Fluid, Electrolyte, and Acid-Base Disturbances in Liver Disease

Joao Felipe de Brito Galvao and Sharon A. Center

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).[174] Separate hepatic and ductular transport mechanisms allow regulation of bile composition and volume in response to changing physiologic needs.[110] 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.[142] The canaliculus is a confined space formed by a junction between specialized portions of cell membranes from two adjacent hepatocytes. The surfaces defining the canaliculus 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 canaliculus 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. Almost 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 concentrated when water and inorganic electrolytes (e.g., sodium, chloride, bicarbonate) 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 choleresis (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

Species	Flow (μL/min/g liver)	Na$^+$ (mEq/L)	K$^+$ (mEq/L)	Cl$^-$ (mEq/L)	HCO$_3^-$ (mEq/L)	Taurocholate (Canalicular Bile) (mM/L)
Dog	0.19 (n = 24)*	171 (n = 75)	5.1 (n = 73)	66 (n = 83)	61 (n = 83)	37 (n = 80)
Cat	0.23 (n = 5)	163 (n = 16)	4.2 (n = 16)	109 (n = 16)	24 (n = 16)	26 (n = 10)

*n = Number of observations reported.
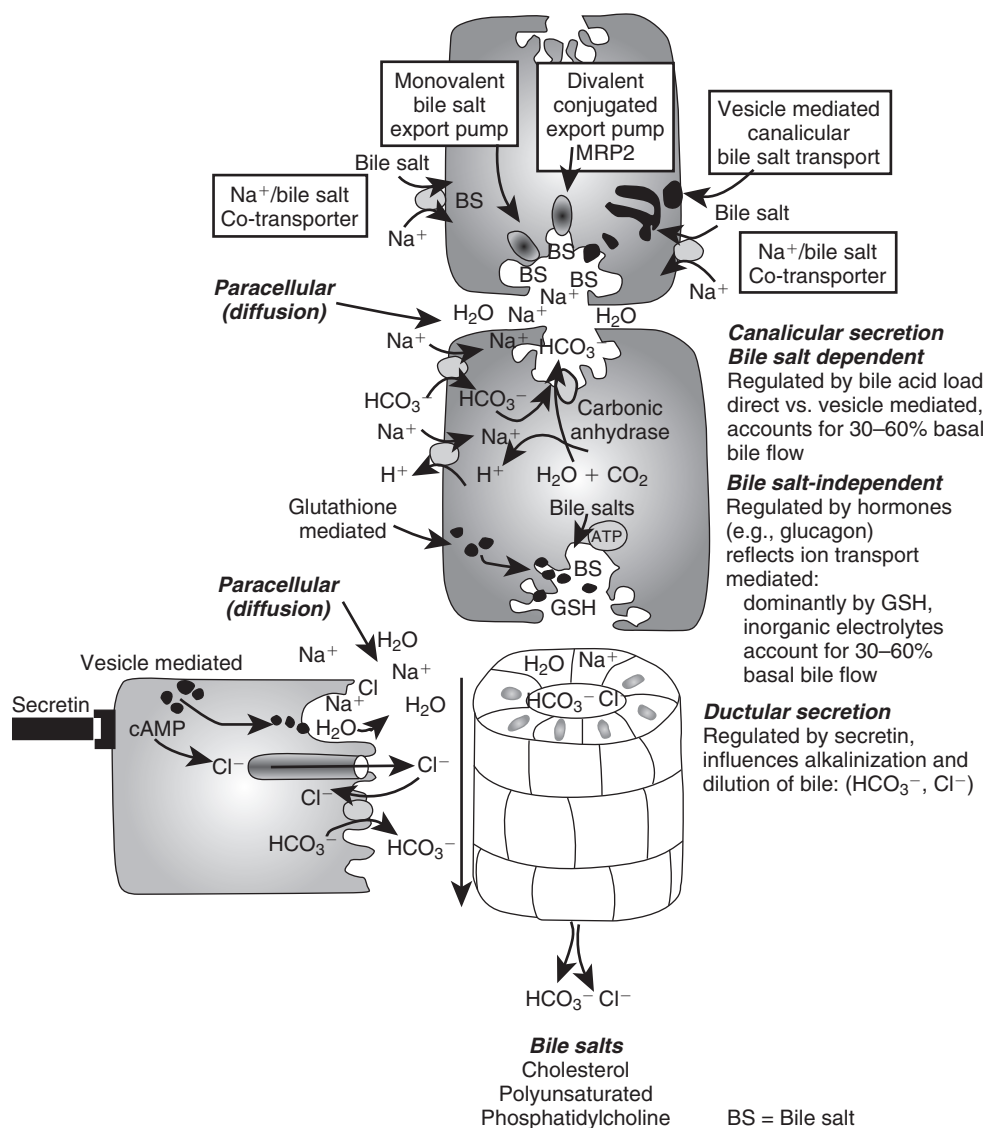
Figure 19-1 Transcellular (active pump-dependent) and paracellular (diffusion-dependent) mechanisms of bile formation in the hepatocyte and bile duct epithelium. Canalicular secretion depends on bile salt-dependent and salt-independent mechanisms. Efflux of bile acids into canaliculi involves facilitated diffusion dependent on canalicular carrier proteins, ATP-dependent mechanisms, and exocytosis of cytosolic vesicles; these involve specific monovalent bile salt, bivalent bile salt, sodium/bile salt cotransport, and vesicle-mediated bile acid transport. Bile acid-independent bile flow is mediated by a Na transport/Na^+, K^+-ATPase-linked mechanism, bicarbonate transport (associated with carbonic anhydrase and a canalicular membrane pump), and transport of organic solutes (principally glutathione [GSH]). Transcellular mechanisms in ducts primarily transport bicarbonate and chloride. Secretin initiates expression of a Cl^- transmembrane channel (cystic fibrosis transmembrane regulator) and subsequent activation of the Cl^-/HCO_3^- exchanger leading to bicarbonate secretion in ductal bile. Whereas bile formation occurs continuously, hormones (e.g., glucagon) can increase bile salt-independent mechanisms. Ductular secretions are stimulated by secretin causing bile alkalinization and dilution.

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 canalicular 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.[142] Protein carriers facilitate cytosolic transport of bile acids to canalicular membranes. Efflux of bile acids into canaliculi involves several mechanisms including facilitated diffusion dependent on canalicular carrier proteins, an adenosine triphosphate (ATP)-dependent mechanism, and exocytosis of cytosolic vesicles. Collectively, transcellular transport of bile acids and micelle formation maintain a marked concentration 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. Membrane pumps (canalicular multispecific organic anion transporter [cMOAT], also termed the multidrug resistance associated protein-2 [MRP2]) facilitate GSH exportation. The strong osmotic influence of GSH on bile flow derives from its hydrophilic nature, active membrane exportation, and hydrolysis by membrane affiliated χ-glutamyltransferase (χGT) 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 spontaneous 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 alkalinization and dilution. Disease states causing bile ductule proliferation also increase bile flow (e.g., cirrhosis, extrahepatic bile duct occlusion, inflammatory disorders). Bile ductules and ducts can also reabsorb bile as shown in cholecystectomized dogs.[74]

HEPATIC NITROGEN METABOLISM: DETOXIFICATION, EXCRETION, AND ROLE IN ACID-BASE BALANCE
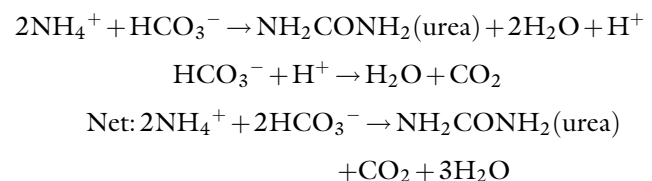### Urea Cycle and Glutamine Cycle

The liver converts waste nitrogen to an excretable form.[55] Nitrogen derived from amino acids can be converted to ammonia directly or indirectly after incorporation into glutamate or aspartate in the liver. Ammonia subsequently is detoxified by conversion to urea (Figure 19-2). Two mechanisms exist for hepatic nitrogen detoxification. 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. Regulation 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 homeostasis, as explained by the following reaction (using the amino acid alanine as an example of a nitrogen source)[55]:

$$(alanine)CH_3CH(CO_2)NH_3 + 3O_2 \rightarrow 2CO_2 + HCO_3^- + NH_4^+ + H_2O$$
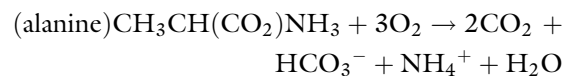
Generation of one positive (NH_4^+) and one negative (HCO_3^-) charge has the potential to maintain electroneutrality. However, because physiologic pH is in the range of 7.0 to 7.4, only 1% of ammonia exists as ammonia. Therefore the protons represented by the ammonium ions cannot be readily transferred to HCO_3^-, 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[55]:

$$2NH_4^+ + HCO_3^- \rightarrow NH_2CONH_2(urea) + 2H_2O + H^+$$
$$HCO_3^- + H^+ \rightarrow H_2O + CO_2$$
$$Net: 2NH_4^+ + 2HCO_3^- \rightarrow NH_2CONH_2(urea) + CO_2 + 3H_2O$$

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 tubular production of ammonium from glutamine. Traditional 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
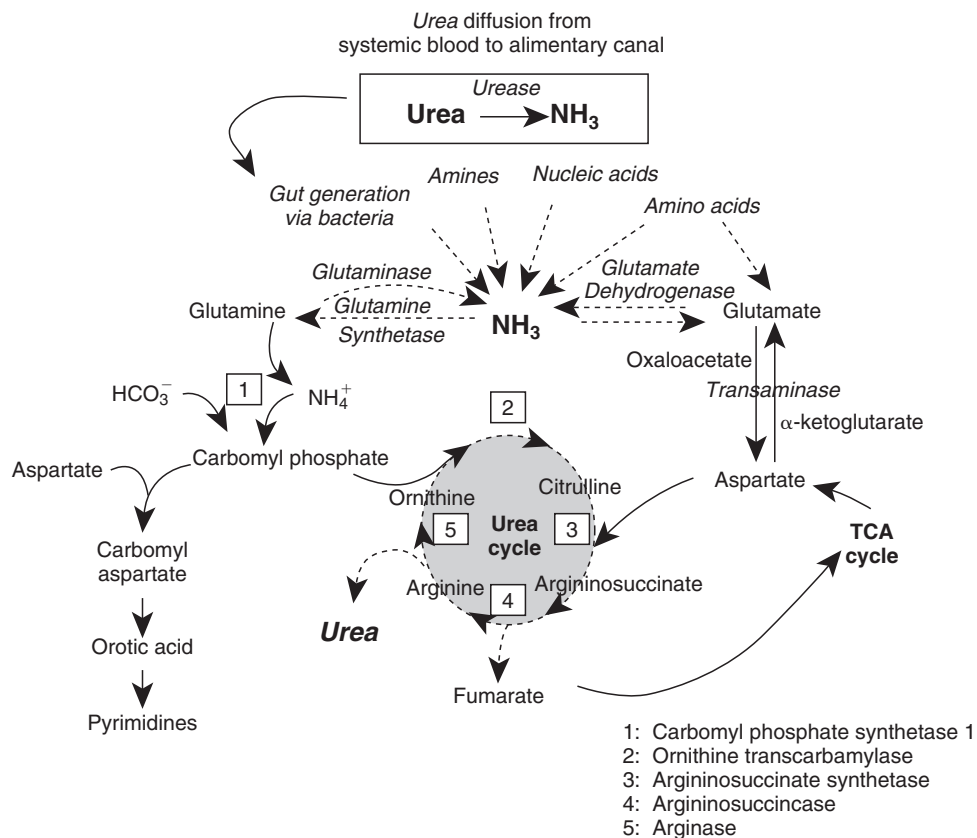
Figure 19-2 Diagram showing the biochemical reactions involved with nitrogenous waste production, detoxification, and elimination in the liver. See text for explanations.

already protonated.[55] An alternative view is that urinary excretion of NH_4^+ 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.
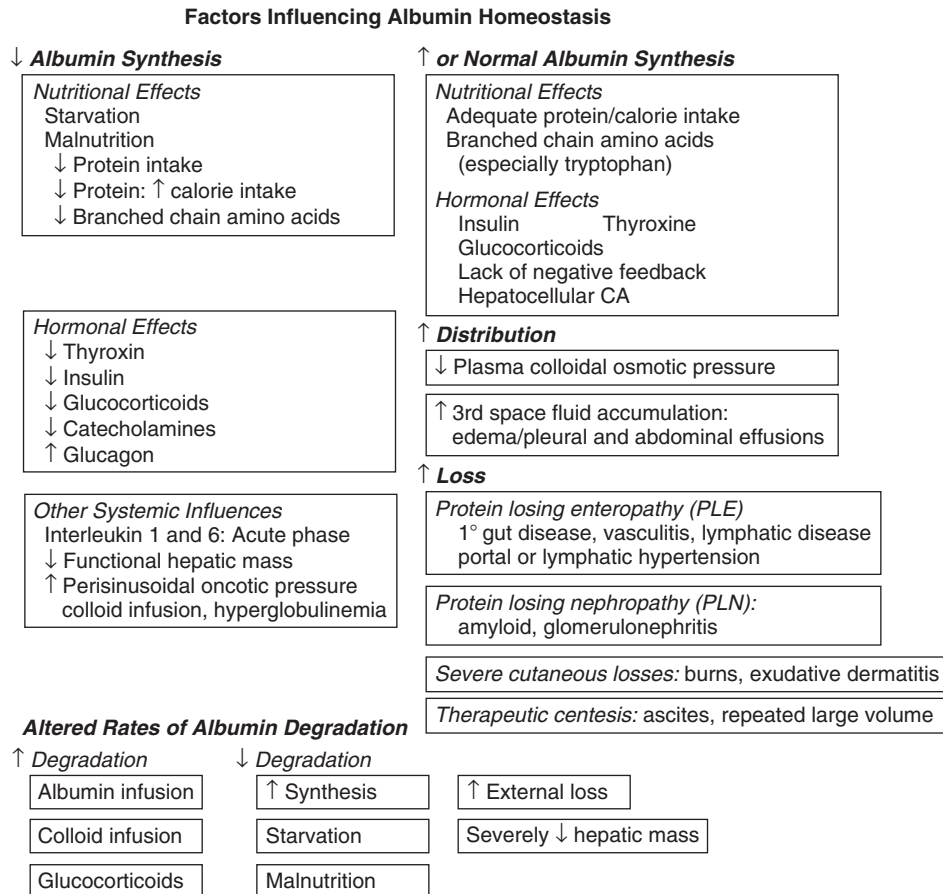
SERUM PROTEINS: ALBUMIN AND GLOBULINS

Albumin

Albumin accounts for 25% of the proteins synthesized by the liver.[151] 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., glomerulo-nephritis, 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.[179] Normally, only 20% to 30% of the hepatocytes produce albumin, and synthesis can be increased as needed by a factor of 200% to 300%.[75]

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.[178] 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.[115,132,179] 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).[66,178] Synthesis of albumin also decreases, sometimes dramatically, during critical illness as part of a negative acute-phase response.[32,38]

Hepatocellular synthesis of albumin is affected by a number of factors, the most important of which is the COP of the hepatic interstitial matrix.[179] 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

Factors Influencing Albumin Homeostasis

↓ Albumin Synthesis

Nutritional Effects
Starvation
Malnutrition
  ↓ Protein intake
  ↓ Protein: ↑ calorie intake
  ↓ Branched chain amino acids

Hormonal Effects
  ↓ Thyroxin
  ↓ Insulin
  ↓ Glucocorticoids
  ↓ Catecholamines
  ↑ Glucagon

Other Systemic Influences
  Interleukin 1 and 6: Acute phase
  ↓ Functional hepatic mass
  ↑ Perisinusoidal oncotic pressure
    colloid infusion, hyperglobulinemia

↑ or Normal Albumin Synthesis

Nutritional Effects
  Adequate protein/calorie intake
  Branched chain amino acids
    (especially tryptophan)

Hormonal Effects
  Insulin   Thyroxine
  Glucocorticoids
  Lack of negative feedback
  Hepatocellular CA

↑ Distribution
  ↓ Plasma colloidal osmotic pressure
  ↑ 3rd space fluid accumulation:
    edema/pleural and abdominal effusions

↑ Loss
  Protein losing enteropathy (PLE)
    1° gut disease, vasculitis, lymphatic disease
    portal or lymphatic hypertension

  Protein losing nephropathy (PLN):
    amyloid, glomerulonephritis

  Severe cutaneous losses: burns, exudative dermatitis

  Therapeutic centesis: ascites, repeated large volume

Altered Rates of Albumin Degradation

↑ Degradation	↓ Degradation	
Albumin infusion	↑ Synthesis	↑ External loss
Colloid infusion	Starvation	Severely ↓ hepatic mass
Glucocorticoids	Malnutrition	

Figure 19-3 Factors and conditions influencing albumin synthesis and degradation.

