Liver disease can influence many metabolic, hormonal, and hemodynamic processes. Changes in hepatic albumin synthesis affect oncotic pressure; alterations in renal function and disturbances in production and metabolism of hormones contribute to water, electrolyte, and acid-base imbalances; and stimulation of baroreceptors and osmoreceptors can evoke detrimental changes in effective circulating volume and plasma osmolality.

**NORMAL PHYSIOLOGY OF THE HEPATOBILIARY SYSTEM**

**BILE FORMATION: COMPOSITION AND FLOW**

Bile is an aqueous solution containing organic and inorganic compounds and electrolytes (Table 19-1). Separately hepatic and ductular transport mechanisms allow regulation of bile composition and volume in response to changing physiologic needs. Bile acids are amphipathic organic anions synthesized and conjugated by the liver. The hepatocyte is a polarized secretory epithelial cell with specific transporters localized in basolateral and canalicular cell membranes. The canalculus is a confined space formed by a junction between specialized portions of cell membranes from two adjacent hepatocytes. The surfaces defining the canalculus form a tight junction that functions as an anatomic barrier to solute diffusion. Transport processes in the basolateral hepatocellular and canalicular membranes determine bile acid uptake and biliary excretion. Active transport of osmotically active solutes into the canalculus provides the driving force for bile flow.

Bile salts are the most concentrated organic solutes in bile and a major determinant of bile secretion. Rate-limiting secretory mechanisms involve bile acid transporters in the canalicular membranes. Bile acids impart unique properties that attenuate the osmotic forces in bile. Formation of bile acid micelles (polymolecular aggregates) protects the intestinal mucosa from highly concentrated solutes and promotes interaction between bile acids and lipids in the intestinal tract, thus facilitating digestion. Most all bile acids are conjugated (exclusively to taurine in the cat and to taurine or glycine in the dog) and exist as organic anions rather than undissociated acids. Nonabsorbable constituents of bile (e.g., bile acids, phospholipids, cholesterol) are absorbed from the gallbladder and biliary ducts. Stasis of bile flow or dehydration can promote a pathologic thickening of bile (inspissated or sticky consistency), whereas choleretic (increased bile flow) produces watery or dilute bile. The bicarbonate concentration of bile exceeds that of plasma and is largely under the influence of secretin. Most of the bicarbonate in bile arises

**TABLE 19-1 Flow and Electrolyte Concentrations of Hepatic Bile**

<table>
<thead>
<tr>
<th>Species</th>
<th>Flow (μL/min/g liver)</th>
<th>Na⁺ (mEq/L)</th>
<th>K⁺ (mEq/L)</th>
<th>Cl⁻ (mEq/L)</th>
<th>HCO₃⁻ (mEq/L)</th>
<th>Taurocholate (Canalicular Bile) (mM/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>0.19 (n = 24)</td>
<td>171</td>
<td>5.1</td>
<td>66</td>
<td>61</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>(n = 24)</td>
<td>(n = 75)</td>
<td>(n = 73)</td>
<td>(n = 83)</td>
<td>(n = 83)</td>
<td>(n = 80)</td>
</tr>
<tr>
<td>Cat</td>
<td>0.23 (n = 5)</td>
<td>163</td>
<td>4.2</td>
<td>109</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>(n = 16)</td>
<td>(n = 16)</td>
<td>(n = 16)</td>
<td>(n = 16)</td>
<td>(n = 16)</td>
<td>(n = 10)</td>
</tr>
</tbody>
</table>

* n = Number of observations reported.
during bile transport through biliary ductules. Bile formation and flow are driven mainly by osmotic mechanisms. Flow is initiated by bile acid-dependent and acid-independent mechanisms. In the basal state, equal contributions to flow are derived from canalicular bile salt-dependent and bile salt-independent mechanisms and from ductule processes. In the absence of bile salts, bile flow reaches only 40% to 50% of normal. Transcellular rather than paracellular mechanisms are most important in determining bile composition. Transcellular mechanisms concentrate bile acids and other solutes, whereas paracellular mechanisms permit simple diffusion (water and electrolytes) down electrochemical or osmotic gradients (Figure 19-1).
There is a direct linear relationship between canalicu-
lar bile acid concentrations and bile flow. Non–micelle-
forming bile acids (e.g., dehydrocholate) have the greatest
effect. Hepatocellular uptake of bile acids is an energy-
dependent process linked to sodium transport. This process
accounts for approximately 80% of taurocholate uptake but
only 50% of unconjugated cholate uptake. Protein
carriers facilitate cytosolic transport of bile acids to canali-
cular membranes. Eflux of bile acids into canaliculi involves
several mechanisms including facilitated diffusion depend-
on canalicular carrier proteins, an adenosine triphos-
phate (ATP)-dependent mechanism, and exocytosis of
cytoplasmic vesicles. Collectively, transcellular transport of bile
acids and micelle formation maintain a marked concentra-
tion gradient between bile and blood, permitting biliary
concentrations to exceed plasma bile acid concentrations
by 100- to 1000-fold.

Bile acid–independent bile flow is mediated by a sodium
transport Na⁺, K⁺-ATPase–linked mechanism, bicarbonate
transport (associated with carbonic anhydrase and a
canalicular membrane pump), and transport of organic solutes (e.g., glutathione [GSH]). As the most abundant
organic molecule in canalicular bile (approximating 8 to
10 mM/L), GSH imposes the greatest osmotic effect even
exceeding that of free bile salts. Approximately 50% of
hepatic GSH, most GSSG (oxidized GSH), and all
GSH-conjugates are exported into the canaliculus. Mem-
brane pumps (canalicular multispecific organic anion
transporter [cMOAT], also termed the multidrug resis-
tance associated protein-2 [MRP2]) facilitate GSH export-
tion. The strong osmotic influence of GSH on bile flow
derives from its hydrophilic nature, active membrane
exportation, and hydrolysis by membrane affiliated
γ-glutamyltransferase (γGT) into its three constituent
amino acids (cysteine, glutamate, glycine), yielding three
osmolar equivalents. The osmotic effect of catabolized
GSH draws water and electrolyte solutes through paracellular pathways or other hepatocellular conduits.

Bile ducts contribute to bile formation and modification
as well as to bile flow. Production of ductular fluid primarily
is under the influence of secretin, which regulates spontane-
ous or basal bile flow. Gastrin (but not pentagastrin) also
increases bile duct secretion in dogs, whereas somatostatin
decreases ductular bile flow. Increased ductular bile flow
results in bile alkalization and dilution. Disease states
causing bile ductule proliferation also increase bile flow
(e.g., cirrhosis, extrahepatic bile duct occlusion, inflamma-
tory disorders). Bile ductules and ducts can also reabsorb
bile as shown in cholecystectomized dogs.

HEPATIC NITROGEN METABOLISM:
DETOXIFICATION, EXCRETION, AND
ROLE IN ACID-BASE BALANCE

Urea Cycle and Glutamine Cycle

The liver converts waste nitrogen to an excretable form. Nitrogen derived from amino acids can be converted
to ammonia directly or indirectly after incorporation
into glutamate or aspartate in the liver. Ammonia subse-
quentl is detoxified by conversion to urea (Figure 19-2).
Two mechanisms exist for hepatic nitrogen detoxifica-
tion. The hepatic urea cycle is best known and involves
a linked series of enzymatic reactions carried out in the
mitochondria and cytosol of the hepatocyte (see
Figure 19-2). The second mechanism, the glutamine
cycle, involves transport of glutamine into mitochondria,
where it is converted to ammonia and used as a precursor
of carbamoyl phosphate (see Figure 19-2). The urea cycle
is a low affinity system, most important during alkalosis,
whereas the glutamine cycle is a high affinity system, most
important during acidosis. Collectively, these systems
efficiently cleanse portal blood of ammonia. Approximately 25% of the ammonia for urea synthesis is derived
directly from portal blood, and the remainder is derived
from catabolism of proteins, peptides, and amino acids.

Urea synthesis depends on substrate supply, hormonal
regulation, nutritional status, and liver cell volume. Reg-
ulation of urea cycle enzymes corresponds to the level of
dietary nitrogen intake and possibly liver cell volume. The
urea cycle may play an important role in acid-base homeo-
"stasis, as explained by the following reaction (using the
amino acid alanine as an example of a nitrogen source):

\[
(\text{alanine}) \text{CH}_3\text{CH}(\text{CO}_2)\text{NH}_3 + 3\text{O}_2 \rightarrow 2\text{CO}_2 + \text{HCO}_3^- + \text{NH}_4^+ + \text{H}_2\text{O}
\]

Generation of one positive (NH₄⁺) and one negative
(HCO₃⁻) charge has the potential to maintain electroneutrality. However, because physiologic pH is
in the range of 7.0 to 7.4, only 1% of ammonia exists as
ammonia. Therefore the protons represented by the
ammonium ions cannot be readily transferred to
HCO₃⁻, and thus catabolism of large amounts of amino
acids or protein can generate high bicarbonate concentrations resulting in metabolic alkalosis. Normally,
detoxification of ammonia to electroneutral urea prevents
changes in systemic pH.

\[
2\text{NH}_4^+ + \text{HCO}_3^- \rightarrow \text{NH}_2\text{CONH}_2(\text{urea}) + 2\text{H}_2\text{O} + \text{H}^+
\]

\[
\text{HCO}_3^- + \text{H}^+ \rightarrow \text{H}_2\text{O} + \text{CO}_2
\]

Net: \(2\text{NH}_4^+ + 2\text{HCO}_3^- \rightarrow \text{NH}_2\text{CONH}_2(\text{urea}) + \text{CO}_2 + 3\text{H}_2\text{O}\)

The preceding model probably is an oversimplification. Consumption of a diet composed of a complex mixture
of amino acids (anionic, cationic, and sulfate-containing
amino acids) results in a net gain of protons that must
be excreted or neutralized. Urinary excretion occurs via
dihydrogen phosphate (titratable acidity) and renal tubu-
lar production of ammonium from glutamine. Tradi-
tional concepts of renal tubular acid titration consider
ammonium ion formation an important mechanism of
acid-base regulation. However, ammonium ions excreted
in urine are incapable of titrating acid because they are
already protonated. An alternative view is that urinary excretion of NH₄⁺ represents a mechanism by which the liver is deprived of substrates for urea synthesis, resulting in less bicarbonate neutralization and mitigation of acidosis. According to this hypothesis, the kidneys determine the route of nitrogen disposal, whereas the liver plays a more active role in systemic acid-base balance.

**SERUM PROTEINS: ALBUMIN AND GLOBULINS**

**Albumin**

Albumin accounts for 25% of the proteins synthesized by the liver. Serum albumin concentration reflects the net result of synthesis by hepatocytes, systemic distribution, and degradation. Being relatively small in size (66,000 Da), albumin can be lost from the circulation through pathologically altered vessels (e.g., vasculitis), gut wall (e.g., lymphangiectasia), or glomeruli (e.g., glomerulonephritis, amyloidosis) or into the peritoneal cavity as a result of hepatic sinusoidal hypertension. Impaired or down-regulated hepatic albumin synthesis or losses exceeding synthetic capability result in hypoalbuminemia of variable severity. The liver has a tremendous reserve capacity for albumin synthesis. Normally, only 20% to 30% of the hepatocytes produce albumin, and synthesis can be increased as needed by a factor of 200% to 300%. Hepatic albumin production fluctuates depending on physiologic conditions and requirements (Figure 19-3). The most important variables are nutrition and interstitial osmotic pressure as sensed by the hepatocyte. The influence of nutrition on albumin production can be dramatic. Albumin synthesis decreases by 50% within 24 hours after a fast or with consumption of a protein-deficient diet. Serum albumin concentration reflects this change only after a lag period ranging from days to weeks as a new balance is achieved between exchangeable albumin pools. Feeding excessive calories in a protein-restricted ration augments development of hypoalbuminemia, as does dietary depletion of branched-chain amino acids.

Hypoalbuminemia, caused in part by reduced albumin synthesis, also can be a consequence of changes in serum oncotic pressure related to hyperglobulinemia and treatment with synthetic colloids (e.g., dextran). Synthesis of albumin also decreases, sometimes dramatically, during critical illness as part of a negative acute-phase response.

Hepatocellular synthesis of albumin is affected by a number of factors, the most important of which is the COP of the hepatic interstitial matrix. A decrease in COP stimulates albumin production whereas an increase in COP results in decreased albumin synthesis. After synthesis in the hepatocyte, albumin is released into the space
of Disse by exocytosis. It then diffuses into the hepatic sinusoids, where it mingles with the systemic circulation. It then is dispersed into the interstitial space, returning to the systemic circulation via lymphatics and the thoracic duct. In normal animals, 50% to 70% of albumin is located extravascularly, with the largest amounts in interstitial spaces in skin and muscle. Normal transcapillary escape approximates 5% per hour, but inflammation may increase this several fold. This phenomenon commonly contributes to the “negative-acute-phase” effect that modestly lowers serum albumin concentrations in inflammation.

Catabolism of albumin probably occurs within or adjacent to vascular endothelium of tissues. The half-life of plasma albumin is 7 to 10 days in dogs and 6 to 9 days in cats. The rate of albumin catabolism is highly variable, but its fractional catabolic rate is directly proportional to the plasma albumin concentration and pool size. In conditions that cause hypoalbuminemia, the fractional and absolute rate of albumin catabolism decreases. The rate of albumin catabolism increases after albumin or synthetic colloid transfusion. Thus transfusion of albumin or infusions of synthetic colloids may potentiate endogenous hypoalbuminemia by two separate mechanisms. As a consequence of the large space of distribution and numerous mechanisms influencing the synthesis, distribution, and catabolism of albumin, serum albumin concentration does not accurately reflect contemporary changes in total body albumin resources or its hepatic synthesis.

The strong net negative charge of albumin (−17) explains its important contribution to the strong ion difference (SID) and allows it to bind weakly and reversibly with a variety of ions. In this capacity, albumin functions as a circulating depot and transport molecule for many ions (e.g., Ca²⁺, Mg²⁺, Cu²⁺) and metabolites (e.g., fatty acids, thyroxine, bilirubin, bile salts, amino acids). Albumin accounts for most of the plasma thiol content (i.e., sulfhydryl bonds) and provides protection against oxidative stress. Albumin also provides antioxidant activity by binding reactive transition metals (e.g., Cu²⁺) that catalyze free radical generation. Other important effects of albumin involve anticoagulant, antithrombotic, and antiinflammatory effects.

Oxidized and glycosylated forms of albumin occur in human patients with cirrhosis and these forms increase in concentration as total serum albumin concentration decreases. The increase in the oxidized form of albumin reflects its role as a scavenger of reactive oxygen species. Glycosylation of albumin influences its binding...
and permeability characteristics and augments platelet aggregation, which may predispose to thromboembolic complications. The clinical implication of a lower reduced/oxidized albumin ratio lies in its relationship to oxidative stress imposed by low thiol substrate availability.

Numerous factors influence serum albumin concentration (see Figure 19-3). Modest hypoalbuminemia may reflect reduced albumin synthesis or enhanced catabolism, but these usually are slow in onset. Protein catabolism caused by illness usually spares albumin and targets muscle. The acute-phase response to tissue injury enhances transcapillary escape of albumin and may reduce lymphatic clearance. The most dramatic rapid reduction in serum albumin concentration is dilutional in nature and associated with crystalloid administration (with or without synthetic colloid). Such therapeutic dilutional effects typically aggravate acute severe extracorporeal losses (e.g., hemorrhage). Albumin loss resulting from protein-losing enteropathy or nephropathy initially is compensated for by albumin flux between intravascular and interstitial pools. With chronicity, a net body albumin deficit becomes apparent, and hypoalbuminemia develops. The most severe chronic hypoalbuminemia arises from disorders that impair albumin synthesis while simultaneously increasing catabolism or extracorporeal loss (e.g., protein-losing enteropathy, protein-losing nephropathy).

Hypoalbuminemia in patients with cirrhosis is a result of many factors, including ascites associated with portal hypertension, decreased synthesis, reduced nitrogen intake, dilutional effects from expansion of splanchnic and systemic circulating volume, concurrent diseases causing extracorporeal albumin loss and an acute-phase response (e.g., decreased albumin synthesis, increased transcapillary loss).

