

# Acid-Base and Potassium Disorders in Liver Disease

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Acid-base and potassium disorders occur frequently in the setting of liver disease. As the liver's metabolic function worsens, particularly in the setting of renal dysfunction, hemodynamic compromise, and hepatic encephalopathy, acid-base disorders ensue. The most common acid-base disorder is respiratory alkalosis. Metabolic acidosis alone or in combination with respiratory alkalosis also is common. Acid-base disorders in patients with liver disease are complex. The urine anion gap may help to distinguish between chronic respiratory alkalosis and hyperchloremic metabolic acidosis when a blood gas is not available. A negative urine anion gap helps to rule out chronic respiratory alkalosis. In this disorder a positive urine anion gap is expected owing to suppressed urinary acidification. Distal renal tubular acidosis occurs in autoimmune liver disease such as primary biliary cirrhosis, but often is a functional defect from impaired distal sodium delivery. Potassium disorders are often the result of the therapies used to treat advanced liver disease. *Semin Nephrol* 26:466-470 © 2006 Elsevier Inc. All rights reserved.

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Acid-base and potassium disorders are found commonly in the setting of liver disease.<sup>1-16</sup> In the initial stages of portal hypertension development, there is splanchnic arterial vasodilation associated with the production of nitric oxide.<sup>17</sup> This explains at least in part the increased sodium avidity and water retention.<sup>18-20</sup> In the setting of compensated liver disease, there is an increase in cardiac index, heart rate, and plasma volume. In the setting of decompensated liver disease, arterial pressure decreases, which leads to an increase in antidiuretic hormone (ADH) receptor activity, plasma catecholamine levels, aldosterone level, and renin-angiotensin system, and ADH levels, causing sodium and water retention.<sup>21-24</sup> The development of ascites, a reduction in renal perfusion, and a reduction in glomerular filtration rate follow, leading to a prerenal state. If persistent, severe, and unresponsive to volume, this condition is known as the *hepatorenal syndrome* and occurs in 5% to 18% at 1 year and 39% at 5 years in patients with cirrhosis and ascites.<sup>25</sup> Hyponatremia occurs from a reduction in filtered sodium, an increase in sodium reabsorption in the proximal tubule, and a reduction in free water clearance. Diuretics and paracentesis

often exacerbate hyponatremia by causing volume depletion and ADH release.<sup>25</sup>

Acid-base and potassium disorders also occur commonly in the setting of liver disease.<sup>1-16</sup> In patients with well-compensated cirrhosis, the abnormality may not be evident clinically. The most common acid-base disorder is respiratory alkalosis. However, metabolic alkalosis, respiratory acidosis, and metabolic acidosis all can be seen. As liver disease progressively worsens, the acid-base abnormality becomes more evident. As the liver's metabolic function decreases, particularly in the setting of renal dysfunction, hemodynamic compromise, hepatic encephalopathy, and further exacerbation of acid-base and potassium disorders often ensue.<sup>4,26</sup> Hyperventilation is an almost universal finding with advanced liver disease, leading to chronic respiratory alkalosis.<sup>27,28</sup>

A number of factors contribute to acid-base imbalance in liver disease: impaired gluconeogenesis reduces the metabolism of lactic acid and leads to metabolic acidosis, abnormalities in the efficiency of the urea cycle can cause a reduction in bicarbonate use, and a reduction in protein synthesis and primarily albumin in the setting of liver disease all contribute to changes in acid-base balance.<sup>29-32</sup>

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## Metabolic Acidosis

### High Anion Gap Metabolic Acidosis

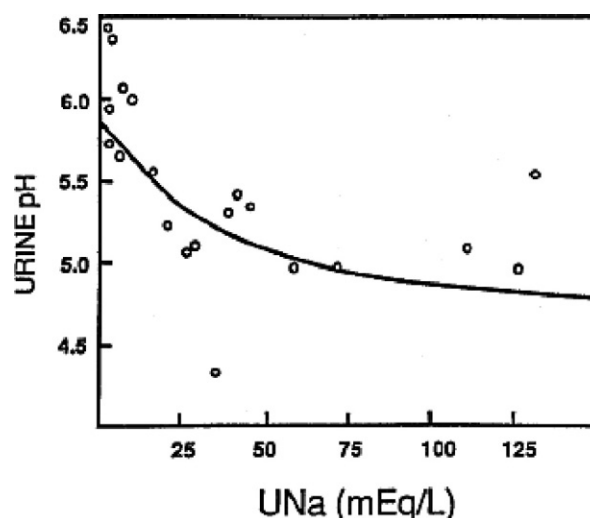
Initial studies reported the development of metabolic acidosis with progressively severe liver disease.<sup>11,13</sup> Increased an-