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.[132] 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.[241] The half-life of plasma albumin is 7 to 10 days in dogs and 6 to 9 days in cats.[68,69,79] The rate of albumin catabolism is highly variable, but its fractional catabolic rate is directly proportional to the plasma albumin concentration and pool size.[104] 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., Ca^{2+}, Mg^{2+}, Cu^{2+}) and metabolites (e.g., fatty acids, thyroxine, bilirubin, bile salts, amino acids).[136] Albumin accounts for most of the plasma thiol content (i.e., sulfhydryl bonds) and provides protection against oxidative stress.[175] Albumin also provides antioxidant activity by binding reactive transition metals (e.g., Cu^{2+}) that catalyze free radical generation.[136] Other important effects of albumin involve anticoagulant, antithrombotic, and antiinflammatory effects.

Oxidized and glycosylated forms of albumin occur in human patients with cirrhosis,[231] 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.[231] 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.[56,157]

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
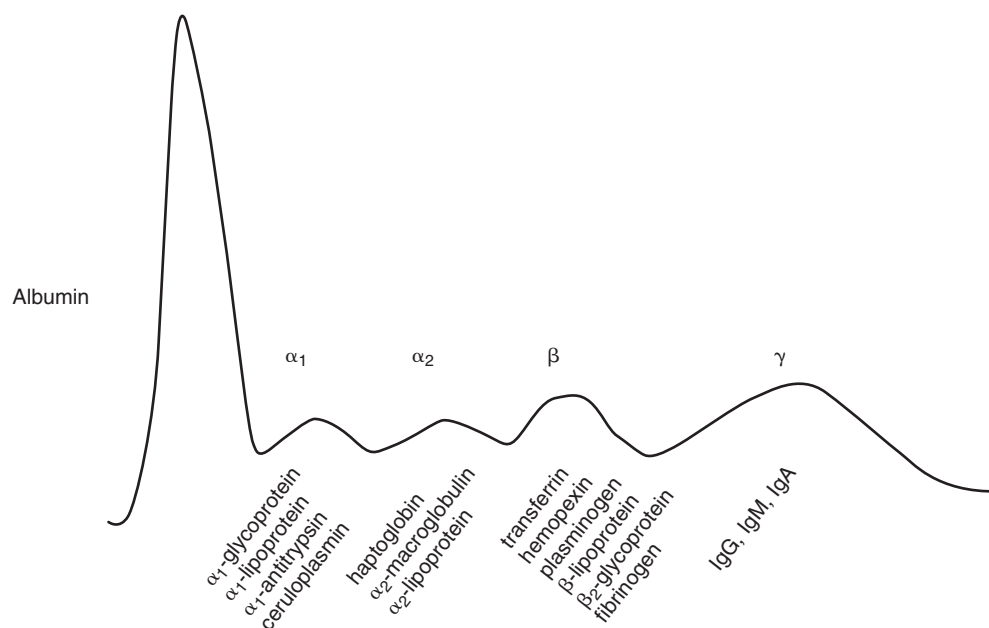
Figure 19-4 Diagram showing a cellulose acetate electrophoretogram with representative proteins in their respective regions.

development of autoantibodies. In severe hepatic insufficiency, decreased α-globulins (e.g., haptoglobin, α_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 (NH_3) to an excretable form (urea). Hepatic 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 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 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 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 NH_3 through glutamine synthesis, as occurs in muscle, is only temporary except in the kidney where glutamine is metabolized to release 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
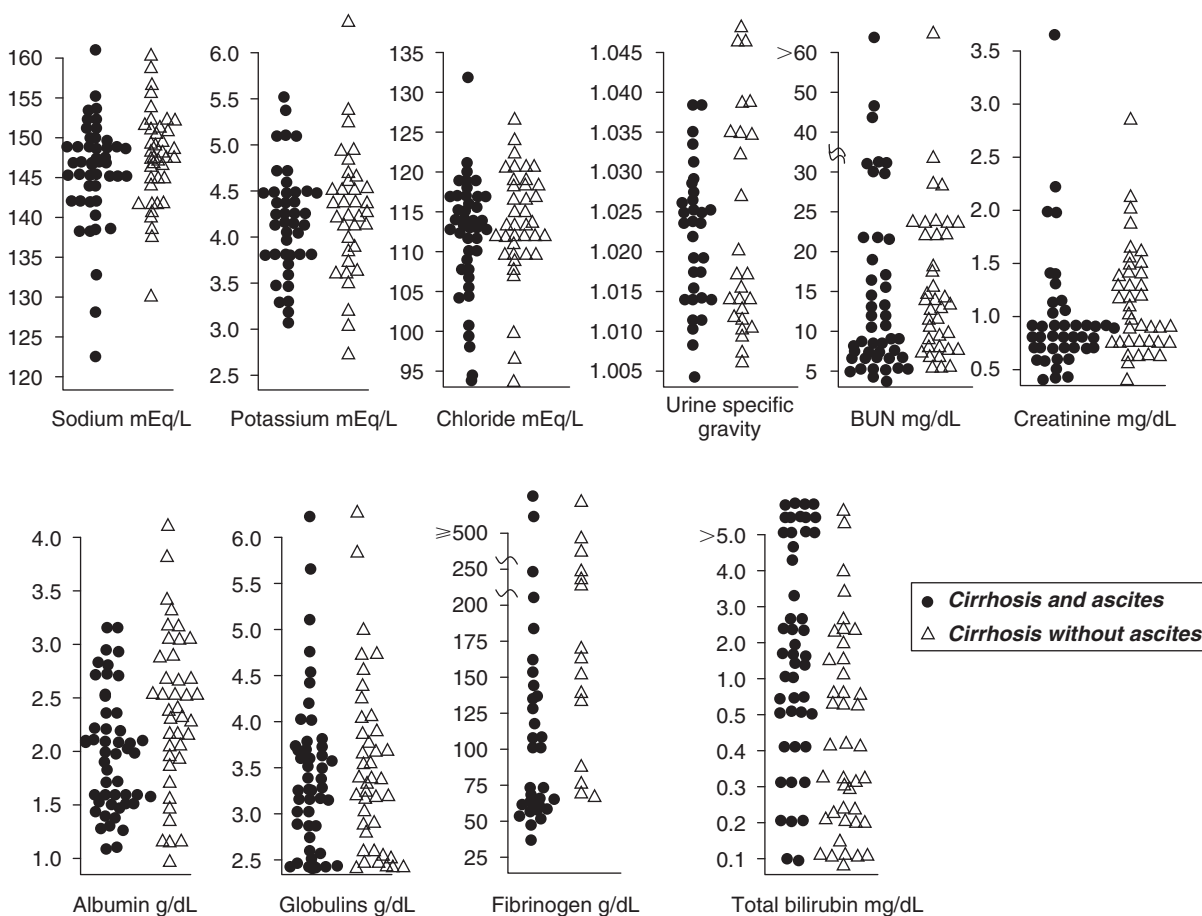
Figure 19-5 Scattergram showing the serum electrolytes, blood urea nitrogen (BUN), creatinine, proteins, and total bilirubin and urine specific gravity in dogs with hepatic cirrhosis with and without ascites. (Data from SA Center: College of Veterinary Medicine, Cornell University, 1998).

concentrations in dogs and could be used to assess the clinical importance of hypocalcemia.[24,144] However, total calcium concentration does not predict ionized calcium concentration in dogs.[185] Therefore, it is not reliable to correct total serum calcium concentration based on serum albumin concentration.[143,144] A reliable relationship between albumin, protein, and calcium concentrations also does not occur in cats.[24,80]

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.[178,243] 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.[19,38,118,152] 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 splanchnic vasodilatation and transcapillary leakage of albumin.[136] 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
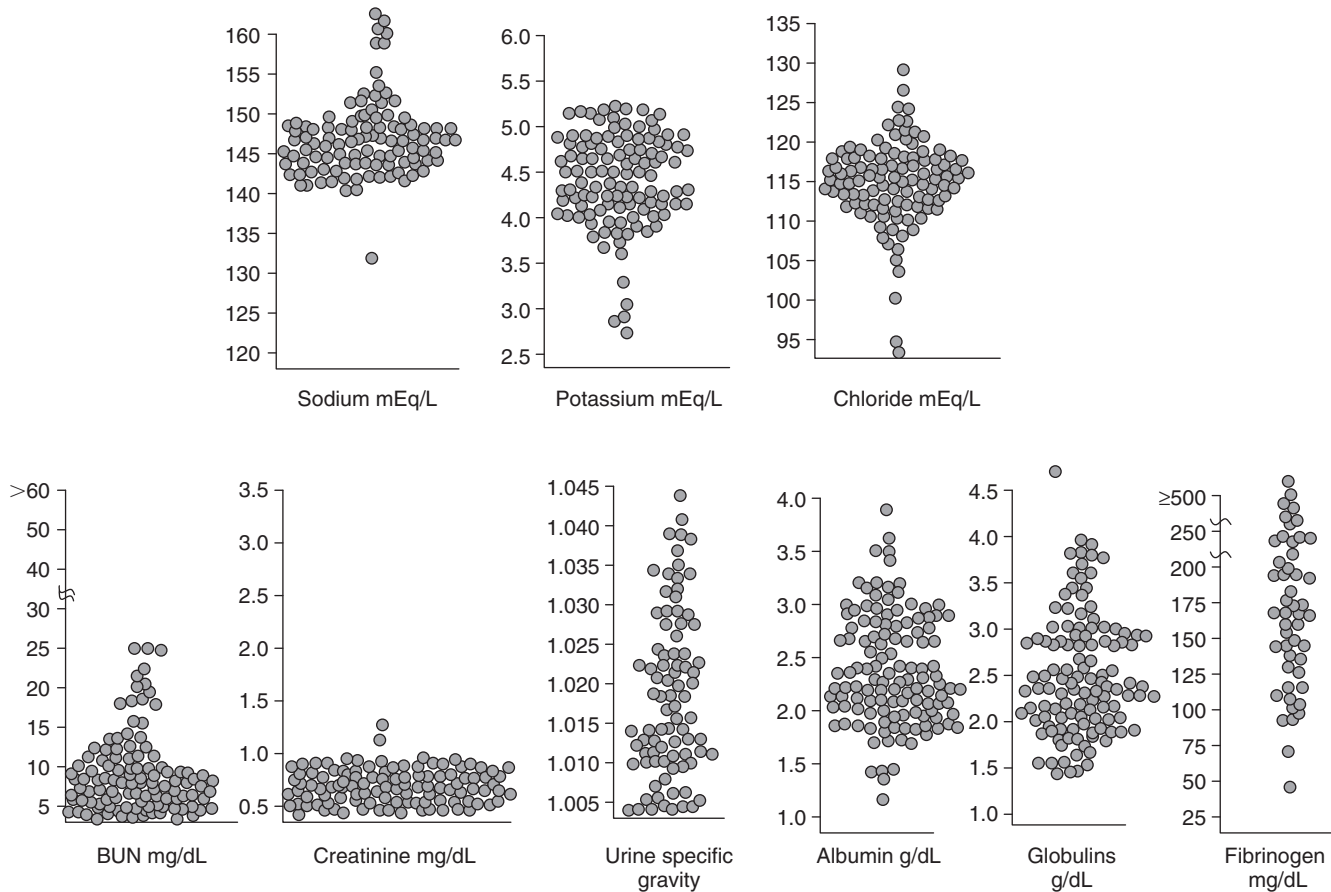
Figure 19-6 Scattergram showing the serum electrolytes, blood urea nitrogen (BUN), creatinine, and proteins, and urine specific gravity in dogs with portosystemic vascular anomalies. (Data from SA Center: College of Veterinary Medicine, Cornell University, 1998).

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 α-globulins and acute-phase proteins. α-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. α-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
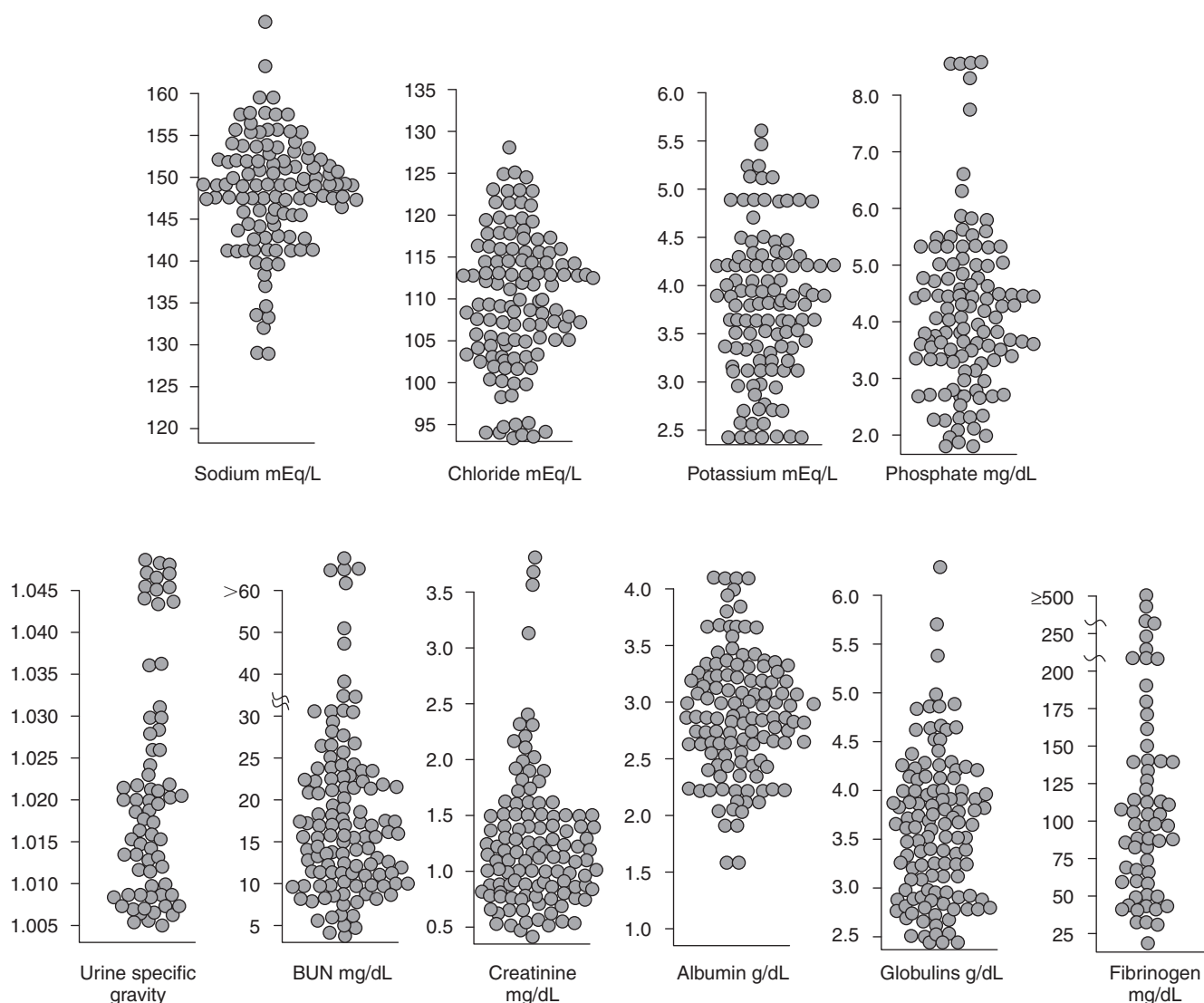
Figure 19-7 Scattergram showing the serum electrolytes, blood urea nitrogen (BUN), creatinine, proteins, and urine specific gravity in cats with hepatic lipidosis; n = 73. (Data from SA Center: College of Veterinary Medicine, Cornell University, 1998).

