

Treatment options for lactic acidosis and metabolic crisis in children with mitochondrial disease

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Abstract The mitochondrial pyruvate oxidation route is a tightly regulated process, which is essential for aerobic cellular energy production. Disruption of this pathway may lead to severe neurometabolic disorders with onset in early childhood. A frequent finding in these patients is acute and chronic lactic acidemia, which is caused by increased conversion of pyruvate via the enzyme lactate dehydrogenase. Under stable clinical conditions, this process may remain well compensated and does not require specific therapy. However, especially in situations with altered energy demands, such as febrile infections or longer periods of fasting, children with mitochondrial disorders have a high risk of metabolic decompensation with exacerbation of hyperlactatemia and severe metabolic acidosis. Unfortunately, no controlled studies regarding therapy of this critical condition are available and clinical outcome is

often unfavorable. Therefore, the aim of this review was to formulate expert-based suggestions for treatment of these patients, including dietary recommendations, buffering strategies and specific drug therapy. However, it is important to keep in mind that a specific therapy for the underlying metabolic cause in children with mitochondrial diseases is usually not available and symptomatic therapy especially of severe lactic acidosis has its ethical limitations.

Introduction

Mitochondria play a central role in the production of ATP via the process of oxidative phosphorylation (OXPHOS). Basically, this biochemical system consists of the respiratory chain enzymes (mitochondrial complex I–IV), which are coupled to ATP synthase (complex V). Disruption of this pathway may lead to severe neurodegenerative disorders. The overall incidence of mitochondrial diseases is estimated at 1–5 in 10,000 live births, making this one of the commonest inherited errors of metabolism (Thorburn 2004; Schaefer et al 2008). The umbrella term “mitochondriopathy” comprises a large number of heterogeneous diseases with diverse clinical phenotypes. This aspect is further illustrated by the fact that to date, disease-causing mutations have been identified in more than 230 different genes (Koopman et al 2012; Rotig 2014). The resulting biochemical defects may affect any OXPHOS complex (isolated or as a combined deficiency). Moreover, coenzyme Q₁₀ metabolism and pyruvate oxidation including pyruvate dehydrogenase complex (PDHC) may be impaired. In addition, secondary mitochondrial disorders may arise from an indirect impairment of OXPHOS function (for example alterations in cardiolipin metabolism as in Barth syndrome [OMIM:302060], disturbance of mitochondrial protein import as in Mohr-Tranebjaerg syndrome [OMIM:304700], inhibition of the respiratory chain in organic acidurias like propionic

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acidemia [OMIM:606054] or impaired uptake of cofactors of the OXPHOS system). In this review the term mitochondrial diseases is used for disorders affecting aerobic energy metabolism with a main focus on OXPHOS defects.

In general, although no good correlation exists between the biochemical defect measured in tissue samples or cultured skin fibroblasts and clinical disease expression, severe biochemical OXPHOS defects mostly present already in the neonatal period or in young infants, leading to rapid deterioration and death in early childhood (Baertling et al 2014). Clinical phenotypes include fatal neonatal lactic acidosis, classical Leigh syndrome (OMIM:256000), Leigh-like syndrome, and Alpers-Huttenlocher syndrome (OMIM:203700).

From a biochemical perspective, dysfunction of OXPHOS enzymes causes a relative increase in the production of ATP via anaerobic glycolysis, leading to intracellular accumulation of pyruvate and NADH. Under aerobic conditions, pyruvate is converted into acetyl-CoA and further oxidized via the Krebs cycle. The first irreversible reaction of glucose oxidation is catalyzed by PDHC (Mizock 1989). Therefore the activity of PDHC determines whether pyruvate is oxidized to CO₂ and H₂O or converted either to lactate via lactate dehydrogenase or to alanine via alanine transaminase (or alanine aminotransferase; ALAT) (Felig 1973). The activity of the PDHC is

modulated by reversible phosphorylation. PDHC is inactivated by phosphorylation catalyzed by a PDH kinase (in humans there exist four distinct isoforms of this enzyme: PDK1–4), the latter of which is stimulated by ATP, NADH and acetyl-CoA. Two specific PDHC phosphatases dephosphorylate the complex and reactivate it. PDHC is further controlled by end-product inhibition (Patel and Korotchkina 2006). In the case of disturbances of the respiratory chain, NADH may accumulate in the cells (Enns et al 2000) leading to an inhibition of the PDH followed by an activation of lactate dehydrogenase, resulting in a regeneration of NAD⁺ and subsequent elevation of lactate (an overview of lactate metabolism is depicted in Fig. 1).

Accordingly, hyperlactatemia is a common feature among children with mitochondrial disorders (Robinson 2006). Especially in situations with altered energy requirements, such as febrile infections or longer periods of fasting, patients with mitochondrial disorders have a high risk of a severe aggravation of hyperlactatemia with metabolic decompensation. Unfortunately, acute metabolic crisis is often difficult to control in these children and may have a rapidly fatal course (Koene et al 2012; Leary et al 2013). This is mainly based on the fact that treatment of lactic acidosis in mitochondrial disorders is only symptomatic and causal treatment options are very limited (Pfeffer et al 2012).

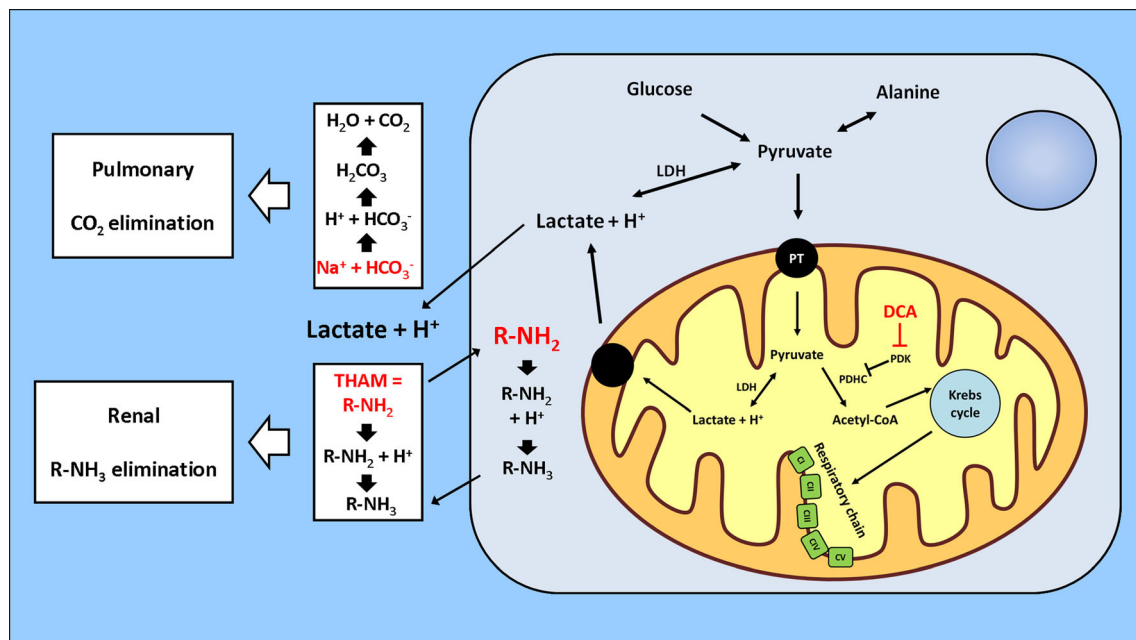


Fig. 1 Lactate metabolism and basic concepts of small molecule interventions. Pyruvate is the end-product of glycolysis and degradation of small amino acids like alanine. In the presence of oxygen, it is transported into mitochondria via a pyruvate transporter (PT), where it is converted to acetyl-CoA catalyzed by the pyruvate dehydrogenase complex (PDHC) and finally oxidized to CO₂. PDH may be inactivated through phosphorylation by pyruvate dehydrogenase kinase (PDK). PDK can be inactivated by the drug dichloroacetate (DCA). On the other hand, where there is hypoxia or

impaired function of the respiratory chain, pyruvate is reduced to lactate via lactate dehydrogenase (LDH). Thus, NAD⁺ required for glycolysis is regenerated. Accumulated lactate is released from the cell, which may cause acidosis. The buffer solution sodium bicarbonate (Na⁺ + HCO₃⁻) acts via the reaction of bicarbonate with protons. The resulting CO₂ is exhaled, thereby reducing acidosis. The amine group of the buffer solution Tris(hydroxymethyl)aminomethane (THAM) takes up one proton and the protonated form of THAM is eliminated via the kidneys

Pathophysiology of lactic acidosis

Of note, lactate per se is not toxic and there is even evidence for a neuroprotective effect (Berthet et al 2009; Wyss et al 2011). However, excessive lactate levels and severe/prolonged metabolic acidosis have finally deleterious effects on many cellular functions:

- 1) Cardiovascular system: Increased proton concentrations in blood lead to decreased cardiac contractility, which is caused by reduced myofilament calcium sensitivity and lowered influx of calcium into the cells (Orchard and Kentish 1990). Furthermore, arterial vasodilation with simultaneous constriction of venous vessels occurs during acidosis (Mitchell et al 1972; Kellum et al 2004a, b). At the same time, acidosis leads to stimulation of the sympathetic nervous system. The functional consequences are pH dependent. At pH values above 7.2, cardiac contractility increases due to enhanced release of catecholamines. However, at pH values below 7.2, opposite effects are observed (Mitchell et al 1972). Generally, tissue response to catecholamines is decreased during acidosis (Huang et al 1995). In addition, a closure of gap junctions slows the impulse conduction of the heart and leads to a high incidence of arrhythmias (Orchard and Cingolani 1994).
- 2) Respiratory system: By stimulation of peripheral and central chemoreceptors, breathing rate increases due to the elevated concentration of protons in order to compensate for metabolic acidosis (O'Regan and Majcherczyk 1982). The high energy consumption of this process may lead to respiratory decompensation after prolonged acidosis.
- 3) Central nervous system (CNS): To correct intracellular acidosis, different cerebral membrane transporters are activated, leading to an intracellular accumulation of Na^+ and Cl^- . This results in an increased influx of water into the cells. As a consequence, cerebral edema may develop (Staub et al 1996).
- 4) Immune system: An additional systemic effect of acidosis is a reduced immune response with increased susceptibility to serious infections caused by an elevated release of interleukins from macrophages and impaired leukocytes function (Lardner 2001; Kellum et al 2004a, b).
- 5) Endocrine system: The response of the cells is pH dependent. Insulin resistance increases at $\text{pH} < 7.2$ and normalizes above (Walker et al 1963). Impaired insulin sensitivity of the cells is probably caused by a pH-dependent binding of insulin to its receptor (Cuthbert and Alberti 1978).
- 6) General effects: Multiple organs are limited in their function during prolonged acidosis, which leads to decreased tissue oxygenation, impaired ATP production and increased apoptosis (Halperin et al 1994).

Management of lactic acidosis in children with mitochondrial disorders

There are no controlled studies on treatment of lactic acidosis in children with mitochondrial diseases. Recommendations in the literature are primarily based on retrospective analyzes in children with lactic acidosis in the context of shock, sepsis or unknown underlying conditions (Hatherill et al 2003; Beveridge and Wilkinson 2006; Aschner and Poland 2008; Berg et al 2010; Parker and Parshuram 2013). While lactate elevations associated with shock or sepsis are mainly due to tissue hypoperfusion, and treatment of the underlying causes is most important to manage this condition, hyperlactatemia due to primary mitochondrial dysfunctions is caused by an impaired cellular energy metabolism with usually no causal treatment available. Accordingly, intensive care management of these patients constitutes a major challenge. Against this background, the aim of this review was to formulate expert-based suggestions for treatment of lactic acidosis in children with mitochondrial disorders. However, based on the lack of well-designed controlled studies, the level of evidence is unfortunately low. Therefore, our recommendations only represent a consensus between our clinical centers and specific details may be handled differently. Moreover, despite the treatment options described in the following sections, it is essential to keep in mind that therapy specific for the underlying metabolic cause is usually not available. Acute metabolic crisis may cause irreversible brain damage that severely affects quality of life. Therefore, decision-making regarding intensive care treatment might differ from patient to patient and should be done in close interaction with the family. If available, involvement of a specialized palliative care team should be considered.

Fluid management during metabolic crisis

Initially, normocaloric feeding and adequate fluid supplementation should be administered orally or via gastric tube. If this is not possible due to the poor clinical condition of the patient during metabolic crisis, early placement of a central venous line for buffering and parenteral nutrition is required. Catabolism should be avoided. However, infusion therapy should be done with caution since high glucose supplementation/glucose bolus application might worsen lactic acidosis (Prietsch et al 2002). As a starting point, we suggest starting infusion at a moderate glucose rate of 5–6 mg/kg/min (of note, the infusion rate might be optimized depending on age and clinical condition) (Sheridan et al 1998; Prietsch et al 2002). Serum glucose and lactate levels should be monitored closely after start of infusion therapy. After starting infusion therapy, further steps depend on close clinical re-assessment of the patient. If tolerated well, glucose rate might be further increased up to 7–8 mg/kg/min. Importantly, a parallel increase

in glucose and lactate levels may indicate disturbed glucose utilization and the infusion rate should be lowered accordingly. In our experience, serum glucose levels should not exceed values between 100 and 120 mg/dl (5.6–6.7 mmol/L). The application of additional insulin to lower glucose levels and to increase cellular glucose uptake should only be used with caution because it might worsen the intracellular glucose utilization problem and aggravate acidosis. Moreover, laboratory monitoring of the critical balance between glucose and lactate levels becomes unreliable under these conditions and further therapeutic decisions may be hindered. Generally, if glucose infusion is not tolerated well, increased administration of fat (2–3 g/kg/day) should be tried to achieve adequate calorie supplementation. Of note, during the acute crisis, fat intake above 3 g/kg/day should be avoided because evidence from the literature suggests that an increased NADH/NAD⁺ ratio generated by reduced flux through the respiratory chain leads to a secondary inhibition of β -oxidation (Infante and Huszagh 2000). Importantly, in patients (especially neonates) where the differential diagnosis of a fatty acid oxidation disorders is not yet excluded, administration of fat should be avoided.

Specific treatment options

Unfortunately, causal treatment for children with mitochondrial diseases is usually not available. Nevertheless, specific interventions should be considered in certain conditions. In patients where the etiology of the lactic acidosis is unclear, several (not exclusively mitochondrial) metabolic diseases/transporter defects should also be kept in mind. For most of the supplementations listed below no well-designed clinical trials have been performed and the results of the often anecdotic reports summarized below should be read in this context (Pfeffer et al 2013).

1) Thiamine supplementation might be effective in thiamine responsive PDHC deficiency or thiamine pyrophosphokinase deficiency (dosage: 15–30 mg/kg/day; (Mayr et al 2011)). Moreover, thiamine (and biotin) administration may be life saving in unclear disease conditions with possible differential diagnoses of thiamine deficiency (Manzanares and Hardy 2011) or thiamine metabolism disorders (biotin-thiamine-responsive basal ganglia disease; (Distelmaier et al 2013)). 2) Riboflavin supplementation was shown to improve the clinical status of patients with mitochondrial complex I deficiency caused by *ACAD9* mutations (dosage: 10 mg/kg/day up to max. 300 mg/day) (Gerards et al 2011). To date the mechanism of these therapeutic effects is not sufficiently clear. It might act as cofactor and also has electron donor and acceptor properties and may thus interfere with the respiratory chain (Tarnopolsky and Raha 2005). 3) Coenzyme Q₁₀ application should be considered in suspected coenzyme Q₁₀ deficiency (OMIM:607426) disorders (dosage:

5–20 mg/kg/day up to max. 1 g/day) (Rotig et al 2000). To increase coenzyme Q₁₀ oral bioavailability, application of a self-emulsifiable composition is recommended (Sato et al 2013). 4) Carnitine supplementation should be provided in cases of secondary carnitine deficiency (dosage: 50–100 mg/kg/day). 5) Ketogenic diet is well established as therapy for patients with PDHC deficiency and has neuroprotective, antiepileptic and mitochondriotropic effect also for other mitochondrial diseases (Wexler et al 1997; Klepper et al 2002). It is contraindicated in patients with known fatty acid oxidation disorders and pyruvate carboxylase deficiency. 6) Phenylbutyrate therapy might be a future option to treat lactic acidosis especially in patients with PDHC deficiency (Ferriero et al 2013). However, human studies are lacking so far. 7) Some patients with pyruvate carboxylase deficiency may profit from administration of biotin or from an anaplerotic diet containing 130 cal/kg/day with 30 % of glucose, 30 % of long-chain fatty acids, 5 % of protein, and 35 % of triheptanoin (Mochel et al 2005; Roe and Mochel 2006). Furthermore different anaplerotic substrates are tried for therapy of pyruvate carboxylase deficiency including high doses of citrate (7.5 mmol/kg/day) (Ahmad et al 1999). 8) Biotinidase deficiency can be successfully treated by administering biotin (dosage: 10–20 mg/day) (Bousounis et al 1993; Wolf 2012). For an overview see also Table 1. Details regarding mitochondrial medications and supplements are also given in the review of Parikh et al (2009).

Buffer therapy during metabolic acidosis

There is conflicting literature on the effects of infusing a buffer solution during metabolic acidosis (Kecskes and Davies 2002; Andrade et al 2007; Lim 2007; Kraut and Madias 2012). This debate is a consequence of the lack of controlled studies regarding benefits, side effects and outcome of this therapy, especially in the context of rare metabolic diseases. Nevertheless, based on the idea that severe acidosis may cause cellular tissue damage and the fact that respiratory compensation via hyperventilation is an energy consuming process, buffer therapy is frequently used during severe lactic acidosis.

Recommendations regarding timing of initiation of therapy differ in the literature and range from pH values <7.2 down to pH <7.0 (Andrade et al 2007; Lim 2007; Sabatini and Kurtzman 2009; Kraut and Madias 2012). However, many patients are able to maintain normal pH values via excessive hyperventilation. This creates a critical condition, which might decompensate later on. Therefore, it is essential that pH values, pCO₂ levels and base deficit are monitored in parallel. Importantly, rapid correction of blood pH may worsen cerebral acidosis since abrupt suppression of hyperventilation stimuli may cause increased blood pCO₂, which crosses the blood brain barrier faster than HCO₃⁻. As a consequence, brain oedema may develop (Herrera and Kazemi 1980; Staub

Table 1 Drugs and supplements that might be beneficial in children with suspected mitochondrial disease and metabolic crisis

	Thiamine	Biotin	Riboflavin	Coenzyme Q ₁₀	L-carnitine
Mode of action	Cofactor of several enzymes including PDHC	Enzyme cofactor	Enzyme cofactor; electron donor and acceptor properties	Cofactor of the electron transport chain; antioxidant properties	Facilitates fatty acyl group transport into mitochondria; maintains the ratio of acyl-CoA to free CoA
Dosage	15–30 mg/ body weight (kg)/day	15 mg/ body weight (kg)/day	10 mg/ body weight (kg)/day up to max. 300 mg/day	5–20 mg/ body weight (kg)/day up to max. 1 g/day	50–100 mg/ body weight (kg)/day
Administration	Intravenous and oral application possible	Oral application	Intravenous and oral application possible	Oral application	Usually oral application, intravenous application is also possible
Main indications	Thiamine deficiency or thiamine metabolism disorders; PDHC deficiency	Biotin-thiamine-responsive basal ganglia disease; biotinidase deficiency	Mitochondrial complex I deficiency (<i>ACAD9</i> mutations); multiple acyl CoA dehydrogenase deficiency; may be helpful also in other mitochondrial diseases	Suspected coenzyme Q ₁₀ deficiency disorders; mitochondrial myopathies	Mitochondrial myopathies; secondary carnitine deficiency
Main side effects	Generally considered safe; dermatitis may occur after intravenous application	Rarely, allergic skin reaction may occur	May rarely cause anorexia and nausea	It may increase the risk of bleeding; may lower blood sugar levels; may cause gastrointestinal distress; may cause sleep disruption	Gastrointestinal distress; “fishy” body odour; allergic reactions are rare; rarely, seizures may occur

et al 1996). Therefore, buffering should be started rather early at a slow infusion rate. The initial hours of buffer therapy should be monitored closely with regular blood gas analyses. Of note, in situations of severe metabolic acidosis and decreased blood pressure, capillary blood sampling becomes unreliable and arterial blood gas analyses should be performed.

Sodium bicarbonate buffering

Sodium bicarbonate buffering is the most commonly used therapy for the management of acidosis due to different disorders. After injection, sodium bicarbonate dissociates to Na⁺ and HCO₃⁻. Of these two, hydrogen carbonate takes up protons to form CO₂ and water. Acidosis can be subsequently reduced by exhalation of CO₂ (for basic mechanism see also Fig. 1).

Of note, sodium bicarbonate buffering has several side effects, including hypernatremia, volume overload, exacerbation of intracellular acidosis, hyperosmolality and potential development of cerebral edema, hypokalemia, hypocalcaemia, and reduced cardiac contractility (Glaser et al 2001).

To minimize negative effects of sodium bicarbonate, there are several recommendations to its application. 1) If possible,

isoosmotic solutions should be used, whereby hyperosmolality may be prevented (Lim 2007). However, volume overload should be avoided. 2) To minimize the increase in the intracellular acidosis, a slow application rate is recommended (see below), although there are no studies in humans available (Kecskes and Davies 2002).

To calculate the quantity of required bicarbonate volume, the distribution of bicarbonate is equated to the extracellular body fluid. In young children, this corresponds to 50–70 % of body weight. Often, the administration of 30 % is sufficient to stabilize the metabolic situation and to minimize potential side effects. This results in the following two formulas (Debray et al 2007):

$$\text{HCO}_3^- (\text{mmol}) = (\text{HCO}_3^- [\text{target value}] - \text{HCO}_3^- [\text{initial value}]) \times \text{body weight (kg)} \times 0.3$$

or

$$\text{HCO}_3^- (\text{mmol}) = \text{BE} \times 0.3 \times \text{body weight (kg, .)}$$

The value of 0.3 is derived from the 30 % described above. Importantly, in neonates a value of 0.4 and in preterm infants a value of 0.5 should be inserted in the calculations. When using

an undiluted 8.4 % solution for infusion (1 ml = 1 mmol sodium bicarbonate) it should be administrated through a central venous system due to its high osmolarity. Depending on the severity of acidosis and clinical condition, half of the calculated sodium bicarbonate amount can be infused over 1–2 h. The remaining amount should be infused at a slower rate. Importantly, blood gases should be monitored closely, especially during the initial buffering phase (for an overview see Table 2).

THAM (Tris-hydroxymethyl-amino-methane) buffering

THAM is a Na^+ -free buffer solution that can be used in conditions of respiratory or metabolic acidosis (Nahas et al 1998). Importantly, THAM does not generate increased CO_2 levels, which is ideal in situations where CO_2 elimination is impaired (Nahas et al 1998). During lactic acidosis, THAM reacts according to the following chemical equation: $\text{R-NH}_2 + \text{H}^+ + \text{Lactate}^- \rightarrow \text{R-NH}_3^+ + \text{Lactate}^-$. The protonated R-NH_3^+ is eliminated via the kidneys (for the basic mechanism see also Fig. 1).

Despite some advantages, THAM is used less frequently than bicarbonate for buffer therapy during metabolic acidosis because several potential side effects including, hyperkalaemia, hypoglycaemia, hepatotoxicity, apnoea/hypopnoea, and skin necrosis after extravasation may occur (Robertson 1970; Nahas et al 1998; Holmdahl et al 2000; Gehlbach and Schmidt 2004).

In children with mitochondrial disease and severe lactic acidosis, THAM buffering might be an alternative where the affected individual is hypernatraemic, which limits the use of bicarbonate. The THAM dosage can be calculated according to the following equation (Kraut and Madias 2012): THAM

(amount in ml of a 0.3 mol/L solution) = body weight (kg) \times base deficit (HCO_3^- [target value] – HCO_3^- [initial value]) \times 1.1. It is recommended that the calculated THAM dose is infused at a slow rate (at least 1 h). The maximum daily dose is 15 mmol/kg for an adult patient. However, in newborns THAM dosage should not exceed 5–7 mmol/kg body weight because of the reduced kidney function (for an overview see Table 2).

Sodium citrate buffering

Sodium citrate buffering is mainly used for long-term treatment of patients with chronic metabolic acidosis. However, it might also be considered in the acute situation depending on the clinical condition of the patient and the wishes of the family (e.g. intravenous buffering has several side effects and may require a central venous catheter, etc.). After oral application, sodium citrate leads to a decrease in blood proton levels and a parallel increase in HCO_3^- concentrations (for the defined underlying mechanism see (Kowalchuk et al 1989)). Compared with oral sodium bicarbonate application, sodium citrate does not induce gastrointestinal gas production and is usually better tolerated (McNaughton 1990). Based on our experience, therapy can be started with a dosage between 0.5 and 1.0 mmol/kg/day (divided into three doses). Further dosages should be adjusted according to blood gas analyses (for an overview see Table 2).

Dichloroacetate therapy

Dichloroacetate stimulates the enzyme pyruvate dehydrogenase kinase, and in doing so, the enzyme pyruvate dehydrogenase remains in its unphosphorylated catalytically active

Table 2 Symptomatic drug treatment of acute and chronic lactic acidosis

	Sodium bicarbonate	THAM	Sodium citrate	Dichloroacetate
Type of acidosis	Acute	Acute	Chronic	Acute and chronic
Mode of action	Extracellular buffering of protons with generating CO_2	Extra- and intracellular buffering of protons without generating CO_2	Extracellular buffering of protons with generating CO_2	Intracellular reduction of lactate production via stimulation of pyruvate dehydrogenase kinase
Dosage	HCO_3^- (mmol) = base excess \times 0.3 \times body weight (kg)	THAM (ml of a 0.3 mol/L solution) = body weight (kg) \times base deficit (mmol/L) \times 1.1	0.5 to 1 mmol/body weight (kg)/day (divided into three doses)	25 mg/body weight (kg)/day (divided into two doses)
Administration	Slow intravenous infusion of the first half of the amount over 1–2 h	Slow intravenous infusion over 1 h	Oral application	Oral application; in exceptional cases intravenous application possible (see main text)
Main side effects	Exacerbation of intracellular acidosis; hypernatremia; hypokalemia; hypocalcaemia; reduced cardiac contractility; local injury in cases of extravasation	Hyperkalemia; hypoglycaemia; respiratory depression; liver necrosis in newborns; local injury in cases of extravasation	Hypernatremia; muscle spasms; gastrointestinal distress	Peripheral neuropathy; liver dysfunction

state (Stacpoole 1989). The resulting pyruvate is mainly converted via the Krebs cycle and lactate production decreases (for the basic mechanism see also Fig. 1). Dichloroacetate crosses the blood–brain barrier effectively and can be used in cases of chronic as well as acute lactic acidosis (Berendzen et al 2006; Kaufmann et al 2006; Stacpoole et al 2008a, b). For long-term administration in children, a dose of 25 mg/kg/d has been recommended (Abdelmalak et al 2013). A single report described the application of intravenous dichloroacetate during acute lactic acidosis in a preterm newborn with septicaemia using a dose of 50 mg/kg twice daily (Aron et al 2001) (for an overview see Table 2). In general, dichloroacetate therapy is tolerated well in most cases and may lead to short-term improvement. However, long-term use may induce peripheral neuropathy, and there have been no studies showing clear benefits of long term DCA usage on the overall disease prognosis (Kurlemann et al 1995; Kaufmann et al 2006). A promising future option could be phenylbutyrate, which has a comparable mode of action but potentially less side effects (Ferriero et al 2013). However, clinical studies are required to evaluate this therapy.

Renal replacement therapy

Hemofiltration or hemodialysis can potentially be used for treatment of lactic acidosis. However, these are invasive procedures with the risk of side effects (see below). Moreover, they may not be feasible in unstable patients. Therefore, the use of these approaches should be critically assessed and might only be applied to exceptional cases.

In general, several studies dealing with the use of renal replacement therapy in critical situations of inborn errors of metabolism demonstrated the successful use of hemofiltration or hemodialysis to remove toxic substrates (McBryde et al 2006; Tsai et al 2014a, b). Possible advantages of using a renal replacement therapy over buffering with alkalizing substrates include the prevention of hyperosmolality and volume overload. Furthermore, the effect of alkalizing on ionized calcium concentration can be reduced by providing calcium. Renal replacement therapy leads to a quick removal of lactate but a rebound can occur. In addition, renal replacement therapy might be the treatment of choice in conditions with lactic acidosis in combination with hyperammonemia, for example in patients with mitochondrial complex V deficiency due to *TMEM70* mutations (Honzik et al 2010).

Experienced personnel are required to perform renal replacement therapy, as it is technically challenging. Reliable vascular access is needed to allow adequate blood flow. The placement of catheters can be complicated by vascular stenosis, thrombosis, air emboli, or hemorrhage. A smaller vascular access in combination with lower flow rates of the blood in children increase

the risk of clotting (Basu et al 2011; Bridges et al 2012). Systemic anticoagulation can result in a higher risk of developing hemorrhage. Furthermore, it might happen that the required rapid volume shifts are not well tolerated by small or critically ill children with hemodynamic instability (Tsai et al 2014a, b). Additionally, there is a risk of disequilibrium syndrome caused by an osmotic gradient between plasma and the brain because of a fast removal of urea leading to cerebral edema accompanied with potential death (Kennedy et al 1962; Arieff 1994). Thus, although renal replacement therapy has some advantages over buffering, it should only be performed in regard of the risks and by an experienced team.

Therapeutic hypothermia

Therapeutic hypothermia (TH) has been shown to be neuroprotective in newborns suffering neonatal encephalopathy after perinatal asphyxia (Jacobs et al 2013). However, the role of TH in mitochondrial disease remains unknown. Rango et al (2014) suggested that brain temperature might be reduced in patients with mitochondrial disease due to malfunctioning OXPHOS (Rango et al 2014). They hypothesized that this could be one of the reasons for impaired neurological outcome in these patients. Whether children would benefit from TH during a phase of cellular stress and severe lactic acidosis remains to be analysed in preclinical and clinical studies, and no clear recommendation can be given at this stage.

Conclusions

Metabolic crisis and severe lactic acidosis in children with mitochondrial diseases are a challenging situation. Adequate caloric supply is essential for these patients. Although discussed still somewhat controversial, buffer therapy is a mainstay of lactic acidosis management. For this purpose, different buffer solutions are available including sodium bicarbonate, THAM, and sodium citrate. Buffering should be started rather early at a slow infusion rate. In addition, dichloroacetate may be used to lower lactate levels. Of note, in certain disease conditions, the application of thiamine (alone or in combination with biotin) might improve the clinical condition (e.g. thiamine deficiency, thiamine metabolism disorders, thiamine responsive pyruvate dehydrogenase deficiency). In cases of uncontrollable lactic acidosis (especially in combination with hyperammonemia), hemofiltration therapy might be an option. Importantly, despite these symptomatic treatment options, prognosis is often unfavorable, which should be discussed openly with the relatives.

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