Absolute hyperalbuminemia is exceedingly rare, but has been reported in one dog and one human patient with hepatocellular carcinoma. Hyperalbuminemia was hypothesized to be a consequence of increased synthesis of albumin by malignant hepatocytes or due to decreased negative feedback from impaired hepatocellular osmoreceptivity.

**Globulins**

The plasma globulin concentration represents many different proteins, some of which are shown in Figure 19-4. The majority of nonimmunoglobulin serum globulins are synthesized and stored in the liver. Many of these proteins function as acute-phase reactants, a group of functionally diverse proteins normally present in very small quantities. The synthesis of acute-phase proteins rapidly and markedly increases after tissue injury or inflammation under the influence of cytokines. These proteins can contribute substantially to an increased total globulin concentration. Nevertheless, determination of the total globulin concentration is not a good measure of liver synthetic function because of the contribution of immunoglobulins to the total globulin concentration. Hyperglobulinemia is common in animals with acquired hepatic disease, and the magnitude of this response may mask hypoalbuminemia if only total serum protein concentration is determined. Along with the acute-phase response, increased globulins reflect systemic immune stimulation secondary to impaired Kupffer cell function, disturbed B- and T-cell function, and

---

**Figure 19-4** Diagram showing a cellulose acetate electrophoretogram with representative proteins in their respective regions.
development of autoantibodies. In severe hepatic insufficiency, decreased \( \alpha \)-globulins (e.g., haptoglobin, \( \alpha_1 \)-antitrypsin) and hypoalbuminemia portend a poor prognosis.\(^{190}\)

**PATHOPHYSIOLOGY OF THE HEPATOBILIARY SYSTEM**

**INFLUENCE OF LIVER FUNCTION ON BLOOD UREA NITROGEN AND SERUM CREATININE**

**Urea Synthesis**

The liver detoxifies waste nitrogen in two biochemical cycles, converting its primary waste product ammonia (\( \text{NH}_3 \)) to an excretable form (urea). Hepatic \( \text{NH}_3 \) detoxification occurs in designated acinar zones, with urea synthesis dominating periportally (zone 1) and glutamine synthesis prevailing in perivenous hepatocytes (zone 3, adjacent to hepatic venules). Working cooperatively, these systems efficiently cleanse nitrogenous wastes from portal blood, thereby restricting access to the systemic circulation. Since most \( \text{NH}_3 \) produced within the liver as well as that derived from the splanchnic circulation is incorporated into urea, hepatic glutamine synthesis is considered a “backup system” scavenging residual \( \text{NH}_3 \) after splanchnic blood has traversed the hepatic sinusoid.

The hepatic urea cycle is a low affinity, high capacity system that dominates in the face of alkalosis while the glutamine cycle is a high affinity, low capacity system that is most important in the face of acidosis. Thus, during acidosis, less \( \text{NH}_3 \) is incorporated into urea partitioning relatively greater amounts for glutamine synthesis. In this way the liver vacillates between functioning as a net “importer” to a net “exporter” of glutamine, effectively sparing bicarbonate use in urea synthesis. Detoxification of \( \text{NH}_3 \) through glutamine synthesis, as occurs in muscle, is only temporary except in the kidney where glutamine is metabolized to release \( \text{NH}_3 \) into urine.

Blood urea nitrogen (BUN) concentration is directly affected by hepatic urea synthesis. Dietary protein restriction and an expanded volume of distribution for urea (e.g., hypoalbuminemia, third-space fluid accumulation, splanchnic and systemic vasodilatation) can exaggerate low BUN concentrations. Consequently, patients with acquired hepatic insufficiency and those with portosystemic shunting commonly develop abnormally low BUN concentrations. Increased water turnover associated with polydipsia and polyuria also may contribute to low BUN concentrations, whereas enteric hemorrhage in dogs with cirrhosis can increase BUN concentration into the normal range. These extrarenal factors make interpretation of BUN concentration as an indicator of renal function more difficult. BUN concentrations in dogs with cirrhosis (with and without ascites), dogs with portosystemic vascular anomaly (PSVA), and cats with hepatic lipidosis (HL) are shown in Figures 19-5, 19-6, and 19-7.

**Creatinine Synthesis**

The liver also plays a major role in the biosynthesis of creatine, an organic nitrogenous compound essential for cell energy metabolism (Figure 19-8). Creatine is derived from two amino acids (arginine and lysine), and the initial synthetic step is dependent on a rate-limiting enzyme (glycine amidinotransferase) present in a wide variety of organs. The next synthetic step occurs primarily in the liver and involves the transfer of a methyl group from S-adenosylmethionine (SAMe). Decreased hepatic synthesis of creatine in liver disease can result from insufficient methylation reactions and may cause subnormal serum creatinine concentrations. Approximately 98% of creatine is located in muscle tissue. Consequently, loss of muscle mass secondary to a negative nitrogen balance (or small body size in young animals with PSVA) can cause subnormal serum creatinine concentrations (see Figures 19-5, 19-6, and 19-7). Increased water turnover associated with polydipsia and polyuria can accentuate subnormal creatinine concentrations in patients with hepatic insufficiency. In humans with hepatic cirrhosis and concurrent renal dysfunction, serum creatinine concentration fails to reflect the decreased glomerular filtration rate (GFR); a similar phenomenon may occur in animals.\(^{34,162}\)

**HYPOALBUMINEMIA IN LIVER DISEASE**

Hypoalbuminemia (serum albumin concentration, <1.5 g/dL) alters Starling’s forces and favors loss of fluid from the vascular space, hypovolemia, and decreased systemic perfusion pressure. In conjunction with other disturbances in Starling’s forces, a transudative effusion, edema, or both may develop. The location of third-space fluid accumulation often reflects local causal factors. With sodium retention and hepatic sinusoidal or portal hypertension, as may occur in patients with liver disease, a pure or modified transudate accumulates as ascites.

Many endogenous and exogenous compounds (including drugs) are bound to albumin, and transport of such substances is an important function of albumin. Adverse clinical consequences may arise in hypoalbuminemic patients treated with drugs that are highly protein-bound. A larger amount of unbound (free) drug may increase interactions with receptors and facilitate movement of drug across the blood-brain barrier, potentially resulting in adverse effects.

Hypoalbuminemia usually is accompanied by hypocalcemia (as reflected by measurement of serum total calcium concentration) as a result of decreased protein binding of calcium. It was previously thought that a linear relationship existed between serum protein and calcium...
concentrations in dogs and could be used to assess the clinical importance of hypocalcemia. However, total calcium concentration does not predict ionized calcium concentration in dogs. Therefore, it is not reliable to correct total serum calcium concentration based on serum albumin concentration. A reliable relationship between albumin, protein, and calcium concentrations also does not occur in cats.

Although usually attributed to synthetic failure, hypoalbuminemia in liver disease is multifactorial. In addition to decreased synthetic capacity, increased distribution into ascites, malnutrition, and a negative acute-phase response also may affect serum albumin concentration. Increased ultrafiltration into the space of Disse (caused by sinusoidal hypertension) may overwhelm the absorptive capacity of hepatic lymphatics despite a nearly tenfold increase in lymphatic flow. Hydrostatic leakage of protein-poor ultrafiltrate from the liver aggravates abdominal effusion. In such patients, newly synthesized albumin released directly into ascitic fluid may not reach the intravascular compartment and may take weeks to equilibrate with the exchangeable albumin pool. Some human patients with severe liver disease and hypoalbuminemia maintain normal rates of albumin synthesis. In these patients, water and sodium retention are primarily responsible for hypoalbuminemia and ascites. Serum protein concentrations in dogs with hepatic cirrhosis (with and without ascites), dogs with PSVA, and cats with HL are shown in Figures 19-5, 19-6, and 19-7.

In patients with inflammatory liver disease, albumin synthesis may be suppressed by inflammatory mediators. Suppression of albumin synthesis usually is inversely proportional to the rate of acute-phase protein synthesis and thus has been called a negative acute-phase response. However, the acute-phase response also increases transcapillary diffusion of albumin. Endotoxin can increase vascular permeability to albumin, and enhanced transmural passage of endotoxins during portal hypertension may contribute to splanchic vasodilatation and transcapillary leakage of albumin. Abnormal polyamine metabolism caused by altered urea cycle function and methionine metabolism also can impair albumin synthesis. Dietary restriction of protein is the most common correctable cause of hypoalbuminemia in liver disease patients. By increasing
protein intake as tolerated and observing the response over weeks, the role of dietary protein restriction in hypoalbuminemia can be evaluated.

Hypoalbuminemia in liver disease generally is not accompanied by decreased globulin concentration (see Figures 19-5, 19-6, and 19-7). Rather, globulin concentration is normal or increased because of a disproportionate increase in $\alpha$-globulins and acute-phase proteins. $\alpha$-Globulin concentrations increase as a result of increased systemic exposure to gut-derived antigens, microorganisms, and debris normally removed by the hepatic mononuclear phagocytes (Kupffer cells) and presence of inflammatory and immune-mediated processes associated with the underlying disease. $\alpha$-Globulins (particularly haptoglobin), fibrinogen, and antithrombin III are abnormally low in dogs with end-stage cirrhosis and hepatic synthetic failure. $^{190}$ Portosystemic shunting and severe hepatic insufficiency also decrease plasma concentration of protein C, an important anticoagulant also involved in the inflammatory response. $^{222,223}$ The diagnostic utility of the serum total protein concentration is complicated by the induction of haptoglobin by glucocorticoids and development of coagulopathies that can further deplete fibrinogen, antithrombin III, and protein C. $^{98,112}$

The wide range of serum albumin concentrations in normally hydrated cirrhotic dogs with and without ascites demonstrates that hypoalbuminemia is only one factor influencing ascites formation (see Figure 19-5). In dogs with ascites ($n = 52$), median serum albumin concentration was 2.0 g/dL (range, 1.2 to 3.2 g/dL), and in dogs without ascites ($n = 50$), median serum albumin concentration was 2.4 g/dL (range, 0.7 to 4.2 g/dL). Median serum globulin concentrations in these dogs were similar, whereas median plasma fibrinogen concentration was significantly decreased in ascitic dogs (median, 105 mg/dL; range, 30 to 780 mg/dL) compared with dogs without ascites (median, 165 mg/dL; range, 64 to 550 mg/dL).

**SERUM ELECTROLYTES**

**Hypokalemia in Liver Disease**

Hypokalemia is a serious electrolyte disturbance associated with hepatic insufficiency. $^{37}$ Contributing factors include insufficient energy intake, enteric losses
(e.g., vomiting, diarrhea, nutrient malassimilation), treatment with loop diuretics, and secondary hyperaldosteronism. Magnesium deficiency also can complicate hypokalemia by potentiating kaliuresis through its effects on aldosterone. Hypokalemia may go unrecognized because of the transcellular shift that occurs between potassium and hydrogen ions. Serum potassium concentrations of dogs with cirrhosis, dogs with PSVA, and cats with HL are shown in Figures 19-5, 19-6, and 19-7. Frank hypokalemia was present in 11 of 48 cirrhotic dogs with ascites, in 10 of 42 of cirrhotic dogs without ascites, in 6 of 113 dogs with PSVA, and in 32 of 116 cats with HL. A total of 34 of 90 cirrhotic dogs (19 of 48 with ascites and 15 of 42 without ascites), 24 of 104 dogs with PSVA, and 44 of 116 cats with HL had subnormal or low normal serum potassium concentrations. Although the prognosis is worse for cats with HL and hypokalemia, the prognostic significance of hypokalemia has not been evaluated in the other disorders.

It is important to recognize and correct hypokalemia for several reasons. Most importantly, a reciprocal relationship exists between intracellular and extracellular potassium concentrations and renal ammoniagenesis. Infusion of potassium chloride in hypokalemic patients significantly improved central nervous system (CNS) function in early hepatic encephalopathy (HE) and prolonged survival in cirrhotic humans. Patients given potassium chloride to establish normokalemia experienced decreased arterial NH₃ concentration and pH, increased arterial NH₄⁺/NH₃ ratio, decreased urine pH, and slightly increased 24-hour urinary ammonia excretion with a significantly
increased urine NH₄⁺/NH₃ ratio. Mechanistically, potassium infused into the hypokalemic patient replaces intracellular hydrogen ions. The displaced cellular hydrogen ions decrease blood pH, promoting conversion of NH₃ to the less-diffusible NH₄⁺ form. This small shift in pH is not great enough to stimulate renal ammoniagenesis, but reduced urine pH leads to increased excretion of NH₄⁺. This effect may be augmented by increased plasma aldosterone given its ability to increase hydrogen ion delivery into distal renal tubular fluid.

Serum Potassium Concentration and Ammoniagenesis

Experimental and clinical observations of potassium depletion and loading suggest that renal NH₃ production is intimately linked with potassium homeostasis. Low serum potassium concentrations stimulate and high serum potassium concentrations suppress renal ammoniagenesis. A closed-loop regulatory system modulates NH₃ production, hydrogen ion homeostasis, and urinary potassium excretion in response to acute and chronic changes in serum potassium concentration. Potassium deficiency stimulates H⁺ secretion in the distal nephron and may stimulate HCO₃⁻ production by increasing collecting duct expression of an H⁺-K⁺-ATPase that facilitates reabsorption of K⁺ in exchange for H⁺. Potassium deficiency also may increase luminal electronegativity in the proximal tubule, stimulating HCO₃⁻ secretion. Hypokalemia arising from diuretics used to treat ascites can cause hyperammonemia secondary to metabolic alkalosis resulting from renal H⁺ loss.

Hypophosphatemia in Liver Disease

Hypophosphatemia also may complicate hepatic insufficiency. In human patients, hypophosphatemia and early phosphorus administration are associated with a good prognosis in acute liver failure, whereas hyperphosphatemia is predictive of poor recovery. Cats with HL are at increased risk for development of hypophosphatemia, especially when associated with diabetes mellitus or pancreatitis. Although symptomatic hypophosphatemia may develop after rehydration and insulin therapy, it is most common as a result of refeeding in cats with HL. Serum potassium, magnesium, and phosphorus concentrations in 157 cats with severe HL are shown in Figure 19-9. In this population, only 22 of 157 (14%) HL cats had hypophosphatemia at presentation, but more than 35% of those undergoing nutritional support became hypophosphatemic with
refeeding. Hypophosphatemia in patients with liver disease is thought to reflect intracellular shifts of phosphate.\textsuperscript{81,206} Although less common on presentation than hypokalemia, severe hypophosphatemia can produce many clinical signs including weakness (e.g., ventilatory failure severe enough to cause respiratory acidosis, neck ventroflexion in cats), vomiting, gastric atony, hemolysis, bleeding tendencies (i.e., platelet dysfunction), hemolytic anemia, and neurologic signs that can be confused with HE.\textsuperscript{59,81} Mechanisms of hemolysis involve depletion of red cell energy related to impaired glycolysis and ATP production and diminished ability to maintain reduced GSH in erythrocytes. Muscle weakness in hypophosphatemia may be severe enough to impair ventilation, leading to ventilatory failure and respiratory acidosis. Hypophosphatemia induced by refeeding in cats with HL typically appears within the first 48 hours of alimentation, and overt clinical effects are observed with serum phosphorus concentrations less than 1.5 mg/dL.

