Review

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Acid-base disorders in liver disease

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Summary

Alongside the kidneys and lungs, the liver has been recognised as an important regulator of acid-base homeostasis. While respiratory alkalosis is the most common acid-base disorder in chronic liver disease, various complex metabolic acid-base disorders may occur with liver dysfunction. While the standard variables of acid-base equilibrium, such as pH and overall base excess, often fail to unmask the underlying cause of acid-base disorders, the physical–chemical acid-base model provides a more in-depth pathophysiological assessment for clinical judgement of acid-base disorders, in patients with liver diseases.

Patients with stable chronic liver disease have several offsetting acidifying and alkalinising metabolic acid-base disorders. Hypoalbuminaemic alkalosis is counteracted by hyperchloraemic and dilutional acidosis, resulting in a normal overall base excess. When patients with liver cirrhosis become critically ill (*e.g.*, because of sepsis or bleeding), this fragile equilibrium often tilts towards metabolic acidosis, which is attributed to lactic acidosis and acidosis due to a rise in unmeasured anions. Interestingly, even though patients with acute liver failure show significantly elevated lactate levels, often, no overt acid-base disorder can be found because of the offsetting hypoalbuminaemic alkalosis.

In conclusion, patients with liver diseases may have multiple co-existing metabolic acid-base abnormalities. Thus, knowledge of the pathophysiological and diagnostic concepts of acid-base disturbances in patients with liver disease is critical for therapeutic decision making.

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Key point

Patients with liver disease often have various complex acid-base disorders. Pathophysiological and diagnostic concepts as well as potential therapeutic interventions are reviewed in this article.

Introduction

A functioning acid-base balance results in normal blood pH and is critical for regular cellular and organ function.[1,2] Next to the kidneys and lungs, the liver is now recognised as an important organ of acid-base regulation,[3] playing a crucial role in various homeostatic pathways, such as the metabolism of organic acid anions like lactate and certain amino acids.[4] Consequently, patients with liver dysfunction often show acid-base disorders. Interestingly, the literature on acid-base disorders in liver disease is very limited. In addition, standard acid-base variables frequently fail to unmask the underlying acid-base disorders in liver disease.[5,6]

In contrast to the traditional model of acid-base equilibrium based on the Henderson-Hasselbalch-formula,[7,8] the more recent physical-chemical approach (also known as Stewart's approach)[9] provides a better understanding of the underlying mechanisms of acid-base disorders in liver disease. The most common acid-base disturbance in patients with liver disease is respiratory alkalosis; however, various complex metabolic disorders of acid-base equilibrium also occur in patients with both stable and decompensated cirrhosis.[10] This review will thus focus on the pathophysiological role of the liver in acid-base disorders that result from liver injury in the setting of cirrhosis, critical illness and acute liver failure; it will also cover diagnostic approaches, as well as specific therapeutic interventions in order to optimise patient management.

The physiological role of the healthy liver in acid-base regulation

Lactate metabolism and the Cori Cycle

Lactic acidosis is the most important type of metabolic acidosis in intensive care patients. It results from tissue hypoxia secondary to circulatory failure,[11,12] reduced lactate removal due to

sympathoadrenal-induced vasoconstriction and reduced blood flow to the liver, kidney and resting muscles.[13] Lactate is also produced in the working muscle during anaerobic glucose utilisation. The healthy liver acts as the main consumer of lactate and contributes to 30–70% of lactate metabolism (Fig. 1).[14,15] Experimental data indicated that liver lactate consumption is directly related to arterial lactate concentrations,[16] rather than liver blood flow.[17] Even after major hepatectomy with a 50% loss of functional liver tissue, blood lactate concentrations remain unchanged, underlining the functional reserve of a healthy liver to counterbalance lactic acidosis.[18] After hepatic uptake, lactate is first converted to pyruvate and then retransformed to glucose in a process called gluconeogenesis. Together, the release of lactate from the working muscle and its retransformation to glucose in the liver is called the Cori Cycle, and it releases equimolar amounts of HCO_3^-.[19]

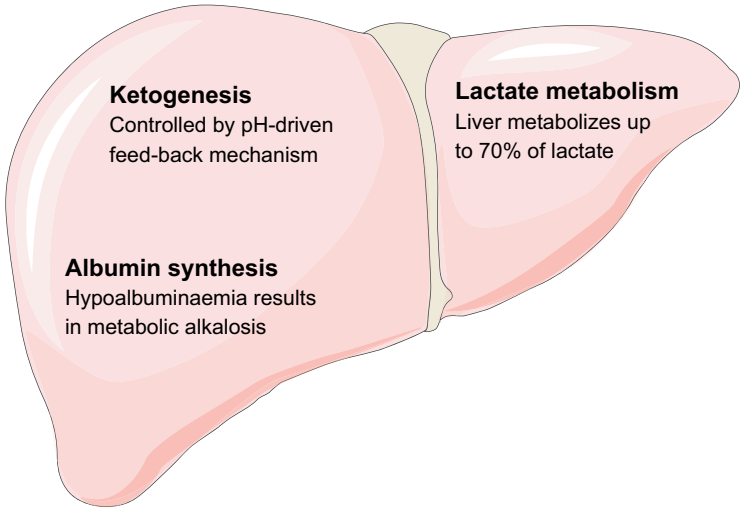

Fig. 1. Summary of the physiological role of the healthy liver in maintaining acid-base