ion gap metabolic acidosis may be seen in 10% to 20% of patients with chronic liver disease, often as a result of type B lactic acidosis.<sup>8</sup> Patients with chronic stable and compensated liver disease, however, do not have increased lactate levels. Patients with decompensated liver disease, however, for example in the setting of sepsis or hemorrhage, may have increased blood lactic acid levels (ie, type A lactic acidosis). In the setting of end-stage liver disease, one study noted that 30% to 40% of patients had some degree of lactic acidosis.<sup>13</sup> Other types of metabolic acidosis include ketoacidosis, for example, in the setting of alcoholic liver disease with starvation, dehydration, impaired gluconeogenesis, and increased lactic acid production.<sup>2</sup> Metabolic acidosis also may be caused by the ingestion of methanol or ethylene glycol.<sup>8</sup> If an osmolar gap is noted in this setting, ingestion of either of these alcohols should be suspected immediately and imperative treatment such as ethanol infusion and hemodialysis should be initiated given the high mortality.<sup>8</sup> Other causes of metabolic acidosis include those developing in the absence of liver disease, such as salicylate overdose and renal failure when present.

### Hyperchloremic Metabolic Acidosis

Nonanion gap metabolic acidosis in patients with liver diseases also can be the result of diarrhea or renal tubular acidosis.<sup>26,33</sup> Diarrhea is a common cause of metabolic acidosis, particularly in patients on lactulose therapy for hepatic encephalopathy. The association between renal tubular acidosis and liver disease has long been recognized.<sup>6,7,12,26,33</sup> This issue, however, is somewhat controversial. Clearly, there are cases in which the distal acidification effect seems to be caused by an intrinsic tubular defect associated with autoimmune disease.<sup>7,12,34-36</sup> In primary biliary cirrhosis, for instance, there are well-documented series.<sup>7,12,34-36</sup> Many patients, however, may have a distal acidification defect that may be secondary to impaired distal sodium delivery as a result of liver failure. This in itself may interfere with the normal decrease of urine pH.<sup>37,38</sup> Urinary sodium availability affects the ability to decrease urine pH (Fig 1). In salt-retaining states with urine sodium levels of less than 25 mmols/L, urine pH cannot be decreased maximally.<sup>38</sup> In patients with liver disease and impaired distal sodium delivery, the finding of a high urine pH may be taken as evidence of distal renal tubular acidosis (RTA), although in reality this is not the case. Hence, urine pH is a misleading index of distal acidification in that the intrinsic renal capacity for distal H<sup>+</sup> secretion is normal once sodium delivery is increased. This may be accomplished by the administration of a loop diuretic.<sup>39</sup>

Whenever a hyperchloremic metabolic acidosis is present without any obvious cause (eg, diarrhea) and with a relatively normal glomerular filtration rate, distal RTA should be excluded. With appropriate suspicion, the diagnosis usually can be confirmed by the findings of an inappropriately low rate of acid excretion. In the presence of metabolic acidosis, ammonium is the most important component of acid excretion.<sup>37</sup> Ammonium is either measured directly or estimated by calculating the urine anion gap. The urine anion gap will



