SECTION 20

The Liver and the Kidney

CHAPTER 127

Liver-Kidney Interaction

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OBJECTIVES

This chapter will:

1. Give the reader an overview of the liver as an acid-base organ.
2. Describe the complexities of the liver-kidney interaction at the molecular level.
3. Relate the pathophysiologic abnormalities of liver-kidney interactions to outcomes of kidney injury in patients with liver disease.

The kidney is the primary organ for body-wide homeostasis, and disruption to its multiple functions has significant impact upon on all organ systems. Correspondingly, the interaction between the liver and kidney is complex and currently poorly understood. Both organs have similar physiologic roles in metabolic and endocrine homeostasis, protein, carbohydrate, and lipid metabolism, and the clearance of many pharmaceutical agents. In particular, they share a combined role in the provision of acid-base balance in the body. Given the large number of shared functions, it is perhaps not surprising that kidney disease is associated with liver impairment and more commonly, liver disease is associated with kidney impairment. This is clinically relevant because critically ill patients with kidney and liver dysfunction have a significantly higher morbidity and mortality.[1–3] In this chapter we provide an overview of the liver's role in acid-base balance and briefly present the clinical significance of acid-base balance abnormalities in the setting of liver disease.

ROLE OF AMMONIA AND GLUTAMINE

Traditionally, it was thought that ammonia (NH_3) has a key role in the acid-base balance because of its combination with hydrogen ions and subsequent formation of ammonium ions (NH_4^+) that are excreted readily via urine for a net loss of acid. However, the ammonia precursor, glutamine, exists in its ionized form in vivo (Fig. 127.1) and not the un-ionized form. Like other amino acids, it is a dipolar ion containing an anionic carboxylate group ($-COO^-$) and a cationic-substituted ammonium ($-NH_3^+$) group. The formation and excretion of ammonia in this pathway are electrochemically neutral with no uptake or loss of protons and therefore do not appear to influence body-wide acid-base balance, so an alternative explanation is required.

After glutamine has been reduced by the removal of two NH_4^+ groups, the remaining carbon skeleton, α-ketoglutarate, has two negatively charged carboxylate groups. Most of this α-ketoglutarate is metabolized within the kidney to glucose or CO_2, and consequently two HCO_3^- ions are produced according to the conservation of charge. However, these changes do not correlate with other changes occurring in the setting of metabolic acidosis. During metabolic acidosis, renal utilization of metabolic fuels switches away from α-ketoglutarate and other carboxylate-containing bicarbonate precursors, including lactate, resulting in net normal bicarbonate generation in acidosis and alkalosis.[4,5] More important, if an increase in renal bicarbonate production were to occur, it would not affect systemic acid-base balance. Glutamine that is not used in the kidney will be metabolized elsewhere (Fig. 127.2).[6] Metabolic acidosis, in addition to increasing renal glutamine utilization, deceases hepatic glutamine utilization. Regardless of the location of metabolism, two bicarbonate ions are generated from each molecule of glutamine, and the alkalinizing effect on the blood is the same in both cases.

UREAGENESIS

A key tenet of this model of acid-base balance is that ureagenesis is a bicarbonate-consuming process (Fig. 127.3).[7–10] In hepatocytes, NH_4^+, derived partly from the portal blood and partly from the action of pH-dependent glutaminase, reacts with bicarbonate from carbamoyl phosphate, with the self-evident consumption of bicarbonate. In the subsequent formation of citrulline in the urea cycle, a proton is released; it, in turn, converts HCO_3^- to CO_2 and H_2O. Thus two bicarbonates are consumed with each revolution of the urea cycle. This can be represented in summary fashion as follows:

$$2NH_4^+ + 2HCO_3^- \rightarrow NH_2 — CO — NH_2 + CO_2 + 3H_2O$$

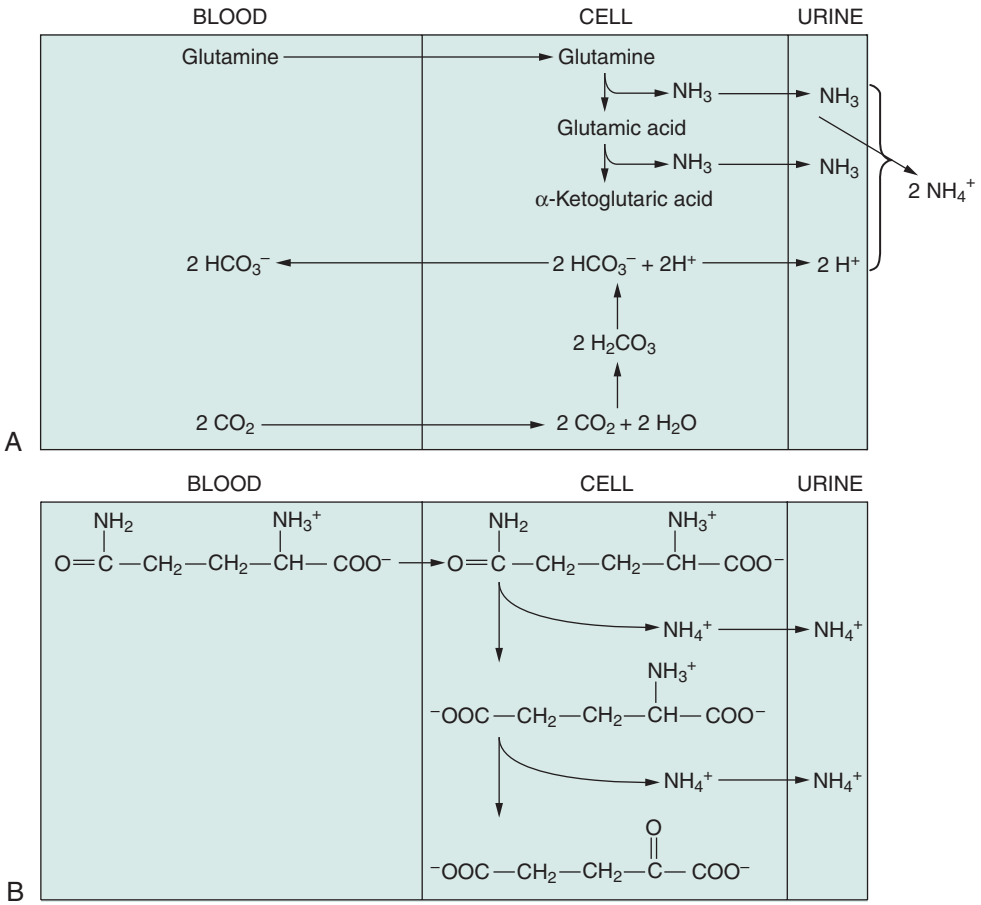

FIGURE 127.1 Deamidation and deamination of glutamine in the kidney. **A,** The conventional Pitts formulation. NH_3, derived from glutamine, moves into the lumen and combines with H^+ that was obtained from the body buffer, with generation of an equimolar amount of HCO_3^-, which moves into the blood. **B,** The chemically valid formulation, taking ionization into account. NH_4^+, rather than NH_3, is the product of deamidation and deamination of glutamine, and excretion of NH_4^+ has no effect on the body buffer.