Albumin synthesis

In the physiological range of blood pH, albumin behaves as a weak acid. Hypoalbuminaemia due to decreased production (*e.g.*, in liver disease or malnutrition) or increased loss (*e.g.*, nephrotic syndrome, intestinal loss or large, chronic wounds) results in mild metabolic alkalosis. In contrast, hyperalbuminaemia, which can be seen in patients with severe dehydration but is rarely observed, contributes to mild metabolic acidosis.[20,21]

Ketogenesis and ketoacidosis

Keto acids are produced in the mitochondria of the liver when carbohydrate or fat is incompletely oxidised. The keto acids, 3-hydroxybutyric acid and acetoacetic acid dissociate at physiologic pH, resulting in increased H^+ concentration, and may ultimately lead to ketoacidosis. Therefore, the net production of keto acids as well as their urinary excretion is controlled by a feedback mechanism, leading to reduced endogenous acid production if pH decreases[22] and increased keto acid production if pH rises.[23] This rapid up- or downregulation applies both to hepatic ketogenesis and lactate production. It can be sustained and it reverses completely as an acid-base challenge disappears.[24] Hepatic ketogenesis and its regulation are negligible and do not cause relevant acidosis under normal conditions. However, starvation or massive alcohol consumption can cause ketogenesis with substantial metabolic acidosis.

Urea production

The neurotoxic weak acid NH_4 arises during protein breakdown, with a daily amount of approximately 1 mol NH_4 based on an average protein intake of 100 g per day.[25] In the liver, NH_4 is further processed to urea, which can be excreted via urine. The process of urea production consumes equal amounts of the strong base HCO_3^-.[6] Therefore, urea production is not only a detoxification process; it may also play a role in acid-base regulation.[26] Indeed, early studies suggested that the liver has a direct acid-base regulating effect by altering ureagenesis and therefore HCO_3^- consumption.[5,25] However, these results could not be reproduced in other studies.[27–31] Furthermore, ureagenesis, an acidifying process, increased rather than decreased in experimental human acidosis.[32] Boon *et al.*[33,34] showed that the reduction of urea synthesis in acute and chronic acidosis was due to a marked decrease of hepatic amino acid transport and uptake, rather than a change in the activity of the ornithine cycle *per se*. In summary, ureagenesis has no discernible homeostatic effect on acid-base equilibrium in humans.

The physical-chemical acid-base model

Traditional acid-base analysis according to Siggaard-Andersen acknowledges the influence of $PaCO_2$, as well as organic acids and is based on blood pH.[8] However, it neglects the effects of electrolytes and weak acids (albumin and phosphate) on acid-base balance. The more recent physical-chemical acid-base approach according to Stewart integrates all potential modifiers of the acid-base balance.[9] While Stewart originally proposed a somewhat complex mathematical model, the simplified model by Gilfix *et al.* describes all possible metabolic acid-base disorders based on base excess (BE) subsets (Fig. 2).[20] It includes BE changes explained by variations in the following variables: (i) water (plasma dilution/concentration), (ii) chloride (Cl), (iii) albuminaemia, (iv) lactate and (v) unmeasured anions (UMA). Analogous to the regular BE, negative and positive values of BE subset indicate acidosis and alkalosis, respectively.

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Review

Key point

While respiratory alkalosis is the most common acid-base disorder in patients with liver disease, a normal pH and base excess do not exclude underlying metabolic acid-base disorders.

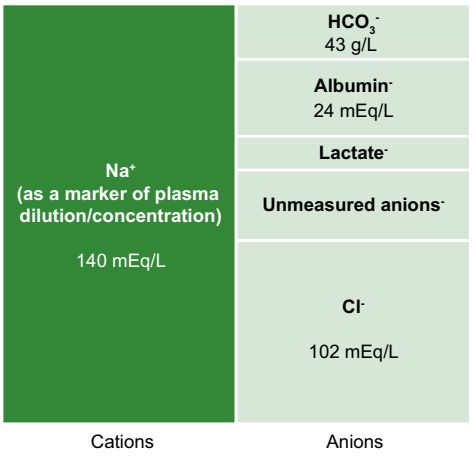

Fig. 2. Gamblegram showing the variables included in the physical-chemical acid-base approach as well as normal values.

(i) Plasma dilution due to an excess of free water causes dilutional acidosis (Na^+ normal value: 140 mEq/L): $BE_{Na} = 0.3 \times (Na^+_{measured} - Na^+_{normal})$; the multiplicator 0.3 derives from the calculation of: $\frac{normal\ strong\ ion\ difference = 40\ mEq/L}{normal\ Na^+\ value = 140\ mEq/L}$ as any differences from normal strong ion difference result in the respective BE changes.

(ii) Loss and retention of HCO_3^- followed by changes in serum chloride result in hyperchloraemic acidosis and hypochloraemic alkalosis, respectively: $BE_{Cl^-} = Cl^-_{normal} - (Cl^-_{observed} \times Na^+_{normal}/Na^+_{observed})$.

(iii) Albumin is a weak, non-volatile acid. Thus, hypoalbuminaemia represents a lack of acid and results in hypoalbuminaemic alkalosis: $BE_{albuminaemia} = (0.148 \times pH - 0.818) \times (albuminaemia_{normal} - albuminaemia_{observed})$.

(iv) Hyperlactataemia results in lactic acidosis: $BE_{Lactate} = lactate_{normal} - lactate_{measured}$.

(v) Any change in BE not caused by changes in free water, chloride, albumin or lactate is attributed to UMA (*e.g.* ketone bodies and organic anions): $BE_{UMA} = BE\ (overall\ base\ excess) - (BE_{Na} + BE_{Cl} + BE_{albuminaemia} + BE_{Lactate})$.