**Figure 1** Urinary pH in relation to urinary sodium concentration in 8 patients with diarrhea. Urinary sodium ( $U_{Na}$ ) was increased by the administration of either furosemide or sodium chloride. The relation between urinary pH ( $y$ ) and urinary sodium ( $x$ ) could be expressed as a curvilinear line, according to the following equation:  $y = -0.16 \ln(x) + 5.8$  ( $r = 0.75$ ,  $P < .001$ ). Reprinted from Battle et al.<sup>38</sup>

be low (often a negative value) if there is a decrease in unmeasured anions or an increase in unmeasured cations (eg,  $NH_4^+$ ). The urine anion gap will be increased (usually a positive value) if there is an increase in unmeasured anions or a decrease in unmeasured cations. Because the concentrations of unmeasured anions in the urine do not change considerably and because  $NH_4^+$  is the major unmeasured cation in the presence of metabolic acidosis, the urine anion gap is a useful estimate of urine  $[NH_4^+]$  in this setting. Patients with an acidification defect typically have a positive gap because of inappropriately low  $NH_4^+$  excretion, whereas in diarrheal states (providing that distal  $Na^+$  delivery is adequate) the gap is negative, reflecting the fact that  $NH_4^+$  excretion is not impaired. In proximal RTA, the urine anion gap is negative (provided plasma  $[HCO_3^-]$  is low), reflecting normal distal acidification. The urine anion gap also is useful to suspect the diagnosis of respiratory alkalosis.<sup>39</sup> In this acid-base disorder, the chronic alkalosis results in suppression of ammonium excretion and this is manifested by a positive urine anion gap (see later) (Table 1).

Diseases that had been associated with distal renal tubular acidosis in patients with liver disease include primary biliary cirrhosis, Wilson's disease, galactose union, amyloidosis, glycogen storage disorders, heavy metal intoxication, and hydrocarbon inhalation.<sup>40</sup> Fanconi syndrome also has been reported, although rarely.<sup>41</sup> Copper deposition injuring the renal tubules is thought to be the mechanism for acidosis in Wilson's disease.<sup>42</sup> Bicarbonate levels in the setting of these diseases generally are between 12 and 20 mEq/L. However, renal tubular acidosis also has been noted in patients in the absence of these types of liver disease. Golding<sup>6</sup> studied 100 patients with chronic liver disease showing the presence of a mild renal acidification defect this disorder was found more

**Table 1** The Urine Anion Gap as a Way to Distinguish Metabolic Acidosis From Respiratory Alkalosis

	Urine Anion Gap*	Plasma Bicarbonate	Plasma Chloride
Metabolic acidosis (diarrhea)	Negative	Low	High
Metabolic acidosis (distal RTA)	Positive	Low	High
Chronic respiratory alkalosis	Positive	Low	High

\*The urinary anion gap as a marker of ammonium excretion has not been validated in patients with chronic liver disease in whom ammonium excretion may be high independently of the renal excretion, which varies depending on the acid-base status. (Increased in metabolic acidosis as a result of diarrhea and decreased in distal RTA and respiratory alkalosis).

commonly in patients with biliary cirrhosis. Clinical renal tubular acidosis was observed infrequently. Some of these patients underwent a kidney biopsy examination, which showed marked renal interstitial nephritis with tubular damage. Another possibility is the presence of gammaglobulinemia as a cause for tubular dysfunction. In those with clinically significant renal tubular acidosis, hypokalemia and hypercalciuria may occur. Gabow et al<sup>5</sup> showed that patients with chronic liver disease on spironolactone developed metabolic acidosis. This is an almost predictable consequence of inhibition of aldosterone-driven sodium transport in the cortical collecting tubules. In the face of decreased distal sodium delivery, aldosterone is critical for sodium reabsorption and H<sup>+</sup> secretion. In fact, patients with advanced liver disease typically have low urine sodium and high urine potassium levels, the hallmark of secondary hyperaldosteronism.

## Respiratory Alkalosis

Respiratory alkalosis is thought to be the most common acid-base derangement found in patients with liver disease as a result of hyperventilation and an increase in blood ammonia levels. In 1967, Mulhausen et al<sup>11</sup> observed the relationship of acid-base status and lactate-pyruvate levels in 91 patients with liver disease; 64% had respiratory alkalosis but all varieties of acid-base abnormalities were observed. In addition, an inverse correlation between plasma bicarbonate and lactate-pyruvate levels was seen and it was proposed that primary respiratory alkalosis progresses to metabolic acidosis from lactic acidosis. Funk et al<sup>3</sup> studied 50 patients with stable liver disease and 10 healthy subjects and observed that patients with the mildest form of liver disease (Child-Pugh class A) had a normal acid-base state, whereas those with class B or C had respiratory alkalosis, although the creatinine clearance by any estimation was not provided for these patients. Proposed causative factors for respiratory alkalosis include hypoxemia in the setting of massive ascites, anemia, hepatopulmonary syndrome, hepatic hydrothorax, or bacterial infection; the exact cause of hyperventilation remains unclear but high progesterone levels owing to liver disease