**Hypomagnesemia in Liver Disease**

Symptomatic hypomagnesemia is observed infrequently in patients with liver disease. Recognition of low serum magnesium concentration is important because of the

---

**Figure 19-9** Scattergram showing the serum potassium, magnesium, phosphate, sodium, chloride, albumin, blood urea nitrogen (BUN), and creatinine from a survey of 157 cats with severe hepatic lipidosis. Normal range indicated by slashed boxes. (Data from SA Center: College of Veterinary Medicine, Cornell University, 2004).
essential role of magnesium as an enzyme cofactor. The mechanisms underlying clinical signs have not been clarified but likely involve transcellular shifting of magnesium into cells with glucose. Hypomagnesemia also may be induced by citrate toxicity after large-volume transfusion with citrate-phosphate-dextrose (CPD)-anticoagulated blood in patients with limited ability for hepatic metabolism of citrate. The most important clinical manifestations of hypomagnesemia are muscle weakness, impaired contractility of the diaphragm, aggravation of preexisting cardiomyopathy, and altered sensorium that may mimic HE. These clinical signs also can be mistakenly attributed to abnormal serum potassium or phosphorus concentrations. Additionally, severe hypomagnesemia can impair the response to potassium supplementation because it perpetuates renal potassium wasting.46

**WATER AND SODIUM DISTURBANCES IN CHRONIC LIVER DISEASE**

The most common fluid and electrolyte abnormalities in hepatic insufficiency accompanied by portal hypertension are impaired ability to excrete sodium and water and a decreased GFR. Sodium retention occurs first, and water retention and an impaired GFR follow. Disturbances of body water and electrolyte homeostasis become apparent with progressive liver dysfunction and precede ascites formation. When most severe, disparity between water ingestion and excretion causes dilutional hyponatremia.

**Iso-osmotic Renal Sodium Retention**

In many patients with hepatic insufficiency prone to ascites formation, iso-osmotic renal sodium retention expands extracellular volume such that total body sodium is not reflected in the serum sodium concentrations (see Figure 19-5). In humans, the magnitude of sodium retention varies among individuals. Hyponatremia in critically ill cirrhotic patients is associated with a poor short-term prognosis. Serum sodium concentration is an important predictor of survival among candidates for liver transplantation.17,19–22 Serum sodium concentrations less than 123 to 135 mEq/L have been associated with a poor outcome.23,35,86,108,113 In one study, however, low serum sodium concentration was found to reflect poor renal function, and did not affect survival when corrected for the GFR.129 Sodium retention also varies in cirrhotic dogs and is indicated by their diverse urine specific gravity (USG) values and serum sodium concentrations at presentation and their apparent resistance to diuretic therapy.

**Impaired Excretion of Solute-Free Water**

Up to 35% of human patients with cirrhosis develop impaired free water excretion causing dilutional hyponatremia.163,165,193 A similar phenomenon may occur in dogs (see Figure 19-5).17,21,140,194,227 When dogs with cirrhosis with and without ascites were compared, the overall frequency of hyponatremia on initial presentation was approximately 25% with the lowest serum sodium concentrations found in dogs with ascites (see Figure 19-5). In humans, serum sodium concentrations of 130 mEq/L corresponded with higher risk of ascites, hepatic encephalopathy, bacterial peritonitis, and hydrothorax, compared with the risks in patients with serum sodium concentration of 136 mEq/L. However, serum sodium concentration has not been associated with the presence of varices.113 In dogs, marked hyponatremia was only observed in association with substantial free water retention and ascites.

Decreased free water excretion is linked to increased vasopressin (AVP) secretion. The most plausible theories involve the sympathetic nervous system (SNS) as both a detector and effector mechanism that adjusts extracellular fluid (ECF) volume and arterial pressure. Decreased total body sodium or decreased arterial pressure reduces SNS inhibition of AVP secretion, whereas vascular distention causes inhibition of AVP secretion and adjustments in vascular tone, cardiac rate, and cardiac contractility. Endothelin may play a modulatory role in the renal AVP response.

**Pathophysiology of Fluid Retention in Cirrhosis**

In cirrhosis, disturbances in fluid balance precede ascites formation by several weeks. In this phase, intravascular volume expansion results from renal sodium retention.140 Renal tubular sodium retention also precedes changes in renal blood flow, GFR, filtration fraction, and intrarenal vascular resistance associated with cirrhosis.127 A 36% plasma volume expansion occurred in cirrhotic dogs during this active salt-retaining, preascitic phase, with two thirds of the newly acquired volume distributed to the vasodilated splanchnic circulation.126 Ascites formation is hastened by sodium ingestion or intravenous administration of sodium-containing fluids. Surgical creation of portosystemic shunting in dogs with hepatic cirrhosis abolished portal hypertension and the early tendency for renal sodium retention and ascites. In such studies, 20- to 30-lb cirrhotic dogs with shunts were able to maintain normal sodium balance with intakes as high as 85 mEq/day. Cirrhotic dogs without shunts accumulated sodium at this level of intake.225

Peripheral arterial and splanchnic vasodilatation initiates water and sodium conservation in cirrhosis.90 Peripheral arterial vasodilatation ("underfilling") reenforces the signal initiating renal sodium retention (i.e., perceived reduction in circulating ECF volume). The physiologic responses observed after acute portal vein constriction (i.e., systemic arterial vasodilatation and hypotension, ECF expansion, increased cardiac output) are similar to those associated with the hyperdynamic circulatory syndrome of cirrhosis.21
These hemodynamic maladjustments are mediated by the renin-angiotensin-aldosterone system (RAAS) and SNS in response to underfilling of the systemic arterial circulation and decreased renal perfusion.\textsuperscript{25,86} Abnormal intrarenal accumulation of angiotensin II occurs early in the disease process, even before activation of the RAAS.\textsuperscript{125} Renal sodium conservation may be related in part to enhanced sensitivity to aldosterone.

**Effect of Portosystemic Shunting on Sodium and Water Retention**

Portosystemic shunting also may affect sodium and water retention, and surgically created portosystemic shunts in experimental dogs have been used to study the effects of diverted hepatoportal perfusion on sodium and water balance. Ten weeks after end-to-side portocaval shunt formation, plasma volume, systemic blood pressure, and central venous pressures were maintained, and no changes in GFR, plasma renin activity, or aldosterone concentrations were identified.\textsuperscript{124} Some dogs maintained normal sodium balance after ingestion of 150 mEq/day of sodium, but others developed ascites.\textsuperscript{124} These findings indicate that in some situations portosystemic shunting alone can impair ability to adapt to increased sodium loads. This finding may explain the tendency to form ascites in some dogs with PSVA (especially those with ductus venosus) and hypoalbuminemia or after administration of sodium-rich crystalloids.

**Specific Mechanisms of Water and Electrolyte Disturbances in Cirrhosis and Portosystemic Shunting**

**Nonosmotic Vasopressin Stimulation**

Nonosmotic stimulation of AVP is a central factor mediating water retention in cirrhosis.\textsuperscript{90} Acute changes in portal venous pressure in cirrhotic dogs initiate AVP-mediated antidiuresis. Both systemic and splanchnic arterial vasodilation can stimulate nonosmotic AVP release and activate other antidiuretic and vasopressor systems.\textsuperscript{86,90} Early in cirrhosis (“compensated cirrhosis”), transient neurohormonal responses increase plasma volume and temporarily suppress baroreceptor signaling. As the disease progresses, arterial vasodilation worsens, and neurohormonal responses are no longer able to compensate. At this point, vasoconstrictor systems become continuously stimulated and promote the sodium and water retention that causes edema and ascites. The response is exaggerated by abnormal retention of AVP as a result of impaired metabolism. Normally, the kidney and liver metabolize AVP, but decreased AVP clearance in hepatic disease correlates with disease severity.\textsuperscript{200} Conivaptan, a nonpeptide, dual V1a/V2 AVP receptor antagonist has shown promising results in both animals\textsuperscript{240} and humans.\textsuperscript{9} It binds competitively and reversibly with high affinity to the V1a and V2 receptors that mediate vasoconstriction and water permeability, respectively. Conivaptan has been shown to correct hyponatremia in euvolemic or hypervolemic patients.\textsuperscript{9}

**Increased Basal Cortisol and ACTH Concentrations**

Increased basal cortisol and adrenocorticotrophic hormone (ACTH) concentrations complicate hepatic insufficiency associated with acquired portosystemic shunting in dogs, but normal adrenal response to low-dose dexamethasone suppression is maintained.\textsuperscript{180} High basal cortisol concentrations also were found in dogs with congenital PSVA, and concentrations normalized after successful shunt ligation.\textsuperscript{205} In another report, baseline cortisol concentrations in dogs with congenital PSVA and in healthy dogs undergoing ovariohysterectomy were similar. Response to ACTH did not correlate with postoperative hypoglycemia or prolonged anesthetic recovery, which was previously thought to be due to inadequate adrenal response.\textsuperscript{105} Dogs with PSVA also have high free-water flux and an abnormally high GFR that normalize after shunt ligation.\textsuperscript{95} It is unknown if this response relates to abnormal cortisol concentration or hemodynamic adjustments. Other potential causes for hypercortisolemia in dogs with congenital PSVA include decreased hepatic synthesis of cortisol binding proteins, decreased hepatic clearance of cortisol, peripheral resistance to cortisol, or stress associated with chronic nonadrenal illness.\textsuperscript{105}

**Altered Steroid Hormone Metabolism**

Altered steroid hormone metabolism also may contribute to sodium retention in cirrhosis. Abnormally increased serum bile salt concentrations may inhibit 11\textbeta-hydroxysteroid dehydrogenase-2 (11\textbeta-HSD-2), the enzyme that interconverts endogenous and exogenous biologically active 11\textbeta-hydroxysteroids and their inactive 11-ketosteroid counterparts. 11\textbeta-HSD-2 selectively modulates access of aldosterone to mineralocorticoid receptors and normally is located in mineralocorticoid-responsive tissues (including the distal nephron). Absence or inhibition of 11\textbeta-HSD-2 can mimic mineralocorticoid excess by allowing inappropriate access of 11\textbeta-hydroxyglucocorticoids to mineralocorticoid receptors.\textsuperscript{4,114,171} The up-regulation of the vasopressin-regulated water channel aquaporin-2 (AQP2) and increased targeting of AQP2 to luminal membranes likely contribute to the increased water reabsorption and urinary concentration in hepatic cirrhosis.\textsuperscript{114}

**Abnormal Aldosterone Release and Responsiveness to Aldosterone**

High (or inappropriately normal) aldosterone concentrations precede and accompany pathologic sodium retention in humans and animals with cirrhosis. Experimentally, hepatic venous congestion and acute portal hypertension stimulate aldosterone secretion.\textsuperscript{23} The importance of aldosterone in sodium and water retention
in cirrhosis in humans is demonstrated by the efficacy of spironolactone (a specific aldosterone antagonist) in mobilizing ascites and alleviating sodium retention in patients without underlying renal dysfunction. The influence of aldosterone on renal sodium retention is enhanced by increased renal sensitivity to the hormone. This phenomenon is reflected clinically by decompensation (i.e., ascites induction) of cirrhotic dogs given glucocorticoids with minimal mineralocorticoid activity (e.g., prednisone).

**Splanchnic Arterial Vasodilatation**
Although the cause of systemic and splanchnic arterial vasodilatation that stimulates AVP production and other antiuretic and vasopressor mechanisms is not completely understood, nitric oxide (NO) plays an integral role. Splanchnic NO is produced by inducible NO synthetase activity in the mesenteric splanchnic endothelium. Splanchnic vasodilatation also reflects formation of arteriovenous shunts, acquired portosystemic communications, and other endothelial (e.g., prostacyclin, endothelin) and nonendothelial (e.g., glucagon, vasoactive intestinal peptide) vasodilatory mechanisms.11 Vasodilatation of splanchnic vasculature also may reflect increased exposure to bacterial endotoxins from enhanced transmural passage of endotoxin from the gut lumen.208

**Diminished Renal Prostaglandin Synthesis**
Decreased renal prostaglandin production increases pathologic water accumulation and dilutional hyponatremia in cirrhosis and hepatorenal syndrome (HRS [see the Hepatorenal Syndrome section]).90 Endogenous renal prostaglandins normally play an important role in regulation of renal perfusion and tubular response to AVP, especially when vasoconstrictor forces predominate (as in cirrhosis). Renal synthesis of vasodilatory eicosanoids (e.g., prostaglandin [PG] I2 and PGE2) normally counterbalances vasoconstrictive stimuli (e.g., angiotensin II, AVP, increased renal sympathetic tone) and preserves renal blood flow and GFR. The protective effect of renal prostaglandins becomes apparent when cirrhotic patients with ascites are treated with nonsteroidal antiinflammatory drugs (NSAIDs). These patients may experience decreased renal blood flow and GFR, activation of vasoconstrictor systems, and sodium and fluid retention that can cause acute renal failure and HRS.

**Water and Sodium Disturbances in Cats with Liver Disease**
Cats with HL do not have consistent changes in serum electrolyte concentrations (see Figure 19-7). This finding is not unexpected because many conditions that cause anorexia and rapid weight loss lead to HL. In a survey of cats with severe HL, 14 of 72 had USG values less than 1.010, 29 of 114 were hyponatremic, and only 1 was hypernatremic. Cats with chronic cholangitis or cholangiohepatitis also do not have consistent changes in serum sodium concentration or USG.

**Summary of Effects of Cirrhosis on Total Body Sodium and Water and Ascites Formation**
In cirrhotic patients, there is a relative inability to adjust water excretion to the amount of water ingested and decreased ability to eliminate sodium in the urine. Impaired water and sodium elimination arises from several factors: (1) enhanced sodium reabsorption in the proximal nephron and decreased delivery of glomerular filtrate to the distal nephron; (2) decreased GFR caused by splanchnic vasodilatation, low systemic blood pressure, altered cardiac output, and inappropriate vasoconstriction of the glomerular efferent arterioles; (3) decreased renal prostaglandin synthesis (PGE2) and impaired autoregulation of renal blood flow; (4) pathologic redistribution of renal blood flow away from the cortex; (5) increased response to, or activity of, aldosterone; and (6) nonosmotic stimulation of AVP release. The most important factors favoring dilutional hyponatremia are disturbed hemodynamics involving the splanchnic and systemic circulation and nonosmotic AVP release. Medical treatment of impaired water and sodium is difficult and may be facilitated by aquaretic agents and vaspressors specific for the splanchnic circulation.89,116,235 In the future, some patients may benefit from treatment with conivaptan to antagonize the effects of AVP.240 The importance of sodium retention in ECF volume expansion associated with portal hypertension is evidenced by patient response to dietary sodium restriction and diuretic stimulation of natriuresis. The severity of sodium retention relative to water retention varies among individuals, and serum sodium concentration does not predict ascites formation (see Figure 19-5). Some patients produce urine that is virtually free of sodium, whereas others produce inappropriately concentrated urine because of excessive AVP release and are at high risk for dilutional hyponatremia.

**ASCITES RESULTING FROM LIVER DISEASE**
Pathophysiologic mechanisms underlying ascites formation are complex, and no specific clinical features clearly identify patients prone to ascites formation. Serum electrolyte, BUN, creatinine, protein, and total bilirubin concentrations for 109 cirrhotic dogs with and without ascites are shown in Figure 19-5. Better understanding of the pathophysiology of ascites formation has led to a shift from the classical underfilling and overflow hypotheses to the forward theory (Figure 19-10). Currently, splanchnic arterial vasodilatation and associated systemic and renal counter-regulatory responses are thought to be the main pathophysiologic events
underlying ascites formation. Decreased systemic vascular resistance initially arises as a consequence of marked splanchnic arterial vasodilatation. The mechanisms underlying splanchnic vasodilatation are poorly understood but likely involve enhanced availability, synthesis, or activity of vasodilatory factors such as NO, glucagon, vasoactive intestinal peptide, endotoxin, bile acids, prostaglandins, and increased local autonomic tone. Splanchnic vasodilatation promotes abnormal distribution of circulating blood volume away from the systemic circulation. The resulting systemic hypoperfusion is sensed by arterial baroreceptors, which signal a need for vasoconstriction and sodium and water retention by the kidneys (e.g., activation of the RAAS and SNS, release of AVP). These events establish a hyperdynamic state characterized by increased cardiac output, decreased systemic vascular resistance, and arterial vasodilatation affecting both the splanchnic and systemic circulation.

Increased splanchnic capillary hydrostatic pressure arises from increased splanchnic blood flow and portal hypertension, which are caused by increased hepatic sinusoidal resistance resulting from hepatic fibrosis. Increased intrasinusoidal pressure combined with high splanchnic capillary pressure and decreased oncotic pressure can cause an up to a twentyfold increase in hepatic lymph formation, exceeding the drainage capacity of the thoracic and hepatic lymphatics. Lymph subsequently weeps from the surface of the liver or splanchnic vasculature into the peritoneal space, causing ascites. Hypoalbuminemia is notably absent early in this syndrome. Formation of ascites continues in response to the ongoing systemic counter-regulatory response (e.g., RAAS-mediated renal sodium retention, nonosmotic stimulation of AVP release). In some patients, these compensatory responses can culminate in development of HRS and acute renal failure.