In summary, BE is calculated as: $BE_{Na} + BE_{Cl} + BE_{albuminaemia} + BE_{Lactate} + BE_{UMA}$. Underlying acid-base disorders might be overlooked when only the overall BE is used as BE_{subset} changes may offset each other.[20,35–37]

While BE_{Na}- and BE_{Cl}- deviations are clinically important, changes in the plasma levels of inorganic phosphate (Pi), potassium (K), magnesium (Mg) and calcium (Ca) do not play an essential role; their serum levels are too low to have a significant impact on BE.[37,38]

Acid-base disorders in liver disease

Considering the various physiologic functions of the liver, it seems obvious that advanced chronic liver disease can result in a variety of acid-base disorders.[2] Furthermore, extrahepatic organ dysfunction in liver cirrhosis (*e.g.*, encephalopathy, renal dysfunction) may also cause or aggravate acid-base disorders.[39] However, several studies using standard techniques for determining metabolic or respiratory acid-base disturbances, including pH-value, HCO_3^- and standard base excess, could not detect significant metabolic acid-base abnormalities in liver disease.[30,31,37] In contrast, analyses performed using a physical-chemical approach (as described earlier)[9,38] revealed several underlying acidifying and alkalinising metabolic acid-base disorders.[37] These acidifying and alkalinising factors will be discussed. While the treatment of extrahepatic conditions (*e.g.*, hepatorenal syndrome) is not a focus of this review, specific therapeutic interventions to stabilise acid-base homeostasis will be outlined.

Alkalinising factors in patients with liver cirrhosis

Even though several studies using standard techniques for evaluating acid-base equilibrium could not find any metabolic acid-base disorders, they reported the most well-established acid-base disorder in chronic liver disease, respiratory alkalosis,[30,31,40–42] with a more pronounced hypocapnia in patients with severe liver disease or viral hepatitis.[37,43,44] While the reason for this commonly observed respiratory acid-base disorder is not ultimately clear, there are several theories and underlying conditions leading to dyspnoea and compensatory hyperventilation.[45,46] While massive ascites and/or hepatic hydrothorax[47] cause hypoxaemia and thus hyperventilation, hyperammonaemia and hepatic encephalopathy[48] induce hyperventilation *per se*. A study by Lustik *et al.*[49] showed a correlation between increased progesterone and oestradiol levels (caused by impaired hepatic metabolism in advanced liver disease) that may directly stimulate ventilation by the activation of progesterone receptors in the central nervous system. Furthermore, dyspnoea can be aggravated in the case of hepatopulmonary syndrome or portopulmonary hypertension (Fig. 3).[46,50,51]

Some studies from the 1980s reported overt metabolic alkalosis in patients with stable chronic liver disease. It was hypothesised that decreased hepatic urea cycle enzyme activity would result in reduced bicarbonate elimination and thus metabolic alkalosis.[5,6,25] However, this theory was challenged as metabolic alkalosis was not actually observed in any other patient populations with cirrhosis,[29–31,37,52] unless patients were treated with diuretics, had taken antacids, or showed secondary hyperaldosteronism or low potassium levels.[42,53] Furthermore, the decrease in urea cycle enzyme activities seems to result from reduced hepatic amino acid uptake in acute and chronic acidosis rather than from downregulated enzyme activity.[33,34]

A physical-chemical acid-base analysis[37] revealed that hypoalbuminaemic alkalosis is the

main alkalinising metabolic disorder in patients with cirrhosis. As albumin is a weak acid, a decrease in albumin levels by 1 g/dl is followed by an approximate base excess increase by 3.7 mEq/L,[20,54] which explains the fact that $BE_{Albumin}$ increases with more severe liver disease.[37] However, hypoalbuminaemia may already be present in the early stages of liver cirrhosis as a result of diminished protein intake, increased protein requirements and altered protein and amino acid metabolism.[55] Therefore, it can be postulated that hypoalbuminaemia represents a major alkalinising factor that is present in a large majority of patients with cirrhosis;[44] hypoalbuminaemia is also a common reason for metabolic alkalosis in critically ill patients.[37,56]

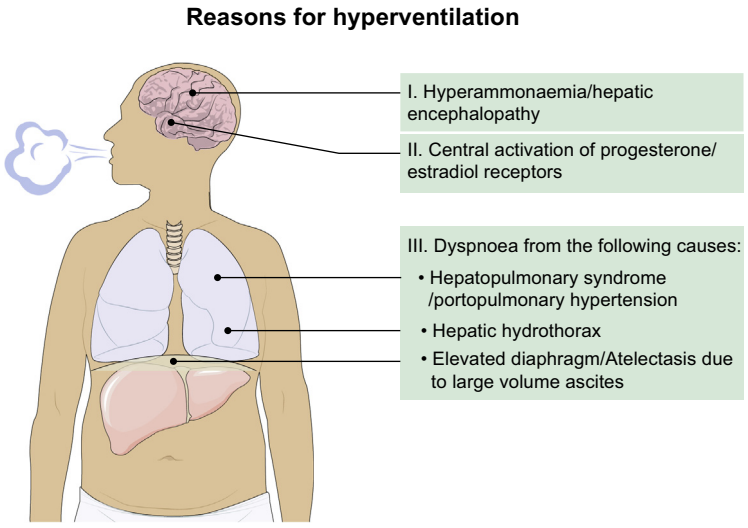

Fig. 3. Mechanisms of hyperventilation and respiratory alkalosis in liver disease.