seems the best explanation. Patients with fulminant hepatitis and hepatic coma can have a pH greater than 7.50.<sup>14</sup> The cause of hyperventilation is not clear; proposed causes include brain hypoxia and direct stimulation of the respiratory center by increased progesterone levels. In addition, estradiol has been proposed to be associated indirectly with respiratory alkalosis because it increases the number of progesterone receptors in animals and hence may increase its overall actions.<sup>28</sup> Progesterone is a respiratory stimulant in human beings and is degraded by the liver. Eiseman and Clark<sup>29</sup> observed that there is a direct correlation with hyperventilation and ammonia; however, subsequent studies with intravenous infusion of ammonia did not produce any increase in ventilation.

Chronic respiratory alkalosis, similar to hyperchloremic metabolic acidosis, presents with hypobicarbonatemia and hyperchloremia (Table 1). In the absence of blood gas determination, this combination often is diagnosed erroneously as a chronic metabolic acidosis. In this respect, the urine anion gap is useful in distinguishing these 2 disorders: if a metabolic acidosis other than distal RTA is present then the urine anion gap should be negative (Table 1). A positive urine anion gap in this setting suggests the presence of a respiratory alkalosis on distal RTA. A negative urine anion gap helps to rule out chronic respiratory alkalosis (Table 1). In this disorder a positive urine anion gap is expected as a result of suppressed urinary acidification, which is an adaptive response to chronic alkalemia. Although the definitive diagnosis requires a blood gas, the urine gap provides an index of suspicion alerting to the possible presence of a chronic respiratory alkalosis. There are no found studies validating the use of the urine anion gap in patients with respiratory alkalosis in the setting of chronic liver disease, in which ammonia levels may be increased.

Respiratory acidosis may occur also, but this is rare except when the patient is exposed to sedatives or in the context of associated lung disease.

## Metabolic Alkalosis

Metabolic alkalosis is another common base disorder found in patients with liver disease, often as a result of thereby with loop diuretics. This occurs owing to increased urinary hydrogen loss from enhanced distal hydrogen secretion. High aldosterone levels and hypokalemia further increase distal hydrogen secretion. A study by Haussinger et al<sup>30</sup> suggested that metabolic alkalosis occurs as a result of abnormal hepatic bicarbonate disposal and urea synthesis in cirrhosis. However, Shangraw and Jahoor<sup>32</sup> showed that impaired urea synthesis may not precipitate metabolic alkalosis.

Metabolic alkalosis often results from diuretic therapy with loop diuretics or thiazides and often is accompanied by hypokalemia. The administration of potassium or the use of potassium-sparing diuretics such as spironolactone may prevent or reduce metabolic alkalosis. Metabolic alkalosis also may occur in the setting of vomiting. As mentioned earlier, alkalosis, similar to hypokalemia, is thought to exacerbate hepatic coma; an increase in extracellular pH increases the

conversion of ammonium to ammonia.<sup>32</sup> Ammonia is lipid soluble and may diffuse into brain cells, thereby exacerbating encephalopathy.

## Potassium Disturbances in the Setting of Liver Disease

Potassium levels may vary in patients with liver disease; both hypokalemia and hyperkalemia may occur, but usually normokalemia is observed. Although there is increased secretion of aldosterone, which leads to sodium and potassium secretion, distal sodium delivery is decreased, thereby counteracting the stimulatory effect of aldosterone on potassium secretion.