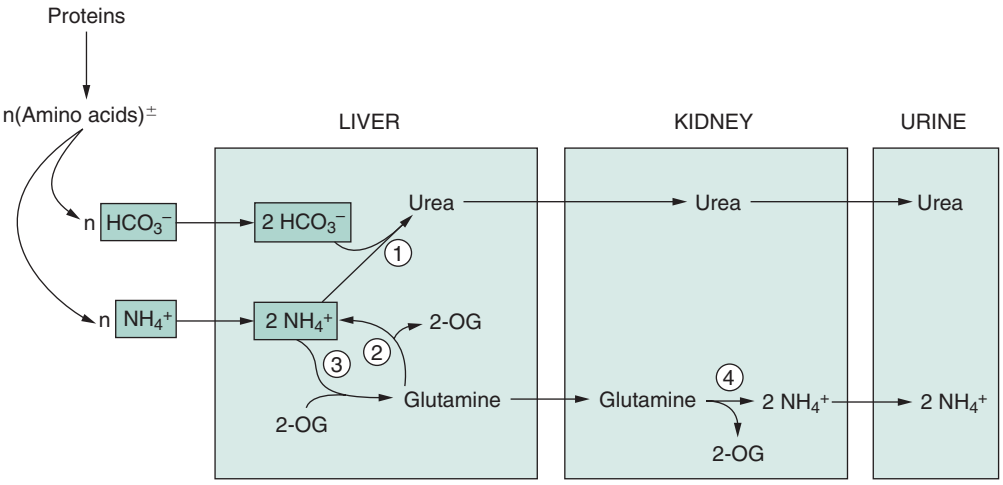

FIGURE 127.2 Ammonium metabolism and bicarbonate homeostasis. NH_4^+ and HCO_3^- generation are ultimately linked in a 1:1 stoichiometry during protein catabolism because of the irreversible elimination of both compounds via hepatic urea synthesis. Flux through the urea cycle is sensitively controlled by the extracellular acid-base status. The mechanisms involved adjust bicarbonate-consuming urea synthesis to the requirements of acid-base homeostasis. When urea synthesis decreases relative to the rate of protein catabolism in acidosis, bicarbonate is spared and NH_4^+ is excreted as such in the urine; there is no net production or consumption of α-ketoglutarate (2-oxoglutarate, or 2-OG) in the organism. Numbers in circles refer to major points of flux controlled by the acid-base status. In metabolic acidosis, flux through the area cycle (reaction 1) and hepatic glutaminase (reaction 2) are decreased, whereas flux through hepatic glutamine synthesis (reaction 3) and renal glutaminase (reaction 4) are increased. This interorgan "team effort" between the liver and the kidney results in NH_4^+ disposal without concomitant removal of HCO_3^- from the organism. (From Haussinger D, Gerok W, Sies H. The effect of urea synthesis on extracellular pH in isolated perfused rat liver. *Biochem J.* 1986;236:261–265.)

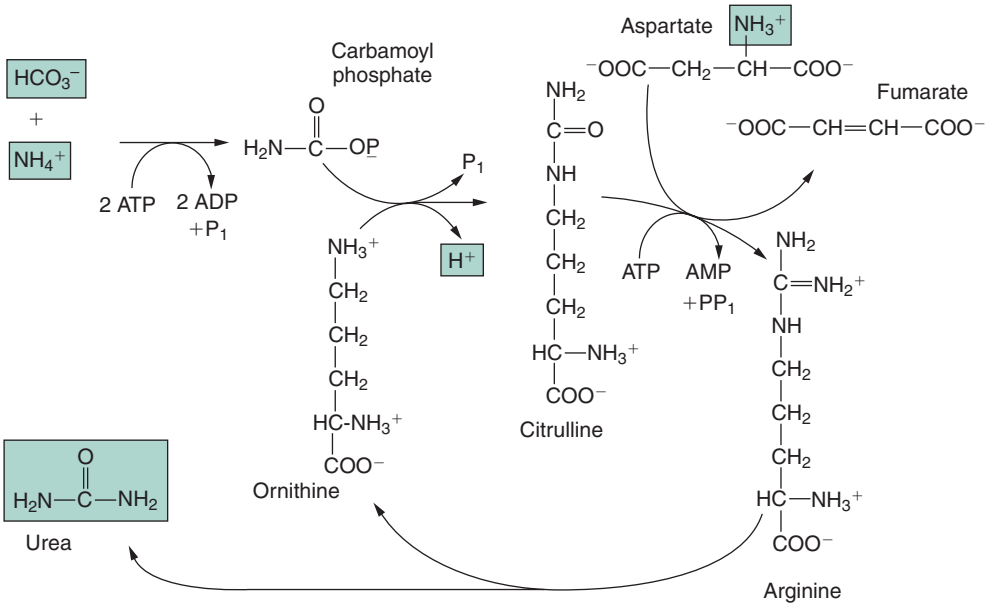

FIGURE 127.3 The pathway of urea synthesis. Compounds and ions that are consumed or produced are enclosed in boxes. In each turn of the cycle, two bicarbonate ions (one of which is retained in the product, urea) are titrated with protons derived from two ammonium ions. This titration, which would be thermodynamically impossible as a direct reaction, is made energetically favorable by being coupled to the conversion of four molecules of adenosine triphosphate (ATP) to adenosine diphosphate (ADP). (From Atkinson DE, Boorke E. pH Homeostasis in terrestrial vertebrates: Ammonium ion as a proton source. In Heisler N [ed]. *Mechanisms of Systemic Regulation: Acid-Base Regulation, Ion Transfer and Metabolism,* no. 22 [Advances in Comparative and Environmental Physiology]. Berlin, Springer, 1995, pp 1–26.)