Acidifying factors in patients with liver cirrhosis

In compensated liver cirrhosis, the aforementioned alkalinising acid-base disorders are partially balanced by several counteracting acidifying disorders that are discussed in this section.[37]

Hyponatraemia is a common finding in cirrhosis[57,58] and almost 50% of ascites patients present with serum sodium levels below the physiological range.[59] Hyponatraemia in cirrhosis is a phenomenon caused by portal hypertension-induced systemic, especially splanchnic, vasodilation. This results in a relative decrease of effective circulating blood volume. To compensate for this arterial "underfilling", water and sodium retention occurs through activation of the renin-angiotensin-aldosterone system (RAAS), non-osmotic, anti-diuretic-hormone (ADH)-release followed by tubular water reabsorption and the activation of the sympathetic nervous system.[57,58,60,61] This hypervolemia results in dilutional hyponatraemia.

Therefore, dilution with free water (pH = 7.00) plays a role in hyponatraemia and has an acidifying effect on plasma (pH ~7.40).[37,44] Furthermore, hyponatraemia is often aggravated by repeated paracentesis (which temporarily activates water-retention mechanisms during post-paracentesis circulatory dysfunction, when sufficient volume

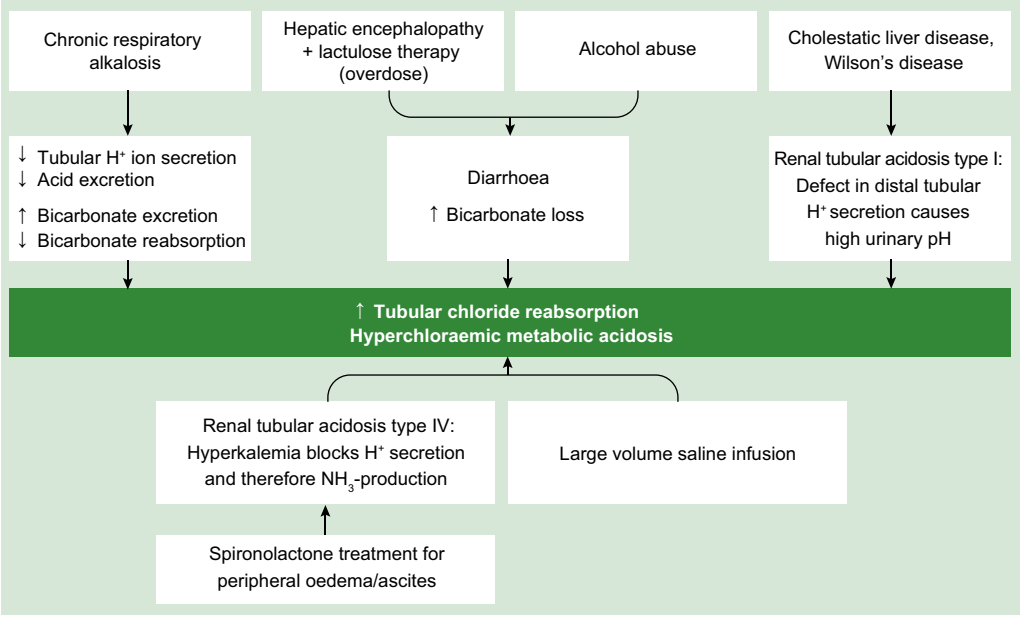

Fig. 4. Reasons for hyperchloraemic metabolic acidosis in patients with chronic liver disease.

expansion is not achieved) in patients with decompensated cirrhosis.[62]

Hyperchloraemic acidosis is another acidifying disorder that is frequently observed in cirrhosis and in critically ill patients.[63] In general this acid-base disorder is characterised by replacement of bicarbonate with chloride, owing to various mechanisms (Fig. 4).[64] In stable cirrhosis, hyperchloraemic acidosis might be considered a compensation for chronic respiratory alkalosis. In acute respiratory alkalosis, the compensatory mechanism is based on alkaline titration of the body's non-bicarbonate buffers,[65] with plasma proteins and inorganic phosphate (Pi) being the most important ones.[38] These mechanisms occur within approximately 5–10 minutes, but have limited compensatory potential.[65] In chronic respiratory alkalosis, the kidney reacts and reduces acid excretion by lowering tubular hydrogen ion secretion, which can be observed by a reduction in ammonium excretion. Furthermore, bicarbonate excretion is increased and a new steady state develops as the kidney chronically suppresses bicarbonate reabsorption in return for an increased chloride reabsorption, resulting in hyperchloraemic acidosis (quantified by a negative $BE_{Chloride}$). This adaptation takes approximately two to three days, but has a high compensatory potential.[65–68]

Diarrhoea and the associated gastrointestinal HCO_3^- loss and Cl^- retention are another cause of hyperchloraemic acidosis, especially in patients on lactulose therapy (overdose) for hepatic encephalopathy,[69] or in patients with alcoholic diarrhoea.[70] In addition, distal renal tubular acidosis (RTA Type I), which is based on a defect in distal tubular H^+ secretion and followed by inadequately high urinary pH (>5.3) during acidosis,[63,71] may occur principally in patients with cholestatic disorders, such as primary biliary cholangitis (PBC),[72] Wilson's disease, amyloidosis and glycogen storage disorders.[69] Mild renal acidification defects were found in patients with various chronic liver diseases and might be explained by the impaired distal renal Na^+ delivery, followed by inadequate Cl^- and H^+ excretion.[73] However, these defects were more common in patients with PBC. In addition, missing urine acidification is often linked to spironolactone-treatment, as hypoaldosteronism is associated with increasing serum potassium blocking NH_3-production and promoting metabolic acidosis (known as RTA Type IV).[70] Furthermore, hyperchloraemic acidosis is a potential limitation for the administration of large volume saline. It is an ongoing debate whether saline-induced hyperchloraemic acidosis also leads to unfavourable clinical outcomes.[74,75]

In patients with compensated cirrhosis, metabolic acid-base disorders, based on lactate or UMA, only play a minor role. However, lactate and UMA, such as ketone bodies, may become important in critically ill patients with cirrhosis[37,42] and will be reviewed later.