Albumin infusions do not consistently improve circulatory and renal function in cirrhotic patients with ascites because of enhanced movement of albumin from vessels into the interstitium and severe vasodilatation of the
splanchnic circulation. Although acute volume expansion in cirrhotic human patients increases peripheral blood volume, limited improvement occurs in central blood volume (i.e., splanchnic, hepatic, and cardiopulmonary circulation). However, infusion of albumin in combination with administration of terlipressin, a long-acting synthetic AVP analog, can cause splanchnic vasoconstriction and improved systemic perfusion. 

Assessment of Ascites
A sample of the abdominal effusion should be evaluated biochemically, cytologically, and by culture if cytology suggests infection. Ascites arising from liver disease typically is a pure transudate with a total protein concentration of less than 2.5 g/dL and a specific gravity between 1.010 and 1.015. Cytologically, the fluid has low cellularity with only a few mesothelial cells and neutrophils present. In the jaundiced patient, the fluid is yellow and bilirubin crystals may be observed, but the bilirubin concentration of the effusion is less than that of serum. A serum-to-effusion albumin gradient greater than 1.1 suggests portal hypertension as a causative mechanism. Body weight and abdominal girth measurements should be taken as a reference for evaluating changes in fluid accumulation. Girth measurements are meaningful only if a consistent method is used. A mark is made on the abdomen with a permanent ink pen, and the owner is taught to monitor ascites accumulation by measuring girth circumference using a consistent technique.

ABNORMAL RENAL FUNCTION IN LIVER DISEASE
As liver function deteriorates and portal hypertension worsens, several maladaptive responses threaten renal function. Decreased GFR reduces delivery of glomerular filtrate to the distal diluting segments of the nephron. Coupled with increased resorption in the proximal tubule, this increases renal sodium and water resorption, impairs renal escape from abnormally increased aldosterone, and favors resistance to atrial natriuretic peptides. Systemic counter-regulatory responses that normally preserve filtration fraction increase production of angiotensin II and further provoke vasoconstriction of the efferent arterioles. Although these events maintain glomerular capillary pressure, increase filtration fraction, and alter peritubular Starling’s forces favoring fluid reabsorption, they do so at the expense of decreased renal blood flow. Functional disruption of solute conservation in Henle’s loop by loop diuretics (e.g., furosemide) may further impair the ability of the nephron to dilute or concentrate urine.

Increased Water Turnover and Glomerular Filtration Rate
The influence of hepatic insufficiency on BUN and serum creatinine concentrations is aggravated by increased water turnover and development of a supranormal GFR as observed in dogs with PSVA. Primary polydipsia associated with HE, stimulation of hepatoportal osmoreceptors, and an impaired renal medullary concentration gradient (e.g., chronic hypokalemia, decreased urea synthesis) may contribute to abnormal water balance in these animals.

Polyuria and Polydipsia
Polydipsia, polyuria, and renal dysfunction may be associated with liver disease in both dogs and cats. Dogs with PSVA may be presented primarily for evaluation of polyuria and polydipsia. Mechanisms may include psychogenic polydipsia associated with HE; sensory input signaling splanchnic vasodilatation, decreased hepatic portal perfusion, or altered osmolality; renal medullary washout caused by low urea concentration; renal tubular dysfunction associated with potassium depletion; or increased concentrations of endogenous steroids.

Evaluation of USG before fluid therapy in dogs with PSVA showed that 47 of 87 had a USG less than 1.020, and 12 of 87 were hyposthenuric (see Figure 19-6). Serum electrolyte concentrations were not significantly correlated with USG, but subnormal BUN concentrations occurred in 58 of 123 dogs, and low normal or subnormal creatinine concentrations were found in 83 of 123. These findings suggest that diuresis contributes to low USG in these patients, as supported by presence of a supranormal GFR in dogs with PSVA. Subnormal BUN concentrations in dogs with PSVA could impair maintenance of the renal medullary solute gradient necessary for water reabsorption in response to AVP. Low serum creatinine concentration probably reflects reduced muscle mass associated with the young age and small size of many affected dogs, hepatic insufficiency, and increased water turnover.

Similar mechanisms are likely to be operative in dogs with acquired hepatic insufficiency. Of cirrhotic dogs with ascites, 15 of 26 with urinalysis performed before treatment had a USG less than 1.020 (see Figure 19-5). Of these, only 3 of 26 were hyposthenuric. In the same group, 11 of 42 had low BUN concentrations, and 21 of 42 had low or subnormal serum creatinine concentrations. In cirrhotic dogs without ascites, 16 of 34 with urinalysis performed before treatment had a specific gravity less than 1.020, and only 1 of 34 was hyposthenuric. In the same group, 20 of 47 had low BUN concentrations, and 36 of 47 had low normal or subnormal serum creatinine concentrations.

Altered Intrarenal Hemodynamics
Subtle changes in intrarenal hemodynamics contribute to deranged renal function in cirrhosis. Normally, renal blood flow is predominantly distributed to cortex (90%) with less blood flow to the outer (9%) and inner medulla (1%). Autoregulation of renal blood flow maintains proper balance between afferent and efferent
arteriolar tone to regulate the GFR and filtration fraction. Redistribution of blood flow from the outer cortical to juxamedullary nephrons occurs in approximately 60% of human patients with ascites. Redistribution of renal blood flow and increased intrarenal arterial resistance are correlated with increased plasma renin activity.\textsuperscript{21,117} Changes in systemic and splanchnic hemodynamics (e.g., low systemic arterial blood pressure, decreased systemic vascular resistance, splanchnic vasodilatation) associated with the hyperdynamic circulatory state of cirrhosis initiate renal vasoconstrictor responses that further compromise renal perfusion. Arterial vasodilatation expands vascular capacity and makes effective circulating blood volume difficult or impossible to maintain. High SNS activity further reduces renal cortical blood flow, whereas low systemic pressure and increased renal interstitial pressure compromise renal blood flow, GFR, sodium excretion, and water diuresis.

**Hepatorenal Syndrome**

HRS is a state of functional renal failure associated with a low GFR, preserved tubular function, and normal renal histology that occurs in some human patients with cirrhosis and ascites.\textsuperscript{147} A similar syndrome rarely may occur in veterinary patients. Reduced renal cortical perfusion resulting from increased renal vascular resistance precedes renal failure in this syndrome. The cause of intrarenal vasoconstriction is complex and poorly understood (Figure 19-11). Factors associated with development of HRS in humans are listed in Box 19-1. Essential diagnostic criteria for HRS in humans include a spontaneously acquired acute decline in the GFR, impaired urinary sodium excretion (<10 mEq/day), urine osmolality greater than plasma osmolality, and the absence of other causes of renal failure.

Prevention of HRS requires early intervention to minimize circulatory instability and renal hypoperfusion. Treatment in human patients has included plasma expanders (e.g., albumin, colloids), the long-acting \(\alpha\)-adrenergic agonist midodrine to improve systemic blood pressure and renal perfusion, and the somatostatin analog octreotide and the AVP analog terlipressin to attenuate splanchnic vasodilatation.\textsuperscript{3,12,116,183,226} In the future, endothelins, adenosine antagonists, long-acting vasoconstrictors, and antileukotriene drugs may play a role in preventing and treating HRS.\textsuperscript{146}
ACID-BASE DISTURBANCES IN LIVER DISEASE

Although experimental studies support a role for hepatic urea and glutamine cycles in regulation of systemic pH by their effects on renal ammoniagenesis, there is no consistent pattern of acid-base disturbances in patients with liver disease. The most common disturbance in humans with hepatic insufficiency and coma is respiratory alkalosis, but metabolic acid-base disturbances may also occur. Patients with stable cirrhosis and those with portal hypertension attenuated by surgically created portosystemic shunts commonly develop compensated respiratory or metabolic alkalosis. Respiratory alkalosis is closely associated with the extent of functional liver impairment rather than the presence of portosystemic shunting and nearly always is compensated.

Mechanism of Respiratory Alkalosis
Respiratory alkalosis in cirrhosis may evolve subsequent to reduced arterial oxygen saturation secondary to acquired venaarterial shunting, ventilation-perfusion mismatch (derived from ascites-induced restriction of ventilatory efforts or changes in pulmonary capillaries), a shift to the right in the oxyhemoglobin dissociation curve, direct stimulation of the respiratory center by encephalopathic toxins (e.g., NH₃), or development of CNS acidosis. Respiratory alkalosis may also develop as compensation for metabolic acidemia (e.g., lactic acidosis, increased concentrations of free fatty acids, impaired renal tubular acid excretion, or renal hypoperfusion).

Mechanism of Metabolic Alkalosis
Hypoalbuminemia produces an apparent metabolic alkalosis even in the presence of a normal serum bicarbonate concentration because of loss of the buffering capacity of the negative charges on the albumin molecule. A decrease of 1 g/dL of plasma albumin results in a calculated base excess of 3.7 mEq/L. Hypoalbuminemia appears to be the dominant alkalinizing influence in cirrhotic dogs, whereas hypochloremia appears to be more influential in cats with severe HL.

Metabolic alkalosis in some patients is caused by excessive diuretic therapy, repeated vomiting of gastric secretions, or alkali loading arising from transfusion of citrate-anticoagulated blood. Immediately after blood collection, CPD-preserved blood has low bicarbonate and high citrate concentrations. During storage, red cell metabolism consumes bicarbonate as a result of glycolysis and lactic acid production. After infusion, citrate-preserved blood products favor development of metabolic alkalosis because both lactate and citrate can be metabolized to HCO₃⁻. The total potential bicarbonate concentration in 450 mL of CPD-preserved human blood is approximately 58 mEq/L (i.e., the initial 24 mEq/L in the plasma itself and an additional 34 mEq/L as citrate). Although transfused blood is transiently acidifying because of free citric acid, this effect is quickly counteracted by the metabolism of citrate to CO₂ and water.

Persistent secondary hyperaldosteronism, as occurs in some patients prone to ascites formation, also contributes to metabolic alkalosis. This effect is augmented when administered diuretics increase distal renal tubular delivery of sodium and water. Metabolic alkalosis also is favored by loss of effective extracellular volume (i.e., concentration alkalosis).

Mechanisms of Metabolic Acidosis
Metabolic acidosis is more common in patients in the terminal stages of cirrhosis complicated by hypoxia, systemic hypotension, lactic acidosis, and renal dysfunction. Patients that develop lactic acidosis have severely compromised hepatic function and cardiovascular stability. Both dogs and cats with severe liver disease accumulate unidentified anions, presumably lactate. As compared with cirrhotic dogs, cats with severe HL appear to be at greater risk for acidemia, metabolic acidosis, accumulation of unmeasured anions, and dilutional acidosis.

Lactate Metabolism in Liver Disease
All cells can produce lactate and can add it to the systemic circulation, and all cells (with the exception of red blood cells [RBCs]) also can extract lactate from the blood for metabolism. Estimates of the lactate flux (production and use under basal conditions) indicate production primarily in the skin, RBCs, brain, and skeletal muscle (Table 19-2). Skeletal muscle contributes considerably more lactate to the systemic circulation after strenuous exercise or generalized seizure activity (as may occur in patients with HE). The liver and kidneys are the primary...
sites of lactate removal, with the liver predominating at rest (see Table 19-2). The normal dog liver can extract at least 19% of a physiologic lactate load per hour.\textsuperscript{168} Lactate use is governed by conversion to pyruvate via lactate dehydrogenase (LDH), and the pyruvate formed is either metabolized to glucose or oxidized in the tricarboxylic acid (Krebs) cycle to carbon dioxide and water (Figure 19-12). Lactate generation by RBCs, brain, and skin with subsequent gluconeogenesis by liver and kidneys is known as the Cori cycle, an important mechanism of energy provision during starvation.

Pyruvate, an intermediate common to several metabolic pathways, is the immediate precursor of lactic acid. Glucose and alanine are the physiologically important pyruvate precursors. Pathologic conditions stimulating conversion of glucose or alanine to pyruvate predispose to lactic acidosis. The enzyme pyruvate dehydrogenase (PDH) plays an integral role in lactate metabolism, catalyzing the intramitochondrial conversion of pyruvate to acetyl coenzyme A (acetyl CoA), which enters the Krebs cycle (see Figure 19-12).

Removal of lactic acid normally occurs through three pathways: two depend on hepatic function and the third on renal excretion.\textsuperscript{121} At rest, the liver metabolizes 40% to 60% of endogenously produced lactate by oxidation in the mitochondrial tricarboxylic acid cycle or by conversion of lactate to glucose in the cytosolic Cori cycle (see Figure 19-12). Each mechanism of lactate metabolism regenerates bicarbonate. Hepatic use of lactate depends on substrate uptake, hepatic gluconeogenic capacity, and hepatic blood flow. In the absence of metabolic acidosis or tissue perfusion deficits, hyperlactatemia usually is associated with conditions that favor glycolysis (e.g., high catecholamine concentrations, alkalosis) and an

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Basal Lactate Production (mmol/day/kg in Humans)</th>
<th>Basal Lactate Use (mmol/day/kg in Humans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>5.0</td>
<td>10.3</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>4.3</td>
<td>5.5</td>
</tr>
<tr>
<td>Brain</td>
<td>3.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Muscle</td>
<td>3.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Intestinal mucosa</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>White blood cells, platelets</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18.4</td>
<td>Total 18.4</td>
</tr>
</tbody>
</table>


![Figure 19-12](image-url) Metabolic generation and interactions of lactate (A) and the mechanisms leading to lactic acidosis in liver failure (B). PFK, Phosphofructokinase; PDH, pyruvate dehydrogenase.
increased conversion of pyruvate to lactate. Respiratory alkalosis, common in cirrhotic patients, is thought to increase lactate production by enhancing phosphofructokinase (PFK) activity. Lactate accumulation also is favored when symptomatic hypoglycemia increases catecholamine release, when high blood ammonia concentrations inhibit PDH and cause preferential conversion of pyruvate to lactate, and when acidosis inhibits pyruvate carboxylase and impairs hepatic gluconeogenesis from lactate. Reduction in systemic pyruvate carboxylase and impairs hepatic gluconeogenesis, and when acidosis inhibits pyruvate carboxylase and impairs hepatic gluconeogenesis from lactate (see Figure 19-12). Reduction in systemic pH compromises hepatic uptake of lactate, and decreased hepatic pH arising from lactic acidosis directly disables hepatic lactate metabolism in dogs.

Lactic acidosis results in a high anion gap metabolic acidosis caused by excessive production or decreased use of lactic acid. It is most commonly associated with tissue hypoxia, hypoperfusion, or fulminant hepatic failure. Lactate production is a late sign of inadequate oxygen supply and therefore is neither a sensitive nor early indicator of impending hepatic insufficiency. Lactic acidemia also may develop in some conditions without perfusion deficits or hypoxic injury (e.g., diabetes mellitus, renal failure, fulminant hepatic failure, sepsis).

Hypoperfusion, hypoxia, and ischemic damage of the liver convert it from a lactate-consuming to a lactate-producing organ. Intraoperative hypotension, hepatic ischemia, vascular thrombosis, and fulminant hepatic failure each can lead to lactic acidemia. In fulminant hepatic failure, lactic acidemia indicates severe cirulatory insufficiency, anaerobic metabolism, and diffuse panlobular parenchymal damage. The direct relationship between plasma lactate concentrations and the severity of parenchymal damage permits prognostic use of systemic lactate concentrations in human hepatic transplant patients.