(e.g., vomiting, diarrhea, nutrient malassimilation), treatment with loop diuretics, and secondary hyperaldosteronism.[30,213,221] Magnesium deficiency also can complicate hypokalemia by potentiating kaliuresis through its effects on aldosterone.[84] 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.[39]

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.[93,212,213] 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.[242] Patients given potassium chloride to establish normokalemia experienced decreased arterial NH_3 concentration and pH, increased arterial NH_4^+/NH_3 ratio, decreased urine pH, and slightly increased 24-hour urinary ammonia excretion with a significantly
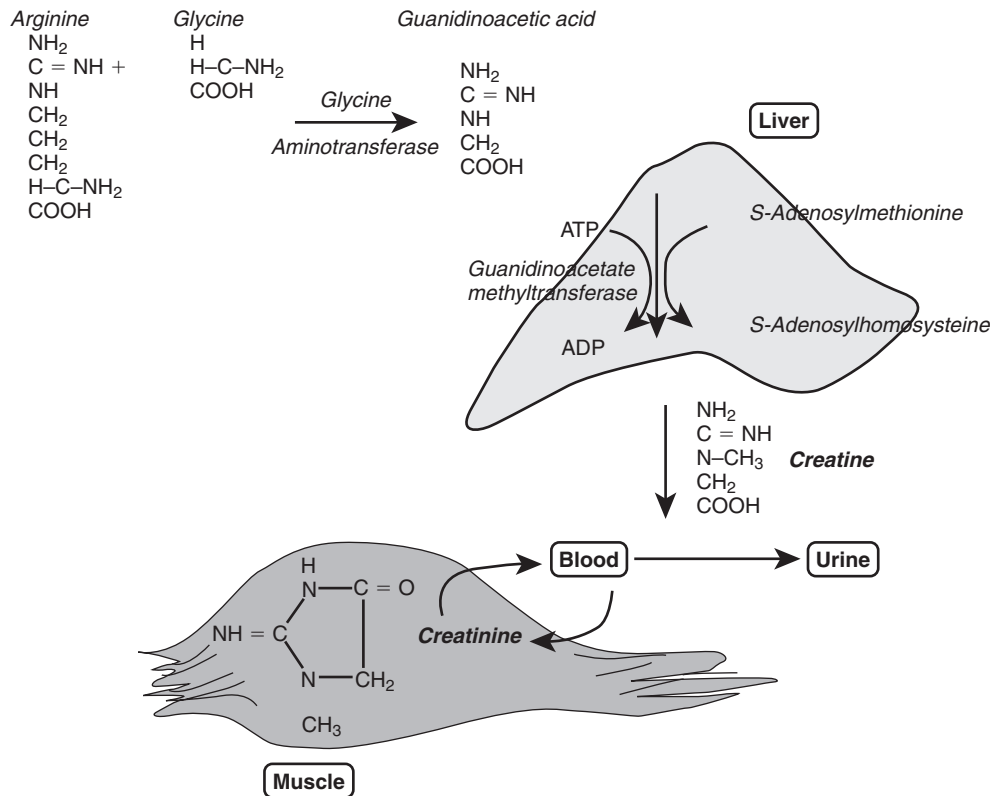
Figure 19-8 Diagrammatic representation of hepatic contribution to creatine synthesis. (Adapted from Heymsfield SB, Arteaga C, McManus C, et al. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. Am J Clin Nutr 1983;37:478–494.)

increased urine NH_4^+/NH_3 ratio. Mechanistically, potassium infused into the hypokalemic patient replaces intracellular hydrogen ions. The displaced cellular hydrogen ions decrease blood pH, promoting conversion of NH_3 to the less-diffusible NH_4^+ form. This small shift in pH is not great enough to stimulate renal ammoniagenesis, but reduced urine pH leads to increased excretion of NH_4^+. This effect may be augmented by increased plasma aldosterone given its ability to increase hydrogen ion delivery into distal renal tubular fluid.[188]

Serum Potassium Concentration and Ammoniagenesis

Experimental and clinical observations of potassium depletion and loading suggest that renal NH_3 production is intimately linked with potassium homeostasis. Low serum potassium concentrations stimulate and high serum potassium concentrations suppress renal ammoniagenesis.[154,214] A closed-loop regulatory system modulates NH_3 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 HCO_3^- production by increasing collecting duct expression of an H^+-K^+-ATPase that facilitates reabsorption of K^+ in exchange for H^+.[119,154] Potassium deficiency also may increase luminal electronegativity in the proximal tubule, stimulating HCO_3^- secretion.[31] 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.[18] 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.[6] 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
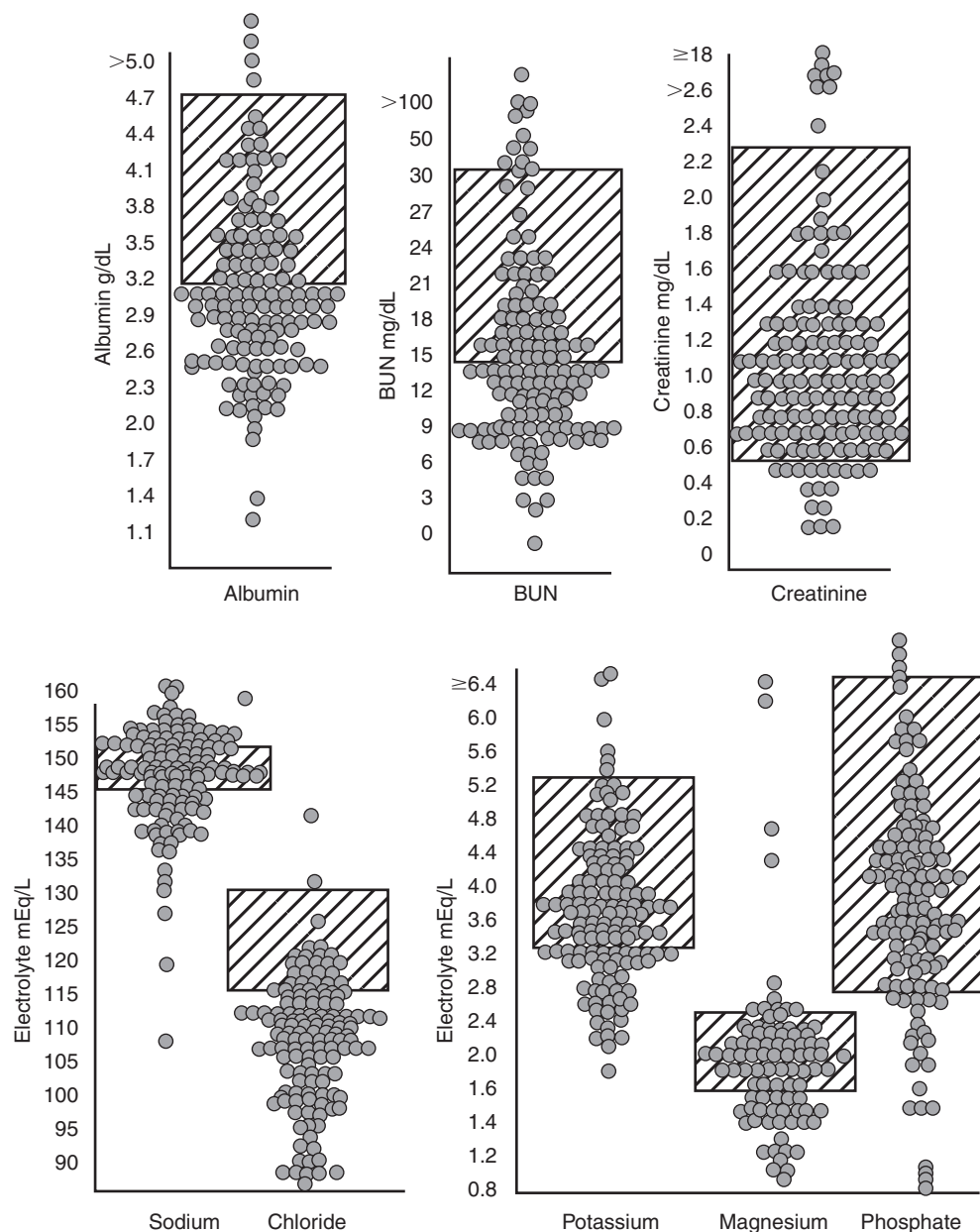
Figure 19-9 Scattergram showing the serum potassium, magnesium, phosphate, sodium, chloride, albumin, blood urea nitrogen (BUN), and creatinine from a survey of 157 cats with severe hepatic lipidosis. Normal range indicated by slashed boxes. (Data from SA Center: College of Veterinary Medicine, Cornell University, 2004).

refeeding. Hypophosphatemia in patients with liver disease is thought to reflect intracellular shifts of phosphate.[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.[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

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.[25,35,86,108,113] 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).[17,73,140,164,227] 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.[25,86] Abnormal intrarenal accumulation of angiotensin II occurs early in the disease process, even before activation of the RAAS.[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.[124] Some dogs maintained normal sodium balance after ingestion of 150 mEq/day of sodium, but others developed ascites.[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.[90] Acute changes in portal venous pressure in cirrhotic dogs initiate AVP-mediated antidiuresis. Both systemic and splanchnic arterial vasodilatation can stimulate nonosmotic AVP release and activate other antidiuretic and vasopressor systems.[86,90] Early in cirrhosis ("compensated cirrhosis"), transient neurohormonal responses increase plasma volume and temporarily suppress baroreceptor signaling. As the disease progresses, arterial vasodilatation 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.[200] Conivaptan, a nonpeptide, dual V1a/V2 AVP receptor antagonist has shown promising results in both animals[240] and humans.[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.[9]

Increased Basal Cortisol and ACTH Concentrations

Increased basal cortisol and adrenocorticotropic hormone (ACTH) concentrations complicate hepatic insufficiency associated with acquired portosystemic shunting in dogs, but normal adrenal response to low-dose dexamethasone suppression is maintained.[180] High basal cortisol concentrations also were found in dogs with congenital PSVA, and concentrations normalized after successful shunt ligation.[203] 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 respose.[105] Dogs with PSVA also have high free-water flux and an abnormally high GFR that normalize after shunt ligation.[65] 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.[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 11β-hydroxysteroid dehydrogenase-2 (11β-HSD-2), the enzyme that interconverts endogenous and exogenous biologically active 11β-hydroxysteroids and their inactive 11-ketosteroid counterparts. 11β-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 11β-HSD-2 can mimic mineralocorticoid excess by allowing inappropriate access of 11β-hydroxyglucocorticoids to mineralocorticoid receptors.[4,114,171] The up-regulation of the vasopressin-regulated water channel aquaporin-2 (AQP2) and increased targeting of AQP2 to luminal membranes likely to contribute to the increased water reabsorption and urinary concentration in hepatic cirrhosis.[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.[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 antidiuretic 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 1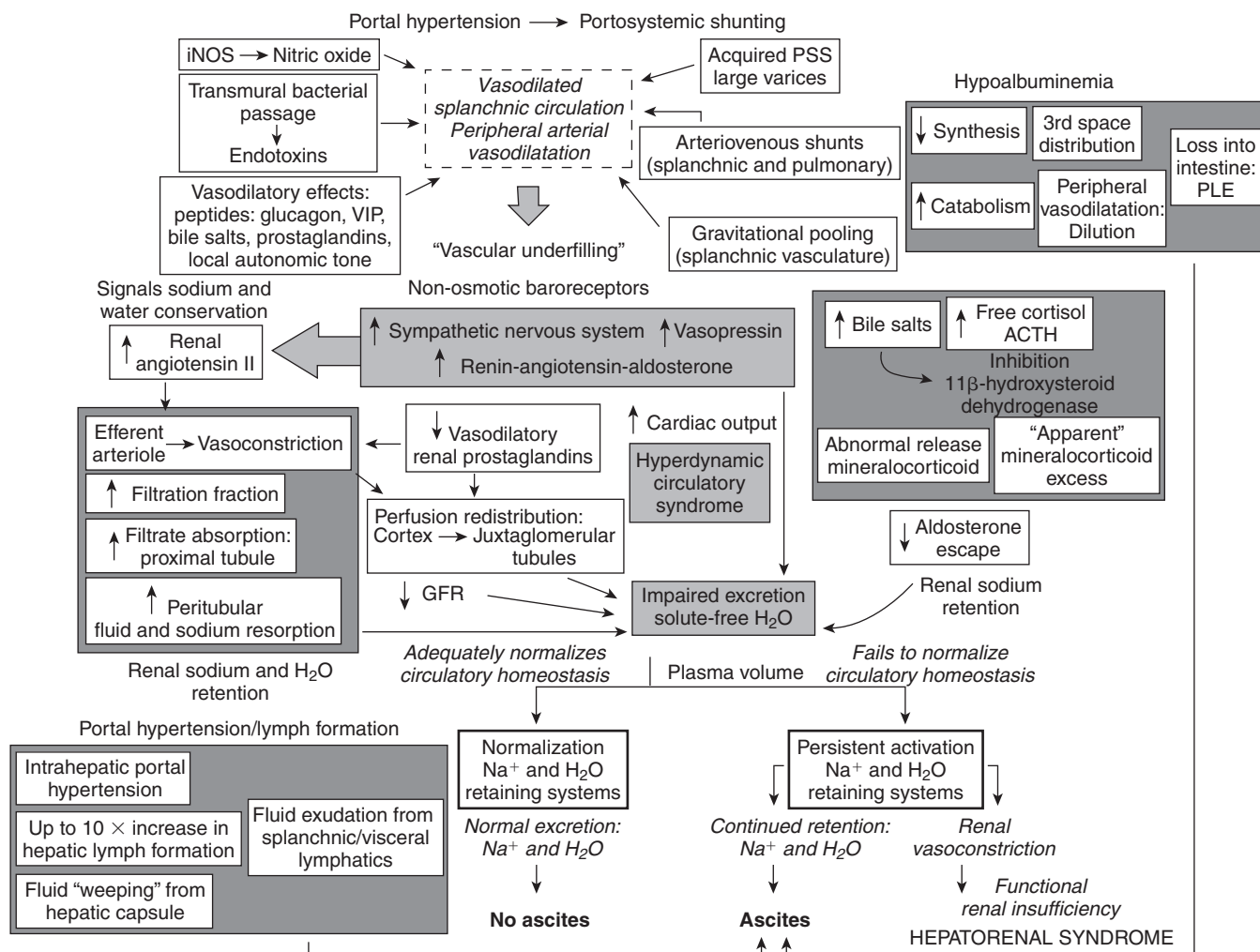14 were hyponatremic, and only 1 was hypernatremic. Cats with chronic cholangitis or cholangiohepatitis also do not have consistent changes in serum sodium concentration or USG.

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 vasopressors 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

Portal hypertension ⟶ Portosystemic shunting

iNOS ⟶ Nitric oxide

Transmural bacterial passage ⟶ Endotoxins

Vasodilatory effects: peptides: glucagon, VIP, bile salts, prostaglandins, local autonomic tone

Vasodilated splanchnic circulation Peripheral arterial vasodilatation

Acquired PSS large varices

Arteriovenous shunts (splanchnic and pulmonary)

Gravitational pooling (splanchnic vasculature)

Hypoalbuminemia

↓ Synthesis | 3rd space distribution | Loss into intestine: PLE

↑ Catabolism | Peripheral vasodilatation: Dilution

"Vascular underfilling"

Signals sodium and water conservation

Non-osmotic baroreceptors

↑ Renal angiotensin II

↑ Sympathetic nervous system | ↑ Vasopressin
↑ Renin-angiotensin-aldosterone

↑ Bile salts | ↑ Free cortisol ACTH
Inhibition 11β-hydroxysteroid dehydrogenase

Abnormal release mineralocorticoid | "Apparent" mineralocorticoid excess

Efferent arteriole ⟶ Vasoconstriction

↓ Vasodilatory renal prostaglandins

↑ Cardiac output

Hyperdynamic circulatory syndrome

↑ Filtration fraction

↑ Filtrate absorption: proximal tubule

Perfusion redistribution: Cortex ⟶ Juxtaglomerular tubules

↓ Aldosterone escape

Renal sodium retention

↑ Peritubular fluid and sodium resorption

↓ GFR

Impaired excretion solute-free H_2O

Renal sodium and H_2O retention

Adequately normalizes circulatory homeostasis

Plasma volume

Fails to normalize circulatory homeostasis

Portal hypertension/lymph formation

Intrahepatic portal hypertension

Up to 10 × increase in hepatic lymph formation

Fluid exudation from splanchnic/visceral lymphatics

Fluid "weeping" from hepatic capsule

Normalization Na^+ and H_2O retaining systems

Normal excretion: Na^+ and H_2O

No ascites

Persistent activation Na^+ and H_2O retaining systems

Continued retention: Na^+ and H_2O

Ascites

Renal vasoconstriction

↓ *Functional renal insufficiency*

HEPATORENAL SYNDROME

Figure 19-10 Diagram showing the pathophysiologic mechanisms associated with ascites formation in patients with chronic hepatic insufficiency.