Because NH_4^+ (pK = 9.3) is a very weak proton donor at physiologic pH levels, it would be thermodynamically impossible to titrate HCO_3^- (pK = 6.1) directly. The only means by which protons of NH_4^+ can be obtained for titration of HCO_3^- is through incorporation of the nitrogen into an uncharged group of an organic molecule with liberation of protons. Metabolic energy is required, and the process is made energetically feasible by being coupled to the conversion of four molecules of adenosine triphosphate (ATP) to adenosine diphosphate (ADP); this forces the titration of HCO_3^- by a proton donor that is much too weak to effect the titration directly. This generation of protons appears to be a major metabolic function of ureagenesis. The relevance of this energy-consuming biosynthesis becomes evident from numerous studies showing that hepatic ureagenesis is responsive to the needs of systemic pH regulation[8]; indeed, the increase in urinary ammonium long known to accompany hydrochloremic acidosis in humans has been shown to be accompanied by an equimolar decrease in urea excretion.[11] By decreasing urea production, the liver decreases the consumption of bicarbonate stores, which is what induced the adaptation in the first place. However, these models of how acid-base status is regulated by the liver and kidney have been challenged by alternative paradigms.

ALTERNATIVE APPROACH

The traditional model, as described earlier, has significant limitations in the interpretation of acid-base balance of the body.[12] Although it is superficially appealing, it fails to take into account the complex acid-base abnormalities that can develop during critical illness.[13] An alternative, the Stewart approach, also can be used to examine and explain the complex handling of nonvolatile acids by the liver and kidney. The Stewart approach uses three properties of physical chemistry—namely electroneutrality, conservation of mass, and electrolyte disassociation—to identify only three independent variables that control acid-base balance in the body.[14] The three variables are the partial pressure of carbon dioxide, the strong ion difference (SID), and total weak acid concentration (A_{tot}). According to the Stewart model, the kidneys remain the primary organ for acid-base balance but by maintaining the SID. This is completed mechanistically by the excretion of the strong Cl^- ion.[15] Ammonium (and consequently glutamine) has a key role in providing electrochemical neutrality by the production of the weak cation NH_4 by the kidneys to be excreted in electrochemical neutrality with the strong Cl^- anion. In contrast to the proposed physiologic pathway for the alkalinization described earlier, glutamine can be seen as alkalinizing because it is used in this manner to facilitate the excretion of Cl^- as opposed to the traditional view of HCO_3 production.

The Stewart approach also offers important insight into other acid-base abnormalities not fully explained by other models. In animal models it has been shown that, when assessed by the SID, the liver is responsible for anion removal but, in the setting of endotoxemia, is a net producer of anions.[16] Because the liver is responsible for protein synthesis, its role in acid-base balance via A_{tot} is significant. The weak acids that compose A_{tot} are largely hepatically synthesized carrier proteins, of which albumin is the most abundant and provides the remainder of the balance required to maintain electrochemical neutrality (i.e., SID = 0). Subsequently, a decrease in A_{tot} has an alkalizing effect on acid-base balance by increasing the SID. Although liver disease and critical illness are associated commonly with hypoalbuminemia, the overall effects of the lower A_{tot} on acid-base balance are negligible. Most studies have shown

that despite low A_{tot}, these patient groups have normal pH, SID, and standard-base excess.[17] It was postulated, on the basis of animal models, that the SID can be reset to ensure acid-base balance in the face of alkalizing hypoalbuminaemia.[15]