Key point

In stable liver cirrhosis, hypoalbuminaemic alkalosis is counteracted by hyperchloraemic and dilutional acidosis resulting in normal pH.

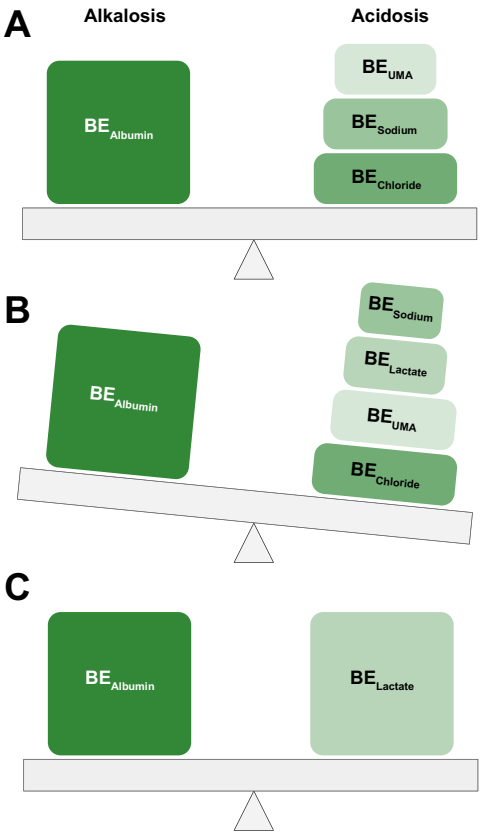

Fig. 5. Acid-base status in patients with chronic liver disease using the physical-chemical approach: (A) Equilibrium of acidifying and alkalinising factors in stable cirrhosis; (B) Net metabolic acidosis in critically ill patients with cirrhosis; (C) Hypoalbuminaemic alkalosis "neutralises" lactic acidosis in acute liver failure. $BE_{Albumin}$ Base excess due to the alkalinising effect of hypoalbuminaemia; BE_{UMA}: Base excess due to the acidifying effect of unmeasured anions (*e.g.*, keto acids); BE_{Sodium}: Base excess due to the acidifying effect of plasma dilution by free water; $BE_{Chloride}$: Base excess due to the acidifying effect of hyperchloraemia; $BE_{Lactate}$: Base excess due to the acidifying effect of elevated lactate.

Balance of acidifying and alkalinising acid-base factors in stable cirrhosis

As shown in Fig.5A, several offsetting acidifying and alkalinising metabolic factors can be observed in stable chronic liver disease, leaving the overall BE and pH unchanged. It is unknown whether this balance is a consequence of successful physiologic acid-base regulation to avoid overt acidosis and alkalosis, or if it is a coincidental finding.

Acid-base status in critically ill patients with cirrhosis

Gastrointestinal bleeding, hepatic encephalopathy, acute renal failure, respiratory failure and sepsis

Table 1. Complications in critically-ill cirrhotic patients with acidosis and comparison of adaptive mechanisms to acidosis in cirrhotic and liver-healthy subjects.

Complications in critically-ill cirrhotic patients with acidosis[36,91–95]	
Complications:	
• Development of acute on chronic liver failure (ACLF)	
• Increased cardiac output/hyperdynamic circulation	
• Lower systemic vascular resistance values	
• More pronounced oxygen debt due to decreased oxygen extraction and impaired tissue perfusion	
• Blood volume sequestration in the splanchnic venous plexus due to splanchnic vasodilation followed by effective hypovolemia and RAAS activation leading to renal vasoconstriction and impaired renal function	
• More pronounced septic shock-associated hyperlactatemia	
• Adrenal insufficiency is common	
• Elevated unmeasured anions in patients with liver disease	
Adaptive mechanisms in patients with cirrhosis:	Adaptive mechanisms in liver-healthy subjects:
• Delayed/missing lactate clearance associated with prolonged acidaemia • Susceptibility for extracellular oedema, ascites and pulmonary oedema – complicating fluid resuscitation and therefore restoring kidney function	• More rapid clearance/normalization of hyperlactataemia potentially improving lactic acidosis • More aggressive fluid resuscitation potentially improving UMA-acidosis

are the main reasons patients with cirrhosis are admitted to ICUs, and have high mortality rates.[36,76] Next to severity of pre-existing liver disease quantified by Child-Pugh-Score,[77] for example, development of organ failure resulted in significantly elevated 30-day mortality rates of over 50%.[78] From an acid-base point of view, in a study of 181 critically ill patients with cirrhosis, 39% of patients presented with acidaemia and 27% with alkalaemia at the time of ICU admission. In these patients, the overall BE was substantially decreased and the metabolic acid-base disorders due to hypoalbuminaemia, hyperchloraemia, elevated lactate and UMA were also profoundly different from those observed in patients with compensated cirrhosis (Table 1).[36,37] Therefore, unlike patients with compensated cirrhosis, critically ill patients with cirrhosis showed net metabolic acidosis, owing to UMA, lactic acidosis and mild dilutional acidosis compensated by hypoalbuminaemic alkalosis (Fig. 5B). Acute renal failure was associated with an even more negative BE and BE_{UMA}. Acute renal failure and the presence of acidaemia and lactic acidosis were independently associated with increased ICU mortality.[36]