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.[226]

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.[170] 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 reabsorption, impairs renal escape from abnormally increased aldosterone, and favors resistance to atrial natriuretic peptides.[72] 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.[90] 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.[65] 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.[95,120,214]

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.[41,95] 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.[120]

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.[65] 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.[34,65,103,162]

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 juxtamedullary 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.[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.[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 α-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.[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.[146]
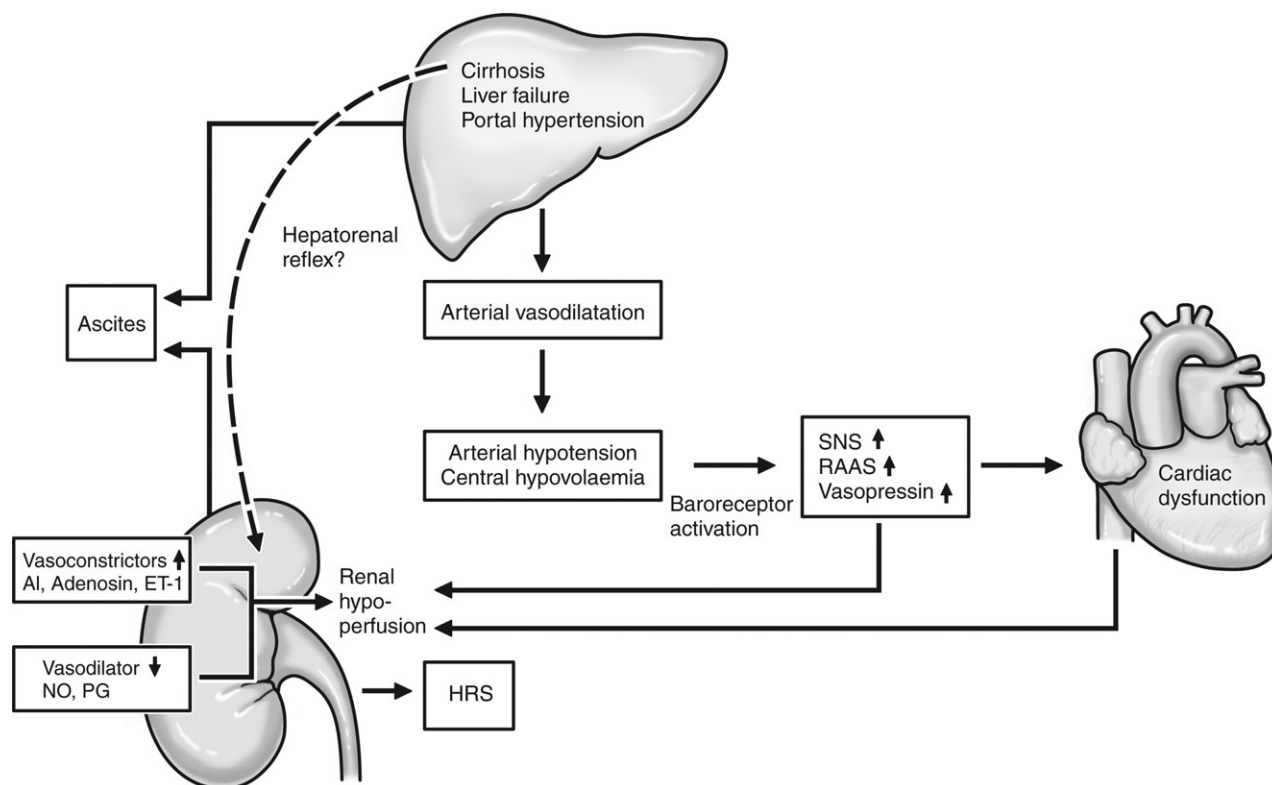
Figure 19-11 Pathophysiologic mechanisms of the hepatorenal syndrome based on human clinical studies and experimental animal modeling of cirrhosis. (From Moller S, Henriksen JH. Review article: pathogenesis and pathophysiology of hepatorenal syndrome: is there scope for prevention? Aliment Pharmacol Ther 2004;20 Supp. 3:31–41; discussion 42–43.)

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.[150,191] The most common disturbance in humans with hepatic insufficiency and coma is respiratory alkalosis, but metabolic acid-base disturbances may also occur.[150,173,191] 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.[173]

Mechanism of Respiratory Alkalosis

Respiratory alkalosis in cirrhosis may evolve subsequent to reduced arterial oxygen saturation secondary to acquired venoarterial 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., NH_3), or development of CNS acidosis.[101] 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).[10,176]

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.[139] 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.[71] 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 HCO_3^-. 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).[71] Although transfused blood is transiently acidifying because of free citric acid, this effect is quickly counteracted by the metabolism of citrate to CO_2 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).[71]

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).[167] 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.[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

**TABLE 19-2 Rates of Basal Lactate Production and Use (mmol/day/kg) in Humans**

Tissue	Basal Lactate Production	Tissue	Basal Lactate Use
Skin	5.0	Liver	10.3
Red blood cells	4.3	Kidney	5.5
Brain	3.4	Heart	1.1
Muscle	3.1	Other	1.5
Intestinal mucosa	1.6		
White blood cells, platelets	1.0		
Total	18.4	Total	18.4

From Park R, Arieff AI. Lactic acidosis. Adv Intern Med 1980;25:33–68.

(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.[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
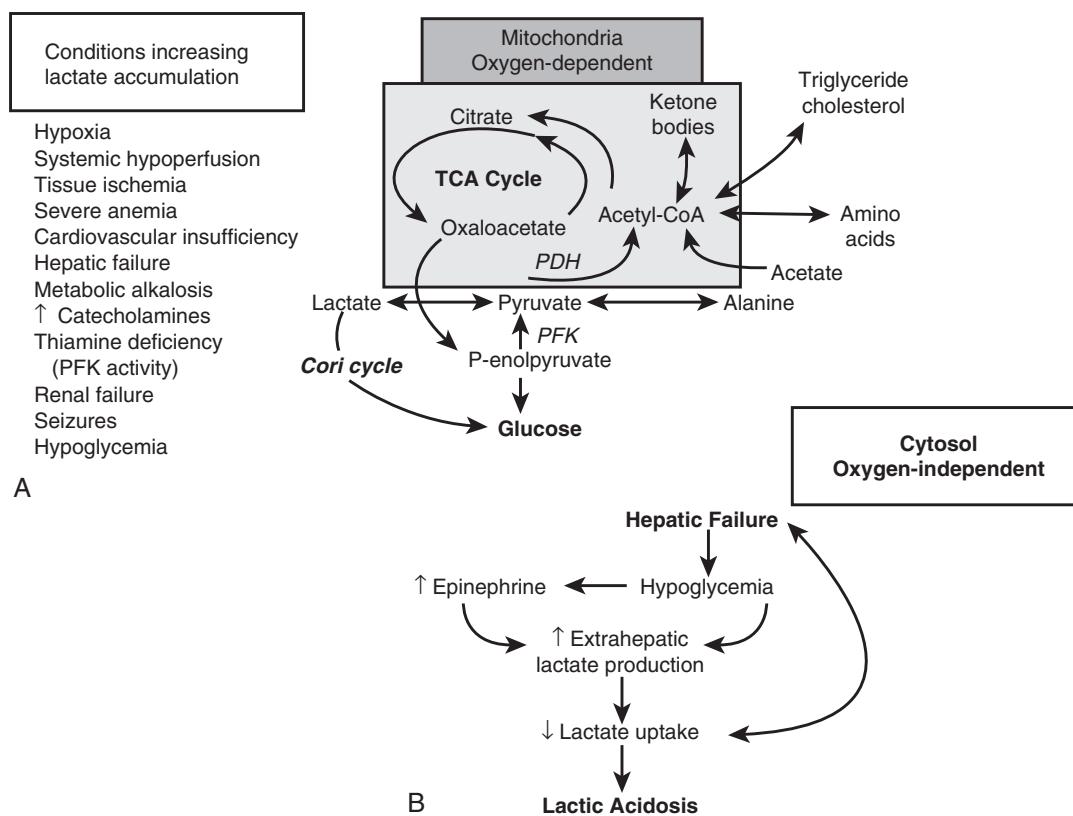
Figure 19-12 Metabolic generation and interactions of lactate (A) and the mechanisms leading to lactic acidosis in liver failure (B). *PFK,* Phosphofructokinase; *PDH,* pyruvate dehydrogenase.

increased conversion of pyruvate to lactate.[64] Respiratory alkalosis, common in cirrhotic patients, is thought to increase lactate production by enhancing phosphofructokinase (PFK) activity.[85] 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 (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.[14,52]

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.[26,27] Lactic acidemia also may develop in some conditions without perfusion deficits or hypoxic injury (e.g., diabetes mellitus, renal failure, fulminant hepatic failure, sepsis).[64,85,131]

Hypoperfusion, hypoxia, and ischemic damage of the liver convert it from a lactate-consuming to a lactate-producing organ.[64] Intraoperative hypotension, hepatic ischemia, vascular thrombosis, and fulminant hepatic failure each can lead to lactic acidemia. In fulminant hepatic failure, lactic acidemia indicates severe circulatory insufficiency, anaerobic metabolism, and diffuse panlobular parenchymal damage.[26] 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.[64]

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.[43] 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).[158] 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.[158]

*References 134, 135, 161, 204, 205, 209, 220.

High blood lactate concentrations also have been associated with intracranial neoplasia (e.g., meningioma) and lymphoma.[134,135,209] 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.[36] 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).[156]

Transfusion of stored blood also can cause lactic acidosis. Immediately after collection into CPD solution, human blood has reduced bicarbonate concentration, increased Pco_2 (CO_2 slowly diffuses through the plastic), and high citrate concentration.[71] 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.[71] 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
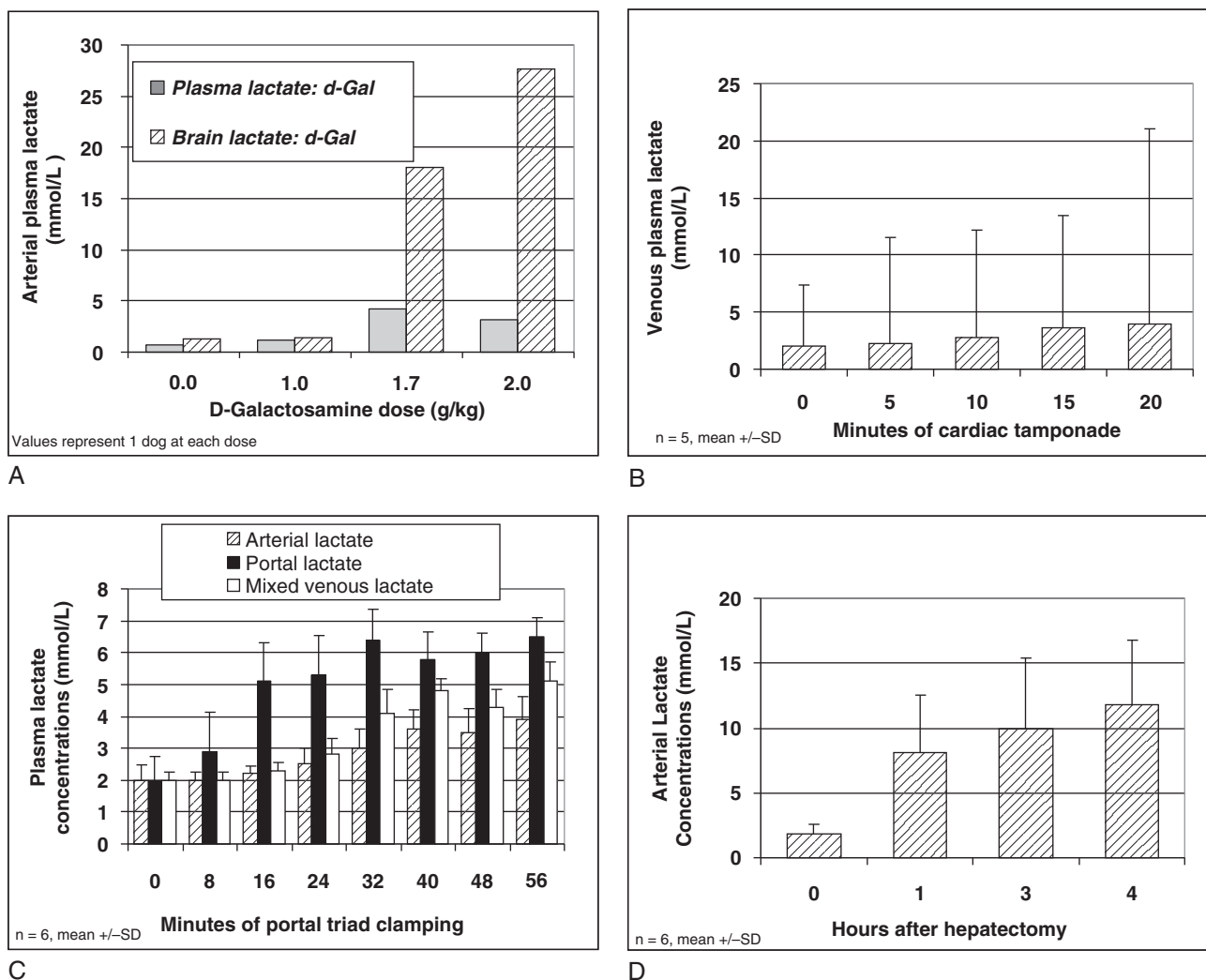
Figure 19-13 Graphic display of plasma and brain lactate concentrations in dogs with fulminant hepatic failure (n = 4) and plasma lactate concentrations in dogs with induced cardiac tamponade (n = 5), dogs with portal triad clamping (n = 6), and in hepatectomized dogs (n = 6). Plasma concentrations of lactate in dogs with fulminant hepatic failure were significantly lower than lactate values achieved within the central nervous systems. Plasma lactate concentrations in dogs with fulminant hepatic failure were similar to those associated with systemic hypotension induced by pericardial tamponade and portal triad clamping. (Data adapted from A, Nyberg SL, Cerra FB, Gruetter R. Brain lactate by magnetic resonance spectroscopy during fulminant hepatic failure in the dog. Liver Transpl Surg 1998;4:158–165; B, Mathias DW, Clifford PS, Klopfenstein HS. Mixed venous blood gases are superior to arterial blood gases in assessing acid-base status and oxygenation during acute cardiac tamponade in dogs. J Clin Invest 1988;82:833–838; C, Nemec A, Pecar J, Seliskar A, et al. Assessment of acid-base status and plasma lactate concentrations in arterial, mixed venous, and portal blood from dogs during experimental hepatic blood inflow occlusion. Am J Vet Res 2003;64:599–608; D, Park R, Arieff AI, Leach W, et al. Treatment of lactic acidosis with dichloroacetate in dogs. J Clin Invest 1982;70:853–862.)