Serum lactate concentrations have been measured in veterinary patients, but the prevalence of lactic acidemia is unknown in dogs and cats with most forms of liver disease. Cats with severe HL have been shown to develop hyperlactatemia. The tendency for affected cats to develop lactate intolerance may be related to impaired mitochondrial function, thiamine deficiency (thiamine is a cofactor for PDH activity), impaired sinusoidal blood flow resulting from hepatocellular cytosolic expansion with triglyceride causing sinusoidal compression, or other underlying disorders causing hypoxia or a predilection for lactic acidosis (e.g., diabetes mellitus, pancreatitis). Dogs with experimentally induced acute hepatic failure developed mild increases in plasma lactate concentrations despite markedly increased concentrations in the brain (Figure 19-13). High brain lactate concentrations are associated with cerebral edema, increased intracranial pressure (>50 mm Hg), decreased cerebral perfusion pressure (<40 mm Hg), and death within 2 days.

High blood lactate concentrations also have been associated with intracranial neoplasia (e.g., meningioma) and lymphoma. Unexpectedly, dogs with partial or complete temporary (2-minute) occlusion of congenital PSVA had unchanged mesenteric venous lactate concentrations (a reflection of portal venous lactate concentration). High portal plasma lactate concentration was expected given the decrease in splanchnic circulation secondary to shunt occlusion, and the elapsed time may not have been sufficient for the changes to become apparent. These results are consistent with previous data showing only a minimal increase in portal plasma lactate concentration at 8 minutes after hepatic blood inflow occlusion (Figure 19-13, C).

Transfusion of stored blood also can cause lactic acidosis. Immediately after collection into CPD solution, human blood has reduced bicarbonate concentration, increased Pco2 (CO2 slowly diffuses through the plastic), and high citrate concentration. Glycolysis in RBC generates lactic acid during storage, and concentrations of approximately 12 mEq/L can be achieved in anticoagulated blood within 14 days. Comparable studies have not been performed using canine or feline blood.

**Citrate Metabolism in Liver Disease**

Citrate-rich blood products can lead to symptomatic hypercitratemia in patients with hepatic insufficiency caused by impaired metabolism of citrate. This effect is most common in very small animals (<5 kg) when large amounts of blood components are transfused. Owing to the chelating capacity of citrate, hypercitratemia can provoke symptomatic ionized hypocalcemia and more rarely hypomagnesemia. Clinical effects include coagulopathy, cardiac arrhythmias, and neuromuscular signs. Large citrate loads also can cause metabolic alkalosis as a result of hepatic metabolism of citrate to bicarbonate. The CPD solution used as an anticoagulant and preservative for blood components is a mixture of sodium citrate, citric acid, sodium phosphate, and dextrose. A 450-mL unit of blood mixed with 63 mL of CPD solution has a final sodium citrate concentration of 34 mEq/L. Hemorrhagic tendencies initiated or aggravated by transfusion of large amounts of citrate-containing blood products should prompt measurement of serum ionized calcium concentration. Symptomatic ionized hypocalcemia requires treatment with intravenously administered calcium gluconate or calcium chloride (see Chapter 6).

**Acid-Base Disturbances in Dogs with Cirrhosis**

Evaluation of clinical data from dogs with cirrhosis indicates that conventional interpretation can cause unmeasured anions to be overlooked and result in underestimation of the complexity of the acid-base disturbance (Figure 19-14). Mixed acid-base disturbances in these dogs may include metabolic alkalosis associated...
with hypoalbuminemia (83%) and hypochloremia (13%) and metabolic acidosis associated with unmeasured anions (67%). Overall, alkalemia was detected in 30% (25% of these animals had clinical signs and laboratory data consistent with emerging HRS), and acidemia was found in 17%. Conventional calculation of anion gaps resulted in an abnormal value in 10%, but after correction of serum sodium concentration for water excess or deficit, 30% had abnormal anion gap values. Low serum sodium concentration (water excess) was found in 17% of dogs with cirrhosis.

**Acid-Base Disturbances in Cats with Severe Hepatic Lipidosis**

Clinical data from cats with severe HL also support the idea that conventional interpretation may underestimate the complexity of acid-base disturbances in patients with liver disease (Figure 19-15). Mixed acid-base disturbances in
these cats may include metabolic alkalosis associated with hypochloraemia (74%) and hypoalbuminemia (48%), and metabolic acidosis associated with unmeasured anions (96%). Alkalemia was detected in 17% and acidemia was found in 26% of these cats. Conventionally calculated anion gaps were abnormal in 39%, but abnormal values increased to 52% after correction of serum sodium concentration for water excess or deficit. Low serum sodium concentration (water excess) was found in 57% of cats with severe HL.

**HEPATIC ENCEPHALOPATHY**

HE is a complex neurophysiologic syndrome involving the CNS that implies a critical loss of functional hepatic mass (65% to 70%) or extensive hepatofugal circulation (portosystemic shunting). The pathogenesis of HE is multifactorial. The most highly suspected contributing factors and their mechanisms are summarized in Box 19-2, Table 19-3, and Figure 19-16. Abnormal cerebral function may arise from a variety of neuroactive toxins, as well as functional and structural alterations affecting neurotransmission and energy metabolism. Most changes are reversible with recovery of hepatic function and appropriate management of the acute metabolic crisis.

Diagnosis of HE is based on clinical signs and clinicopathologic features in the setting of confirmed severe liver disease or portosystemic shunting. In companion animals, HE is rarely associated with acute hepatic failure. The onset of clinical signs can be acute or chronic and episodic or progressive. Progressive HE is characterized by widely variable signs that include a decreased level of consciousness progressing to lethargy, somnolence, stupor, and coma.
CLINICAL MANAGEMENT OF PATIENTS WITH LIVER DISEASE

Important therapeutic considerations in the patient with liver disease include provision of appropriate nutrition for the stage of disease including assessment of protein and sodium tolerance, as well as maintenance of euglycemia, hydration, and electrolyte balance. Circumstances that promote development of HE should be avoided, and HE should be treated aggressively if it does develop. Therapy to eliminate or ameliorate ascites should be carried out as necessary, and coagulation abnormalities should be identified and managed.

NUTRITIONAL CONSIDERATIONS IN LIVER DISEASE

The primary goal of nutritional support is to achieve positive (or at least neutral) nitrogen balance and to provide adequate energy, vitamin, and micronutrient intake.

Protein and Sodium Intake

Protein intake should be restricted only in the presence of hyperammonemia, ammonium biurate crystalluria, or clinically apparent HE or as a therapeutic trial when subtle clinical signs suggest occult HE. In the latter situation, protein intake should be increased cautiously according to individual patient tolerance so as to avoid inadequate nutrition. Nitrogen tolerance is estimated based on...
TABLE 19-3 Conditions Associated with Development of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>Prerenal azotemia</td>
</tr>
<tr>
<td></td>
<td>Renal azotemia</td>
</tr>
<tr>
<td>Azotemia</td>
<td>↑ NH₃</td>
</tr>
<tr>
<td>Alkalemia</td>
<td>↑ NH₃, ↑ diffusion across BBB into CNS</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>↑ NH₃, ↑ renal ammoniagenesis</td>
</tr>
<tr>
<td></td>
<td>Promotes alkalemia</td>
</tr>
<tr>
<td></td>
<td>Polyuria and anorexia</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Neuroglycopenia: augments NH₃ toxicity</td>
</tr>
<tr>
<td>Catabolism</td>
<td>↑ Protein turnover: ↑ NH₃</td>
</tr>
<tr>
<td></td>
<td>↓ Muscle NH₃ detoxication</td>
</tr>
<tr>
<td>Infection</td>
<td>↑ Protein turnover: ↑ NH₃</td>
</tr>
<tr>
<td></td>
<td>Urease producers → urea → ↑ NH₃</td>
</tr>
<tr>
<td>Polydipsia/polyuria</td>
<td>↓ K⁺ → alkali, ↑ NH₃</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Catabolism</td>
</tr>
<tr>
<td></td>
<td>↓ K⁺: promotes alkalemia → augments NH₃ toxicity</td>
</tr>
<tr>
<td></td>
<td>↓ Zinc: impairs urea cycle NH₃ detoxification</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Constipation</td>
<td>↑ Toxin production</td>
</tr>
<tr>
<td></td>
<td>↑ Toxin absorption</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>↑ RBC breakdown → ↑ Protein</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>↑ RBC breakdown →</td>
</tr>
<tr>
<td></td>
<td>↑ Protein: ↑ NH₃</td>
</tr>
<tr>
<td></td>
<td>↑ NH₃ content in stored blood, endotoxins</td>
</tr>
<tr>
<td>GI hemorrhage</td>
<td>↑ Protein: ↑ NH₃</td>
</tr>
<tr>
<td>RBC digestion</td>
<td>↑ Protein: ↑ NH₃</td>
</tr>
<tr>
<td>Inflammation</td>
<td>↑ Protein: ↑ NH₃</td>
</tr>
<tr>
<td>Parasitism</td>
<td>↑ Protein: ↑ NH₃</td>
</tr>
<tr>
<td>High dietary protein</td>
<td>↑ Protein load: ↑ NH₃</td>
</tr>
<tr>
<td>(animal, fish, eggs)</td>
<td>Aromatic amino acids</td>
</tr>
<tr>
<td>Drugs: (examples)</td>
<td>↑ Many other toxins</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Methionine</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Organophosphates</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Diuretic overdosage</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Certain anesthetics</td>
</tr>
</tbody>
</table>

BBB, Blood-brain barrier; CNS, central nervous system; RBC, red blood cell.

Response to initial protein intake and sequential assessments of clinical status. Dogs experiencing nitrogen intolerance require dietary modification of both protein quantity and quality along with treatments targeting enteric toxin production (see the Acute and Chronic Hepatic Encephalopathy section).

Sodium intake should be limited to the 100 mg/100 kcal energy requirement in hypoalbuminemic dogs and cats and in those with ascites. A diet that is less than 0.1% sodium on a dry matter basis is considered very low in sodium for dogs.

Vitamin Supplementation

Water-soluble vitamins should be given to all patients with liver disease. Intravenous fluids should be supplemented with a water-soluble B complex vitamin preparation. Anorectic cats seem to be predisposed to B-vitamin depletion.

Signs of vitamin B₁ deficiency (i.e., hypothyaminosis or Wernecke’s encephalopathy) are easily confused with those of HE but can be rapidly corrected with 50 to 100 mg of thiamine given parenterally or orally every 12 hours followed by every 24 hours for 3 days. Thereafter, thiamine can be adequately provided using a B-vitamin preparation added to intravenous fluids. Oral administration of thiamine is preferred to parenteral administration to prevent the rare but severe vasovagal or anaphylactic reactions to injectable thiamine observed in some animals.

Cats with intestinal malassimilation or pancreatic dysfunction are at increased risk for vitamin B₁₂ deficiency because of inadequate intrinsic factor or impaired cobalamin uptake in the small intestine; a link between cobalamin insufficiency and HL is suspected. Cobalamin deficiency occasionally is severe enough to produce neuromuscular signs, such as neck ventralflexion, anisocoria, papillary dilatation, vestibular signs, postural reaction deficits, and seizures. Parenteral treatment with vitamin B₁₂ is begun after a sample for measurement of baseline serum B₁₂ concentration has been obtained. Pretreatment determination of serum B₁₂ concentration is mandatory because it is on this basis that chronic repletion therapy is prescribed. Initially, parenteral cobalamin treatment should provide 0.5 to 1.0 mg of B₁₂ intramuscularly or subcutaneously every 7 days to every 21 days. Others have recommended 0.25 mg B₁₂ per injection once weekly for 6 weeks, once every 2 weeks for 6 weeks, and then monthly as determined by measurement of serum cobalamin concentration.

Hepatic (and possibly systemic) depletion of fat-soluble vitamin E (α-tocopherol) may complicate inflammatory and cholestatic liver disease. Specific deficiencies have not been quantified in companion animals with spontaneous liver disease, but experimental evidence, information from human medicine, and evidence of deficient hepatic thiol antioxidant status in companion animals argue that α-tocopherol supplementation is appropriate. Vitamin E can protect both lipid-soluble and water-soluble cell constituents from oxidative damage, and experimentally provides antioxidant protection.
in various types of liver injury, including those associated with cholestasis. The amount of vitamin E needed to protect membrane polyunsaturated fatty acids (PUFAs) from oxidative damage ranges from 0.4 to 0.8 mg of vitamin E/g of dietary PUFA. However, patients on diets rich in long-chain PUFA may require more than 1.5 mg of vitamin E/g of dietary PUFA. The complex relationship between vitamin E status and dietary PUFA intake makes definitive recommendations difficult. Vitamin E uptake by enterocytes is dependent on the presence of enteric bile acids, and cholestasis may increase vitamin E requirement because of impaired enterohepatic bile acid circulation. Using a water-soluble form of \( \alpha \)-tocopherol can circumvent problems created by impaired enteric bile acid circulation (e.g., \( \alpha \)-tocopherol formulated with polyethylene glycol-1000 succinate, Eastman Chemical Company, Kingsport, Tenn.). A dosage of at least 10 U/kg body weight per day is recommended but has not been critically evaluated for efficacy in dogs and cats with spontaneous liver disorders.

Vitamin K\(_1\) is given to all jaundiced patients during the first 12 hours of hospitalization to prevent coagulopathies associated with its deficiency. Since vitamin K is a fat-soluble vitamin, its enteric availability may be substantially reduced by impaired enterohepatic bile acid circulation. Consequently, intramuscular or subcutaneous administration of vitamin K is recommended. A vitamin K\(_1\) dosage of 0.5 to 1.5 mg/kg, repeated three times at 12-hour intervals, has been clinically shown to ameliorate coagulation abnormalities in most cats and many dogs with liver disease. The dose of vitamin K should be calculated carefully because excessive amounts can cause oxidant damage to the liver, erythrocytes, and other organs (especially in sick cats). The risk of anaphylaxis should be considered when administering vitamin K\(_1\), but the incidence of anaphylaxis due to intravenous phytonadione (vitamin K\(_1\)) injection in humans was 3 per 10,000 doses in a retrospective study over 5 years. The subcutaneous route is preferred over other routes, especially intravenous.

**Maintenance of Euglycemia**

Patients with hepatic dysfunction may have insufficient liver and muscle glycogen reserves to maintain glycogenolysis. If hepatic gluconeogenesis also is impaired, these
patients are prone to symptomatic hypoglycemia. Animals with portosystemic shunting and those with fulminant hepatic failure are at greatest risk. Neuroglycopenia must be avoided in animals with PSVA during surgical and anesthetic procedures because neurologic recovery can be permanently impaired. In HE, hypoglycemia can intensify neurologic signs by augmenting ammonia-associated brain energy deficits. Intravenous fluids initially should be supplemented with 2.5% dextrose with sequential determinations of blood glucose concentration guiding maintenance treatment. Symptomatic hypoglycemia is managed by administration of 0.5 to 1.0 mL/kg of a 50% dextrose solution given by bolus intravenous injection (diluted 1:2 to 1:8 in saline). Thereafter, glucose supplementation is sustained by adding glucose to fluids to effect using a continuous 24-hour infusion.

**TREATMENT OF HEPATIC ENCEPHALOPATHY**

**General Considerations**

Treatment of HE is based on clinical signs and a comprehensive understanding of the underlying pathophysiologic mechanisms. Syndrome severity is difficult to quantify with biochemical tests and does not correlate with hepatic histologic lesions. The degree of HE reflects circulatory complications, portosystemic shunting, fluid and electrolyte disturbances, hypoglycemia, accumulation of toxins associated with HE (especially ammonia), systemic complications caused by liver dysfunction, and concurrent disease processes. Stratification of patients into two major categories facilitates therapeutic decisions. The first category consists of patients with episodic HE that are relatively normal between episodes and likely have a resolvable precipitating circumstance (see Table 19-3). The second category consists of patients with spontaneous acute encephalopathy in which an underlying cause cannot be found. Management of HE involves detection and treatment of precipitating events, modulation of causative mechanisms, and treatment of the underlying liver disease.

