharmD, FCCP; *The Pharmacy Practice News*, December 2000.

A group of canadian researchers have shown that sodium lauryl sulfate (SLS), a common ingredient in shampoo and toothpaste, is a potent microbicide against HIV and herpes viruses. The mechanism of action appears to be the prevention of the virus's attachment and entry to target cells by extracting proteins from the envelope of the virus. Whether SLS would prevent infection *in vivo* has not been studied but is certainly of interest.

Based upon their results, they have developed a topical gel formulation of SLS for intravaginal use and are performing preclinical trials. In animal studies, they have shown that animals pretreated with the gel formulation survived infection and showed no signs of toxicity.

COMMENT BY THOMAS G. SCHLEIS, MS, RPh

With the cost of new pharmaceuticals for treatment of HIV continuing to escalate, it is interesting to see how a simple, inexpensive substance such as SLS (essentially soap) can provide a potential advance in preventing HIV infection. While condoms provide the best barrier to HIV transmission between sexual partners, they are not 100% effective and the potential of SLS lessening the likelihood of infection is certainly worth pursuing.

Pharmaceutical manufacturers are currently working on 137 new infectious disease medicines. This is in addition to the 103 medicines in development for AIDS and AIDS-related conditions. Manufacturers have invested an estimated $3.6 billion in infectious diseases research in 2000 and this dollar value is sure to increase in 2001.[1]

When considering the high cost of treatment of HIV, the need for continued emphasis on prevention cannot be over-emphasized. As more and more dollars are poured into pharmaceutical development, the net result will be more expensive medications on the market. This is occuring at a time when consumers are being asked to pay a higher percentage of pharmaceutical costs by their medical insurance providers. ❖

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Effectiveness and Cost-Benefit of Influenza Vaccination of Healthy Working Adults

ABSTRACT & COMMENTARY

Synopsis: *Influenza vaccination in healthy working adults younger than 65 years of age can reduce the rates of influenza-like illness, lost work days, and physician visits during years when the vaccine and circulating viruses were similar, but vaccination was not cost effective.*

Source: Bridges CB, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial. *JAMA* 2000;284:1655-1663.

The cost-effectiveness of influenza vaccination in reducing influenza illness, hospitalization, and death is well established in persons aged 65 years or older.[1-3] However, the benefit of annual influenza vaccination in healthy young adults is less clear. The purpose of this study was to determine the clinical efficacy and cost benefits of influenza vaccination in healthy young adults.

Bridges and colleagues conducted a double-blind, randomized, placebo-controlled trial of influenza vaccine among healthy working adults during the 1997-1998 and 1998-1999 influenza seasons. The primary outcome measures were clinically defined respiratory illness based on ICD-9 codes, associated physician visits, lost workdays during the influenza season, and the cost benefits.

Patients between the ages of 18 and 64 years were randomly assigned to receive either trivalent inactivated influenza vaccine or placebo. Study participants were sent follow-up surveys via e-mail twice monthly and information was obtained on respiratory illness and related physician visits, medications, hospitalization, and lost work days. During November through April of each study year, throat swabs, nasopharyngeal swabs, or both were collected from

participants who notified the study nurse of an influenza-like illness (ILI) and who had been ill for four days or less. Specimens were sent for viral culture. Influenza isolates were sent to the Centers for Disease Control and Prevention (CDC) and antigenically characterized. A total of 1184 participants were randomized in the 1997-1998 and 1191 in the 1998-1999 seasons. Complete follow-up was available for 95% (1130/1184) and 99% (1178/1191) of participants in each period, with 23% in each year having serologic testing. In 1997-1998, when the vaccine virus was different from the predominant circulating viruses, vaccine efficacy against serologically confirmed influenza illness was 50% (P = 0.33). The vaccination did not reduce ILI, physician visits, or lost workdays; the net societal cost was $65.59 per person compared with no vaccination. In 1998-1999, the vaccine and predominant circulating viruses were well matched. Vaccine efficacy was 86% (P = 0.001), and vaccination reduced ILI, physician visits, and lost workdays by 34%, 42%, and 32%, respectively. However, vaccination resulted in a net societal cost of $11.17 per person compared with no vaccination.

Bridges et al thus conclude that in years in which there is a good match between vaccine and the circulating virus, vaccination against influenza can have substantial health benefits by reducing rates of ILI, physician visits, and work absenteeism. However, it does not provide societal economic benefits for healthy young adults.

COMMENT BY DAVID OST, MD

The strategy for influenza vaccination in the United States has emphasized prevention of influenza in persons most likely to experience complications: those aged 65 years or older and younger individuals with cardiac, pulmonary, and other chronic conditions. Studies have shown that vaccination is cost effective in the elderly population.[1] Although vaccination of healthy adults is known to be effective in preventing clinical influenza, cost-effectiveness has not been demonstrated conclusively in this population.