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
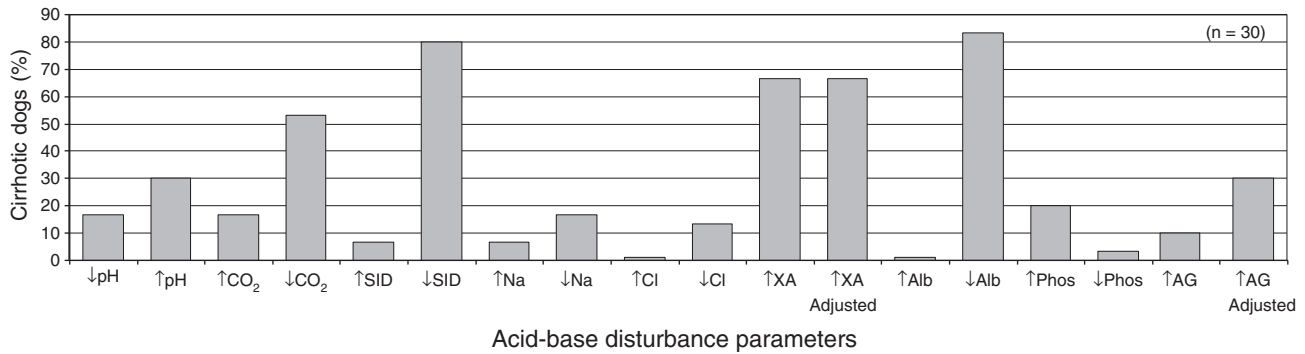
Figure 19-14 Graphic representation of parameters and calculated values used to identify acid-base derangements (number of patients with abnormal values) derived from dogs with hepatic cirrhosis (n = 30). *Alb,* Albumin; *AG,* anion gap; *Cl,* chloride; *Phos,* phosphorus; *SID,* strong ion difference; *XA,* unmeasured anions; *Adjusted,* value adjusted for change in free water as represented by serum sodium concentration. Values used to determine SID were calculated using conventional formulas as described in Chapter 13. (Data from SA Center: College of Veterinary Medicine, Cornell University, 2004).
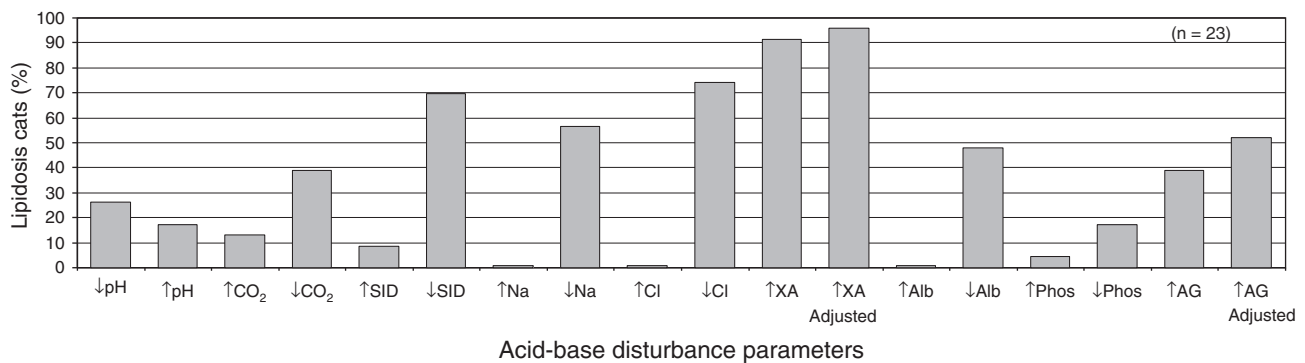
Figure 19-15 Graphic representation of parameters and calculated values used to identify acid-base derangements (number of patients with abnormal values) derived from cats with severe HL (n = 23). *Alb,* Albumin; *AG,* anion gap; *Cl,* chloride; *Phos,* phosphorus; *SID,* strong ion difference; *XA,* unmeasured anions; *Adjusted,* value adjusted for change in free water as represented by serum sodium concentration. Values used to determine SID were calculated using conventional formulas as described in Chapter 13. (Data from SA Center: College of Veterinary Medicine, Cornell University, 2004).

these cats may include metabolic alkalosis associated with hypochloremia (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.[47] 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 clinico-pathologic 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.

BOX 19-2	**Putative Hepatoencephalopathic Toxins and Their Mechanisms**

Ammonia
↓ Microsomal Na^+, K^+-ATPase in the brain
↓ ATP availability (ATP consumed in glutamine production)
↑ Excitability (if mild ↑ NH_3)
Disturbed malate-aspartate shuttle: ↓ energy
↓ Glycolysis
Brain edema (acute liver failure)
↓ Glutamate, altered glutamate receptors
↑ BBB transport: glutamate, tryptophan, octopamine

Bile Acids
Membranocytolytic effects alter cell or membrane permeability
BBB more permeable to other HE toxins
Impaired cellular metabolism because of cytotoxicity

Endogenous Benzodiazepines
Neural inhibition: hyperpolarize neuronal membrane
Induction of peripheral (mitochondrial) benzodiazepine receptors

GABA
Neural inhibition: hyperpolarize neuronal membrane
↑ BBB permeability to GABA in HE
↓ α-Ketoglutarate: impairs energy metabolism, NH_3 detoxification
Diversion from TCA cycle for NH_3 detoxification
↓ ATP availability

Aromatic Amino Acids
↓ Neurotransmitter synthesis: ↓ dopa
↓ Gluconeogenesis: compete with BCAA for CNS transporter
Accumulation of octopamine, phenylethanolamine, Serotonin
Octopamine and phenylethanolamine compete with dopa, Norepinephrine

Altered Neuroreceptors
Abnormal mediators and response
↑ Production false neurotransmitters

Methionine → Toxic Metabolites: Mercaptans
(Methanethiol and dimethyldisulfide)
Synergistic with other toxins: NH_3, SCFA
Gut derived → fetor hepaticus (distinct breath odor in HE)
↓ NH_3 detoxification in brain
↓ Microsomal Na^+, K^+-ATPase

Tryptophan
Directly neurotoxic
↑ Serotonin: neuroinhibition

Glutamine
Alters BBB amino acid transport
NH_3 transfer

SCFA
↓ Microsomal Na^+, K^+-ATPase in brain
Uncouples oxidative phosphorylation
Impairs oxygen use
Displaces tryptophan from albumin → ↑free tryptophan

Phenol (Derived from Phenylalanine and Tyrosine)
Synergistic with other toxins
↓ A multitude of cellular enzymes
Neurotoxic and hepatotoxic

False Neurotransmitters (Tyrosine → Octopamine, Phenylalanine → Phenylethylamines)
Impair norepinephrine action

ATP, adenosine triphosphate; *BBB,* blood-brain barrier; *HE,* hepatic encephalopathy; *GABA,* γ-aminobutyric acid; *TCA,* tricarboxylic acid; *BCAA,* branched chain amino acids; *CNS,* central nervous system; *SCFA,* short-chain fatty acids.

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

Condition	Mechanism
Dehydration	Prerenal azotemia
	Renal azotemia
Azotemia	$\uparrow NH_3$
Alkalemia	$\uparrow NH_3$, $\uparrow$diffusion across BBB into CNS
Hypokalemia	$\uparrow NH_3$, $\uparrow$ renal ammoniagenesis
	Promotes alkalemia
	Polyuria and anorexia
Hypoglycemia	Neuroglycopenia: augments NH_3 toxicity
Catabolism	$\uparrow$ Protein turnover: $\uparrow NH_3$
	$\downarrow$Muscle NH_3 detoxication
Infection	$\uparrow$ Protein turnover: $\uparrow NH_3$
	Urease producers $\rightarrow$ urea $\rightarrow$ $\uparrow NH_3$
Polydipsia/polyuria	$\downarrow K^+ \rightarrow$ alkalosis, $\uparrow NH_3$
	Provokes: inappetence, weakness
Anorexia	Catabolism
	$\downarrow K^+$: promotes alkalemia $\rightarrow$ augments NH_3 toxicity
	$\downarrow$ Zinc: impairs urea cycle NH_3 detoxification
	Dehydration
	Hypoglycemia
Constipation	$\uparrow$ Toxin production
	$\uparrow$ Toxin absorption
Hemolysis	$\uparrow$ RBC breakdown $\rightarrow$ $\uparrow$Protein
Blood transfusion	$\uparrow$ RBC breakdown $\rightarrow$ $\uparrow$ Protein: $\uparrow NH_3$
	$\uparrow NH_3$content in stored blood, endotoxins
GI hemorrhage	
RBC digestion	$\uparrow$ Protein: $\uparrow NH_3$
Inflammation	$\uparrow$ Protein: $\uparrow NH_3$
Parasitism	$\uparrow$ Protein: $\uparrow NH_3$
High dietary protein (animal, fish, eggs)	$\uparrow$ Protein load: $\uparrow NH_3$, Aromatic amino acids $\uparrow$ Many other toxins
Drugs: (examples)	
Benzodiazepines	Tetracyclines
Antihistamines	Methionine
Barbiturates	Organophosphates
Phenothiazines	Diuretic overdosage
Metronidazole	Certain anesthetics

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 B_1 deficiency (i.e., hypothiaminosis 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 B_{12} deficiency because of inadequate intrinsic factor or impaired cobalamin uptake in the small intestine;[194] a link between cobalamin insufficiency and HL is suspected.[46] Cobalamin deficiency occasionally is severe enough to produce neuromuscular signs, such as neck ventriflexion, anisocoria, papillary dilatation, vestibular signs, postural reaction deficits, and seizures.[15] Parenteral treatment with vitamin B_{12} is begun after a sample for measurement of baseline serum B_{12} concentration has been obtained. Pretreatment determination of serum B_{12} 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 B_{12} intramuscularly or subcutaneously every 7 days to every 21 days.[194] (149) Others have recommended 0.25 mg B_{12} 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.[15,202]

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
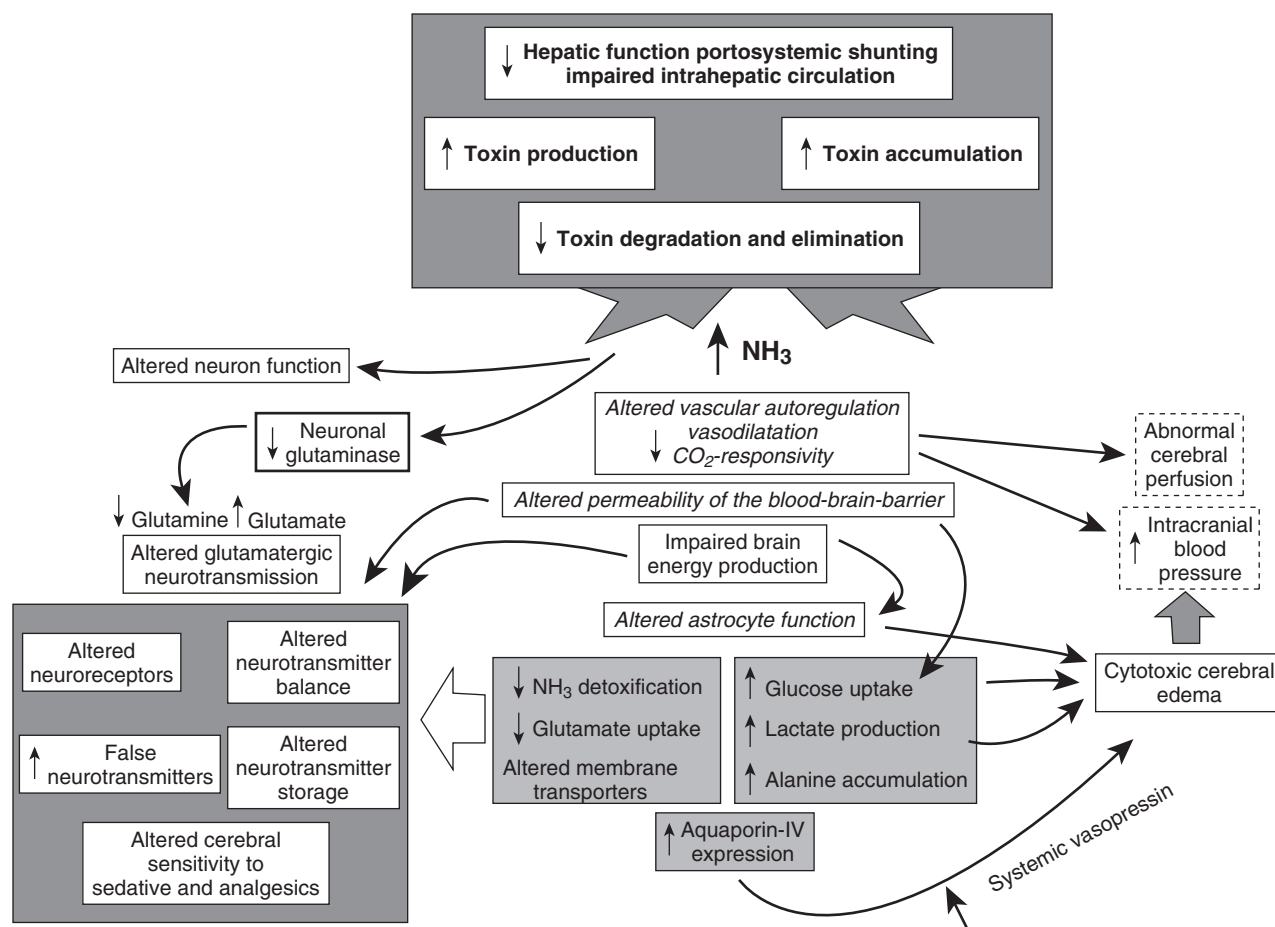
Figure 19-16 Diagram demonstrating pathomechanisms contributing to hepatic encephalopathy, as discussed in the text.

in various types of liver injury, including those associated with cholestasis.[197,198] 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.[233] 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.[141] 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.[62] Using a water-soluble form of α-tocopherol can circumvent problems created by impaired enteric bile acid circulation (e.g., α-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.[44] 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.[177] 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 NH_3 concentrations by therapeutically targeting the gastrointestinal tract (the primary source of NH_3 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 NH_3 metabolism or ameliorate NH_3 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 NH_3 tolerance. Cachexia, starvation, and glucocorticoid administration increase nitrogenous waste production from muscle catabolism, including NH_3 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 NH_3 concentrations. Metabolic alkalosis facilitates brain uptake and intracerebral trapping of NH_3. Hypokalemia promotes renal ammoniagenesis and H^+ loss, promoting metabolic alkalosis and increasing renal tubular NH_3 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 osmolal 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 NH_3 production and hyperammonemia. Volume expansion can attenuate hyperammonemia caused by enteric hemorrhage when NH_3 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 hypoalbuminemia 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 NH_3 concentrations, strategies targeting enteric NH_3 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.[50] 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 hyperglycemia 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 NH_3 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.[15,123] 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.[123] 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.[82] However, recent findings have not supported its routine use in human medicine.[130]

Chronic Hepatic Encephalopathy

Dietary Management

The mainstay of nutritional support is judicious protein restriction taking care to avoid a catabolic state.[49] 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 NH_3 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.[172] Whether the lower plasma ammonia concentration reflected better control of HE has been a topic of debate.[232] Some dogs developed very low albumin concentration, likely due to the negative energy balance.[172,232] 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.[192] 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.[192] Although no double-blinded, placebo-controlled studies have been done to date, clinical experience still supports the use of these treatments in human patients.[29,57,230] 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).[15] Protein and caloric intake should only be restricted in animals with clinical HE.[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 β-hydroxybutyrate concentrations in obese cats with experimentally induced hepatic lipidosis, but concentrations were not significantly different during the treatment phase.[28] L-CN may be provided orally at a dose of 250 to 500 mg/day.[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.[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**

Dietary Modifications
↓ Protein quantity
Altered protein quality: dairy and vegetable preferred
↑ Dietary soluble fiber

Modification of Enteric Microbial Population

Alter enteric pH:	Lactose, lactulose, lactitol, fiber		
Antimicrobials:			
Neomycin	22 mg/kg	PO	bid-tid
Metronidazole	7.5 mg/kg	PO	bid-tid
Amoxicillin	11 mg/kg	PO	bid-tid
Administration of lactobacilli: live yogurt cultures			
Modify enteric substrates: dietary, nonabsorbable disaccharide fiber			
Lactulose	0.25-0.5 mL/kg	PO	bid-tid

(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.)

Lactitol	0.5-0.75 g/kg	PO	bid
Lactose	Slightly sweet solution		bid-tid
Fiber	Metamucil, psyllium		

(Each of the above are used to effect, attaining several soft stools per day.)

Direct Elimination of Enteric Microorganisms, Substrates, and Products

Cleansing enemas	5-10 mL/kg, repeat until clear; use warm polyionic fluids	
Retention enemas	As necessary, respect total systemic drug dose	
Neomycin	15-20 mL 1% solution	tid
	(No >22 mg/kg body weight tid)	
Lactulose	5-15 mL diluted 1:3 with water	tid
Lactitol	0.5-0.75 g/kg	bid
Metronidazole	7.5 mg/kg (systemic dose) with water	bid
Betadine	Dilute 1:10 with water, flush out within 10 min	
Dilute vinegar	Dilute 1:10 with water, alters pH	bid-tid
Activated charcoal	Administered and retained in crisis situation	

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 osmolal 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 borborygmus), and causes watery diarrhea. Generation of organic acids from lactulose rarely can result in metabolic acidosis, dehydration, and hypernatremia.[155] Lactulose may be contraindicated in patients with hypercalcemia if increased absorption of calcium from the gut exacerbates hypercalcemia.[189]

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, hypokalemia, 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 NH_3 excretion. Enhanced renal NH_3 elimination occurs secondary to increased glutamine delivery to the proximal tubules, increased urine flow rate (i.e., decreased NH_3 reabsorption), and suppression of antidiuretic hormone secretion. Total body NH_3 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 NH_3 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 HCO_3^- maintains electroneutrality, it contributes to metabolic alkalosis that can increase NH_3 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^+/HCO_3^- cotransport.[122]

Administration of a carbonic anhydrase inhibitor (e.g., acetazolamide) or a thiazide (e.g., chlorothiazide) diuretic can indirectly augment hyperammonemia by inhibiting HCO_3^- 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 hypothiaminosis (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

---

*References 9, 78, 89, 160, 235, 240.