Lactic acidosis is a common finding in ICU patients.[79] Considerable progress has been made in understanding hyperlactataemia in sepsis, which is not only driven by overproduction due to tissue hypoxia, dysfunction of the microcirculation[80] and increased glycolysis,[81] but also by underutilisation caused by impaired mitochondrial oxidation.[79] Furthermore, as 5% of lactate is metabolised by the kidney, acute kidney injury (AKI) in the setting of critical illness can worsen hyperlactataemia.[82] While the healthy liver has a huge functional reserve of metabolising lactate,[18] this lactate clearance is impaired in chronic liver diseases because of a decrease in the functional hepatocyte mass.[83,84] Accordingly, when compared to liver-healthy subjects, fasting lactate levels were significantly elevated in patients with chronic liver diseases.[82] However, fasting lactate levels were still within the range of normal and lactate levels were not correlated with Child-Pugh score,[37,82] indicating no direct correlation with the severity of compensated liver disease. Nevertheless, liver function and lactate clearance are further compromised in the presence of acute illness.[85,86] A dysfunctional liver may even become a net lactate producer in sepsis. While the splanchnic area was reported to be a major source of lactate production in patients with sepsis and acute liver dysfunction,[87] others could not confirm these results and reported a net splanchnic lactate production in only 7% of patients with sepsis.[12] However, both studies were not performed in a population of patients with cirrhosis.[87,88] An experimental study (animal model of sepsis) showed that the liver can become a major site of acid production in early sepsis, as measured by the strong-ion difference.[89] Another study suggested that the elevated lactate levels in patients with liver disease are a result of defects in hepatic pyruvate metabolism with a reduction in hepatic gluconeogenesis following severe hepatic necrosis.[90] In conclusion, complex disturbances of lactate metabolism can be found in acute and chronic liver disease. More studies directly targeting this question are needed.

Dichloroacetate, a drug stimulating the enzyme pyruvate dehydrogenase and therefore reducing pyruvate concentration as a substrate for lactate production,[96] was tested as a treatment for lactic acidosis.[97] This drug was found to be safe in several settings, including patients with sepsis,[98] patients with end-stage liver disease and patients with cirrhosis undergoing orthotopic liver transplantation.[97,99] While dichloroacetate treatment significantly reduced lactate levels,[52] no survival benefit was observed.[100]

Metformin-treatment in patients with diabetes and liver cirrhosis was thought to be associated with an increased incidence of lactic acidosis.[101] However, a recent study showed that metformin therapy was not only safe in patients with cirrhosis, but it also improved survival in patients with diabetes

Table 2. Summary of specific therapeutic interventions in cirrhotic patients with acid-base balance disorders. PaO_2 (mmHg), $PaCO_2$ (mmHg), HCO_3 (mEq/L), BE (mEq/L), Na (Sodium, mmol/L), K (Potassium, mmol/L), Cl (Chloride, mmol/L), Ca (Calcium, mmol/L), Mg (Magnesium, mmol/L), Pi (Phosphate, mmol/L), Alb (Albumin, g/L), Crea (serum creatinine, mg/dL), Lactate (mmol/L), $BE_{subsets}$ (mEq/L).

