Feline liver disease usually involves Zone 1 (portal triad region) and focuses on components of the biliary system (bile ductules, bile ducts, common bile duct, gallbladder). Inflammatory effacement of the limiting plate (hepatocytes surrounding the portal triad) and associated apoptotic or necrolytic hepatocyte death is uncommon without involvement of biliary structures. The cholangitis/cholangiohepatitis syndrome (CCHS) is the feline equivalent to canine chronic hepatitis. Despite early suggestion of a Siamese predisposition, there is no consistent evidence for breed predilection. Affecting cats of any age (3 months–19 years), CCHS is usually diagnosed in middle aged or older cats, with the most common form involving non-suppurative inflammation. An ongoing study at the author’s hospital is clarifying the histologic features and subclassifications of this feline syndrome and their responses to therapeutic interventions.

Polycystic liver disease in cats is often confused with feline CCHS, because affected animals may not manifest overt cystic lesions in other organs (kidneys or pancreas). Initially, cystic biliary structures may be very small and are not observed by ultrasonographic imaging. Later, as cyst fluid accumulates (in middle to old age), lesions become ultrasonographically apparent. Liver biopsy from a cat with early polycystic disease discloses dysplastic epithelial structures (low or flat epithelium) and an increase in circumferential extracellular matrix. As the syndrome advances, cats may develop portal hypertension, abdominal effusion, and signs of hepatic encephalopathy. Development of hyperthyroidism may augment onset of clinical signs.

Hepatic lymphoproliferative disease and lymphoma also may be confused with nonsuppurative CCHS. Collection of adequate biopsy samples from several liver lobes, application of stains detailing change in hepatic architecture, immunohistochemical differentiation of cell populations, PCR for bacterial organisms, and T cell receptor rearrangement (clonality) are emerging methods for definitive diagnosis of a diverse spectrum of disorders falling under the CCHS umbrella.

**Suppurative CCHS**

This form of CCHS does not appear to be antecedent to the nonsuppurative form, based on prospective studies at Cornell. Underlying disorders promoting bile stasis are often discovered in cats with suppurative CCHS (e.g., extrahepatic bile duct occlusion [EHBDO], cholelithiasis, acute severe inflammatory bowel disease [IBD], and pancreatitis). Choleliths may play a causal role or develop consequent to associated cholestasis, choledocholithiasis, or hemobilia. Suppurative CCHS may be more common in young, male cats, and presents with acute clinical signs (lethargy, fever, inappetence, painful abdomen, acute vomiting/diarrhea, dehydration, +/- jaundice). Less than <50% of cats are hepatomegalic. Some cats present for hepatic lipidosis (HL) consequent to their inappetence, vomiting, and diarrhea. Some cats are infected secondary to therapeutic immunosuppression (e.g., treatment if nonsuppurative CCHS or lymphoma). In these, infections may derive from feeding appliances (esophagostomy or gastrostomy tubes). Histologically, suppurative CCHS is characterized by neutrophilic infiltrates around and within intrahepatic bile ducts, periductal edema, and hepatocellular cholestasis (canalicular bile plugs). With chronicity (> several weeks), a circumferential periportal fibrolamellar mantle surrounds and bridges between ducts. There is no distinct ultrasonographic (US) appearance aside from recognition of abnormalities involving large bile ducts, GB, or pancreas; coexistent HL complicates US interrogation.

**Cultured Organisms**

Cultures of liver, bile, or choleliths are positive in 18–25% of feline submissions. One report described positive cultures in 7/49 (14%) liver and 5/14 (36%) bile samples. Single bacterial (75–90%) and polymicrobial infections (10–15%) may be encountered. Gram negative aerobes (E. coli, Enterococcus, Streptococcus) are most common; anaerobes include Bacteroides spp and Clostridium spp. Finding bacteria does not confirm a causal relationship to CCHS because any form of cholestasis predisposes to infection (translocating enteric opportunists). In addition to intestinal translocation (fostered by IBD), bacteria may ascend the biliary tree or be hematogenously dispersed from infections elsewhere in the body. Vomiting and diarrhea common to CCHS may coincide with portal bacteremia or reflux of enteric flora into biliary or pancreatic ducts.
Treatment
Elimination of cholestatic factors and systemic infection is imperative. Antimicrobials (4–6 wks) are select based on cytologic morphology of infecting organisms (organism often seen on cytologic imprints but not on histology) and gram stains of these imprints if tissue/bile cultures are negative. Hydrocholeresis with ursodeoxycholate (UDCA) and s-adenosylmethionine (SAMe) provides hepatoprotective and antioxidant benefits in addition to augmenting mechanical cleansing. Vitamin supplementation (water soluble, ensure B12 repletion, vitamin E 10 U/kg/day) is recommended along with a balanced protein-replete feline diet. Adequate nutritional support is pivotal. The role of silibinin is unclear, and lipoic acid is not recommended (can be lethal). Vitamin K (0.5–1.5 mg/kg) is usually provided independent of PIVKA analysis (based on data published by the author) in 3 doses at 12-hour intervals in jaundiced patients.