### Hypokalemia

Patients may be hypokalemic owing to a variety of reasons including low dietary intake of potassium-rich foods or intracellular shifting of extracellular potassium in the setting of alkalemia.<sup>27</sup> Alternatively, patients may become hypokalemic, commonly in the setting of potassium loss with diuretic use, hyperaldosteronism, magnesium depletion (as in the case of chronic alcoholic liver disease), or vomiting.<sup>43</sup> Oftentimes hypokalemia is multifactorial. Early studies showed that the total body potassium level was decreased 30% to 40% in patients with liver disease irrespective of the stage of liver disease.<sup>43,44</sup> Hypokalemia can exacerbate hepatic encephalopathy by increasing renal ammoniogenesis and systemic ammonia levels.<sup>45</sup> Chlorothiazide treatment has been associated with hypokalemia and worsening of hepatic encephalopathy.<sup>45</sup> One of the first descriptions of this was by Read et al<sup>45</sup> in 1959. Subsequent studies reported that most patients on diuretics developed marked renal potassium wasting.<sup>46,47</sup> Another study in 1966 showed that induction of hypokalemia correlated with an increase in blood ammonia levels.<sup>4</sup> The degree of hypokalemia is dependent on the degree of natriuresis and hyperaldosteronism. Typically, those patients with hypokalemia had very high aldosterone levels but low distal Na<sup>+</sup> delivery, so that collecting tubule K<sup>+</sup> secretion is kept close to normal as a result of opposite influences canceling each other. A study in 1966 showed that induction of hypokalemia correlated with an increase in blood ammonia levels.<sup>4</sup> Hypokalemia also can result in muscle weakness, myocardial irritability, polyuria, polydipsia, and ileus. Exacerbation of hypokalemia was reported in a patient given terlipressin, a vasopressin analog used in the treatment of bleeding varices.<sup>48</sup> The patient developed urine potassium wasting and it was postulated that perhaps terlipressin potentiated the effect of aldosterone on potassium secretion.<sup>48</sup>

### Hyperkalemia

Hyperkalemia also can be seen in the setting of liver disease, although this is a less frequent complication and usually is caused by drugs such as the potassium-sparing diuretics spironolactone, eplerenone, amiloride, or triamterene, or angiotensin-converting enzyme inhibitors and angiotensin II

blockers.<sup>5</sup> This is exacerbated further by increased potassium intake, decreased glomerular filtration rate, and decreased distal delivery of sodium. Severe hyperkalemia also may occur in the setting of acidemia in the setting of end-stage or terminal liver disease. It also can occur if there is concomitant rhabdomyolysis as in the case of alcohol intoxication, gastrointestinal bleeding, or hemolysis.<sup>5,40,43,49</sup>

## Conclusion

Acid-base disorders in the setting of liver disease are frequent and complex; mixed acid-base disturbances are not uncommon in the setting of the underlying disease process and the therapy used to treat it. Respiratory alkalosis either alone or associated with a metabolic acidosis is the most common acid-base disorder. Metabolic acidosis often occurs from diarrhea associated with lactulose therapy and it is aggravated further by decreased distal Na<sup>+</sup> delivery. The urine anion gap is a useful tool in distinguishing chronic respiratory alkalosis from metabolic acidosis. The presence of multiple and mixed acid-base disorders may lead to a normal blood pH and the erroneous conclusion that there is no acid-base disorder. Even the most minor of therapies such as the infusion of normal saline, the administration of albumin, glucose infusion, and the initiation of diuretic therapy may alter the delicate acid-base balance. In addition, common complications in this patient population such as sepsis shock and hemorrhage can lead to a metabolic acidosis. The severity and complications of liver disease, presence of renal dysfunction and its potential cause, intravenous infusions, and all medications such as diuretics, vasopressin analogs, and lactulose therapy must be considered in the evaluation of acid-base and potassium disorders.