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 H_2 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 impending 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 NH_3 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.[33,48]

Lactic Acidosis

With the exception of cats with HL and animals in fulminant 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.[237] 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 crystalloid 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 CO_2 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 hypoventilation 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-Pao_2 gradient identifies impaired gas diffusion and ventilation-perfusion mismatch in patients with normal arterial Po_2 values. A PA-Pao_2 gradient greater than 15 mm Hg warrants consideration of oxygen therapy. Respiratory acidosis and increased PA-Pao_2 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 dosages in healthy dogs.[109] 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.[148] 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. Dextrans are linear polymers 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.[238] 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.[145] 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.[145,153,169,218] Although HES expands plasma in humans for 12 to 48 hours, it increased oncotic pressure for less than 12 hours in hypoalbuminemic dogs.[99,106,149] When used for oncotic 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).[195]

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 acquired fibrinogen deficiency likely caused dilutional coagulopathy, and ex vivo addition of fibrinogen completely corrected the coagulopathy.[77] 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.[187] Regardless of cause, hemostatic abnormalities are notable in animals with hepatobiliary disease given dextran 70.[48] Intraoperative use of dextran 70 in dogs with PSVA has resulted in bleeding tendencies in patients assessed presurgically as having normal hemostasis (i.e., normal results for mucosal bleeding time, prothrombin time, activated partial thromboplastin time, activated coagulation time, and proteins induced by vitamin K absence or antagonism [PIVKA]). In addition to rapid hemodilution causing moderate to severe reduction in 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.[97] 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.[97]

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.[244] 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.[196]

Acute allergic reactions are possible with use of dextrans 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,[201] 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.[70]

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.[182] The most common complications of therapeutic abdominocentesis in humans include HE, decreased renal function, and hyponatremia.[16] 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
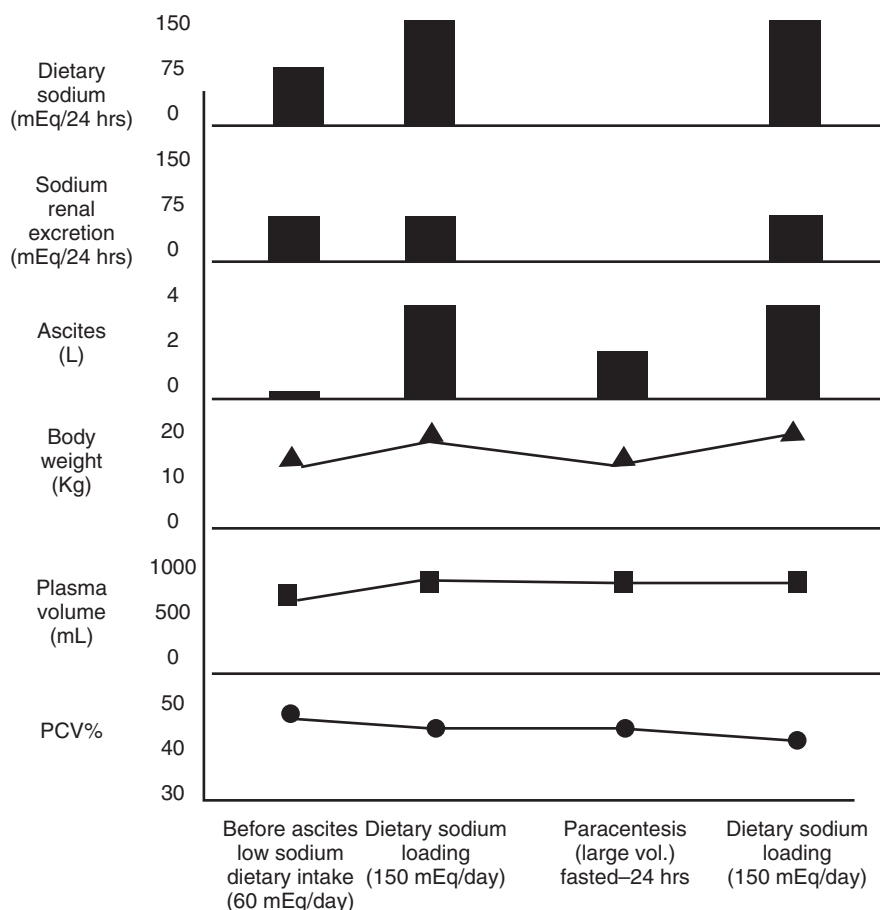
Dogs (n = 5) with dimethylnitrosamine-induced cirrhosis

Figure 19-17 Experimental data showing the response of cirrhotic dogs to different levels of sodium ingestion, ascites formation, and response to paracentesis. Data derived from five dogs with cirrhosis induced with dimethylnitrosamine. (Adapted from Levy M. Sodium retention and ascites formation in dogs with experimental portal cirrhosis. Am J Physiol 1977;233:F572–F585.)

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.[126] 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.[90] 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).[215] Patients receiving dextran 70 concurrently with paracentesis did not develop significant hemodynamic changes in the first 24 hours after paracentesis.[215] 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.[216] 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).[76] 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).[58,199]

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 K_1, 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 K_1 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 K_1 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 NH_3 that may exacerbate HE, and also may introduce pyrogens or endotoxins that are poorly tolerated in patients with liver disease.[186] 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. Hemostatic responses to DDAVP administration to dogs include liberation of preformed endothelial von Willebrand factor monomers and increased factor VIII activity (Figure 19-18).[22] The benefits in patients with liver disease seem too great to be explained based on these
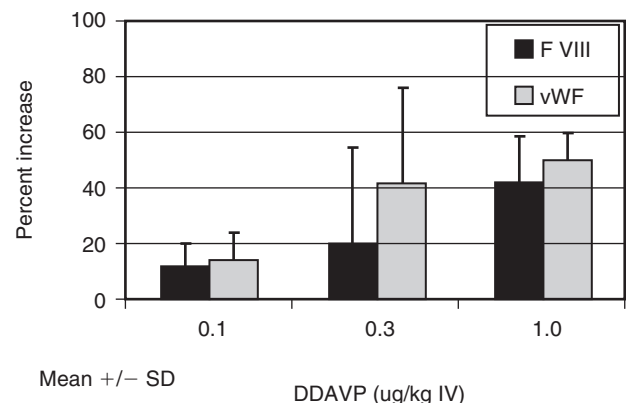
Figure 19-18 Graphic depiction of the influence of desmopressin (DDAVP) on von Willebrand factor and factor VIII activity in healthy dogs. (Adapted from Bernat A, Hoffmann P, Dumas A, et al. V2 receptor antagonism of DDAVP-induced release of hemostasis factors in conscious dogs. J Pharmacol Exp Ther 1997;282:597–602.)

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 microvasculature 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% $CaCl_2$ 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

1. Aberg M, Bergentz S, Hedner U. Effect of dextran and induced thrombocytopenia on the lysability of ex vivo thrombi in dogs. Acta Chir Scand 1977;143:91–4.
2. Aberg M, Hedner V, Bergentz S. Effect of dextran on factor VIII and platelet function. Ann Surg 1979;189:243–7.
3. Abraldes JG, Bosch J. Somatostatin and analogues in portal hypertension. Hepatology 2002;35:1305–11.
4. Ackermann D, Vogt B, Escher G, et al. Inhibition of 11b-hydroxysteroid dehydrogenase by bile acids in rats with cirrhosis. Hepatology 1999;30:623–9.
5. Adamantos S, Chan DL, Goggs R, et al. Risk of immunologic reactions to human serum albumin solutions. J Small Anim Pract 2009;50:206.
6. Adams LG, Hardy RM, Weiss DJ, et al. Hypophosphatemia and hemolytic anemia associated with diabetes mellitus and hepatic lipidosis in cats. J Vet Intern Med 1993;7:266–71.
7. Adrogue HJ, Tannen RL. Ketoacidosis, hyperosmolar states, and lactic acidosis. In: Kokko JP, Tannen RL, editors. Fluids and electrolytes. 3rd ed Philadelphia: WB Saunders; 1996. p. 643–74.
8. Aizawa Y, Ohmori T, Imai K, et al. Depressant action of acetate upon the human cardiovascular system. Clin Nephrol 1977;8:477–80.
9. Ali F, Raufi MA, Washington B, et al. Conivaptan: a dual vasopressin receptor v1a/v2 antagonist [corrected]. Cardiovasc Drug Rev 2007;25:261–79.
10. Amatuzio DS, Nesbitt S. A study of pyruvic acid in the blood, spinal fluid and urine of patients with liver disease with and without hepatic coma. Clin Invest 1950;29:1486–90.
11. Angeli P, Volpin R, Gerunda G, et al. Reversal of type 1 hepatorenal syndrome with administration of midodrine and octreotide. Hepatology 1999;29:1690–7.
12. Angeli P. Prognosis of hepatorenal syndrome: has it changed with current practice? Aliment Pharmacol Ther 2004;20(Suppl. 3):44–8.
13. Arai K, Kawamoto M, Yuge O, et al. A comparative study of lactated Ringer and acetated Ringer solution as intraoperative fluids in patients with liver dysfunction. Masui 1986;35:793–9.
14. Arieff AI, Park R, Leach J, et al. Pathophysiology of experimental lactic acidosis in dogs. Am J Physiol 1980;239:F135–F142.
15. Armstrong PJ, Blanchard G. Hepatic lipidosis in cats. Vet Clin North Am Small Anim Pract 2009;39:599–616.
16. Arroyo V, Gines P, Planas R. Treatment of ascites in cirrhosis. Diuretics, peritoneovenous shunt, and large-volume paracentesis. Gastroenterol Clin North Am 1992;21:237–56.
17. Arroyo V, Rodes J, Gutierrez-Lizarraga MA, et al. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Am J Dig Dis 1976;21:249–56.
18. Baquerizo A, Anselmo D, Shackleton C, et al. Phosphorus as an early predictive factor in patients with acute liver failure. Transplantation 2003;75:2007–14.
19. Baumann H, Gauldie J. The acute phase response. Immunol Today 1994;15:74–80.
20. Bergqvist D. Dextrans and haemostasis: a review. Acta Chir Scand 1982;31:320–4.
21. Bernardi M. Renal sodium retention in preascitic cirrhosis: expanding knowledge, enduring uncertainties. Hepatology 2002;35:1544–7.
22. Bernat A, Hoffmann P, Dumas A, et al. V2 receptor antagonism of DDAVP-induced release of hemostasis factors in conscious dogs. J Pharmacol Exp Ther 1997;282:597–602.
23. Better OS, Schrier RW. Disturbed volume homeostasis in patients with cirrhosis of the liver. Kidney Int 1983;23:303–9.
24. Bienzle D, Jacobs RM, Lumsden JH. Relationship of serum total calcium to serum albumin in dogs, cats, horses and cattle. Can Vet J 1993;34:360–4.
25. Biggins SW, Rodriguez HJ, Bacchetti P, et al. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 2005;41:32–9.
26. Bihari D, Gimson AE, Waterson M, et al. Tissue hypoxia during fulminant hepatic failure. Crit Care Med 1985;13:1034–9.
27. Bihari D, Smithies M, Gimson A, et al. The effects of vasodilatation with prostacyclin on oxygen delivery and uptake in critically ill patients. N Engl J Med 1987;317:397–403.
28. Blanchard G, Paragon BM, Milliat F, et al. Dietary L-carnitine supplementation in obese cats alters carnitine metabolism and decreases ketosis during fasting and induced hepatic lipidosis. J Nutr 2002;132:204–10.
29. Blei AT. Treatment of hepatic encephalopathy. Lancet 2005;365:1383–6.
30. Boag AK, Coe RJ, Martinez TA, et al. Acid-base and electrolyte abnormalities in dogs with gastrointestinal foreign bodies. J Vet Intern Med 2005;19:816–21.
31. Boron VF, Hediger MA, Boulpaep EL, et al. The renal electrogenic Na+: HCO_3^- cotransporter. J Exp Biol 1997;200:263–8.
32. Brenner DA, Buck M, Feitelberg SP, et al. Tumor necrosis factor-alpha inhibits albumin gene expression in a murine model of cachexia. J Clin Invest 1990;85:248–55.
33. Brown SA, Spyridakis LK, Crowell WA. Distal renal tubular acidosis and hepatic lipidosis in a cat. J Am Vet Med Assoc 1986;189:1350–2.
34. Caregaro L, Menon F, Angeli P, et al. Limitations of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. Arch Intern Med 1994;154:201–5.
35. Carey RG, Bucuvalas JC, Balistreri WF, et al. Hyponatremia increases mortality in pediatric patients

listed for liver transplantation. Pediatr Transplant 2010;14:115–20.

36. Cariou MP, Lipscomb VJ, Hughes D, et al. Plasma lactate concentrations and blood gas values in dogs undergoing surgical attenuation of a single congenital portosystemic shunt. Vet Rec 2009;165:226–9.

37. Casey TH, Summerskill WHJ, Bickford RG, et al. Body and serum potassium in liver disease: II. Relationships to arterial ammonia, blood pH, and hepatic coma. Gastroenterology 1965;48:208–15.

38. Castell JV, Gomez-Lechon MJ, David M, et al. Acute-phase protein synthesis by interleukin-6. Hepatology 1990;12:1179–86.

39. Center SA, Crawford MA, Guida L, et al. A retrospective study of cats (n=77) with severe hepatic lipidosis: (1975-1990). J Vet Intern Med 1993;7:349–59.

40. Center SA, Harte J, Watrous D, et al. The clinical and metabolic effects of rapid weight loss in obese pet cats and the influence of supplemental oral l-carnitine. J Vet Intern Med 2000;14:598–608.

41. Center SA, Magne M. Historical, physical examination, and clinicopathologic features of portosystemic vascular anomalies in the dog and cat. Sem Vet Med Surg Small Anim 1990;5:83–93.

42. Center SA, Sunvold GD. Investigations of the effect of l-carnitine on weight reduction, body condition, and metabolism in obese dogs and cats. In: Reinhart GA, Carey DP, editors. Recent advances in canine and feline nutrition, vol III, Iams Nutrition Symposium Proceedings. Wilmington, Ohio: Orange Frazer Press; 2000. p. 113–22.

43. Center SA, Thompson M, Wood PA, et al. Hepatic ultrastructural and metabolic derangements in cats with severe hepatic lipidosis, In: Proceedings of the 9th ACVIM Forum; 1991. p. 1993–6.

44. Center SA, Warner K, Corbett J, et al. Proteins invoked by vitamin K absence and clotting times in clinically ill cats. J Vet Intern Med 2000;14:292–7.

45. Center SA, Warner KL, Erb HN. Liver glutathione concentrations in dogs and cats with naturally occurring liver disease. Am J Vet Res 2002;63:1187–97.

46. Center SA. Feline hepatic lipidosis. Vet Clin North Am Small Anim Pract 2005;35:225–69.

47. Center SA. Pathophysiology of liver disease: normal and abnormal function. In: Guilford GA, Center SA, Strombeck DR, et al., editors. Strombeck's small animal gastroenterology. 3rd ed. Philadelphia: WB Saunders; 1996. p. 553–632.

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

49. Center SA. Nutritional support for dogs and cats with hepatobiliary disease. J Nutr 1998;128:2733S–2746S.

50. Chung C, Vaquero J, Gottstein J, et al. Vasopressin accelerates experimental ammonia-induced brain edema in rats after portocaval anastomosis. J Hepatol 2003;39:193–9.

51. Cochrane Injuries Group Albumin Reviewers . Human albumin administration in critically ill patients: systematic review of randomized controlled trials. BMJ 1998;317:235–9.

52. Cohen RD, Iles RA, Barnett D, et al. The effect of changes in lactate uptake on the intracellular pH of the perfused rat liver. Clin Sci 1971;41:159–70.

53. Cohn LA, Kerl ME, Lenox CE, et al. Response of healthy dogs to infusions of human serum albumin. Am J Vet Res 2007;68:657–63.

54. Concannon KT, Haskins S, Feldman BF. Hemostatic defects associated with two infusion rates of dextran 70 in dogs. Am J Vet Res 1992;53:1369–75.

55. Cooper AJL. Role of the liver in amino acid metabolism. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. 3rd ed, Philadelphia: WB Saunders; 1996. p. 563–604.

56. Cooper ES, Wellman ML, Carsillo ME. Hyperalbuminemia associated with hepatocellular carcinoma in a dog. Vet Clin Pathol 2009;38:516–20.

57. Córdoba J, Minguez B, Vergara M. Treatment of hepatic encephalopathy. Lancet 2005;365:1384–6.

58. Cotrim HP, Garrido V, Parana R, et al. Paracentesis associated with dextran-70 in the treatment of ascites in patients with chronic liver diseases: a randomized therapeutic study. Arq Gastroenterol 1994;31:125–9.