Major treatment strategies for HE include (1) reducing systemic and cerebral NH3 concentrations by therapeutically targeting the gastrointestinal tract (the primary source of NH3 production); (2) maintaining stable systemic blood pressure; (3) ensuring euhydration (i.e., avoiding dehydration or overhydration); (4) correcting or avoiding detrimental electrolyte disturbances (e.g., hypokalemia, hypophosphatemia); (5) maintaining euglycemia; (6) controlling hemorrhage (especially enteric bleeding); (7) avoiding catabolic events and maintaining body condition and muscle mass by feeding a diet tailored to the patient’s nitrogen tolerance and energy requirements; (8) providing supplemental vitamins and micronutrients in the event that increased requirements may be present in hepatic insufficiency (i.e., reduced hepatic storage or activation); (9) identifying and eliminating infectious complications including enteric parasites that may provoke catabolism and nitrogenous waste production; and (10) using metabolic strategies to improve NH3 metabolism or ameliorate NH3 toxicity (e.g., supplementing L-carnitine [L-CN], L-ornithine, L-aspartate, and possibly branched-chain amino acids).

Adjusting the enteric bacterial flora, providing fermentable carbohydrates, and avoiding constipation are common strategies used to modify enteric factors contributing to HE. Constipation is detrimental because many encephalopathic toxins are produced and absorbed in the large intestine. Excessively aggressive nitrogen restriction and failure to provide enough energy for maintenance requirements encourages a catabolic state and muscle wasting, which impair protein and NH3 tolerance. Cachexia, starvation, and glucocorticoid administration increase nitrogenous waste production from muscle catabolism, including NH3 and other toxic metabolites.

Antianabolic effects of certain drugs (e.g., tetracyclines) may promote release of nitrogenous waste products, exceeding hepatic capacity for detoxification. Avoiding hypokalemia and metabolic alkalosis are crucial because these disturbances favor high blood NH3 concentrations. Metabolic alkalosis facilitates brain uptake and intracerebral trapping of NH3. Hypokalemia promotes renal ammoniagenesis and H+ loss, promoting metabolic alkalosis and increasing renal tubular NH3 reabsorption. Severe hypokalemia also may impair urinary concentrating ability, leading to diuresis and dehydration. Persistence of either hypokalemia or hypophosphatemia can lead to weakness and anorexia, compromising adequate nutritional support and fluid balance. In some animals, hypoglycemia precipitates encephalopathic signs. While hypoglycemia can directly or indirectly provoke neurologic and systemic signs (e.g., weakness, lethargy, confusion) and increased neuronal susceptibility to cerebral neurotoxins, hyperglycemia can contribute to an increase in astrocyte osmolar load thereby provoking cerebral edema. A number of neuroactive drugs (e.g., sedatives, analgesics, anesthetics) can directly interact with dysfunctional neuroreceptors causing encephalopathic signs. Maintaining adequate hydration is important in preventing prerenal azotemia, which can increase enteric NH3 production and hyperammonemia. Volume expansion can attenuate hyperammonemia caused by enteric hemorrhage when NH3 arises largely from enhanced renal ammoniagenesis. However, avoiding overhydration also is important because it can promote ascites, cerebral edema, or pulmonary edema associated with occult cardiopulmonary complications of hepatic insufficiency. Fluid volumes and drug dosages must be calculated based on estimated lean body mass in patients with ascites. Failure to do so can lead to fluid...
overload or life-threatening drug toxicities. Administration of a highly protein-bound drug to a patient with hypalbuminemia without dosage adjustment potentially can lead to an inadvertent drug overdose that could be lethal.

**Acute Severe Hepatic Encephalopathy or Liver Injury**

Treatments should be targeted at controlling hyperammonemia and cerebral edema. Critical supportive care should address circumstances that increase cerebral blood flow and compromise cerebral or hepatic metabolism. Effort should be made to attenuate systemic inflammatory responses and provoking causative factors. Although acute hepatic failure usually is associated with high blood NH₃ concentrations, strategies targeting enteric NH₃ production generally are less effective in patients with acute HE than in those with episodic HE caused by chronic liver disease or portosystemic shunting.

Careful management of systemic blood pressure is important; both hypotension and hypertension must be prevented. Analogs of AVP used to counteract splanchnic hypoperfusion and enteric bleeding in severe hepatic insufficiency are contraindicated in patients with signs of cerebral edema based on experimental studies and observations in human patients. Body temperature should be monitored, and hyperthermia should be avoided. Hyperthermia increases metabolic rate and cerebral blood flow, which can increase intracranial pressure. Modest hypothermia may prevent emerging cerebral edema in acute HE but cannot be maintained long term. Glucose infusion may ensure euglycemia, but hypoglycemia and hyponatremia may provoke cerebral edema in acute hepatic failure. Hypercapnia must be avoided because it may increase cerebral blood flow and intracranial pressure. However, hyperventilation must also be avoided because severe hypocapnia may decrease cerebral perfusion. Monitoring blood pH to prevent alkalemia or acidemia is essential. Alkalemia can facilitate diffusion of NH₃ across the blood-brain barrier, and acidemia may indicate the presence of unmeasured anions, especially lactate. Hyperlactatemia should be avoided because it contributes to cerebral edema, increased cerebral blood flow, and increased intracranial pressure. Infusion of branched-chain amino acids and supplemental L-CN may be appropriate in patients with acute severe HE and suspected cerebral edema, but these treatments remain controversial. Supplemental vitamin K and water-soluble vitamins should be given, and some clinicians believe that fluids containing lactate should be avoided. However, the benefit of avoiding lactate-containing fluids may be more theoretical than practical. An investigation of endogenous lactate production in septic human patients with acute renal failure found that an acute exogenous load of lactate did not affect basal endogenous lactate production and metabolism. Antimicrobials should be administered to prevent enteric organisms from gaining access to the systemic circulation. Patients with cirrhosis and HE may have increased endogenous benzodiazepines or benzodiazepine-like substances, which can bind to this receptor complex and lead to neuroinhibitory effects from activation of the GABA portion of the receptor complex. Flumazenil, a drug that acts as an antagonist of the benzodiazepine-γ-aminobutyric acid (GABA) receptor complex located in the brain has been proposed to ameliorate HE in the short term. However, recent findings have not supported its routine use in human medicine.

**Chronic Hepatic Encephalopathy**

**Dietary Management**

The mainstay of nutritional support is judicious protein restriction taking care to avoid a catabolic state. Nitrogen allowances should be tailored individually for each patient. Excessively severe protein restriction can contribute to malnutrition patients with chronic liver disease, increasing catabolic loss of muscle. Positive nitrogen balance should be maintained and catabolism should be avoided because muscle is an important site for transient NH₃ detoxification. Vegetable and dairy sources of protein are superior to meat, fish, or egg sources in dogs. A recent study showed that a soy-based, low-protein diet had more impact in decreasing plasma ammonia concentration when compared with a poultry-based, low-protein diet after 4 weeks of treatment. Despite the difference in plasma ammonia concentration, both diets improved HE scores, increased serum fibrinogen concentration, and increased prothrombin times. Whether the lower plasma ammonia concentration reflected better control of HE has been a topic of debate. Some dogs developed very low albumin concentration, likely due to the negative energy balance. Recent studies in animals and humans suggest that the main source of ammonia in the portal blood is the glutaminase activity of small intestinal enterocytes, which use glutamine as their main energy source. The issue of whether or not the standard treatment approach of a low-protein diet and lactulose actually benefits patients with HE has been debated. Although no double-blinded, placebo-controlled studies have been done to date, clinical experience still supports the use of these treatments in human patients. Cats are strict carnivores and require meat-derived protein as part of their restricted protein allowance. Energy requirements may be increased in hepatic insufficiency, and the patient’s body condition and behavior at home should be evaluated sequentially to assess the adequacy of nutritional support.

Conventional recommendations for chronic management of hyperammonemia and HE in dogs include limiting dietary protein intake to between 14% and 16% of energy intake with a minimum of 2.5 g protein/kg body weight per day. Recommendations for cats include...
limiting dietary protein to 25% to 30% of energy intake with a minimum of 4.5 g protein/kg body weight per day. Others recommend a caloric distribution of more than 32% protein (essential amino acids including arginine and taurine), more than 40% fat (essential fatty acids), and approximately 20% carbohydrate (preferably glucose).\textsuperscript{15} Protein and caloric intake should only be restricted in animals with clinical HE.\textsuperscript{15} In cats, insufficient arginine or citrulline may increase susceptibility to hyperammonemia. Titration of individual protein tolerance from an initial severely restricted allocation is done by adding 0.25 to 0.5 g protein/kg body weight per day and evaluating clinical response over time (e.g., sequential body weight, body condition scores, serum albumin and creatinine concentrations, and patient cognition and behavior). Dietary supplementation of L-CN led to significantly lower plasma $\beta$-hydroxybutyrate concentrations in obese cats with experimentally induced hepatic lipodiosis, but concentrations were not significantly different during the treatment phase.\textsuperscript{28} L-CN may be provided orally at a dose of 250 to 500 mg/day.\textsuperscript{46} Use of L-CN (parenteral administration) may avert NH$_3$ toxicity, but this approach has not yet been widely applied clinically. Conventional total parenteral nutrition solutions have been used safely in dogs and cats with HE with formula modification to achieve protein restriction on an individual basis. At Cornell University Companion Animal Hospital, supplemental L-CN (25 to 50 mg/kg body weight per day) is provided in such solutions.

**Modification of the Enteric Environment: Ammonia Detoxification**

Many factors contribute to HE, and no single treatment is appropriate and effective for all patients in all circumstances. A common approach incorporates strategies that reduce enteric and extraintestinal NH$_3$ production and increase enteric NH$_3$ detoxification (Table 19-4). The kidneys may be a major source of NH$_3$ production in patients with enteric hemorrhage, and volume expansion may facilitate renal NH$_3$ elimination.\textsuperscript{159}

Orally administered disaccharides that are fermented in the gut (e.g., lactulose, lactitol, or lactose in lactase-deficient patients) commonly are combined with parenterally administered antimicrobial agents to modify enteric flora and suppress urease-producing bacteria.

---

**TABLE 19-4 Methods Used to Modify Enteric Production and Absorption of Toxins**

<table>
<thead>
<tr>
<th>Dietary Modifications</th>
<th>Modification of Enteric Microbial Population</th>
<th>Direct Elimination of Enteric Microorganisms, Substrates, and Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein quantity</td>
<td>Altered protein quality: dairy and vegetable preferred</td>
<td>Cleansing enemas 5-10 mL/kg, repeat until clear; use warm polyionic fluids</td>
</tr>
<tr>
<td>Alter enteric pH:</td>
<td>Dietary soluble fiber</td>
<td>Retention enemas As necessary, respect total systemic drug dose</td>
</tr>
<tr>
<td>Lactose, lactulose, lactitol, fiber</td>
<td>Antimicrobials: Neomycin 22 mg/kg</td>
<td>Neomycin 15-20 mL 1% solution tid (No &gt;22 mg/kg body weight tid)</td>
</tr>
<tr>
<td></td>
<td>Metronidazole 7.5 mg/kg</td>
<td>Lactulose 5-15 mL diluted 1:3 with water tid</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin 11 mg/kg</td>
<td>Lactitol 0.5-0.75 g/kg bid</td>
</tr>
<tr>
<td>Administration of lactobacilli: live yogurt cultures</td>
<td>Modify enteric substrates: dietary, nonabsorbable disaccharide fiber</td>
<td>Lactose Slightly sweet solution bid-tid</td>
</tr>
<tr>
<td></td>
<td>Lactulose 0.25-0.5 mL/kg PO bid-tid</td>
<td>Fiber Metamucil, psyllium bid-tid</td>
</tr>
<tr>
<td></td>
<td>Lactitol 0.5-0.75 g/kg PO bid</td>
<td>(Each of the above are used to effect, attaining several soft stools per day.)</td>
</tr>
<tr>
<td></td>
<td>Lactose Slightly sweet solution PO bid</td>
<td>Direct Elimination of Enteric Microorganisms, Substrates, and Products</td>
</tr>
<tr>
<td></td>
<td>Fiber Metamucil, psyllium bid-tid</td>
<td>Cleansing enemas 5-10 mL/kg, repeat until clear; use warm polyionic fluids</td>
</tr>
<tr>
<td></td>
<td>(This is a STARTING dose. Start low and gradually work dose up to required amount based on stool consistency and frequency: aim for 2-3 soft pudding-like stools per day.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Each of the above are used to effect, attaining several soft stools per day.)</td>
<td></td>
</tr>
</tbody>
</table>

PO, orally; bid, twice daily; tid, thrice daily.
Transient repopulation of the gut with beneficial (i.e., non–urease-producing) microorganisms (e.g., lactobacilli) may provide short-term benefits. Collectively, these efforts often ameliorate clinical signs of HE. In neurologically impaired patients that cannot tolerate oral medications, cleansing enemas are used to rid the colon of retained toxins and debris and are followed by retention enemas (see Table 19-4). Retention enemas contain enteric-modulating medications with effects similar to those described for oral administration. Simultaneous oral and per-rectal dosing should be avoided to prevent diarrhea, cramping, and potential drug overdose.

**Fermentable carbohydrates** Dietary management of HE optimally is combined with oral administration of a fermentable carbohydrate such as lactulose (β-galactosidofructose, most commonly used), lactitol (β-galactosidosorbitol), or lactose (in lactase-deficient patients) because this strategy increases patient nitrogen tolerance. Lactulose and lactitol are synthetic disaccharides not digested by mammalian enzymes. Lactose may achieve a similar effect in lactase-deficient patients and is much cheaper. These compounds undergo bacterial fermentation in the intestinal tract, yielding lactic, acetic, and formic acids, which acidify the enteric lumen (pH < 5.0). These organic acids constitute an osmolar load, provoking a cathartic influence (softening feces and increasing the frequency of defecation). This cathartic effect increases the gastrointestinal transit rate, which commonly is slow in patients with HE and portal hypertension. The acidic luminal pH suppresses bacterial urease activity, renders the enteric environment inhospitable for many ammonia-generating organisms, and traps NH$_3$ as the NH$_4^+$, thereby increasing its elimination in feces. Carbohydrate fermentation also increases microbial incorporation of nitrogen, thereby decreasing the nitrogen available for systemic absorption. Fecal nitrogen excretion increases up to fourfold because of increased fecal volume and nitrogen trapping. Carbohydrate fermentation also decreases formation of potentially toxic short-chain fatty acids (e.g., propionate, butyrate, valerate) thought to contribute to HE. The dose of fermentable carbohydrate administered must be individually titrated to achieve several soft stools each day. Too much lactulose induces abdominal cramping (because of fermentation and gas production), stimulates peristalsis (causing borborygms), and causes watery diarrhea. Generation of organic acids from lactulose rarely can result in metabolic acidosis, dehydration, and hypernatremia. Lactulose may be contraindicated in patients with hypercalcemia if increased absorption of calcium from the gut exacerbates hypercalcemia.

Given together, lactulose and an enteric antimicrobial synergistically improve nitrogen tolerance in most animals. Lactulose (0.25 to 1 mL/kg orally every 8 to 12 hours) commonly is combined with metronidazole (7.5 mg/kg orally every 8 to 12 hours), amoxicillin (22 mg/kg orally every 8 to 12 hours), or neomycin (22 mg/kg orally every 12 hours) to decrease enteric production of NH$_3$ from urea and other nitrogenous substrates. Caution should be exercised when using neomycin because it potentially can be absorbed from the intestinal tract to an extent sufficient to result in ototoxicity or nephrotoxicity, especially if coexisting inflammatory bowel disease increases its absorption. Rarely, concurrent administration of an antimicrobial may reduce the efficacy of lactulose by decreasing its bacterial fermentation. This effect can be detected by checking fecal pH, which should be less than 6.0 if effective lactulose fermentation has occurred. Transient repopulation of the intestine with non–urease-producing microorganisms (e.g., lactobacilli) may provide only short-term benefit but carries little risk. Products that deliver lactobacilli or similar probiotic organisms also provide fermentable carbohydrate substrates, which may explain their benefits. Rarely, hepatic or systemic infections with the probiotic organism have been encountered.

**Cleansing and retention enemas** Conventional measures that decrease systemic NH$_3$ concentrations are directed at cleansing and removing noxious substrates from the colon and modifying the enteric environment. Initially, this approach involves cleansing rectal lavage using warm isotonic fluids and removal of residual ingesta, nitrogen-containing compounds, urease-producing microorganisms, and encephalopathic toxins. Next, a retention enema containing an antimicrobial, a fermentable carbohydrate, an acidifying solution, or activated charcoal is instilled. Use of a fermentable carbohydrate is preferred because it reduces enteric pH and traps NH$_3$, and eliminates it as NH$_4^+$.