Case presentation	Acid-base interpretation	Clinical interpretation	Further diagnostics and treatment
55-year-old, stable cirrhotic patient (Child-Pugh B); **Acid-base status:** pH 7.45; PaO_2 55; $PaCO_2$ 31; HCO_3 21.2; BE -2 **Lab:** Na 134; K 3.9; Cl 98; Ca 1.22; Mg 0.8; Pi 1.0; Alb 30.0; Crea 0.8; Lactate 1.3 **BE subsets:** BE_{Alb} 4; BE_{Na} -3; BE_{Cl} -2; BE_{UMA} -1; $BE_{Lactate}$ 0	Alkalaemic pH plus hypocapnia indicate **respiratory alkalosis**. Normal base excess (BE) excludes an overall metabolic acid-base disorder. Underlying BE subsets show mild disorders offsetting each other.	This is the typical acid-base pattern of stable cirrhosis (see chapter 3). Potential reasons for hyperventilation are shown in Fig. 1. If severe hyperventilation is present, consider: - Encephalopathy, - Ascites, - Dyspnoea/Hypoxaemia (*e.g.*, due to hepatopulmonary syndrome or portopulmonary hypertension).	- Find and treat cause of hyperventilation (chest x-ray, CT scan to exclude atelectasis/shunt in hypoxaemic patients) - Lab: NH_3 - Echocardiography: systolic pulmonary artery pressure (sPAP) - Contrast-echocardiography (in hypoxaemic patients): intrapulmonary shunt?
50-year-old patient with alcoholic liver cirrhosis (Child-Pugh B) and known benzodiazepine abuse. Admittance to the emergency department because of somnolence. **Acid-base status:** pH 7.24; PaO_2 50; $PaCO_2$ 65; HCO_3 26.9; BE -1 **Lab:** Na 133; K 3.9; Cl 97; Ca 1.22; Mg 0.8; Pi 1.0; Alb 29.0; Crea 0.7; Lactate 1.5 **BE subsets:** BE_{Alb} 3; BE_{Na} -3; BE_{Cl} -1; BE_{UMA} 0; $BE_{Lactate}$ –1	Acidaemic pH plus high $PaCO_2$ indicate **respiratory acidosis**. Normal BE excludes an overall metabolic acid-base disorder. Underlying BE subsets show mild disorders offsetting each other.	This acid-base pattern is found in patients with alveolar hypoventilation (*e.g.*, due to coma, intoxication).	- Find and treat cause of hypoventilation - Lab: NH3, ethanol, drug screening - Consider antidote-treatment (*e.g.* flumazenil) - Consider mechanical ventilation (non-invasive ventilation)
47-year-old patient with posthepatitic cirrhosis (Child-Pugh B) and large oesophageal varices. Admittance to the emergency department because of severe variceal bleeding. **Acid-base status:** pH 7.28; PaO_2 85; $PaCO_2$ 32; HCO_3 14.6; BE -11 **Lab:** Na 130; K 4.1; Cl 95; Ca 1.22; Mg 0.85; Pi 1.05; Alb 30.0; Crea 1; Lactate 7.3 **BE subsets:** BE_{Alb} 3; BE_{Na} -4; BE_{Cl} -2; BE_{UMA} -2; $BE_{Lactate}$ -6	Acidaemic pH plus negative BE indicate **metabolic acidosis**. Calculation of BE subsets reveals **lactic acidosis**.	This acid-base pattern is frequently found in patients with shock (*e.g.* haemorrhagic, septic) but might also be drug-induced (*e.g.*, metformin, betamimetics – compare chapter 4).	- Find and treat cause of lactic acidosis - Assess haemodynamic situation - Consider ICU admission
46-year-old cirrhotic patient (Child-Pugh B) with sepsis due to spontaneous bacterial peritonitis. Patient is treated at a normal ward and received 4 l NaCl 0.9% because of hypotension. **Acid-base status:** pH 7.31; PaO_2 70; $PaCO_2$ 29; HCO_3 14.2; BE -11 **Lab:** Na 133; K 3.7; Cl 105; Ca 1.22; Mg 0.87; Pi 1.1; Alb 28.0; Crea 0.9; Lactate 1.4 **BE subsets:** BE_{Alb} 4; BE_{Na} -3; BE_{Cl} -10; BE_{UMA} -1; $BE_{Lactate}$ -0	Acidaemic pH plus negative BE indicate **metabolic acidosis**. Calculation of BE subsets reveals **hyperchloraemic acidosis** due to chloride-rich infusions.	This acid-base pattern is found in cases of chloride-rich infusions (*e.g.*, normal saline), but also in patients with diarrhoea or renal-tubular acidosis (compare chapter 3).	- Find and treat cause - Measure glomerular filtration rate - Calculate urine anion gap - Measure urine pH

40-year-old cirrhotic patient (Child-Pugh C) undergoing large volume ascites paracentesis (10 l) with state-of-the-art albumin substitution three days before admittance. Patient is now presenting with somnolence at the emergency department. **Acid-base status:** pH 7.26; PaO_2 65; $PaCO_2$ 36; HCO_3 15.6; BE -10 **Lab:** Na 129; K 7; Cl 95; Ca 1.22; Mg 1; Pi 1.3; Alb 25.0; Crea 5.4; Lactate 2.3 **BE subsets:** BE_{Alb} 4; BE_{Na} -4; BE_{Cl} -2; BE_{UMA} -7; $BE_{Lactate}$ -1	Acidaemic pH plus negative BE indicate **metabolic acidosis**. Calculation of BE subsets reveals **acidosis due to unmeasured anions** because of paracentesis-induced circulatory and acute renal failure and **uremic acidosis**.	This acid-base pattern is found in patients with acidosis due to unmeasured anions (*e.g.*, ketoacidosis, uremic acidosis due to renal failure, intoxications).	- Find and treat cause - Test for urinary ketones - Measure glomerular filtration rate - Correct hypovolemia (fluid challenge) - Consider renal replacement therapy
60-year-old cirrhotic patient (Child-Pugh A) with diuretically controlled ascites. Diuretic dose was adjusted by the general practitioner one week ago because of lower leg oedema. **Acid-base status:** pH 7.50; PaO_2 70; $PaCO_2$ 37; HCO_3 28.6; BE 6 **Lab:** Na 131; K 3.5; Cl 88; Ca 1.18; Mg 0.8; Pi 0.95; Alb 35.0; Crea 0.9; Lactate 1.3 **BE subsets:** BE_{Alb} 2; BE_{Na} -3; BE_{Cl} 7; BE_{UMA} 0; $BE_{Lactate}$ 0	Alkalaemic pH plus positive BE indicate **metabolic alkalosis**. Calculation of BE subsets reveals **hypochloraemic alkalosis** caused by diuretic overdose.	This acid-base pattern is found in patients with alkalosis due to hypochloraemia (*e.g.*, vomiting, diuretics, gastric drainage, hypovolaemia).	- Find and treat cause - Reconsider diuretic choice and dose (*e.g.* consider acetazolamide- treatment) - Consider potassium replacement
54-year-old non-cirrhotic patient presenting with fulminant Hepatitis B after starting of anti-TNF-α-treatment for severe rheumatoid arthritis. Patient presents at the emergency department because of progressive jaundice. **Acid-base status:** pH 7.41; PaO_2 75; $PaCO_2$ 30; HCO_3 18.6; BE -5 **Lab:** Na 133; K 4; Cl 96; Ca 1.25; Mg 0.9; Pi 1; Alb 20.0; Crea 1.3; Lactate 6.5 **BE subsets:** BE_{Alb} 6; BE_{Na} -3; BE_{Cl} 0; BE_{UMA} -2; $BE_{Lactate}$ -6	Normal pH-value indicates **no acid-base** disorder. However, calculation of BE subsets reveals offsetting **hypoalbuminaemic alkalosis** and **lactic acidosis**. Furthermore, mild respiratory alkalosis is present.	This acid-base pattern is typically found in patients with acute liver failure (compare chapter 5). Hypoalbuminaemic alkalosis may also be attributed to malnutrition or nephrotic syndrome.	- Find and treat cause - Test for proteinuria - Consider careful albumin substitution in order to improve anasarca and maintain adequate perfusion pressure