In a double-blind, placebo-controlled trial of vaccination against influenza done by Nichol and colleagues, vaccination resulted in substantial health-related and economic benefits with an estimated cost savings of $46.85 per person vaccinated for healthy working adults.[4] This current study differs from the Nichol et al study in several important aspects. It was conducted during two consecutive influenza seasons, it defined the influenza period based on virologic surveillance at the study site, and it used diagnostic testing to confirm influenza infection rates in a subset of participants unlike the previous study where influenza was defined by clinical features only. This study illustrates that the clinical efficacy and the cost-benefit of vaccination depends on the match between vaccine virus and the circulating virus, thus the need to take a multiyear approach in evaluating influenza vaccine programs. The findings of Bridges et al regarding cost-effectiveness are especially important this year, because there is limited availability of influenza vaccine in the United States. It provides important clinical and cost-benefit data to help in the development of strategies for preventing influenza in healthy working adults. In conclusion, influenza vaccine is effective in preventing serologically proven influenza infection in young, healthy adults and may reduce cumulative days of illness and absence. However, programs for vaccination in the workplace may not provide economic benefit in all years. (*Dr. Ost is Assistant Professor of Medicine, NYU School of Medicine, Director of Interventional Pulmonology, Division of Pulmonary and Critical Care Medicine, Northshore University Hospital, Manhasset, NY.*) ❖

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Inhaled Zanamivir for the Prevention of Influenza in Families

ABSTRACT & COMMENTARY

Source: Hayden FG, et al. Inhaled zanamivir for the prevention of influenza in families. *N Engl J Med* 2000;343:1282-1289.

Influenza (flu) remains a major source of morbidity and mortality in the United States, despite the

widespread availability of vaccine and antiviral pharmacotherapies. Prevention of influenza by antiviral drug therapy has, until quite recently, been limited by the fact that amantadine and rimantadine are only efficacious against influenza A. Two new neuraminidase inhibitors—zanamivir and oseltamivir—are not only effective against both influenza A and influenza B, but in contrast to amantadine and rimantadine, they have not been thus far associated with emergence of drug-resistant influenza strains.

At the time of this writing, only oseltamivir (Tamiflu) is approved for prophylaxis of influenza. This study used zanamivir (Relenza) in an attempt to reduce family member influenza in a large group of subjects (n = 321) who developed an influenza-like illness (ILI) during the 1998-1999 flu season.

Once an index case came down with an ILI, either zanamivir 10 mg qd (by inhalation) or placebo was given to household contacts for 10 days. The index case was treated with the therapeutic FLU dose, 10 mg bid for five days.

There was a striking difference in the frequency with which previously healthy household contacts came down with ILI if they received zanamivir: 4% vs. 19% on placebo. No serious adverse events occurred.

COMMENT BY LOUIS KURITZKY, MD

Zanamivir, in a standard dose administered by inhalation once daily, appears to be an effective and safe intervention for prevention of influenza A and B; its efficacy for treatment of FLU has been previously established. (*Dr. Kuritzky is Clinical Assistant Professor, University of Florida, Gainesville, Fla.*) ❖

CME Questions

7. Which one of the following is correct?
- a. SLS, used intravaginally, demonstrates reversible toxicity in animals.
- b. SLS is not used in toothpaste because of the danger of absorption through the mucosa of the mouth.
- c. SLS has not been tested *in vivo* to determine if it can effectively destroy the HIV virus.
- d. SLS is extremely expensive to produce but offers an advance in HIV prevention.

8. Mortality among patients with acute necrotizing pancreatitis with and without infection, respectively, was:
- a. 12% and 7%.
- b. 24% and 3.5%.
- c. 24% and 14%.
- d. 36% and 3.5%.
- e. 36% and 14%.

9. Which one of the following statements is true about acute pancreatitis?
- a. It is most often a mild-to-moderate and self-limited disease that requires supportive therapy and subsequent treatment of the underlying cause.
- b. When infection occurs in necrotic pancreatic tissue, the associated mortality increases by more than 5-fold.
- c. The combination of clinical and radiological (computed tomographic) criteria identifies the majority of patients with severe acute pancreatitis.
- d. All of the above
- e. None of the above

10. Which one of the following is correct?
- a. Influenza vaccination of young adults is highly cost effective (societal perspective) regardless of the match between vaccine strains and circulating strains.
- b. The United States Public Health Service recommends that all working adults receive yearly influenza vaccination.
- c. Influenza vaccination has not been demonstrated to be cost effective in the elderly.
- d. Influenza vaccination of young adults is more effective when there is a good match between vaccine strains and circulating strains than when such a match is absent.