## References

1. Better OS: Renal and cardiovascular dysfunction in liver disease. *Kidney Int* 29:598-607, 1986
2. Cooperman MT, Davidoff F, Spark R, et al: Clinical studies of alcoholic ketoacidosis. *Diabetes* 23:433-439, 1974
3. Funk GC, Doberer D, Osterreicher C, et al: Equilibrium of acidifying and alkalinizing metabolic acid-base disorders in cirrhosis. *Liver Int* 25:505-512, 2005
4. Gabdudza GJ, Hall PW: Relation of potassium depletion to renal ammonium metabolism and hepatic coma. *Medicine (Baltimore)* 45:481-490, 1966
5. Gabow PA, Moore S, Schrier RW: Spironolactone-induced hyperchloremic acidosis in cirrhosis. *Ann Intern Med* 90:338-340, 1979
6. Golding PL: Renal tubular acidosis in chronic liver disease. *Postgrad Med J* 51:550-556, 1975
7. Golding PL, Mason AS: Renal tubular acidosis and autoimmune liver disease. *Gut* 12:153-157, 1971
8. Goodkin DA, Krishna GG, Narins RG: The role of the anion gap in detecting and managing mixed metabolic acid-base disorders. *Clin Endocrinol Metab* 13:333-349, 1984
9. Kee CS, Choi JW, Chang DK, et al: Hyperkalemia due to hyporeninemic hypoaldosteronism with liver cirrhosis and hypertension. *J Korean Med Sci* 8:464-470, 1993
10. Moreau R, Hadengue A, Soupison T, et al: Arterial and mixed venous acid-base status in patients with cirrhosis. Influence of liver failure. *Liver* 13:20-24, 1993
11. Mulhausen R, Eichenholz A, Blumentals A: Acid-base disturbances in