REGULATORY ROLE OF HEPATOCYTE HETEROGENEITY

The role of the liver in acid-base balance is supported further by the sequential distribution of enzymes within the functional units of the liver. The acini, which give precedence to the regulation of ureagenesis over glutamine synthesis, enable the rate of ureagenesis to respond to pH change, while leftover NH_4^+ is packaged into glutamine for export. The arrangement that facilitates this regulated sequence can be summarized as follows (Fig. 127.4): Each acinus extends from a terminal portal venule along a sinusoid to a terminal hepatic venule. The hepatocytes near the sinusoidal inflow are termed *periportal,* and those near the sinusoidal outflow are termed *perivenous* hepatocytes. A remarkable functional hepatocyte heterogeneity with respect to nitrogen metabolism occurs; it involves metabolic zonation of ureagenesis and glutamine synthesis, respectively, which is attributable to a special separation of the key enzymes between the periportal (urea cycle enzymes, glutaminase) and the perivenous (glutamine synthetase) hepatocytes of the hepatic acinus. Accordingly, along the sinusoid, the pathways of urea and glutamine synthesis are arranged in sequence. This organization prevents competition for the available ammonium between the two processes. Instead, there exists an established priority for ureagenesis. From the periportal venule, throughout a substantial length of the hepatic acinus, the enzyme glutaminase that contributes to the supply of ammonium for ureagenesis and also the enzymes the urea cycle share, as it were, a common hepatic compartment, giving prevalence to ureagenesis. Downstream, separately compartmentalized in the last rung of cells of the perihepatic venule, is the enzyme glutamine synthetase, which acts as a high-affinity scavenger for ammonium that has not been used in the periportal synthesis of urea. As the blood moves downstream through the sinusoid from the portal toward the hepatic venule, there is initially the formation of urea from the consumption of bicarbonate, which is derived from the metabolism of carboxylate groups of keto acids, and of ammonium, which is derived in part from the portal blood but is kept in adequate supply by the action of glutaminase. Acidosis reduces this bicarbonate-using process. As a consequence, there is ammonium left over, which is not used for ureagenesis. This leftover ammonium is taken up by the last rung of cells of the acinus, where glutamine synthetase incorporates it into glutamine, thereby controlling the blood ammonium concentration and serving as a transport mechanism for ammonium to the kidney.

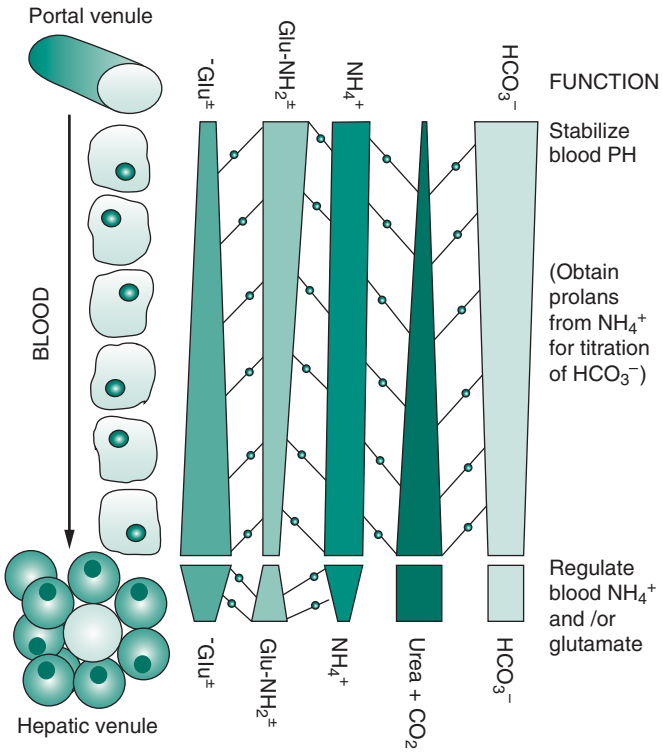

FIGURE 127.4 Schematic representation of nitrogen metabolism in the liver. As blood flows from the portal venule through the sinusoid, it first passes cells that contain glutaminase and the enzymes of the urea cycle. Glutamine is hydrolyzed to a greater or lesser extent. NH_4^+ is generated from the hydrolysis and from the metabolism of amino acids (not shown); incorporation of NH_4^+ into urea generates protons that serve to titrate HCO_3^-, half of which is incorporated into urea, with the other half converted to CO_2. The last rank of cells around the hepatic venule takes up glutamate and NH_4^+ and synthesizes glutamine. Changes in widths of the bars represent changes in concentrations of the corresponding substances. *Glu,* Glutamate; *Glu-$NH_2^{\pm}$,* glutamine. (From Atkinson DE, Boorke E. pH Homeostasis in terrestrial vertebrates: Ammonium ion as a proton source. In Heisler N [ed]. *Mechanisms of Systemic Regulation: Acid-Base Regulation, Ion Transfer and Metabolism,* no. 22 [Advances in Comparative and Environmental Physiology]. Berlin, Springer, 1995, pp 1–26.)