**FLUID THERAPY IN LIVER DISEASE**

**General Considerations**

Selection of the most appropriate fluid for patients with hepatobiliary disease must take into consideration their propensity for third-space fluid accumulation (e.g., edema, ascites), hypoalbuminemia, hyponatremia, hyperkalemia, coagulopathies, and hyperlactatemia and whether preexisting acid-base disturbances put them at risk for HE. In patients without evidence of synthetic failure or HE, balanced polyionic solutions are appropriate and should be supplemented with KCl as routinely recommended for maintenance needs.

When ascites or edema precedes fluid administration or develops after infusion of polyionic solutions, fluid support must be modified to reduce the administered load of sodium. Ascites has been experimentally induced in medium-sized dogs with cirrhosis by ingestion of only 85 mEq of sodium per day. Considering that a 15-kg dog has a maintenance volume requirement of approximately 1 L/day, the sodium content of commonly used polyionic crystalloid solutions may promote ascites formation when maintenance volumes are administered.
Selection of commercially available solutions with restricted sodium content or mixing of commercially available solutions to achieve restricted sodium content is necessary for these patients. Slow infusion of both a crystalloid and a colloid is a useful approach for many of these patients because it expands intravascular volume, limits the requirement for crystalloids, and reduces the tendency for third-space fluid sequestration. Crystalloid administration is reduced to 33% of normal maintenance requirement when administered with 20 mL/kg/day of synthetic colloid. The potential bleeding complications associated with synthetic colloid use and their cost must be carefully considered. (See Chapter 27 for more information on colloid therapy).

Hypoalbuminemic patients with tense ascites require individually tailored fluid therapy combined with a synthetic colloid or plasma, large-volume paracentesis, and diuretics (furosemide and spironolactone). Simply adjusting fluid sodium intake or restricting water intake is not efficacious. Water restriction is hazardous because of inadequate home monitoring. Although providing a synthetic colloid may seem reasonable, this approach alone will not interrupt the complex physiologic signals impairing renal water excretion. Low plasma oncotic pressure is not the sole driving force of ascites in these patients.

Hyponatremia presents a therapeutic challenge in patients with liver disease because the underlying physiology is complex and involves increased secretion of AVP (see Figure 19-10). Availability of aquaretic agents, such as conivaptan (an AVP receptor antagonist) may facilitate management of water retention in the future.* An angiotensin II type one receptor antagonist (e.g., Losartan) may improve the blunted natriuresis observed in cirrhotic human patients with or without ascites.87,91,236,239 This natriuretic effect appears to be more pronounced in ascitic than in nonascitic patients. Low doses are preferred because higher doses may substantially lower mean arterial blood pressure.87 The appropriate dosage and benefit of losartan in dogs and cats with liver disease are not established.

Influence of Diuresis, Fluid Expansion, and Diuretics on Ammonia Concentration

Hyperammonemia in patients with hepatic insufficiency can be attenuated by systemic volume expansion because volume expansion reduces renal and hepatic ammoniagenesis. Renal ammoniagenesis is curtailed by increased renal plasma flow and the GFR, which increases fractional NH₃ excretion. Enhanced renal NH₃ elimination occurs secondary to increased glutamine delivery to the proximal tubules, increased urine flow rate (i.e., decreased NH₃ reabsorption), and suppression of antidiuretic hormone secretion. Total body NH₃ load is decreased by redirection of ammonia into urine rather than into the renal vein. Volume expansion in well-compensated human patients with cirrhosis also decreases plasma renin activity and angiotensin II production. The latter effect may be important because angiotensin II enhances ammoniagenesis in the proximal tubules.107 Improved systemic perfusion increases uptake of NH₃ by liver, skeletal muscle, and brain where it can be detoxified.

Enhanced sodium reabsorption in the ascending limb of Henle’s loop and distal tubule is a disturbance associated with cirrhosis that may cause resistance to conventional doses of furosemide. Decreased response to furosemide also may reflect impaired drug access to the tubular lumen where it achieves its pharmacologic effect. When very large doses of furosemide are administered to initiate diuresis, the risk of hypovolemia and excessive loss of Cl⁻ (in excess of Na⁺) is increased. Although retention of HCO₃⁻ maintains electroneutrality, it contributes to metabolic alkalosis that can increase NH₃ flux through an impaired urea cycle. Collectively, these effects promote persistent hyperammonemia in the patient with hepatic insufficiency. Dopamine may act synergistically with furosemide in this setting because dopamine inhibits proximal renal tubular Na⁺/HCO₃⁻ cotransport.122

Administration of a carbonic anhydrase inhibitor (e.g., acetazolamide) or a thiazide (e.g., chlorothiazide) diuretic can indirectly augment hyperammonemia by inhibiting HCO₃⁻ generation in the renal tubular epithelium. Bicarbonate is necessary for mitochondrial synthesis of carbamoyl phosphate (an essential urea cycle substrate) and urea cycle function may be impaired (see Figure 19-2).100

Fluid Therapy Aggravating Electrolyte Depletions and Transcellular Shifts

Hyperglycemia caused by oral carbohydrate loading, diabetes mellitus, or glucose-supplemented fluids aggravates electrolyte depletion by osmotic diuresis. During the initial stages of refeeding in cats with HL, hyperglycemia also may provoke symptomatic thiamine deficiency (in patients with marginal thiamine reserves) because thiamine is a cofactor for several enzymatic reactions involving glucose use. Provision of thiamine is mandatory during refeeding of cats with HL and is accomplished using a water-soluble B-complex vitamin supplement. Glucose supplementation is contraindicated in cats with HL because it favors metabolic adaptations that precipitate refeeding syndrome, compromises adaptation to fatty acid oxidation, and may potentiate hepatic triglyceride accumulation via enhanced lipogenesis. Carbohydrates should not be used to increase the energy density of diets fed to cats with HL. However, carbohydrate supplementation of parenteral fluids may be necessary in very small or young dogs with PSVA because they may have inadequate gluconeogenic and glycolytic...

enzyme activity and insufficient muscle and liver glycogen stores to maintain euglycemia during anorexia or recovery from anesthesia and surgery.

**TREATMENT OF ACID-BASE DISTURBANCES IN LIVER DISEASE**

### Respiratory and Metabolic Alkalosis

Respiratory alkalosis usually does not cause clinical complications or require intervention. Amelioration of HE often attenuates hyperventilation. If loss of acid-rich gastric juice underlies development of metabolic alkalosis, treatment with an H₂ blocker or acid pump inhibitor (e.g., omeprazole) may allow normalization of systemic pH. In patients with hypokalemia, KCl supplementation of fluids is required for recovery from alkalosis. In the absence of ascites or edema, 0.9% NaCl may be administered to replace the chloride deficit. In the presence of ascites or edema, infusion of 0.45% NaCl in 2.5% dextrose is preferable. Induction of a bicarbonate diuresis by administration of the carbonic anhydrase inhibitor acetazolamide can also be effective if conventional therapy fails.⁶⁷

### Metabolic Acidosis

If alkalinization is necessary, a bicarbonate- or acetate-containing polyionic solution (e.g., Normosol-R, Plasma-Lyte) can be used for patients with hepatic insufficiency. Consideration of the patient’s sodium tolerance is essential because sodium bicarbonate delivers a sodium load that may increase ascites formation. In general, treatment with alkalinizing solutions or medications should be avoided in patients with signs of HE because alkalosis worsens hyperammonemia and increases NH₃ delivery to the CNS. If lactic acidemia is suspected, identification and correction of systemic hypoperfusion are warranted. An important potential cause of metabolic acidosis in animals with severe liver disease is renal dysfunction, which may develop as a result of hemodynamic disruptions associated with portal hypertension and systemic hypoperfusion or the underlying cause of liver injury (e.g., copper toxicosis, immune-mediated injury, infectious disease), chronic interstitial nephritis, or glomerulonephropathy. Renal tubular acidosis also has been recognized in dogs with copper-associated hepatotoxicity, drug-induced fulminant hepatic failure (e.g., carprofen or other NSAIDs), and in cats with HL.³⁴,⁴⁸

### Lactic Acidosis

With the exception of cats with HL and animals in fulminating hepatic failure, the importance of lactic acidosis in patients with spontaneous liver disease remains unclear. High anion gap metabolic acidosis, in the absence of renal failure or administration of unusual drugs, suggests lactic acidemia. Marked lactic acidosis in a patient with liver disease suggests the presence of some other complicating condition (i.e., endotoxemia, severe infection, disorders causing hypoperfusion) or acute fulminant hepatic failure. At a normal rate of lactate production, abrupt cessation of hepatic lactate metabolism does not result in clinically significant lactate accumulation because of a compensatory increase in lactate extraction by extrahepatic tissues.³²⁷ As a result of lack of correlation between systemic and CNS lactate concentrations, however, it is difficult to determine which patients may suffer from lactate administration (see Figure 19-13).¹⁵⁸ Therefore acetated Ringer’s solution (or a comparable crystallloid solution) has been recommended as an alternative alkalinizing solution for patients with serious hepatic dysfunction.¹³,²¹¹ As a bicarbonate precursor, acetate is more readily metabolized by peripheral tissues than is lactate (acetate combines with CoA, forming acetyl CoA). This process consumes one hydrogen ion from carbonic acid and yields one bicarbonate ion for each millimole of acetate metabolized. Although acetate usually is considered nontoxic, excessive administration of acetate may impair myocardial contraction and induce vasodilatation.⁸,²²⁹

It is unclear whether treatment with bicarbonate or a bicarbonate precursor is beneficial in patients with liver disease and lactic acidosis.⁷,⁹⁴ Administration of bicarbonate to dogs with hypoxic lactic acidosis does not facilitate recovery but rather increases blood lactate concentrations. Administered bicarbonate may have detrimental effects on hepatic and splanchnic circulation, increasing CO₂ delivery to the liver and decreasing hepatic intracellular pH.⁹⁴,¹⁶⁶

### Respiratory Acidosis

Respiratory acidosis is a grave prognostic finding in patients with liver disease and requires diagnostic investigation. Ventilatory support should be provided if hypventilation is present, but caution should be exercised to prevent hyperventilation and hypocapnia, which can decrease cerebral blood flow and metabolic rate. Calculation of the PA-Pao₂ gradient identifies impaired gas diffusion and ventilation-perfusion mismatch in patients with normal arterial Po₂ values. A PA-Pao₂ gradient greater than 15 mm Hg warrants consideration of oxygen therapy. Respiratory acidosis and increased PA-Pao₂ gradient justify a grave prognosis in animals with hepatic disease.

### MANAGEMENT OF ASCITES IN PATIENTS WITH LIVER DISEASE

Increased abdominal pressure caused by tense ascites can increase portal venous pressure. This effect can potentiate gastrointestinal hemorrhage from newly expanded varices, ectatic vessels, or ulcerative lesions, as well as protein loss from the intestines. Tense ascites also has negative hemodynamic effects on cardiac output. Studies of patients before and after fluid removal have shown a progressive increase in cardiac output, stroke volume, and
ventricular ejection rate. Tense ascites also can impair ventilation by restricting diaphragmatic movement and chest expansion and also can impair appetite by imposing gastric compression.

Management of factors contributing to ascites formation is essential. Treatment must be carefully supervised because iatrogenic problems related to ascites mobilization (e.g., sodium restriction, paracentesis, diuretic administration) can lead to complications (e.g., abnormalities of hydration, electrolytes, and acid-base balance).

Before treatment, the patient’s body condition score, body weight, and abdominal girth are recorded, and serum sodium, potassium, BUN, and creatinine concentrations and USG are determined to provide baseline information.

**Sodium Restriction**

Sodium restriction as proposed for dogs with cardiac or renal disease is instituted. A positive response to dietary management alone is rare. Low sodium intake for dogs and cats is less than 100 mg/100 kcal energy requirement or less than 0.1% to 0.2% sodium on a dry matter basis. By calculating daily sodium intake and measuring 24-hour urinary excretion of sodium, 24-hour sodium balance can be estimated in patients refractory to dietary sodium restriction. If negative sodium balance has not been achieved, additional sodium restriction can be recommended. In the future, drugs such as losartan and conivaptan may facilitate management of fluid imbalance in ascitic patients with liver failure.

**Diuretics**

Combined use of a loop diuretic (furosemide, 1 to 2 mg/kg orally every 12 hours) and an aldosterone antagonist (spironolactone, loading dosage of 2 to 4 mg/kg followed by 1 to 2 mg/kg orally every 12 hours) is recommended initially. The goal of diuretic therapy is to achieve a net negative sodium balance such that ascites can be resolved and prevented in the future. Combined use of furosemide and spironolactone produces a greater effect in humans than either drug used alone and usually does not result in iatrogenic hypokalemia. A similar strategy has been used in dogs, but at least one study failed to identify a diuretic response to spironolactone even at high doses in healthy dogs. If sequential evaluation of the patient every 5 to 7 days fails to identify sufficient mobilization of ascites but serum electrolyte concentrations and renal function remain normal and the owner has consistently fed a sodium-restricted diet, the dosage of each diuretic may be doubled. The rate of weight loss should not exceed 1% of body weight per day. If treatment still fails to mobilize ascites after an additional 7 to 14 days, large-volume paracentesis is recommended. In some patients with tense ascites, large volume paracentesis is used initially to improve patient comfort and well-being, as other strategies for ascites management are employed.

Complications of diuretic therapy include development or worsening of hyponatremia, a decreased GFR, hypokalemia or hyperkalemia, metabolic acidosis, and induction of HE. Diuretics are contraindicated in patients with preexisting hyponatremia (i.e., serum sodium concentration <130 mEq/L), known renal dysfunction, or active bacterial infection because these factors may predispose the patient to development of HRS. Although water restriction is used to manage hyponatremia in human patients, this approach is discouraged in veterinary medicine because it is difficult to closely monitor water intake in dogs and cats, and dehydration predisposes these animals to acute renal failure.

**Albumin**

Although administration of colloids may expand the intravascular compartment and facilitate mobilization of edema and ascites, these effects are short-lived because of transcapillary escape of albumin. Despite this limitation, hypoalbuminemic patients with liver disease and ascites may benefit from administration of albumin or synthetic colloids during large-volume paracentesis. Colloid infusion also may counter hypovolemia and hypotension during anesthesia and surgical procedures, in sepsis, and at the onset of HRS. Selection of the most appropriate colloid for a given situation depends on the required duration of effect, whether abnormalities of hemostasis are present, and whether other disease processes are aggravating hypoproteinemia. In patients with severe ongoing extracorporeal protein loss (e.g., intestinal loss, urinary loss), administered colloids may have very short retention time in plasma. If hypoalbuminemia is only the result of hepatobiliary disease, colloids have a longer plasma retention time.

Hypoalbuminemia does not appear to be a dominant factor in the pathophysiology of ascites formation in patients with liver disease. In fact, the presence of albumin in the effusion actually aggravates fluid accumulation. Studies in human patients with cirrhosis indicate that large-volume paracentesis of ascites should be coupled with intravascular colloid replacement using autologous albumin or plasma or synthetic colloids.