- patients with cirrhosis of the liver. *Medicine (Baltimore)* 46:185-189, 1967
12. Pares A, Rimola A, Bruguera M, et al: Renal tubular acidosis in primary biliary cirrhosis. *Gastroenterology* 80:681-686, 1981
  13. Prytz H, Thomsen AC: Acid-base status in liver cirrhosis. Disturbances in stable, terminal and portal-caval shunted patients. *Scand J Gastroenterol* 11:249-256, 1976
  14. Record CO, Iles RA, Cohen RD, et al: Acid-base and metabolic disturbances in fulminant hepatic failure. *Gut* 16:144-149, 1975
  15. Roberts KE, Vanamee P, Poppell JW, et al: Electrolyte alterations in liver disease and hepatic coma. *Med Clin North Am* 40:901-914, 1956
  16. Zavagli G, Ricci G, Bader G, et al: The importance of the highest normokalemia in the treatment of early hepatic encephalopathy. *Miner Electrolyte Metab* 19:362-367, 1993
  17. Cardenas A, Arroyo V: Mechanisms of water and sodium retention in cirrhosis and the pathogenesis of ascites. *Best Pract Res Clin Endocrinol Metab* 17:607-622, 2003
  18. Epstein M, Berk DP, Hollenberg NK, et al: Renal failure in the patient with cirrhosis. The role of active vasoconstriction. *Am J Med* 49:175-185, 1970
  19. Wilkinson SP: The kidney and liver diseases. *J Clin Pathol* 34:1241-1244, 1981
  20. Wilkinson SP, Hirst D, Day DW, et al: Spectrum of renal tubular damage in renal failure secondary to cirrhosis and fulminant hepatic failure. *J Clin Pathol* 31:101-107, 1978
  21. Akriviadis EA, Ervin MG, Cominelli F, et al: Hyponatremia of cirrhosis: Role of vasopressin and decreased 'effective' plasma volume. *Scand J Gastroenterol* 32:829-834, 1997
  22. Epstein M, Levinson R, Sancho J, et al: Characterization of the renin-aldosterone system in decompensated cirrhosis. *Circ Res* 41:818-829, 1977
  23. Tulassay T, Tulassay Z, Rascher W: Atrial natriuretic peptide in patients with decompensated hepatic cirrhosis. *Gastroenterol J* 50:140-143, 1990
  24. Cardenas A, Arroyo V: Refractory ascites. *Dig Dis* 23:30-38, 2005
  25. Gines A, Escorsell A, Gines P, et al: Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology* 105:229-236, 1993
  26. Shear L, Bonkowsky HL, Gabuzda GJ: Renal tubular acidosis in cirrhosis. A determinant of susceptibility to recurrent hepatic precoma. *N Engl J Med* 280:1-7, 1969
  27. Krapf R, Beeler I, Hertner D, et al: Chronic respiratory alkalosis. The effect of sustained hyperventilation on renal regulation of acid-base equilibrium. *N Engl J Med* 324:1394-1401, 1991
  28. Lustik SJ, Chhibber AK, Kolano JW, et al: The hyperventilation of cirrhosis: Progesterone and estradiol effects. *Hepatology* 25:55-58, 1997
  29. Eiseman B, Clark GM: Studies in ammonia metabolism. III. The experimental production of coma by carotid arterial infusion of ammonium salts. *Surgery* 43:476-485, 1958
  30. Haussinger D, Steeb R, Gerok W: Metabolic alkalosis as driving force for urea synthesis in liver disease: Pathogenetic model and therapeutic implications. *Clin Invest* 70:411-415, 1992
  31. McAuliffe JJ, Lind LJ, Leith DE, et al: Hypoproteinemic alkalosis. *Am J Med* 81:86-90, 1986
  32. Shangraw RE, Jahoor F: Effect of liver disease and transplantation on urea synthesis in humans: Relationship to acid-base status. *Am J Physiol* 276:G1145-G1152, 1999
  33. Oster JR, Hotchkiss JL, Carbon M, et al: Abnormal renal acidification in alcoholic liver disease. *J Lab Clin Med* 85:987-1000, 1975
  34. Davidson BK, Haslock I: Osteomalacia secondary to renal tubular acidosis masquerading as primary biliary cirrhosis. *Rheumatology (Oxford)* 39:1428-1429, 2000
  35. Kodama T, Imai H, Wakui H, et al: Tubulointerstitial nephritis with renal tubular acidosis and asymptomatic primary biliary cirrhosis accompanied by antibody to a 52-kDa mitochondrial protein alone. *Clin Nephrol* 45:401-405, 1996
  36. Tsantoulas DC, McFarlane IG, Portmann B, et al: Cell-mediated immunity to human Tamm-Horsfall glycoprotein in autoimmune liver disease with renal tubular acidosis. *BMJ* 4:491-494, 1974
  37. Batlle DC, Hizon M, Cohen E, et al: The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. *N Engl J Med* 318:594-599, 1988
  38. Batlle DC, von Rott A, Schlueter W: Urinary sodium in the evaluation of hyperchloremic metabolic acidosis. *N Engl J Med* 316:140-144, 1987
  39. Batlle D: Hyperchloremic metabolic acidosis, in Seldin DW, Giebisch G (eds): *The Regulation of Acid-Base Balance*. New York, Raven Press, 1989, pp 319-351
  40. Anderson R: Electrolyte, water, mineral, and acid-base disorders in liver disease, in Narins R (eds): *Clinical Disorders of Fluid and Electrolyte Metabolism*. New York, McGraw Hill, 1994, pp 1153-1172
  41. Lino M, Binaut R, Noel LH, et al: Tubulointerstitial nephritis and Fanconi syndrome in primary biliary cirrhosis. *Am J Kidney Dis* 46:e41-e46, 2005
  42. Leeson PM, Fourman P: A disorder of copper metabolism treated with penicillamine in a patient with primary biliary cirrhosis and renal tubular acidosis. *Am J Med* 43:620-635, 1967
  43. Casey TH, Summerskill WH, Bickford RG, et al: Body and serum potassium in liver disease. II. Relationships to arterial ammonia, blood pH, and hepatic coma. *Gastroenterology* 48:208-215, 1965
  44. Casey TH, Summerskill WH, Orvis AL: Body and serum potassium in liver disease. I. Relationship to hepatic function and associated factors. *Gastroenterology* 48:198-207, 1965
  45. Read AE, Laidlaw J, Haslam RM, et al: Neuropsychiatric complications following chlorothiazide therapy in patients with hepatic cirrhosis: Possible relation to hypokalaemia. *Clin Sci* 18:409-423, 1959
  46. Isaac G, Holland OB: Drug-induced hypokalaemia. A cause for concern. *Drugs Aging* 2:35-41, 1992
  47. Laffi G, La Villa G, Carloni V, et al: Loop diuretic therapy in liver cirrhosis with ascites. *J Cardiovasc Pharmacol* 22:S51-S58, 1993 (suppl 3)
  48. Stephan F, Paillard F: Terlipressin-exacerbated hypokalaemia. *Lancet* 351:1249-1250, 1998
  49. Siamopoulos KC, Elisaf M, Katopodis K: Iatrogenic hyperkalaemia—points to consider in diagnosis and management. *Nephrol Dial Transplant* 13:2402-2406, 1998