59. Craddock PR, Yawata Y, VanSanten L, et al. Acquired phagocyte dysfunction: a complication of hypophosphatemia of parenteral hyperalimentation. N Engl J Med 1974;290:1403–7.

60. Dalrymple-Hay M, Aitchison R, Collins P, et al. Hydroxyethyl starch induced acquired von Willebrand's disease. Clin Lab Haematol 1992;14:209–11.

61. Damon L, Adams M, Stricker R, et al. Intracranial bleeding during treatment with hydroxyethyl starch. N Engl J Med 1987;317:964–1105.

62. Davit-Spraul A, Cosson C, Couturier M, et al. Standard treatment of alpha-tocopherol in Alagille patients with severe cholestasis is insufficient. Pediatr Res 2001;49:232–6.

63. Dawson DJ, Babbs C, Warnes TW, et al. Hypophosphataemia in acute liver failure. BMJ 1987;295:1312–3.

64. DeGasperi A, Mazz E, Corti A, et al. Lactate blood levels in the perioperative period of orthotopic liver transplantation. Int J Clin Lab Res 1997;27:123–8.

65. Deppe TA, Center SA, Simpson KW, et al. Glomerular filtration rate and renal volume in dogs with congenital portosystemic vascular anomalies before and after surgical ligation. J Vet Intern Med 1999;13:465–71.

66. Dich J, Hansen SE, Thieden HID. Effect of albumin concentration and colloid osmotic pressure on albumin synthesis in perfused rat liver. Acta Physiol Scand 1973;89:352–8.

67. Dillingham MA, Anderson RJ. Electrolyte, water, mineral, and acid base disorders in liver disease. In: Maxwell MH, Kleeman CR, Narins RG, editors. Clinical disorders of fluid and electrolyte metabolism, 4th ed. New York: McGraw-Hill; 1987. p. 879–96.

68. Dixon FJ, Maurer PH, Deichmiller MP. Half-lives of homologous serum albumins in several species. Soc Exp Bio Med 1953;83:287–338.

69. Douglas TA. The half-life of plasma albumin in the cat. Vet Rec 1967;80:738–9.

70. Dubick MA, Zaucha GM, Korte Jr DW, et al. Acute and subacute toxicity of 7.5% hypertonic saline-6% dextran-70 (HSD) in dogs. 2. Biochemical and behavioral responses. J Appl Toxicol 1993;13:49–55.

71. Emmitt M, Narins RG. Mixed acid-base disorders. In: Maxwell MH, Kleeman CR, Narins RG, editors. Clinical disorders of fluid and electrolyte metabolism, 4th ed. New York: McGraw-Hill; 1987. p. 743–88.

72. Epstein M. Atrial natriuretic factor and liver disease. In: Epstein M, editor. The kidney in liver disease. 4th ed Philadelphia: Hanley & Belfus; 1996. p. 339–58.

73. Epstein M. Derangements of renal water handling in liver disease. Gastroenterology 1985;89:1415–25.

74. Erlinger S. Physiology of bile secretion and enterohepatic circulation. In: Johnson LR, editor. Physiology of the gastrointestinal tract. 2nd ed New York: Raven Press; 1987. p. 1557–80.

75. Evans TW. Review article: albumin as a drug: biological effects of albumin unrelated to oncotic pressure. Aliment Pharmacol Ther 2002;16(Suppl. 5):6–11.

76. Fassio E, Terg R, Landeira G, et al. Paracentesis with Dextran 70 vs paracentesis with albumin in cirrhosis with tense ascites. Results of a randomized study. J Hepatol 1992;14:310–6.

77. Fenger-Eriksen C, Tonnesen E, Ingerslev J, et al. Mechanisms of hydroxyethyl starch-induced dilutional coagulopathy. J Thromb Haemost 2009;7:1099–105.

78. Fernandez-Varo G, Ros J, Cejudo-Martin P, et al. Effect of the V1a/V2-AVP receptor antagonist, Conivaptan, on renal water metabolism and systemic hemodynamics in rats with cirrhosis and ascites. J Hepatol 2003;38:755–61.

79. Fink RM, Enns R, Kimball CP, et al. Plasma protein metabolism: observations using heavy nitrogen in lysine. J Exp Med 1944;80:455–75.

80. Flanders JA, Scarlett JM, Blue JT, et al. Adjustment of total serum calcium concentration for binding to albumin and protein in cats: 291 cases (1986-1987). J Am Vet Med Assoc 1989;194:1609–11.

81. Forrester SD, Moreland KJ. Hypophosphatemia: causes and clinical consequences. J Vet Intern Med 1989;3:149–59.

82. Foster KJ, Lin S, Turck CJ. Current and emerging strategies for treating hepatic encephalopathy. Crit Care Nurs Clin North Am 2010;22:341–50.

83. Francis AH, Martin LG, Haldorson GJ, et al. Adverse reactions suggestive of type III hypersensitivity in six healthy dogs given human albumin. J Am Vet Med Assoc 2007;230:873–9.

84. Francisco LL, Sawin LL, Dibona GF. Mechanism of negative potassium balance in the magnesium-deficient rat. Proc Soc Exp Biol Med 1981;168:382–8.

85. Frommer JP. Lactic acidosis. Med Clin North Am 1983;67:815–29.

86. Fukuhara T, Ikegami T, Morita K, et al. Impact of preoperative serum sodium concentration in living donor liver transplantation. J Gastroenterol Hepatol 2010;25:978–84.

87. Fukui H. Does angiotensin II typ. 1 receptor blockade offer a clinical advantage to cirrhotics with ascites? J Gastroenterol 2002;37:235–7.

88. Garzon AA, Cheng C, Lerner B, et al. Hydroxyethyl starch (HES) and bleeding: an experimental investigation of its effect on hemostasis. J Trauma 1967;7:757–66.

89. Gerbes AL, Gulberg V, Gines P, et al. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. Gastroenterology 2003;124:933–9.

90. Gines P, Berl T, Bernardi M, et al. Hyponatremia in cirrhosis: from pathogenesis to treatment. Hepatology 1998;28:851–64.

91. Girgrah N, Liu P, Collier J, et al. Haemodynamic, renal sodium handling, and neurohormonal effects of acute administration of low dose losartan, an angiotensin II receptor antagonist, in preascitic cirrhosis. Gut 2000;46:114–20.

92. Gollub S, Schaefer C, Squitieri A. The bleeding tendency associated with plasma expanders. Surg Gynecol Obstet 1967;124:1203–11.

93. Good DW. Effects of potassium on ammonia transport by medullary thick ascending limbs of the rat. J Clin Invest 1987;80:1358–65.

94. Graf H, Leach W, Arieff AI. Metabolic effects of sodium bicarbonate in hypoxic lactic acidosis in dogs. Am J Physiol 1985;249:F630–F635.

95. Grauer GF, Pitts RP. Primary polydipsia in three dogs with portosystemic shunts. J Am Anim Hosp Assoc 1987;23:197–200.

96. Guzman JA, Rosado AE, Kruse JA. Vasopressin vs norepinephrine in endotoxic shock: systemic, renal, and splanchnic hemodynamic and oxygen transport effects. J Appl Physiol 2003;95:803–9.

97. Hartog C, Reinhart K. CONTRA: Hydroxyethyl starch solutions are unsafe in critically ill patients. Intensive Care Med 2009;15:1337–42.

98. Harvey JW, West CL. Prednisone-induced increases in serum alpha-2-globulin and haptoglobin concentrations in dogs. Vet Pathol 1987;24:90–2.

99. Haupt MT, Rackow EC. Colloid osmotic pressure and fluid resuscitation with hetastarch, albumin, and saline solutions. Crit Care Med 1982;10:159–62.

100. Haussinger D, Kaiser S, Stehle T, et al. Liver carbonic anhydrase and urea synthesis. The effect of diuretics. Biochem Pharmacol 1986;35:3317–22.

101. Heinemann HO, Emirgil C, Mijnssen JP. Hyperventilation and arterial hypoxemia in cirrhosis of the liver. Am J Med 1960;28:239–46.

102. Heymsfield SB, Arteaga C, McManus C, et al. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. Am J Clin Nutr 1983;37:478–94.

103. Heymsfield SB, Waki M, Reinus J. Are patients with chronic liver disease hypermetabolic? Hepatology 1990;11:502–4.

104. Hoffenberg R. Control of albumin degradation in vivo and in the perfused liver. In: Rothschild MA, Waldmann T, editors. Plasma protein metabolism: regulation of synthesis, distribution and degradation. New York: Academic Press; 1970. p. 239–55.

105. Holford AL, Tobias KM, Bartges JW, et al. Adrenal response to adrenocorticotropic hormone in dogs before and after surgical attenuation of a single congenital portosystemic shunt. J Vet Intern Med 2008;22:832–8.

106. Hulse J, Yacobi A. Hetastarch: an overview of the colloid and its metabolism. Drug Intel Clin Pharmacol 1983;17:334–41.

107. Jalan R, Kapoor D. Enhanced renal ammonia excretion following volume expansion in patients with well compensated cirrhosis of the liver. Gut 2003;52:1041–5.

108. Jenq CC, Tsai MH, Tian YC, et al. Serum sodium predicts prognosis in critically ill cirrhotic patients. J Clin Gastroenterol 2010;44:220–6.

109. Jeunesse E, Woehrle F, Schneider M, et al. Spironolactone as a diuretic agent in the dog: is the water becoming muddy (abstract). J Vet Intern Med 2004;18:448.

110. Kanno N, LeSage G, Glaser S, et al. Regulation of cholangiocyte bicarbonate secretion. Am J Physiol 2001;281:G612–G625.

111. Karlson KE, Garzon AA, Shaftan GW, et al. Increased blood loss associated with administration of certain plasma expanders: Dextran 75, Dextran 40, and hydroxyethyl starch. Surgery 1967;62:670–8.

112. Kelly DA, Summerfield JA. Hemostasis in liver disease. Semin Liver Dis 1987;7:182–91.

113. Kim JH, Lee JS, Lee SH, et al. The association between the serum sodium level and the severity of complications in liver cirrhosis. Korean J Intern Med 2009;24:106–12.

114. Kim SW, Schou UK, Peters CD, et al. Increased apical targeting of renal epithelial sodium channel subunits and decreased expression of typ. 2 11beta-hydroxysteroid dehydrogenase in rats with CCl4-induced decompensated liver cirrhosis. J Am Soc Nephrol 2005;16:3196–32210.

115. Kirsch RF, Saunders SJ, Frith L, et al. Plasma amino acid-regulation of albumin synthesis. J Nutr 1969;98:395–403.

116. Kiszka-Kanowitz M, Henriksen JH, Hansen EF, et al. Effect of terlipressin on blood volume distribution in patients with cirrhosis. Scand J Gastroenterol 2004;5:486–92.

117. Knepper MA. Molecular physiology of urinary concentrating mechanism: regulation of aquaporin water channels by vasopressin. Am J Physiol 1997;272:F3–F12.

118. Koj A, Gauldie J, Regoeezi E, et al. The acute-phase response of cultured rat hepatocytes. Biochem J 1984;224:505–14.

119. Kone BC, Higham SC. A novel N-terminal splice variant of the rate H+-K+-ATPase $_2$ subunit. J Biol Chem 1998;273:3543–52.

120. Kozlowski S, Krzysztof D. The role of osmoreception in portal circulation in control of water intake in dogs. Acta Physiol Pol 1973;24:325–30.

121. Kreisberg RA. Lactate homeostasis and lactic acidosis. Ann Intern Med 1980;92:227–37.

122. Kunimi M, Seki G, Hara C, et al. Dopamine inhibits renal Na^++: HCO_3^- cotransporter in rabbits and normotensive rats but not in spontaneously hypertensive rats. Kidney Int 2000;57:534–43.

123. Leverve X, Mustafa I, Novak I, et al. Lactate metabolism in acute uremia. J Ren Nutr 2005;15:58–62.

124. Levy M, Wexler MJ. Renal sodium retention and ascites formation in dogs with experimental cirrhosis but without portal hypertension or increased splanchnic vascular capacity. J Lab Clin Med 1978;91:520–36.

125. Levy M. Pathogenesis of sodium retention in early cirrhosis of the liver: evidence for vascular overfilling. Semin Liver Dis 1994;14:4–13.

126. Levy M. Sodium retention and ascites formation in dogs with experimental portal cirrhosis. Am J Physiol 1977;233:F572–F585.

127. Levy M. Sodium retention in dogs with cirrhosis and ascites: efferent mechanisms. Am J Physiol 1977;233: F586–F592.

128. Lewis JH, Szeto IL, Bayer WL. Severe hemodilution with hydroxyethyl starch and dextrans. Arch Surg 1966;93:941–50.

129. Lim YS, Larson TS, Benson JT, et al. Serum sodium, renal function, and survival of patients with end-stage liver disease. J Hepatol 2010;52:523–8.

130. Lock BG, Pandit K. Evidence-based emergency medicine/systematic review abstract. Is flumazenil an effective treatment for hepatic encephalopathy. Ann Emerg Med 2006;47:286–8.

131. Luft FC. Lactic acidosis update for critical care clinicians. J Am Soc Nephrol 2001;12:S15–S19.

132. Lunn PC, Austin S. Excess energy intake promotes the development of hypoalbuminemia in rats fed on low-protein diets. Br J Nutr 1983;49:9–16.

133. Macintyre E, Mackie IJ, Ho D, et al. The haemostatic effects of hydroxyethyl starch (HES) used as a volume expander. Intensive Care Med 1985;11:300–3.

134. Marconato L, Crispino G, Finotello R, et al. Clinical relevance of serial determinations of lactate dehydrogenase activity used to predict recurrence in dogs with lymphoma. J Am Vet Med Assoc 2010;236:969–74.

135. Marconato L, Crispino G, Finotello R, et al. Serum lactate dehydrogenase activity in canine malignancies. Vet Comp Oncol 2009;7:236–43.

136. Margarson MP, Soni N. Serum albumin: touchstone or totem? Anaesthesia 1998;53:789–803.

137. Martin LG, Luther TY, Alperin DC, et al. Serum antibodies against human albumin in critically ill and healthy dogs. J Am Vet Med Assoc 2008;232:1004–9.

138. Mathews KA. The therapeutic use of 25% human serum albumin in critically ill dogs and cats. Vet Clin North Am Small Anim Pract 2008;38:595–605, xi–xii.

139. McAuliffe JJ, Lind LJ, Leith DE, et al. Hypoproteinemic alkalosis. Am J Med 1986;81:86–90.

140. McCullough AJ, Mullen KD, Kalhan SC. Measurements of total body and extracellular water in cirrhotic patients with and without ascites. Hepatology 1991;14:1102–11.

141. McGuire SO, Alexander DW, Fritsche KL. Fish oil source differentially affects rat immune cell alpha-tocopherol concentration. J Nutr 1997;127:1388–94.

142. Meier PJ. Molecular mechanisms of hepatic bile salt transport from sinusoidal blood into bile. Am J Physiol 1995;269:G801–G812.

143. Meuten DJ, Chew DJ, Capen CC, et al. Relationship of serum total calcium to albumin and total protein in dogs. J Am Vet Med Assoc 1982;180:63–7.

144. Meuten DJ, Chew DJ, Capen CC, et al. Relationship of serum total calcium to albumin and total protein in dogs. J Am Vet Med Assoc 1982;180:63–7.

145. Mishler JM. Pharmacology of hydroxyethyl starch. Use in therapy and blood banking. In: Oxford, UK: Oxford University Press; 1982. p. 1–118.

146. Moller S, Henriksen JH. Review article: pathogenesis and pathophysiology of hepatorenal syndrome: is there scope for prevention? Aliment Pharmacol Ther 2004;20 (Suppl. 3):31–41 discussion 42–43.

147. Moller S, Henriksen JH. Pathogenesis and pathophysiology of hepatorenal syndrome: is there scope for prevention? Aliment Pharmacol Ther 2004;20(Suppl. 3):31–41.

148. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the consensus conference of the international ascites club. Hepatology 2003;38:258–66.

149. Moore LE, Garvey MS. The effect of hetastarch on serum colloid oncotic pressure in hypoalbuminemic dogs. J Vet Intern Med 1996;10:300–3.

150. Moreau R, Hadengue A, Soupison T, et al. Arterial and mixed venous acid-base status in patients with cirrhosis. Influence of liver failure. Liver 1993;13:20–4.

151. Morgan EH, Peters T. The biosynthesis of rat serum albumin: V. Effect of protein depletion and refeeding on albumin and transferrin synthesis. J Biol Chem 1971;246:3500–7.