ACID-BASE BALANCE IN HEPATIC FUNCTIONAL IMPAIRMENT

It is unclear what impact liver impairment has upon acid-base balance. Early experimental research concluded that, despite decreased urinary urea, that there was no major role for the liver in acid-base regulation.[18] This has been supported by other studies looking at postoperative acid-base balance after major hepatic surgery, showing early acidosis but no overall longer-term impact upon acid-base balance.[19,20] A key component of the hepatic resection is to ensure that the liver remnant is of sufficient size to maintain normal hepatic metabolic function. Currently approximately 25% of hepatic tissue is recommended; it is likely that this residual tissue is sufficient to maintain adequate ureagenesis and ammonia detoxification in the absence of profound systemic insult.[21] Chronic liver disease, however, presents a different and more complex picture.[22–24] A study with patients with histologically stratified liver disease revealed increased in vivo plasma bicarbonate with progressive loss of in vivo urea cycle capacity; in these patients, other causes of metabolic alkalosis, such as diuretics, antacids, vomiting, hyperaldosteronism, and renal dysfunction, were excluded.[21] More recent studies have shown that in patients with stable cirrhosis there is apparent net normal acid-base balance, but this was due to the equilibrium of hypoalbuminemia,

hyperchloremia, and lactic acidosis.[22] In addition, this study highlighted the benefits of the physical, chemical, or physicochemical approach to acid-base in liver disease populations. However, this stability appears to be lost as patients with cirrhosis decompensate, with studies demonstrating significantly abnormal standard base excess (SBE), HCO_3, and strong ion difference (SID) values in those admitted with critical illness.[23,24] In addition, these abnormalities were found to be associated significantly with increased patient mortality.[23,24]

It is not clear why patients with cirrhosis are so susceptible to such complex acid-base disturbances, but it is likely that a complex interaction exists between the liver's metabolic function, the pathophysiologic consequences of liver disease, and the primary role of the kidney in acid-base balance. Proponents of the traditional view of acid-base balance propose that a feedback circuit exists between urea synthesis, bicarbonate accumulation, amplification of hepatic ammoniagenesis via glutaminase, and renal ammoniagenesis for excretion is controlled by systemic acid-base status.[22,25,26] Liver disease leads to the decrease of urea cycle capacity and subsequently increased alkalinization and hepatic glutaminase activity. This increases glutamine production and augments urea synthesis and restores a normal urea flux.[22,25,26] Correspondingly, the progressive loss of urea cycle capacity in cirrhosis is paralleled by an increase in renal ammonium excretion, despite coexisting metabolic alkalosis, indicating that the kidney undertakes the task of eliminating ammonium when urea synthesis fails.[22,25,26]

From a physical chemistry perspective, factors that are highly likely to be involved are the vasopressin-associated altered renal free water handling in cirrhosis and subsequent dilutional hyponatremia and relative hyperchloridemia. This, in turn, will influence the handling of strong ions and subsequently acid-base balance within the body. Progressive hepatic dysfunction and the increased risk of developing an episode of critical illness will lower the total amount of weak acids via the reduction in albumin, adding a confounding metabolic alkalosis to the acid-base balance. Finally, the role of the liver as an anion producer or remover has not yet been elucidated fully; it may be that the liver acts as either remover or producer, depending on overall systemic health.

In conclusion, the liver and kidney are intricately related in the maintenance of acid-base balance. It is clear that ureagenesis and ammonia metabolism are crucial steps in maintaining overall systemic acid-base balance. The underlying physiology and its relation to pathophysiology is still under investigation, and it appears that a physical chemical approach to acid-base in liver disease may provide a greater understanding and potentially improved management of patients with liver disease with alterations in acid-base balance.

Key Points

1. Contrary to the traditional view, glutamine does not generate NH_3 and therefore cannot remove H^+.
2. Ureagenesis is an acidifying process, whereas glutaminogenesis is alkalinizing.
3. The kidney's role in acid-base regulation requires cooperation with the liver.
4. Renal ammonium production is activated when ureagenesis decreases; this occurs not only in metabolic acidosis, when urea synthesis is inhibited because of homeostatic regulation, but also during alkalosis, when urea synthesis fails because of liver disease.

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A complete reference list can be found online at ExpertConsult.com.

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