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Management and emergency treatments of neonates with a suspicion of inborn errors of metabolism

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During the neonatal period, inborn errors of metabolism mostly present with an overwhelming illness that requires prompt diagnosis and both supportive and specific treatments. The most frequent situations are due to branched-chain organic acidurias that present with ketoacidosis and urea cycle defects that are characterized by hyperammonaemia. During both situations, toxin removal procedures and nutritional support with a free-protein and high-energy diet are pivotal treatments. In patients presenting with hypoglycaemia blood glucose levels must be corrected. Progress following glucose provision is useful in recognizing the disorders that are mainly implicated. Hyperinsulinism requires high-glucose infusion. Glycogen storage diseases and gluconeogenesis defects are easily treated with a permanent glucose provision while hypoglycaemias quickly recur. In patients with galactosaemia, hereditary fructose intolerance or tyrosinaemia type I, the presentation is dominated by a liver failure requiring galactose and fructose exclusion associated with a low-protein diet. Many patients with β-oxidation defects may present with hypoglycaemia that is usually easily corrected. The precise diagnosis can be easily missed in those patients that do well in the following weeks but may develop cardiac failure, arrhythmia and/or liver failure. Patients presenting with intractable convulsions, vitamin responsiveness to biotin, pyridoxine and folate must be considered.

Key words: ketoacidosis, organic acidurias, hyperammonaemia, urea cycle defects, neoanatal hypoglycaemias, fatty acid oxidation defects, galactosaemia, tyrosinaemia type I, gluconeogenesis defects, glycogen storage diseases

Introduction

During the neonatal period, inborn errors of metabolism have relatively homogeneous expression and the diagnosis is mostly considered in neonates affected with an overwhelming illness that does not rapidly prove its aetiology [1,2]. As soon as the diagnosis is suspected, an emergency management has to be scheduled, even if precise diagnosis is still unknown. The therapeutic approach relies on the clinical and biological situations and has to prevent errors that could weigh on prognosis. Four aspects have to be considered: the kind of supportive care, the potential requirement of a specific nutrition, the indication of an extra-renal toxin removal, and the usefulness of additional therapies. In addition, beside the information on the newborn's state, close clinical and biological survey is useful for final diagnosis.

Many of these severe states must be treated by means that require some medical and technical expertise. In case of insufficient expertise, initial symptomatic treatment must be started and the newborn transferred in emergency to a more trained unit.

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General principles

Supportive care and nutrition

a) Many of these very ill newborns require ventilatory and circulatory support and, most require

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rehydration and correction of electrolyte, calcium and phosphate imbalance, since specific therapeutic approaches will fail unless these derangements are corrected. Conversely, and despite their importance, these treatments must not postpone the initiation of the specific therapeutic means.

b) Many patients affected with a metabolic crisis frequently suffer from concomitant septicaemia. This, in turn, results in persistent catabolism and therapeutic failure. Therefore, infections must be thoroughly searched for and prevented.

c) Whatever the disease, nutrition is a pivotal therapeutic approach and must be rapidly considered in both its composition and its mode of administration. Briefly, four types of composition can be considered: a normal diet, a low-protein diet, a carbohydrate-restricted diet, and a high-glucose diet, with or without lipid restriction.

The mode of administration selected depends on the disorder and the clinical status. Oral nutrition is rarely possible in the very first few days and continuous enteral tube feeding can be temporarily useful in patients with poor initial condition. In many severely affected patients, total parenteral nutrition (TPN) is the method of choice. Therefore, insertion of a central venous catheter should be considered at once to rapidly meet a high energy requirement and, in some to allow extracorporeal dialysis procedure.

Toxin removal procedures

Toxin removal procedures are considered for those patients affected with disorders of the intoxication types, such as branched chain organic acidurias (BCOA) and urea cycle defects (UCD), during which the neurological outcome is compromised. Exchange transfusion (ET), peritoneal dialysis (PD) and, various kinds of extracorporeal blood dialysis are the main techniques used. These latter tools are the most efficient but also the most difficult to perform and require paediatric intensive care units (PICU) already trained in the technique of extracorporeal circulation.

Exchange transfusion

Theoretically, ET is an inadequate removal procedure for metabolites distributed throughout total body water. However, ET with large volumes (1.5–4 volume exchanges) of fresh blood has long been recognized as an effective means in numerous disorders. However, its transient effect limits its use, and ET should be applied in association with other methods such as PD [3] or as a result of long standing patterns, such as multiple or continuous exchanges [4,5].

Peritoneal dialysis

PD for the emergency treatment of newborns was long ago demonstrated to have superior efficacy compared to ET [3,6,7]. Manual PD requires minimal expertise and can be rapidly initiated in any PICU. Warmed and buffered dialysate solutions with volumes of 40–50 ml/kg body weight are delivered by gravity. One-hour cycles (15 min fill-up, 30-min dwell time, 15-min drainage) are repeated over 24–36 hours, during which most the toxin removal occurs. Prolonged PD is usually not necessary, except for UCD. PD has the advantage of simplicity. However, poor drainage, leakage of dialysate, and poor splanchnic blood flow may prevent efficient toxin removal. In addition, the risk of overhydration may postpone nutritional management with large volume of TPN.