Nonsuppurative CCHS
Cats with nonsuppurative CCHS show few clinical signs in the early stage. Even with chronicity, clinical signs may remain vague and cyclic, including lethargy, weight loss, anorexia or polyphagia (sclerosing cholangitis associated malassimilation), vomiting, diarrhea, and polydipsia. Since CCHS often coexists with inflammatory bowel disease (IBD), gastrointestinal signs may dominate. Jaundice may be absent, intermittent, or marked and often is cyclic in severity. Rarely, in advanced disease, cats may display hepatic encephalopathy (ptyalism, aggression, somnolence). Such cats are jaundiced and may also manifest abdominal effusion. Most cats with nonsuppurative CCHS have a palpable “normal to large” liver. Cyclic disease is apparent on sequential liver enzyme and total bilirubin assessments. Typically, inappetence and illness are followed by spontaneous remissions, leading owners to question the gravity of their pet’s condition. Some cats initially present for hepatic lipidosis during cyclic illness; underlying CCHS is often heralded by recognition of a high GGT activity acknowledging disease involving biliary or pancreatic ductal components. Some cats present primarily for pancreatitis associated with periductal inflammation. The feline anatomic association between common bile and pancreatic ducts provides a conduit for sharing infectious agents, inflammatory mediators, and obstructing debris as well as shared antigenic epitopes (ductal epithelium), critical in the most severe form of nonsuppurative syndrome (sclerosing CCHS).

Diagnosis of Nonsuppurative CCHS
Classification of CCHS is based on liver biopsy. Cytologic assessment of liver aspirates can deduce septic versus nonseptic inflammation but is unable to definitively diagnose nonsuppurative CCHS. Development of concurrent hepatic lipidosis in anorectic CCHS affected cats can delay clinical diagnosis of the underlying nonsuppurative CCHS. In some cats, a mixed inflammatory infiltrate is found in the absence of demonstrable or culturable bacteria and negative PCR for eubacterial DNA. The clinical significance of positive PCR results for Helicobacter spp DNA in liver or bile is unclear. Helicobacter was detected by PCR in bile from 4/15 (26%) cats with nonsuppurative CCHS, 8/51 (24%) cats with liver disease other than nonsuppurative CCHS, and 7/12 (58%) cats lacking liver disease. A study investigating Helicobacter species in humans with primary biliary cirrhosis, primary sclerosing cholangitis, and liver disease of known cause (alcoholism, hepatitis B, metabolic liver disease) discovered that 30% of each population was PCR positive, contradicting a causal role of Helicobacter. A feline study using archived paraffin embedded liver tissue found Helicobacter sp in 2/32 (6%) cats with CCHS and 1/17 (6%) control (non-inflammatory liver disease or healthy cats) by PCR amplification. Positive findings were speciated by sequence confirmation. Using FISH, a single semicurved bacterium (2-u long) with Helicobacter-like morphology was observed within an intrabiliary bile duct (cat with suppurative CCHS). DNA of Helicobacter spp other than H. pylori was confirmed (suppurative CCHS: H. fennelliae or H cinaedi; H. bilis was amplified from a cat with portosystemic vascular anomaly). Silver staining (Steiner stain) was uniformly negative in PCR positive cats. Discordancy among culture, in-situ localization, and positive PCR reports is frequent in experimental and clinical studies of Helicobacter. It is possible that PCR detection reflects enterohepatic circulation of intestinal organisms or DNA sojourning in the liver rather than true colonization. However, positive reports might also reflect transient tissue colonization.

Histologic Characterization of Nonsuppurative CCHS
An ongoing study at Cornell is defining subcategorizations of nonsuppurative CCHS. Preliminary information contradicts an initiating neutrophilic inflammatory process or that nonsuppurative CCHS represents tissue response to antecedent bacterial infection (including Helicobacter). Histologic characterization is compromised by differences in disease activity among liver lobes. This complicates accurate pathologic interpretation when only small tissue samples are submitted from a single liver lobe (e.g., needle biopsies). It is best to collect wedge or laparoscopic biopsies, as well as full thickness intestinal and pancreatic samples from these cats. Inflammation often coexists in
these additional organs, suggesting either a common causal factor or similar epithelial epitopes as the focus of immunotargeting. Routine sampling of gallbladder bile (US guidance) is not advised in cats with suspected CCHS. Dull pressure on the gallbladder during cystocentesis can initiate a lethal vasovagal response (severe bradycardia, respiratory arrest, death). A similar response may explain sudden death after needle biopsy of liver in cats. Bile is typically sampled at the time of surgery, with anticipated preparation for possible complications.

At present, 4 categories of CCHS are recognized:

**Group 1:** lymphocytic/lymphoplasmacytic inflammation confined within the portal triad or effacing the limiting plate. Biliary epithelial hyperplasia exists without apparent duct destruction or immunocyte targeting.