Blood component products are used to supply albumin in small patients because concentrated species-specific albumin is not available for veterinary use. Albumin concentrations range from 3.5 to 4.5 g/dL in whole blood or fresh frozen plasma and from 1.5 to 1.9 g/dL in packed RBCs, making it difficult and expensive to adequately correct albumin deficits. An infusion rate of 10 mL/kg/hr typically is used in dogs and cats with liver disease and hypoalbuminemia that require treatment with colloid. This approach provides important coagulation and transport proteins in addition to albumin. Plasma infusion also may decrease tendencies for adverse drug effects with medications that are highly protein-bound. In the absence of extrahepatic routes of
protein loss, albumin has a longer retention time than synthetic colloids.\(^{181}\) The patient’s size determines whether plasma administration can reasonably be expected to achieve adequate colloid repletion. Unfortunately, plasma administration can lead to complications associated with hypercitratemia such as symptomatic hypocalcemia and hypomagnesemia caused by chelation of these cations by citrate. Stored blood products also may be a source of additional NH\(_3\) and may introduce endotoxins, pyrogens, or bacteria if contaminated products are administered.\(^{67}\)

### Benefits and Hazards of Using Human Albumin in Animals

Some clinicians advocate administration of commercially available human albumin to veterinary patients. In particular, this practice has been recommended in patients presented for acute critical care. Veterinary clinicians should carefully consider the benefits and risks of this therapy. Use of albumin for similar purposes in human patients remains controversial.\(^{51,217,234}\) Type III hypersensitivity reaction has been seen in normal dogs when 25% human albumin solution was administered (HSA).\(^{83}\) Two of six dogs in this study died after infusion of human albumin. In another study of normal dogs, administration of HSA resulted in severe reactions in two of nine dogs given a single infusion and in two of two dogs given a second infusion. These studies indicate the risk of life-threatening adverse reactions to HSA infusion in healthy dogs.\(^{53}\) Seventeen of 73 (23%) ill dogs had at least one complication that potentially could be associated with administration of HSA. Three dogs had severe, delayed complications.\(^{224}\) An approximately 20% mortality rate was observed in a retrospective study of 5% HSA in dogs and cats.\(^{228}\) Severe hypersensitivity reactions, such as anaphylaxis, angioedema, and urticaria, were not identified. Moreover, discontinuation of HSA infusion and specific treatment of reactions were not required in any animal in this study.\(^{228}\) Many of these patients were critically ill, which may have contributed to the mortality rate. Serum IgG antibodies against HSA were evaluated in 14 critically ill dogs, and peak antibody response was observed 4 to 6 weeks after HAS administration. Interestingly, 5 of 68 negative control dogs also had a positive antibody response.\(^{137}\) Meta-analysis of autologous albumin compared with crystalloids or synthetic colloids in human patients failed to demonstrate advantage for albumin administration in several diseases. Opponents of its use emphasize the risks of infusing albumin in patients with disorders associated with increased vascular permeability.

Maintaining serum albumin concentration within a defined range theoretically may have clinical benefit, but limited clinical evidence supports this view with a few notable exceptions (e.g., emergency resuscitation, impending HRS, colloid replacement during large-volume paracentesis). The relatively mild clinical signs observed in genetically analbuminemic humans (with serum albumin concentrations <1 g/L) suggest that albumin is far from essential. These patients have other plasma constituents (e.g., globulins, lipids) that compensate for the absence of albumin’s colloidal effects.

Potential complications associated with albumin infusion include facial swelling, prolonged clotting time, increased respiratory effort, vomiting, fever, polyarthritis, vasculitis, dermatitis, glomerulonephritis, type III hypersensitivity reactions, fluid overload (especially pulmonary edema) when infused too rapidly, decreased GFR caused by presence of microaggregates that impede glomerular filtration and impaired renal sodium and water excretion.\(^{5,53,83,138,224,228}\) These renal effects may predispose to acute renal failure and are thought to result from increased peritubular oncotic pressure. Infused albumin also may impede the renal response to furosemide by limiting luminal delivery to the ascending Henle’s loop. Endogenous albumin may have antiinflammatory effects such as binding NO, oxidants, cytokines, and other inflammatory mediators, whereas manufactured albumin appears to permissively foster inflammation. Administered albumin also can have anticoagulant effects, exerting heparin-like activity on antithrombin III and inhibiting platelet aggregation.

Infusing albumin specifically to improve the oncotic pressure gradient and control interstitial fluid accumulation provides only a temporary benefit. Infused albumin initially may draw some fluid from the interstitium into the intravascular compartment, but later, when infused albumin escapes into the interstitium, it favors third-space accumulation of fluid. In septic patients, up to two thirds of administered albumin moves to the interstitial space within 4 hours and thereafter promotes interstitial fluid accumulation. Thus the colloidal benefit of albumin is transient at best, and it may worsen third-space fluid accumulation in the presence of vasculitis or impaired lymphatic function. In cirrhotic patients with ascites, extravasation of albumin into the peritoneal effusion has the potential to aggravate fluid retention. Use of human albumin products derived from pooled donor plasma also has the risk of infectious agent transmission. Consideration must be given to the potential for exposing clinicians and technicians to potentially infectious agents that are transmissible to human beings (e.g., prions).

### Synthetic Colloids

Dextran and hydroxyethyl starch (HES, hetastarch) are macromolecular colloids developed for use as acute volume expanders. Dextran is a linear polymer of glucose produced by bacterial enzyme systems. The preferred dextran for oncotic effect is dextran 70, which has an effective half-life of 24 hours in normal dogs. HES, a highly branched polymer of glucose (synthetic hydroxyethyl substitute of amylopectin), also has a plasma half-life of 24
hours in normal dogs. The pharmacokinetics of HES are complex owing to the molecular size and heterogeneity of component polymers. Elimination of HES occurs by glomerular filtration of small polymers, hydrolysis of larger polymers by α-amylase, or reticuloendothelial phagocytosis and metabolism in the liver, spleen, and lymph nodes. The HES that is retained in reticuloendothelial cells does not appear to have a detrimental effect on organ function in normal dogs, but its effects have not been evaluated in dogs with liver disease or portosystemic shunting where it may impede macrophage surveillance. Although HES expands plasma in humans for 12 to 48 hours, it increased oncotic pressure for less than 12 hours in hypoalbuminemic dogs. When used for oncolytic support, synthetic colloids usually are given at a dosage of 20 mL/kg/day and can be administered by slow infusion over many hours. Infusion of 20 mL/kg for 1 hour increased urine specific gravity in healthy dogs for over 6 hours after stopping the infusion (from 1.020 to 1.030).

**Adverse Effects of Synthetic Colloids in Patients with Liver Disease**

Synthetic volume expanders have predictable effects on hemostasis. The risk of bleeding with dextran is related to the dosage and type of dextran used. Hemostatic abnormalities may be related to dilutional effects on one or more coagulation factors, interference with platelet activity, decreased activity of von Willebrand factor, or increased fibrinolytic activity. Although results have varied, one study indicated that a fibrinogen deficiency likely caused dilutional coagulopathy, and ex vivo addition of fibrinogen completely corrected the coagulopathy. Prolonged clot formation time and decreased clot strength were noted in human patients after infusion of 7, 14, and 21 mL/kg of either HES 130/0.4 or gelatin compared with the Ringer’s acetate solution. Regardless of cause, hemostatic abnormalities are notable in animals with hepatobiliary disease given dextran 70. Intraoperative use of dextran 70 in dogs with PSVA has resulted in bleeding tendencies in patients assessed presurgically as having normal hematocrit, some patients with liver disease treated with synthetic colloids also have developed transient pulmonary edema.

Even though colloids are widely used, at least one author claims no single clinical study or systemic review has shown that administration of HES confers a clinically relevant benefit compared with crystalloids in critically ill patients or surgical patients in need of volume replacement. Contrary to the belief that a 4:1 ratio of crystalloid-to-colloid is needed for adequate volume replacement, recent studies of goal-directed resuscitation have observed crystalloid-to-colloid ratios of 1.0 to 1.6. Furthermore, Hartog et al believe that considering the lack of demonstrated superiority in clinical utility studies and the wide spectrum of severe adverse effects, the use of HES in intensive care units should no longer be continued and the belief that four times as much crystalloid as colloid is needed for successful resuscitation be seriously reconsidered.

In normal dogs and humans, the influence of HES on coagulation is dose-dependent and negligible when small doses are administered. However, normal dogs do develop a dose-dependent increase in bleeding time after blood replacement with HES. Induced hemostatic abnormalities in humans have involved von Willebrand factor and factor VIII coagulation activity, and cumulative dosages greater than 30 mL/kg have induced von Willebrand’s disease or hemophilia-like syndromes. Little information is available regarding HES use in veterinary patients, and no reports describe its effects on coagulation tests in patients with spontaneous hepatobiliary disease. Dogs with hypovolemia, however, did not demonstrate hemostatic abnormalities after being treated with hypertonic saline combined with colloids. Although HES is contraindicated in the presence of severe coagulopathies, its use in dogs with low serum albumin concentration not attributable to liver disease but with preexisting coagulation abnormalities resulted in normalization of coagulation in five of seven dogs.

Acute allergic reactions are possible with use of dextran and HES. Adverse effects associated with nonalbumin plasma extenders have been well studied only in healthy dogs. Isovolemic hemodilution with HES and polymerized bovine collagen did not have adverse effects on hepatic histology, but normal dogs receiving hypertonic saline (6%) and dextran 70 at a maximally tolerated dosage (20 mL/kg) experienced increases in alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase during the first 72 hours.

**Therapeutic or Large-Volume Paracentesis**

Therapeutic or large-volume paracentesis usually is safe. However, severe consequences (including death) have been reported in patients with hepatic cirrhosis. Characteristic hemodynamic maladaptations in these patients include increased plasma renin activity, increased norepinephrine concentrations, decreased systemic vascular resistance, and an increased hepatic venous pressure gradient. The most common complications of therapeutic abdominocentesis in humans include HE, decreased renal function, and hyponatremia. The influence of rapid abdominocentesis on portal pressure and vena caval pressure has been evaluated in humans and dogs. These studies have not identified deleterious effects on portal or
systemic venous pressure. The effect of large-volume paracentesis on reformation of ascites in cirrhotic dogs treated by sodium restriction or high sodium intake is shown in Figure 19-17. These data explain why sodium restriction is so important in overall management of patients with ascites and must be established before or concurrent with therapeutic paracentesis.

Use of Colloids and Large-Volume Paracentesis

Intravenous colloid administration can facilitate mobilization of ascites in the hypoalbuminemic patient when salt restriction and diuretics are ineffective. In these patients, large-volume paracentesis is coupled with intravenous colloid administration. Without colloids, therapeutic or large-volume paracentesis can lead to contraction of effective circulating blood volume, renal dysfunction, and dilutional hyponatremia.

Large-volume paracentesis coupled with albumin administration is safe and useful for management of intractable ascites. Alternative colloids have been investigated because of the high cost of homologous albumin. In comparative studies, postparacentesis circulatory dysfunction occurred twice as frequently in patients receiving synthetic colloids as in those receiving homologous albumin. Humans given dextran 70 at 12 hours after paracentesis experienced resolution of their hemodynamic abnormalities and became normovolemic (84 ± 14 mL of dextran 70 for each 1000 mL of ascites removed). Patients receiving dextran 70 concurrently with paracentesis did not develop significant hemodynamic changes in the first 24 hours after paracentesis. Unfortunately, gastrointestinal bleeding as a complication of dextran infusion precipitated HE in some patients. As a result of the short plasma retention time of dextran 70, some of these patients developed hypovolemia 24 hours after paracentesis. An alternative approach with a more reliable outcome was accomplished by combining smaller volume daily paracentesis with dextran 70 (6 g for each 1000 mL of ascites removed). Compared with single diuretic therapy, large-volume paracentesis combined with intravenous dextran 70 and diuretics
resulted in a better outcome and fewer adverse effects in cirrhotic patients (i.e., a high frequency of HE occurred when diuretics alone were used to mobilize ascites). The use of large-volume paracentesis in dogs and cats is complicated by a lack of available autologous albumin and the necessity to use human albumin, species-specific plasma, or synthetic colloids. Plasma is preferred in small patients, and HES can be used in larger patients (more hemorrhagic complications result from use of dextran 70 than HES in our experience). Fluid removal is completed aseptically using a 14-gauge Teflon catheter. A sterile closed-end polypropylene tomcat catheter can be used to maintain patency of the Teflon catheter. For large-volume paracentesis, fluid is removed over 30 to 45 minutes. After paracentesis, the patient rests quietly with the puncture site positioned uppermost to prevent formation of a subcutaneous seroma; if possible, a pressure bandage is applied to the puncture site. Avoiding the midline as the site of abdominal puncture prevents gravitational pooling of subcutaneous fluid (a ventrolateral flank approach is preferred). Ventral midline puncture may increase the risk of visceral laceration (due to ovariohysterectomy adhesions). Confirming that the urinary bladder is empty, reviewing abdominal radiographs for abnormally positioned organs, and ballotting the puncture site immediately before needle insertion to help prevent visceral laceration.

Management of Bleeding Tendencies in Patients with Liver Disease

Blood Transfusion and Vitamin K1 Administration

Whole-blood transfusions are indicated for patients with symptomatic anemia or coagulopathy. Anemia usually becomes symptomatic in dogs when the packed cell volume (PCV) is 18% or less and in cats when the PCV is 15% or less. Cats with liver disease seem predisposed to hemolysis associated with formation of Heinz bodies. Sometimes hemolysis occurs after treatment with certain drugs or products that provoke oxidative damage (e.g., excessive vitamin K1, propofol, propylene glycol-containing drugs, onion powder used to enhance food palatability) or as a result of hypophosphatemia. Coagulation abnormalities in liver disease result from several different deficiencies or abnormalities. The most commonly considered cause of bleeding is factor deficiency arising from hepatic synthetic failure. However, clinical evidence suggests that these patients more often develop a vitamin K-responsive coagulopathy. This observation may be related to intestinal malabsorption (e.g., secondary to abnormal enterohepatic bile acid turnover), insufficient dietary intake, or impaired enteric synthesis of vitamin K secondary to prophylactic antimicrobial therapy. Vitamin K deficiency is avoided or corrected by administration of vitamin K1 at a dosage of 0.5 to 1.5 mg/kg for two or three treatments at 12-hour intervals initially and then once weekly as required. Sequential PIVKA clotting tests can determine the relationship of a coagulopathy to vitamin K deficiency and the need for weekly vitamin K1 injections. Other conditions that may contribute to bleeding tendencies in patients with liver disease include increased factor consumption or use as occurs with extensive gastrointestinal bleeding and disseminated intravascular coagulation.

If a blood transfusion is required, fresh whole blood is most helpful. Stored blood products may contain lactate, can deliver substantial amounts of NH3 that may exacerbate HE, and also may introduce pyrogens or endotoxins that are poorly tolerated in patients with liver disease. The rate of blood administration depends on the circumstances and urgency imposed by bleeding tendencies. Usually, an infusion rate of 5 to 10 mL/kg/hr is safe and effective.

DDAVP Administration

In addition to blood component therapy, coagulopathies may be ameliorated by administration of 1-deamino-8-D-arginine AVP (DDAVP, desmopressin) at a dosage of 0.5 to 5.0 µg/kg subcutaneously or diluted in 10 to 20 mL of saline and given intravenously slowly over 10 minutes during the perioperative period (e.g., before liver biopsy) or during a bleeding crisis. Administration usually is coupled with transfusion of fresh frozen plasma. Although DDAVP can mitigate bleeding in humans and animals with hepatobiliary disease, its mechanism of action in this circumstance remains uncertain. Hemosstatic responses to DDAVP administration to dogs include liberation of preformed endothelial von Willebrand factor monomers and increased factor VIII activity (Figure 19-18). The benefits in patients with liver disease seem too great to be explained based on these
mechanisms because neither of these factors is notably deficient in hepatic insufficiency. DDAVP may have hemodynamic or vasoactive actions that have a salutary effect on microvascularature in areas of active hemorrhage. DDAVP has a narrow (4 to 6 hours) therapeutic window of effectiveness, and administration must be planned for optimal response (e.g., immediately before an invasive procedure). Administration of additional doses does not offer therapeutic benefit in terms of von Willebrand factor and may aggravate edema or ascites by increasing water retention.

**Hemorrhage Caused by Citrate Loading**

In very small patients (<10 kg) receiving large quantities of blood or blood components preserved with CPD, acquired hemorrhagic tendency is treated with 0.1 mL/kg of 10% CaCl₂ suspended in 10 to 20 mL of 0.9% saline and given over 10 to 20 minutes. Treatment is repeated until ionized hypocalcemia has been corrected.

**REFERENCES**

35. Carey RG, Bucuvalas JC, Balistreri WF, et al. Hyponatremia increases mortality in pediatric patients...


48. Center SA. Unpublished observations College of Veterinary Medicine, Cornell University; 2005.