IPS: intrapulmonary shunt; Hb: Haemoglobin; ICU: intensive care unit.

and cirrhosis due to non-alcohol-steatohepatitis (NASH). However, this study mainly included patients with Child-Pugh A liver disease. Metformin should be used with caution in patients with Child-Pugh B and C cirrhosis.[102]

Acid-base disorders in acute liver failure (ALF)

Most patients with acute liver failure (ALF) have substantially elevated lactate levels. However, these changes were observed without acidaemia.[35,42,103] This counterintuitive phenomenon was described as "stress hyperlactataemia", resulting from a massive increase in glycolysis caused by catecholamine- and other cytokine-mediated increases in cellular glucose uptake without hypoxia,[104,105] as well as a reduction in total body clearance.[106] In accordance, net local production of lactate in the absence of hypoxia was observed in the splanchnic area[107,108] and the lungs, in the setting of ALF,[109] after large burns,[110] in pulmonary injury[111] and in sepsis.[112] However, at physiological pH, lactic acid is almost completely dissociated into lactate$^-$ and H^+ and should therefore cause metabolic acidosis.[113,114] Accordingly, a study using the physical-chemical acid-base model[9] revealed offsetting metabolic acid-base disorders (Fig. 5C). Lactic acidosis was compensated by pronounced hypoalbuminaemic alkalosis in patients with non-paracetamol-induced ALF, resulting in net respiratory alkalaemia due to hyperventilation.[35,103] Another study reported an additional alkalinising effect of hypochloraemia in patients with combined severe hepatic and renal failure.[10] While overt metabolic acidosis seems to be rare in non-paracetamol-induced ALF, there is conflicting data on patients with paracetamol-induced ALF. Record *et al.* published a report on three patients with severe acidosis presenting at 48 hours after paracetamol intoxication with high lactate levels; the patients presented without clinical signs of liver failure, but with an obvious failure of gluconeogenesis.[103] Importantly, most patients with ALF present with a stable overall acid-base state. Whether the presence of these offsetting acid-base disorders is a coincidence, or if the hypoalbuminaemia is a result of hyperlactatemia remains unclear.[35] However, we believe that these beneficial disorders – in terms of acid-base balance – are a result of ALF and do not represent a regulatory mechanism. It is of clinical importance to consider that correction of hypoalbuminaemia by exogenous albumin infusions might lead to net metabolic acidaemia, as observed in severely sick patients with hepatic and renal failure.[10] However, the acidifying effect of 20% albumin solution (1 g/kg of bodyweight) infused in patients with intact liver function was statistically significant, but still very small due to the buffered drug formulation.[115] Therefore, the finding that albumin infusion induced net metabolic acidaemia, as described earlier, might also be explained by an increase in UMA due to the high prevalence of coexisting renal failure in this group.[10]

Key point

In acute liver failure, pronounced lactic acidosis is counteracted by hypoalbuminaemic alkalosis again resulting in normal pH.

Therapeutic implications

The monitoring of acid-base status using the simplified physical-chemical model in patients with cirrhosis has several potential therapeutic consequences and is summarised in Table 2.

While specific treatment of the underlying disease is the only intervention with a proven benefit on mortality (*e.g.*, bleeding control, antibiotic treatment in the setting of sepsis), several supportive therapies have the potential to improve patient management.[11,116,117] In mechanically ventilated patients with cirrhosis and acidaemia due to metabolic acidosis, hyperventilation mitigates the severity of acidaemia. Based on physiologic considerations the targeted decrease in $paCO_2$ from 40 mmHg ($\Delta paCO_2$) should equal the observed decrease in standard base excess (ΔSBE).[118] For example, in a patient with an SBE of −10 mmol/L the target $paCO_2$ is 30 mmHg (subtracting 10 from the normal $paCO_2$ of 40 mmHg).

Conclusions and outlook

In healthy individuals, the most important hepatic contributions to a stable acid-base state are lactate clearance and albumin production, while hepatic ureagenesis does not represent a relevant acid-base regulating mechanism. Patients with stable liver cirrhosis show an equilibrium between acidifying and alkalinising metabolic acid-base disorders, resulting in a normal overall BE and pH. However, during hepatic decompensation or critical illness, this equilibrium may be rapidly destabilised, most often resulting in overt metabolic acidosis. Importantly, a normal pH and BE do not exclude underlying metabolic acid-base disorders in patients with liver disease. Therefore, the physical-chemical model of acid-base evaluation, which considers the acid-base effects of albumin and electrolytes, should be applied to understand and properly treat the underlying disorders in patients with acute and chronic liver disease.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study conception and design: B.S., G.-C.F.; Selection of appropriate literature: B.S., G.-C.F.; Drafting of the manuscript: B.S., T.R., M.T., G.-C.F.; Critical revision of the manuscript for important intellectual content: G.L., T.R., Br.S., M.T., C.Z., G.-C.F.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2017.06.023.

Key point

When patients with liver cirrhosis get critically ill, the acid-base equilibrium often tilts towards metabolic acidosis due to lactic acidosis and unmeasured anions.

Key point

The physical-chemical acid-base model should be applied to diagnose and properly manage underlying disorders of acid-base homeostasis in patients with acute and chronic liver disease.

Review

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