Extracorporeal dialysis

More recently, extracorporeal blood purification is becoming increasingly used, since technological advances have improved the suitability of these techniques in neonates [8]. Continuous haemofiltration techniques appear to be effective means of treatment in newborns suffering acute decompensation of various metabolic disorders [9–12]. Both continuous veno-venous haemofiltration (VVHF) and haemodiafiltration (VVHDF) are suitable. They have the advantages of simplicity of logistics, high tolerance in neonates who present with haemodynamic instability, multiorgan failure, and hypercatabolic state, and the possibility to use a large volume of TPN without the risk of overhydration. Theoretically, HDF increases solute removal but, in terms of clearance, both techniques have similar results that otherwise are, obviously, higher than with PD. Its effectiveness is mostly linked to the technical control of both the blood and the dialysate flow rates. They both allow efficient toxin removal within hours and early reintroduction of protein in the TPN that, in turn, reduces the risk for acute protein malnutrition.

Haemodialysis

HD is the most effective and rapid method of removing small solutes. In hyperammonaemic neonates, ammonia extraction is undoubtedly better than those obtained by any other procedure. However, multiple dialysis sessions are most often necessary due to rebound in the circulation of toxic metabolites and clearance is hampered by vascular instability [4,9,11].

Clinical and biological presentations

From a clinical and management point of view and, whatever the underlying metabolic disorder in cause, three main situations can be identified.

- Neurological distress with ketoacidosis
- Neurological distress with severe hyperammonaemia
- Neurological distress with hypoglycaemia, either isolated or associated with cardiac and/or liver involvement

At last, some neonates have neurological distress without any other organ or biological signs.

Neurological distress with ketoacidosis

The neurological presentation of these neonates is dominated by a coma with hypo/hypertonia and pyramidal signs. Biologically, they have metabolic acidosis with low blood and urine pH, low blood bicarbonate level, and an anionic gap due to the accumulation of abnormal organic acids. Acidosis is associated with ketonuria, a major key to diagnosis during the newborn period.

This is the most frequent situation in which branched chain organic acidurias (BCOA) are the main disorders during which accumulation of organic acids are responsible for endogenous intoxication. Besides, some neonates affected with congenital hyperlactacidaemia may present with similar acidosis due to lactate accumulation.

Branched chain organic acidurias

As a whole, these patients require monitored supportive care, toxin removal procedures, high-energy and free-protein nutrition, and specific additional therapies.

From a practical point of view, one can considered two situations.

- Some patients may appear quite well. They have mild acidosis (pH>7.20, HCO_3>15), dehydration is not severe (<10% of birth weight), blood ammonia level is normal or mildly increased (<400 μmol/l). Glycaemia, lactacidaemia, calcaemia, and blood cell count are normal. This presentation could be due to maple syrup urine disease, which is recognizable by its odd odour, and in urine, its negative acetest contrasting with positive 2,4-dintrophenylhydrazine (DNPH)-test. It could also be secondary to methylmalonic, propionic and isovaleric acidurias when the diagnosis has rapidly been suspected after the first signs have appeared.
- In other patients, the situation appears more severe. This is especially the case for patients affected with organic acidurias whose diagnosis has been delayed for a few days. They present with severe ketoacidosis (pH<7.10, HCO_3<10 mEq/l). They are seriously dehydrated (>10% of birth weight), and may have hyperammonaemia (>400 μmol/l), mild hyperlactacidaemia (<5 mmol/l), hypo- or hyperglycaemia, hypocalcaemia, and leukothrombopenia.

Mildly affected patients

These neonates have to be hydrated for a 24-hour period, while a toxin removal procedure is undertaken. Hydration can be performed using a standard 5–10% glucose solution containing 34 mmol/l of Na^+ (2 g/l of NaCl), and 20 mmol/l of K^+ (1.5 g/l of KCl).

At that point, high-caloric and protein-free nutrition must be initiated at once. Parenteral and enteral solutions providing 100 Kcal/kg/day to a 3.5 kg baby are exemplified in Tables 1 and 2. At first parenteral and enteral nutrition are used together for the 24–36 hour period needed for testing the gastric tolerance (Table 2). To prevent acute protein malnutrition, this protein-free diet must not be used for more than 2 days. Thus, once the toxic metabolites have abated, natural proteins are introduced using quantified amounts of infant formula to cover the minimal daily protein requirement which are about 50–60% of the normal requirements for neonates. An appropriate amino acid mixture can be added to meet the protein-recommended dietary allowances (RDA). Next,

Table 1. Example of protein-free solution for parenteral nutrition in a 3.5 kg neonate. Micronutrients and vitamins must be added to these solutions to provide normal requirements for a newborn

Nutrient	Amount	Energy (Kcal)	Prot (g)	Fat (g)	CHO (g)	Na (mEq)	K (mEq)	Ca (mg)	Pi (mg)
Glucose 30%	240 ml	288			72				
Intralipids 20%	50 ml	90		10					
NaCl (sufficient for)						13			
Kcl (sufficient for)							10		
Phosphorus (sufficient for)									200
Calcium gluc. 10%	30 ml							270	
Water (sufficient for a total volume of 500 ml)									
Total	500 ml	378	0	10	72	13	10	270	200
Total energy provision (%)			0	24	76				

Calcium-gluc, calcium-gluconate; CHO, glucose and glucose polymers; Pi, inorganic phosphate; Prot, proteins.
NaCl and KCl solutions have to be added in volumes sufficient to meet 34 mmol/l of Na^+ and 20 mmol/l of K^+, taking in account that other drugs (such as antibiotics or phosphate-salt) may contain significant amount of Na^+.
130 ml/kg/day of this solution provides (per kg/day): 97 Kcal, 3.4 mmol Na^+, 2.6 mmol K^+, 70 mg Ca^{++}, 51 mg P^{--}.
This solution can be used in association with the enteral solution described in Table 2 (see also text page).
For those hyperammonaemic neonates with signs of cerebral oedema, water volume should be restricted (see text page).

Table 2. