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Review

Acid-base disorders in liver disease

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Key points:

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

- 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.

- In stable liver cirrhosis, hypoalbuminemic alkalosis is counteracted by hyperchloremic and dilutional acidosis resulting in normal pH.

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

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

- 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.
Summary

Next to the kidneys and lungs, the liver has been recognized 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. Although 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 allows a more in-depth pathophysiological understanding and clinical judgement of acid-base disorders in patients with liver diseases.

Patients with stable chronic liver disease have several offsetting acidifying and alkalinizing metabolic acid-base disorders. Hypoalbuminemic alkalosis is counteracted by hyperchloremic and dilutional acidosis, resulting in a normal overall base excess. When patients with liver cirrhosis become critically ill (e.g., due to 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 due to the offsetting hypoalbuminemic alkalosis.

In conclusion, patients with liver diseases may have multiple co-existing metabolic acid-base abnormalities and, thus, knowledge of the pathophysiological and diagnostic concepts of acid-base disturbances in patients with liver disease is critical to decisions on adequate therapeutic interventions.
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 kidney and lungs, the liver is now recognized as an important acid-base regulation organ\(^3\), 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 optimize patient management.
1. The physiological role of the healthy liver in acid-base regulation (Figure-1)

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, reduced lactate removal due to sympathoadrenal-induced vasoconstriction and reduced blood flow to the liver, kidney and resting muscles. Lactate is also produced in the working muscle during anaerobic glucose utilization. The healthy liver acts as the main consumer of lactate and contributes to 30–70% of lactate metabolism. Experimental data indicated that liver lactate consumption is directly related to arterial lactate concentrations, rather than liver blood flow. 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. 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 $\text{HCO}_3^-$.

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.

Ketogenesis and ketoacidosis

Keto acids are produced in the mitochondria of the liver when carbohydrate or fat is incompletely oxidized. 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 as well as 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, as a consequence of starvation or massive alcohol consumption,
ketogenesis with substantial metabolic acidosis can occur.

**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\(_3^-\). 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 regulation 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 due to 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.
Figure-1: Summary of the physiological role of the healthy liver in maintaining acid-base homeostasis

2. The physical-chemical acid-base model (Figure-2)

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\textsuperscript{8}. However, it neglects the effects of electrolytes and the 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\textsuperscript{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\textsuperscript{20}. It includes BE changes explained by variations in the following variables: (i) water (plasma dilution/concentration), (ii) chloride (Cl), (iii) albuminemia (Alb), (iv) lactate and (v) unmeasured anions (UMA). Analogous to the regular base excess, negative and positive values of base excess subset indicate acidosis and alkalosis, respectively.

(i) Plasma dilution due to an excess of free water causes dilutional acidosis (Na$^+$ normal value: 140 mEq/L): $BE_{Na} = 0.3 \times (Na^+_{\text{measured}} - Na^+_{\text{normal}})$; the multiplicator 0.3 derives from the calculation of: $\frac{\text{normal strong ion difference}}{\text{normal Na+value}} = \frac{40 \text{ mEq/L}}{140 \text{ mEq/L}}$ as any differences from normal strong ion difference result in the respective BE-changes.
(ii) Loss and retention of $\text{HCO}_3^-$ followed by changes in serum chloride result in hyperchloremic acidosis and hypochloraemic alkalosis, respectively: $\text{BE}_{\text{Cl}} = \text{Cl}^{-}_{\text{normal}} - (\text{Cl}^{-}\text{observed} \times \text{Na}^+_{\text{normal}} / \text{Na}^+_{\text{observed}})$.

(iii) Albumin is a weak, non-volatile acid. Thus, hypoalbuminaemia represents a lack of acid and results in hypoalbuminemic alkalosis: $\text{BE}_{\text{ALB}} = (0.148 \times \text{pH} - 0.818) \times (\text{Alb}_{\text{normal}} - \text{Alb}_{\text{observed}})$.

(iv) Hyperlactataemia results in lactic acidosis: $\text{BE}_{\text{Lac}} = \text{lactate}_{\text{normal}} - \text{lactate}_{\text{measured}}$.

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

In summary, BE is calculated as: $\text{BE}_{\text{Na}} + \text{BE}_{\text{Cl}} + \text{BE}_{\text{Alb}} + \text{BE}_{\text{Lac}} + \text{BE}_{\text{UMA}}$. Underlying acid-base disorders might be overlooked when only the overall BE is used as BE subset changes may offset each other.\textsuperscript{20,35-37}

While $\text{BE}_{\text{Natrium}}$ and $\text{BE}_{\text{Chloride}}$ 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.\textsuperscript{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\(^3\). However, several studies using standard techniques for determining metabolic or respiratory acid-base disturbances, including pH-value, $\text{HCO}_3^-$ and standard base excess, could not detect significant metabolic acid-base abnormalities in liver disease\(^3,31,37\). In contrast, analyses performed using a physical-chemical approach (as described above)\(^9,38\) revealed several underlying acidifying and alkalinizing metabolic acid-base disorders\(^37\). These acidifying and alkalinizing 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 stabilize acid-base homeostasis will be outlined.

**Figure-2:** Gamblegram showing the variables included in the physical-chemical acid-base approach as well as normal values
Alkalinizing factors in patients with liver cirrhosis (Figure-3)

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 hypoxemia 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 $^{46,50,51}$ (Figure-3).

**Reasons for hyperventilation**

I. Hyperammonemia / Hepatic encephalopathy

II. Central activation of progesterone / estradiol receptors

III. Dyspnea from the following causes:
- Hepatic hydrothorax
- Hepatopulmonary syndrome / Portopulmonary Hypertension
- Elevated diaphragm / Atelectasis due to large volume ascites

Figure-3: Mechanisms of hyperventilation and respiratory alkalosis in liver disease
Some studies from the 1980s reported overt metabolic alkalosis in patients with stable chronic liver disease. It was hypothesized that decreased hepatic urea cycle enzyme activity results in reduced bicarbonate elimination and thus metabolic alkalosis. However, this theory was challenged as metabolic alkalosis was not actually observed in any other cirrhotic patient populations unless patients were treated with diuretics, had taken antacids, or showed secondary hyperaldosteronism or low potassium levels. 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.

A physical-chemical acid-base analysis revealed that hypoalbuminemic alkalosis is the main alkalinizing metabolic disorder in cirrhotic patients. 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, which explains the fact that BE increases with more severe liver disease. However, hypoalbuminaemia may be already 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. Therefore, it can be postulated that hypoalbuminaemia represents a major alkalinizing factor that is present in a large majority of cirrhotic patients; hypoalbuminaemia has also been shown to be a common reason for metabolic alkalosis in critically ill patients.

**Acidifying factors in patients with liver cirrhosis (Figure-4)**

In compensated liver cirrhosis, the abovementioned alkalinizing acid-base disorders are partially balanced by several counteracting acidifying disorders that are discussed in this section.

Hyponatraemia is a common finding in cirrhosis and almost 50% of ascites patients present with serum sodium levels below the physiological range. Hyponatraemia in cirrhosis is a phenomenon caused by portal hypertension-induced systemic and especially
splanchnic vasodilation, resulting 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. As a consequence, this hypervolemia results in dilution hyponatraemia.

Therefore, dilution with free water (pH = 7.00) plays a role in hyponatremia and has an acidifying effect on plasma (pH~7.40). Furthermore, hyponatraemia is often aggravated by repeated paracentesis (which temporarily activates water-retention mechanisms during post-paracentesis circulatory dysfunction when sufficient volume expansion is not achieved) in patients with decompensated cirrhosis.

Hyperchloremic acidosis is another acidifying disorder that is frequently observed in cirrhosis as well as in critically ill patients. In general, this acid-base disorder is characterized by replacement of bicarbonate with chloride due to various mechanisms. In stable cirrhosis, hyperchloremic acidosis might be considered a compensation for chronic respiratory alkalosis. In acute respiratory alkalosis, the compensatory mechanism is based on alkaline titration of body’s non-bicarbonate buffers, with plasma proteins and inorganic phosphate (Pi) being the most important ones. These mechanisms occur within approximately 5-10 minutes but have limited compensatory potential. 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 hyperchloremic acidosis (quantified by a negative $BE_{\text{Chloride}}$). This adaptation takes approximately two to three days but has a high compensatory potential.
Diarrhoea and the associated gastrointestinal \(\text{HCO}_3^-\) loss and \(\text{Cl}^-\) retention can be another reason for hyperchloremic 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 \(\text{H}^+\) secretion and followed by inadequately high urinary \(\text{pH}\) (>5.3) during acidosis \(^{63,71}\), may especially occur 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 \(\text{Na}^+\) delivery, followed by inadequate \(\text{Cl}^-\) and \(\text{H}^+\)-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 \(\text{NH}_3\)-production and promoting metabolic acidosis \(^{70}\) (known as RTA Type IV). Furthermore, hyperchloremic acidosis is a potential limitation for the administration of large volume saline. It is an ongoing debate whether saline-induced hyperchloremic acidosis also leads to unfavourable clinical outcomes \(^{74,75}\).

In compensated cirrhotic patients, metabolic acid-base disorders based on lactate or unmeasured anions (UMA) only play a minor role. However, these unmeasured anions, such as ketone bodies, and lactate may become important in critically ill cirrhotics \(^{37,42}\) and will be reviewed later.
**Figure-4:** Reasons for hyperchloremic metabolic acidosis in patients with chronic liver disease

**Balance of acidifying and alkalinizing acid-base factors in stable cirrhosis**

As shown in Figure-5A, several offsetting acidifying and alkalinizing 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.
3. Acid-base status in critically ill patients with cirrhosis (Table-1, Figure-5B)

Gastrointestinal bleeding, hepatic encephalopathy, acute renal failure, respiratory failure and sepsis are the main reasons of ICU admissions in cirrhotic patients, resulting in high mortality rates \(^{36,76}\). Next to severity of pre-existing liver disease as for example quantified by Child-Pugh-Score \(^{77}\), 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 cirrhotic patients, 39\% of patients presented with acidaemia and 27\% with alkalaemia at the time of ICU admission. In those patients, the overall BE was substantially decreased and the metabolic acid-base disorders due to hypoalbuminemia, hyperchloraemia, elevated lactate and unmeasured anions were also profoundly different from what was observed in compensated cirrhotics \(^{36,37}\). Therefore, unlike compensated patients, cirrhotic patients with critical illness showed net metabolic acidosis, owing to UMA, lactic acidosis and mild dilutional acidosis compensated by hypoalbuminemic alkalosis (Figure-5B). Acute renal failure was associated with an even more negative BE and BE\(_{\text{UMA}}\). 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 an overproduction due to tissue hypoxia, dysfunction of the microcirculation \(^{80}\) and increased glycolysis \(^{81}\) but also by an underutilization due to impaired mitochondrial oxidation \(^{79}\). Furthermore, as 5 \% of lactate is metabolized 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 metabolizing lactate \(^{18}\), this lactate clearance is impaired in chronic liver diseases due to 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 septic patients with acute liver dysfunction\(^ {87}\), others could not confirm these results and reported a net splanchnic lactate production in only 7\% of septic patients\(^ {12}\). However, both studies were not performed in a population of cirrhotic patients\(^ {87,88}\). 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.
Complications in critically-ill cirrhotic patients with acidosis

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 cirrhotic patients:

- Delayed / missing lactate clearance associated with prolonged acidemia
- Susceptibility for extracellular edema, ascites and pulmonary edema – complicating fluid resuscitation and therefore restoring kidney function

Adaptive mechanisms in liver-healthy subjects:

- More rapid clearance / normalization of hyperlactatemia potentially improving lactic acidosis
- More aggressive fluid resuscitation potentially improving UMA-acidosis

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

Dichloroacetate, a drug stimulating the enzyme pyruvate dehydrogenase and therefore reducing pyruvate concentration as a substrate for lactate production, was tested as a treatment of lactic acidosis. This drug was found to be safe in several settings, including septic patients, patients with end-stage liver disease and cirrhotics undergoing orthotopic liver transplantation. While it significantly reduced lactate levels, no survival benefit was observed with dichloroacetate treatment.

Metformin-treatment in diabetic patients with liver cirrhosis was thought to be associated with an increased incidence of lactic acidosis. However, a recent study showed that metformin therapy was not only safe in cirrhotic patients, but it also improved survival in diabetic patients with cirrhosis due to non-alcohol-steatohepatitis (NASH). However, this study mainly included
Child-Pugh A-patients. Metformin should be used with caution in patients with Child-Pugh B and C cirrhosis. \(^{102}\).

4. **Acid-base disorders in acute liver failure (ALF; Figure-5C)**

Most patients with acute liver failure (ALF) have substantially elevated lactate levels. However, these changes were observed without acidaemia.\(^{35,42,103}\) This contra-intuitive phenomenon was described as “stress hyperlactataemia” and it resulted from a massive increase in glycolysis caused by catecholamine- and other cytokine-mediated increases in cellular glucose uptake without hypoxia\(^ {104,105}\) and 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 to lactate\(^ {-}\) and protons (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 (Figure-5C). Lactic acidosis was compensated by pronounced hypoalbuminemic alkalosis in patients with non-paracetamol-induced ALF, resulting in net respiratory alkalaemia due to hyperventilation\(^ {35,103}\). Another study reported an additional alkalinizing 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 severely acidotic patients 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 ALF-patients present with a stable overall acid-base state. Whether the presence of these offsetting acid-base disorders is a coincidence or if the hypoalbuminemia 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 1 g/kg bodyweight 20% albumin solution infused in patients with intact liver function was statistically significant, but still very small due to the buffered drug formulation \(^{115}\). Therefore, the finding of albumin infusion-induced net metabolic acidaemia, as described above, might also be explained by an increase in UMA due to the high prevalence of coexisting renal failure in this collective \(^{10}\).

Figure-5: Acid-base status in patients with chronic liver disease using the physical-chemical approach (A) Equilibrium of acidifying and alkalinizing factors in stable cirrhosis;
Net metabolic acidosis in critically ill cirrhotic patients; Hypoalbuminemic alkalosis “neutralizes” lactic acidosis in acute liver failure.

6. Therapeutic implications (Table-2)

The monitoring of acid-base status using the simplified physical-chemical model in patients with cirrhosis has several potential therapeutic consequences and is summarized 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. In mechanically ventilated patients with cirrhosis and acidemia due to metabolic acidosis, hyperventilation mitigates the severity of acidemia. Based on physiologic considerations the targeted decrease in $\text{paCO}_2$ from 40 mmHg ($\Delta \text{paCO}_2$) should equal the observed decrease in standard base excess ($\Delta \text{SBE}$). E.g. in a patient with a SBE of -10 mmol/L the target $\text{paCO}_2$ is 30 mmHg (subtracting 10 from the normal $\text{paCO}_2$ of 40 mmHg).
<table>
<thead>
<tr>
<th>Case presentation</th>
<th>Acid-base interpretation</th>
<th>Clinical interpretation</th>
<th>Further diagnostics and treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-year-old, stable cirrhotic patient (Child-Pugh B); Acid-base status: pH 7.45, PaO\textsubscript{2} 55, PaCO\textsubscript{2} 31, HCO\textsubscript{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\textsubscript{Alb} 4, BE\textsubscript{Na} -3, BE\textsubscript{Cl} -2, BE\textsubscript{UMA} -1, BE\textsubscript{Lactate} 0</td>
<td>Alkalaeic pH plus hypocapnia indicate <strong>respiratory alkalosis</strong>. Normal base excess (BE) excludes an overall metabolic acid-base disorder. Underlying BE subsets show mild disorders offsetting each other.</td>
<td>This is the typical acid-base pattern of stable cirrhosis (see chapter 3). Potential reasons for hyperventilation are shown in Figure 1. If severe hyperventilation is present, consider: - Encephalopathy, - Ascites, - Dyspnea / Hypoxaemia (e.g., due to hepatopulmonary syndrome or portopulmonary hypertension).</td>
<td>- Find and treat cause of hyperventilation (chest x-ray, CT scan to exclude atelectasis / shunt in hypoxic patients) - Lab: NH\textsubscript{3} - Echocardiography: systolic pulmonary artery pressure (sPAP) - Contrast-echocardiography (in hypoxic patients): intrapulmonary shunt?</td>
</tr>
<tr>
<td>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\textsubscript{2} 50, PaCO\textsubscript{2} 65, HCO\textsubscript{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\textsubscript{Alb} 3, BE\textsubscript{Na} -3, BE\textsubscript{Cl} -1, BE\textsubscript{UMA} 0, BE\textsubscript{Lactate} -1</td>
<td>Acidaemic pH plus high PaCO\textsubscript{2} indicate <strong>respiratory acidosis</strong>. Normal BE excludes an overall metabolic acid-base disorder. Underlying BE subsets show mild disorders offsetting each other.</td>
<td>This acid-base pattern is found in patients with alveolar hypoventilation (e.g., due to coma, intoxication).</td>
<td>- Find and treat cause of hypoventilation - Lab: NH\textsubscript{3}, ethanol, drug screening - Consider antidote-treatment (e.g. flumazenil) - Consider mechanical ventilation (non-invasive ventilation)</td>
</tr>
<tr>
<td>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:</td>
<td>Acidaemic pH plus negative BE indicate <strong>metabolic acidosis</strong>. Calculation of BE subsets reveals lactic acidosis.</td>
<td>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).</td>
<td>- Find and treat cause of lactic acidosis - Assess haemodynamic situation</td>
</tr>
<tr>
<td>Patient</td>
<td>Clinical History</td>
<td>Acid-base Status</td>
<td>Lab Values</td>
</tr>
<tr>
<td>---------</td>
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<tr>
<td>46-year-old cirrhotic patient (Child-Pugh B)</td>
<td>Severe sepsis due to spontaneous bacterial peritonitis. Patient treated at a normal ward and received 4 l NaCl 0.9% due to hypotension.</td>
<td>pH 7.31, PaO₂ 70, PaCO₂ 29, HCO₃ 14.2, BE -11</td>
<td>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</td>
</tr>
<tr>
<td>40-year-old cirrhotic patient (Child-Pugh C)</td>
<td>Large volume ascites paracentesis (10 l) with state-of-the-art albumin substitution three days before admittance. Patient now presenting with somnolence at the emergency department.</td>
<td>pH 7.26, PaO₂ 65, PaCO₂ 36, HCO₃ 15.6, BE -10</td>
<td>Na 129, K 7, Cl 95, Ca 1.22, Mg 1, Pi 1.3, Alb 25.0, Crea 5.4, Lactate 2.3</td>
</tr>
<tr>
<td>60-year-old cirrhotic patient (Child-Pugh A)</td>
<td>Diuretically controlled ascites. Diuretic dose was adjusted by the general practitioner one week ago.</td>
<td>pH 7.28, PaO₂ 85, PaCO₂ 32, HCO₃ 14.6, BE -11</td>
<td>Na 130, K 4.1, Cl 95, Ca 1.22, Mg 0.85, Pi 1.05, Alb 30.0, Crea 1, Lactate 7.3</td>
</tr>
</tbody>
</table>
because of lower leg oedema.

**Acid-base status:**
- pH 7.50, PaO₂ 70, PaCO₂ 37, HCO₃ 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

Subsets reveals hypochloraemic alkalosis caused by diuretic overdose.

**diuretics, gastric drainage, hypovolaemia.**

consider acetazolamide-treatment
- Consider potassium replacement

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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, PaO₂ 75, PaCO₂ 30, HCO₃ 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 and normal BE indicate no metabolic acid-base disorder. However, calculation of BE subsets reveals offsetting hypoalbuminemic 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). Hypoalbuminemic 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

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**Table-2:** Summary of specific therapeutic interventions in cirrhotic patients with disorders of acid-base balance; Abbreviations and units:

- PaO₂ (mmHg), PaCO₂ (mmHg), HCO₃ (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)
5. 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 of acidifying and alkalinizing metabolic acid-base disorders, resulting in a normal overall BE and pH. However, during hepatic decompensation or critical illness, this equilibrium may be rapidly destabilized, 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.
Literature


Legends to figures and tables:

Figure 1: Summary of the physiological role of the healthy liver in maintaining acid-base homeostasis

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

Figure 3: Mechanisms of hyperventilation and respiratory alkalosis in liver disease

Figure 4: Reasons for hyperchloremic metabolic acidosis in patients with chronic liver disease

Figure 5: Acid-base status in patients with chronic liver disease using the physical-chemical approach: (A) Equilibrium of acidifying and alkalinizing factors in stable cirrhosis; (B) Net metabolic acidosis in critically ill cirrhotic patients; (C) Hypoalbuminemic alkalosis “neutralizes” lactic acidosis in acute liver failure.

BE_{Albumin}: Base excess due to the alkalinizing effect of hypoalbuminaemia; BE_{UMA}: Base excess due to the acidifying effect of unmeasured anions (e.g., keto acids);

BE_{Natrium}: Base excess due to the acidifying effect of plasma dilution by free water;

BE_{Chloride}: Base excess due to the acidifying effect of hyperchloremia; BE_{Lactate}: Base excess due to the acidifying effect of elevated lactate.

Table 1: Complications in critically-ill cirrhotic patients with acidosis and comparison of adaptive mechanisms to acidosis in cirrhotic and liver-healthy subjects.
Table-2: Summary of specific therapeutic interventions in cirrhotic patients with acid-base balance disorders. IPS: intrapulmonary shunt; Hb: Haemoglobin; ICU: intensive care unit.