**Group 2:** lymphocytic/lympho-plasmacytic inflammation with biliary epithelial targeting, duct destruction, and extension of biliary hyperplasia effacing the limiting plate. Inflammatory cells follow replicating oval/biliary epithelial cells, leaving a trail of lipogranulomas (macrophages filled with membrane debris) and ductopenia (loss of bile ducts) within portal triads. Inflammatory infiltrates may extend into major bile ducts, cystic duct, or gallbladder, and may extend into the pancreatic ductal system. Pancreatic involvement may be associated with disappearance of islets, islet amyloid (amylin), pancreatitis, and clinical diabetes mellitus.

**Group 3:** inflammatory infiltrates ambiguously may represent clonal expansion (histomorphology, immunophenotyping); cats may be ductopenic due to immunotargeting of biliary epithelium. A “paraneoplastic process” is proposed that may at some point transform to lymphoma.

**Group 4:** overtly neoplastic lymphoid infiltrates.

The distinction among the groups is made with special stains (e.g., extent of fibrosis, lobular collapse, biliary epithelial hyperplasia, iron retention), immunophenotyping, cytokeratin immunohistochemistry, PCR for detection of antigen receptor rearrangements (PARR, primers for conserved regions of the V and J genes to amplify desired CDR3 regions, followed by product size separation to identify clonal expansions), and PCR for detection of eubacterial DNA, with FISH applied to positive samples. Pathologic findings are being correlated with clinicopathologic features, treatment response, and survival.

**Treatment of Nonsuppurative CCHS**

Nutritional support involves a balanced protein replete feline diet, vitamin supplements (as above, explore B12 sufficiency), injectable vitamin K before biopsy sampling (as above), antioxidants (SAMe: use 40–50 mg/kg bioavailable product, vitamin E: 10 U/kg), UDCA (15 mg/kg divided BID with meals) given with concurrent supplemental taurine (250 mg/day), and anti-inflammatory and immunomodulatory medications.

Anti-inflammatory and immunomodulatory effects in Group 1 cats are commonly achieved with prednisolone (2–4 mg/kg initially, tapered to 1 mg/kg in tolerant cats; no hyperglycemia) and metronidazole (7.5 mg/kg PO BID, compound into gel caps). SAMe and vitamin E are combined, as these also provide an anti-inflammatory effect. SAMe also may impart immunomodulatory influence. In Group 2 cats with sclerosing CCHS, duct immunotargeting is not well controlled with prednisolone and metronidazole and requires addition of either methotrexate (MTX) or chlorambucil.

MTX is administered using pulse dosing, the drug given on a single day with doses divided into 3 treatments. The total MTX dose given per cat is 0.4 mg, with treatments given at 0, 12, and 24 hours of 0.13 mg MTX PO. In intractable cats, MTX also may be given IV, IM, or IP, but the total dose is reduced by 50%. Folate (0.25 mg/kg) is routinely given to thwart hepatotoxicity. Folate supplementation does not block MTX anti-inflammatory or immunomodulatory effects.

The mechanism of action of MTX is complex, involving an extraordinarily diverse influence on immune and inflammatory mechanisms. Treatment results in increased local release of adenosine as a mediating effect. Anti-inflammatory/immunosuppressive affects include inhibition of monocytes replication and increased monocytes apoptosis, reduced IL-1 and IL-6, increased IL-1 receptor antagonist, increased IL-4 and IL-10 gene expression, and reduced gene expression of proinflammatory TH1 cytokines (IL-2 and interferon-γ). MTX also exerts an indirect inhibition of COX-2 synthesis, neutrophil chemotaxis, and matrix metalloproteinase production. It simultaneously enhances tissue metalloproteinase inhibitors. Uptake after oral administration is dependent on a saturable active
transport system, and rapid uptake into the liver results in prolonged organ retention. Most MTX is excreted in urine within the first 24 hours of administration; consequently, impaired renal function can profoundly increase MTX plasma concentrations and promote toxicity (BM, enteric, hepatic). Renal excretion is inhibited by weak organic acids such as aspirin, other NSAIDs, penicillin, piperacillin, and probenicid. Cephalosporins may reduce renal excretion by competitive inhibition (tubular secretion). Simultaneous folic acid administration can block MTX reabsorption in the distal tubule.

Chlorambucil is usually given at a total dose of 2 mg PO every other day or every third day along with prednisolone at a total dose of 5–10 mg PO q12–24 hours. An alkylating agent, chlorambucil, is a noncytotoxic prodrug metabolized to its active metabolite phenylacetic acid mustard. After biotransformation to inactive products, it is eliminated in urine and feces. As an alkylating agent, chlorambucil forms covalent bonds with nucleic acids, cross-linking of DNA strands. This leads to DNA strand breakage and impaired DNA replication. Effects culminate in cell death (altered gene transcription and impaired cell replication), to which lymphocytes are particularly susceptible. Chlorambucil can influence cells in all phases of the cell cycle.

Group 3 (lymphoproliferative disease) and Group 4 cats with low-grade lymphoma may respond well to combined chlorambucil and prednisolone therapy. However, cats with high-grade lymphoma require a full chemotherapy protocol.

References