152. Moshage H. Cytokines and the hepatic acute phase response. J Pathol 1997;181:257–66.

153. Murphy GP, Demaree DE, Gagnon JA. The renal and systemic effects of hydroxyethyl starch solution infusions. J Urol 1965;93:534–9.

154. Nagami GT. Effect of bath and luminal potassium concentration on ammonia production and secretion by mouse proximal tubules perfused in vitro. J Clin Invest 1990;86:32–9.

155. Nelson DC, McGrew WRG, Hoyumpa AM. Hypernatremia and lactulose therapy. JAMA 1983;249:1295–8.

156. Nemec A, Pecar J, Seliskar A, et al. Assessment of acid-base status and plasma lactate concentrations in arterial, mixed venous, and portal blood from dogs during

experimental hepatic blood inflow occlusion. Am J Vet Res 2003;64:599–608.

157. Nizam R, Ahmed F. Hyperthyroxinemia and elevated lipids as paraneoplastic phenomena in hepatocellular carcinoma. A case report. J Clin Gastroenterol 1995;21:246–8.

158. Nyberg SL, Cerra FB, Gruetter R. Brain lactate by magnetic resonance spectroscopy during fulminant hepatic failure in the dog. Liver Transpl Surg 1998;4:158–65.

159. Olde Damink SWM, Jalan R, Deutz NE, et al. The kidney plays a major role in the hyperammonemia seen after simulated or actual GI bleeding in patients with cirrhosis. Hepatology 2003;37:1277–85.

160. O'Leary JG, Davis GL. Conivaptan increases serum sodium in hyponatremic patients with end-stage liver disease. Liver Transpl 2009;15:1325–9.

161. Pang DS, Boysen S. Lactate in veterinary critical care: pathophysiology and management. J Am Anim Hosp Assoc 2007;43:270–9.

162. Papadakis MA, Arieff AI. Unpredictability of clinical evaluation of renal function in cirrhosis. Prospective study. Am J Med 1987;82:945–53.

163. Papper S, Belsky JL, Bleifer KH. Renal failure in Laennec's cirrhosis of the liver. I. Description of the clinical and laboratory features. Ann Intern Med 1959;51:759–65.

164. Papper S, Saxon L. The diuretic response to administered water in patients with liver disease. II. Laennec's cirrhosis of the liver. Arch Intern Med 1959;103:750–7.

165. Papper S. The role of the kidney in Laennec's cirrhosis of the liver. Medicine (Baltimore) 1958;37:299–309.

166. Park R, Arieff AI, Leach W, et al. Treatment of lactic acidosis with dichloroacetate in dogs. J Clin Invest 1982;70:853–62.

167. Park R, Arieff AI. Lactic acidosis. Adv Int Med 1980;25:33–68.

168. Park R, Leach WJ, Arieff AI. Determination of the liver intracellular pH in vivo and its homeostasis in acute acidosis and alkalosis. Am J Physiol 1979;236:F240–F245.

169. Parth E, Jurecka W, Szepfalusi Z. Histological and immunohistochemical investigations of hydroxyethyl starch deposits in rat tissues. Eur Surg Res 1992;24:13–21.

170. Pembleton-Corbett JR, Center SA, Schermerhorn T, et al. Serum-effusion albumin gradient in dogs with transudative abdominal effusion. J Vet Intern Med 2000;14:613–8.

171. Perschel FH, Buhler H, Hierholzer K. Bile acids and their amidates inhibit 11 beta-hydroxysteroid dehydrogenase obtained from rat kidney. Pflugers Arch 1991;418:538–43.

172. Proot S, Biourge V, Teske E, et al. Soy protein isolate versus meat-based low-protein diet for dogs with congenital portosystemic shunts. J Vet Intern Med 2009;23:794–800.

173. Prytz H, Thomsen AC. Acid-base status in liver cirrhosis. Disturbances in stable, terminal and porta-caval shunted patients. Scand J Gastroenterol 1976;11:249–56.

174. Pugh P, Stone SL. The ionic composition of bile. J Physiol 1969;201:50P–51P.

175. Quinlan GJ, Margarson MP, Mumby S, et al. Administration of albumin to patients with sepsis syndrome: a possible beneficial role in plasma thiol repletion. Clin Sci (Lond) 1998;95:459–65.

176. Record CO, Iles RA, Cohen RD, et al. Acid-base and metabolic disturbances in fulminant hepatic failure. Gut 1975;16:144–9.

177. Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K1): a 5-year retrospective review. Ann Allergy Asthma Immunol 2002;89:400–6.

178. Rothschild MA, Oratz M, Dessler R, et al. Albumin synthesis in cirrhotic subjects with ascites studied with carbonate 14. J Clin Invest 1969;48:344–50.

179. Rothschild MA, Oratz M, Schreiber SS. Serum albumin. Hepatology 1988;8:385–401.

180. Rothuizen J, Biewenga WJ, Mol JA. Chronic glucocorticoid excess and impaired osmoregulation of vasopressin release in dogs with hepatic encephalopathy. Domest Anim Endocrinol 1995;12:13–24.

181. Rudloff E, Kirby R. The critical need for colloids: selecting the right colloid. Compend Contin Educ 1997;19:811–25.

182. Ruiz-del-Arbol L, Monescillo A, Jimenez W, et al. Paracentesis-induced circulatory dysfunction: mechanisms and effect on hepatic hemodynamics in cirrhosis. Gastroenterology 1997;113:579–86.

183. Saner FH, Fruhauf NR, Schafers RF, et al. Terlipressin plus hydroxyethyl starch infusion: an effective treatment for hepatorenal syndrome. Eur J Gastroenterol Hepatol 2003;15:925–7.

184. Sanfilippo MJ, Suberviola PD, Geimer NF. Development of a von Willebrand-like syndrome after prolonged use of hydroxyethyl starch. Am J Clin Pathol 1987;88:653–5.

185. Schenck PA, Chew DJ. Prediction of serum ionized calcium concentration by use of serum total calcium concentration in dogs. Am J Vet Res 2005;66:1330–6.

186. Schenker S, Breen KJ, Hoyumpa AM. Hepatic encephalopathy: current status. Gastroenterology 1974;66:121–51.

187. Schramko A, Suojaranta-Ylinen R, Kuitunen A, et al. Hydroxyethylstarch and gelatin solutions impair blood coagulation after cardiac surgery: a prospective randomized trial. Br J Anaesth 2010;104:691–7.

188. Sebastian A, Sutton JM, Hulter HM, et al. Effect of mineralocorticoid replacement therapy on renal acid-base homeostasis in adrenalectomized patients. Kidney Int 1980;18:762–83.

189. Seki N, Hamano H, Iiyama Y, et al. Effect of lactulose on calcium and magnesium absorption: a study using stable isotopes in adult men. J Nutr Sci Vitaminol (Tokyo) 2007;53:5–12.

190. Sevelius E, Andersson M. Serum protein electrophoresis as a prognostic marker of chronic liver disease in dogs. Vet Rec 1995;137:663–7.

191. Shangraw RE, Jahoor F. Effect of liver disease and transplantation on urea synthesis in humans: relationship to acid-base status. Am J Physiol 1999;276:G1145–G1152.

192. Shawcross D, Jalan R. Dispelling myths in the treatment of hepatic encephalopathy. Lancet 2005;365:431–3.

193. Shear L, Kleinerman J, Gabuzda GJ. Renal failure in patients with cirrhosis of the liver. I. Clinical and pathologic characteristics. Am J Med 1965;39:184–9.

194. Simpson KW, Fyfe J, Cornetta A, et al. Subnormal concentrations of serum cobalamin (vitamin B_{12}) in cats with gastrointestinal disease. J Vet Intern Med 2001;15:26–32.

195. Smart L, Hopper K, Aldrich J, et al. The effect of hetastarch (670/0.75) on urine specific gravity and osmolality in the dog. J Vet Intern Med 2009;23:388–91.

196. Smiley LE, Garvey MS. The use of hetastarch as adjunct therapy in 26 dogs with hypoalbuminemia: a phase two clinical trial. J Vet Intern Med 1994;8:195–202.

197. Sokol RJ, Devereaux M, Khandwala RA. Effect of dietary lipid and vitamin E on mitochondrial lipid peroxidation and hepatic injury in the bile duct-ligated rat. J Lipid Res 1991;32:1349–57.

198. Sokol RJ, McKim JM, Goff MC, et al. Vitamin E reduces oxidant injury to mitochondria and the hepatotoxicity of taurochenodeoxycholic acid in the rat. Gastroenterology 1998;114:164–74.

199. Sola R, Vila MC, Andreu M, et al. Total paracentesis with dextran 40 vs diuretics in the treatment of ascites in cirrhosis: a randomized controlled study. J Hepatol 1994;20:282–8.

200. Solis-Hernuzo JA, Gonzalez-Gamarra A, Castellano G, et al. Metabolic clearance rate of arginine vasopressin in patients with cirrhosis. Hepatology 1992;16:974–9.

201. Standl T, Lipfert B, Reeker W, et al. Acute effects of complete blood exchanges with ultra-purified hemoglobin solution or hydroxyethyl starch on liver and kidney in the animal model. Anasthesiol Intensivemed Notfallmed Schmerzther 1996;31:354–61.

202. Steiner JM. Cobalamin - Diagnostic use and therapeutic considerations. Texas A&M Gastrointestinal Laboratory; 2010.

203. Sterczer A, Meyer HP, Van Sluijs FJ, et al. Fast resolution of hypercortisolism in dogs with portosystemic encephalopathy after surgical shunt closure. Res Vet Sci 1999;66:63–7.

204. Stevenson CK, Kidney BA, Duke T, et al. Evaluation of the Accutrend for lactate measurement in dogs. Vet Clin Pathol 2007;36:261–6.

205. Stevenson CK, Kidney BA, Duke T, et al. Serial blood lactate concentrations in systemically ill dogs. Vet Clin Pathol 2007;36:234–9.

206. Stoff JS. Phosphate homeostasis and hypophosphatemia. Am J Med 1982;72:489–95.

207. Stump DC, Strauss RG, Henriksen RA, et al. Effects of hydroxyethyl starch on blood coagulation, particularly factor VIII. Transfusion 1985;25:230–4.

208. Such J, Frances R, Munoz C, et al. Detection and identification of bacterial DNA in patients with cirrhosis and culture-negative, nonneutrocytic ascites. Hepatology 2002;36:135–41.

209. Sullivan LA, Campbell VL, Klopp LS, et al. Blood lactate concentrations in anesthetized dogs with intracranial disease. J Vet Intern Med 2009;23:488–92.

210. Symington BE. Hetastarch and bleeding complications. Ann Intern Med 1986;105:627–8.

211. Tanifuji Y, Kamide M, Shudo Y, et al. Clinical evaluation of acetated Ringer as intraoperative fluids for patients with liver cirrhosis. Masui 1983;32:1347–52.

212. Tannen RL, Kunin AS. Effect of pH on ammonia production by renal mitochondria. Am J Physiol 1976;231:1631–7.

213. Tannen RL. Ammonia and acid base homeostasis. Med Clin North Am 1983;67:781–98.

214. Tannen RL. Relationship of renal ammonia production and potassium homeostasis. Kidney Int 1977;11:453–65.

215. Terg R, Berreta J, Abecasis R, et al. Dextran administration avoids hemodynamic changes following paracentesis in cirrhotic patients. A safe and inexpensive option. Dig Dis Sci 1992;37:79–83.

216. Terg R, Miguez CD, Castro L, et al. Pharmacokinetics of Dextran-70 in patients with cirrhosis and ascites undergoing therapeutic paracentesis. J Hepatol 1996;25:329–33.

217. The SAFE Study Investigators . A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247–56.

218. Thompson WL, Fukushima T, Rutherford RB, et al. Intravascular persistence, tissue storage, and excretion of hydroxyethyl starch. Surg Gynecol Obstet 1970;131:965–72.

219. Thompson WL, Gadsden RH. Prolonged bleeding times and hypofibrinogenemia in dogs after infusion of hydroxyethyl starch and dextran. Transfusion 1965;5:440–6.

220. Thorneloe C, Bedard C, Boysen S. Evaluation of a hand-held lactate analyzer in dogs. Can Vet J 2007;48:283–8.

221. Torrente C, Silvestrini P, Ruiz de Gopegui R. Severe life-threatening hypokalemia in a cat with suspected distal renal tubular acidosis. J Vet Emerg Crit Care (San Antonio) 2010;20:250–7.

222. Toulza O, Center SA, Brooks MB, et al. Evaluation of plasma protein C activity for detection of hepatobiliary disease and portosystemic shunting in dogs. J Am Vet Med Assoc 2006;229:1761–71.

223. Toulza O, Center SA, Brooks MB, et al. Protein C deficiency in dogs with liver disease. J Vet Int Med 2004;18:445 (abstract).

224. Trow AV, Rozanski EA, Delaforcade AM, et al. Evaluation of use of human albumin in critically ill dogs: 73 cases (2003-2006). J Am Vet Med Assoc 2008;233:607–12.

225. Unikowsky B, Wexler MJ, Levy M. Dogs with experimental cirrhosis of the liver but without intrahepatic hypertension do not retain sodium or form ascites. J Clin Invest 1983;72:1594–604.

226. Uriz J, Gines P, Cardenas A, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol 2000;33:43–8.

227. Vaamonde CA. Renal water handling in liver disease. In: Epstein M, editor. The kidney in liver disease. 3rd ed. Baltimore: Williams & Wilkins; 1988. p. 31–72.

228. Vigano F, Perissinotto L, Bosco VR. Administration of 5% human serum albumin in critically ill small animal patients with hypoalbuminemia: 418 dogs and 170 cats (1994-2008). J Vet Emerg Crit Care (San Antonio) 2010;20:237–43.

229. Vinay P, Cardoso M, Tejedor A, et al. Acetate metabolism during hemodialysis: metabolic considerations. Am J Nephrol 1987;7:337–54.

230. Walshe JM. Treatment of hepatic encephalopathy. Lancet 2005;365:1385–6.

231. Watanabe A, Matsuzaki S, Moriwaki H, et al. Problems in serum albumin measurement and clinical significance of albumin microheterogeneity in cirrhotics. Nutrition 2004;20:351–7.

232. Watson P. Comparing two low-protein diets in the treatment of dogs with congenital portosystemic shunts. J Vet Intern Med 2010;24:1–2. author reply 3.

233. Weber P, Bendich A, Machlin LJ. Vitamin E and human health: rationale for determining recommended intake levels. Nutrition 1997;13:450–60.

234. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. Ann Intern Med 2001;135:149–64.

235. Wong F, Blei AT, Blendis LM, et al. A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. Hepatology 2003;37:182–91.

236. Wong F, Liu P, Blendis L. The mechanism of improved sodium homeostasis of low-dose losartan in preascitic cirrhosis. Hepatology 2002;35:1449–58.
237. Woods HF, Connor H, Tucker GT. The role of altered lactate kinetics in the pathogenesis of type B lactic acidosis. In: Porter R, editor. Metabolic acidosis, CIBA Found Symp 87; 1982:. p. 307–23.
238. Yacobi A, Gibson TP, McEntegart CM, et al. Pharmacokinetics of high molecular weight hydroxyethyl starch in dogs. Res Comm Chem Pathol Pharmacol 1982;36:199–204.
239. Yang YY, Lin HC, Lee WC, et al. One-week losartan administration increases sodium excretion in cirrhotic patients with and without ascites. J Gastroenterol 2002;37:194–9.
240. Yatsu T, Kusayama T, Tomura Y, et al. Effect of conivaptan, a combined vasopressin V(1a) and V(2) receptor antagonist, on vasopressin-induced cardiac and haemodynamic changes in anaesthetised dogs. Pharamacol Res 2002;46:375–81.
241. Yedgar S, Carew RE, Pittman RC, et al. Tissue sites of catabolism of albumin in rabbits. Am J Physiol 1983;244:E101–E107.
242. Zavagli G, Ricci G, Bader G, et al. The importance of the highest normokalemia in the treatment of early hepatic encephalopathy. Miner Electrolyte Metab 1993;19:362–7.
243. Zimmon DS, Oratz M, Kessler R, et al. Albumin to ascites. Demonstration of a direct pathway bypassing the systemic circulation. J Clin Invest 1969;48:2074–8.
244. Zoran DL, Jergens AE, Riedesel DH, et al. Evaluation of hemostatic analytes after use of hypertonic saline solution combined with colloids for resuscitation of dogs with hypovolemia. Am J Vet Res 1992;53:1791–6.