11. Which one of the following is correct?
- a. Rimantidine is effective against both influenza A and influenza B viruses.
- b. Antiviral resistance of influenza A to amantadine develops more readily *in vivo* than does resistance to zanamivir.
- c. Oseltamivir is active against influenza B, but not influenza A.
- d. Amantadine is a neuraminidase inhibitor.

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In Future Issues:

Serum Antibody Response and the Clinical Course of *Clostridium difficile*-Associated Diarrhea

UPDATES

By Carol A. Kemper, MD, FACP

Is it Truly Traveler's Diarrhea?

Source: Yanai-Kopelman D, et al. *J Travel Med* 2000;7:333-335.

Travelers returning from developing countries with diarrhea are obvious suspects for having traveler's diarrhea (TD). But some of these individuals may, in fact, be presenting with their first symptoms of inflammatory bowel disease (IBD). These authors describe five patients, ages 22-44, returning from Central and South America, India, and Asia with persistent diarrheal illness. All of the patients complained of frequent stools, ranging from 2-8 times per day (which were occasionally bloody in 3 patients), abdominal pain, cramping, and bloating. Two patients experienced weight loss and one patient had a rectal fissure. Only one patient experienced fever that resolved with the administration of antibacterials. Symptoms persisted for 3-12 months despite negative stool studies, and empiric treatment with antibiotics and/or antiparasitic agents in two patients. Colonoscopy revealed Crohn's disease in three patients, ulcerative colitis in one and, in one case, nonspecific colitis that responded to salycilates.

It may be easy to overlook the possibility of IBD in returning travelers with diarrhea, but there may be several clues: Patients with TD generally have a self-limited illness lasting less than one week with frequent stooling (up to 12 stools/d). Only 2% of cases of TD develop persistent symptoms for more than one month. Fever may be present. In contrast, IBD may have an insidious onset, with persistent symptoms for several months, often with less diarrhea (2-7 stools/d). Other systemic symptoms may be present, and laboratory studies may reveal anemia or an elevated ESR without significant eosinophilia and unremarkable stool studies. The presence of an anal fissure or ulcer should be an immediate clue to the possibility of IBD, although infrequently due to amebiasis. A careful history may reveal an earlier episode of unexplained diarrheal illness.

Further confusion may result from the identification of infectious etiology in about one-fifth of patients with IBD, in which case the presence of infection may contribute to the unmasking of the underlying colitis. The symptoms may also be mistaken for tropical sprue, or postinfectious tropical malabsorption, in which patients develop persistent diarrheal illness leading to malabsorption. Symptoms of tropical sprue are seldom insidious in onset and patients can often recall a specific episode of acute diarrhea. Although an infectious etiology is typically not identified, the symptoms often respond to empiric antibacterials. A thorough gastrointestinal work-up, including colonoscopy, is warranted in any traveler with persistent diarrhea for which no explanation is found and which does not respond to the usual antimicrobials and antispasmodics. ■

Can You Name This Disease?

A 53-year-old woman living in Spain presented with a history of recurrent tender nodules on the lower extremities for three years. Three to four nodules would appear every 3-4 months, lasting about one month in duration. Laboratory studies were remarkable for leukocytosis and an eosinophil count of 79%. A skin biopsy was consistent with eosinophilic panniculitis and cellulitis. No organisms were identified. A CT scan of the abdomen demonstrated numerous calcifications and multiple low-density lesions in the hepatic parenchyma. A liver biopsy showed necrotizing lesions with giant cells and eosinophils. A diagnostic serology was obtained.

A 36-year-old Somalian male living in The Netherlands since 1986 presented with right upper quadrant pain for one week. His laboratory studies showed a leukocytosis with 51% eosinophils. Liver function studies were unremarkable except for an elevated alkaline phosphatase. A CT scan of the liver revealed a large irregular mass with necrotic areas in the left lobe with enlarged periaortic lymph nodes. Liver biopsy showed noncaseating granulomatous eosinophilic infiltrate. A diagnostic serology was obtained. The patient's only risk factor was chewing fresh khat leaves imported from Kenya.

Can you diagnose the condition in these patients? Please see the answer below.

Answer: Serological studies were positive for *Fasciola hepatica* in both cases. Following ingestion of contaminated watercress or other vegetation, metacercariae of this common liver fluke invade the intestinal wall and migrate to the biliary tree, where they reside for many years. The flukes rarely lose their way and can migrate to the skin, residing in subcutaneous nodules and abscess on the thorax and extremities. Based on a lack of parasitic elements in the first patient's skin biopsy, she may have experienced a recurrent dermal immunological eosinophilic response, similar to erythema nodosum. Investigation in the second case revealed that khat shrubs were grown near sheep housing and irrigated with local water. Fresh khat leaves were kept damp and wrapped in banana leaves for shipment, which preserved the metacercariae during transport. ■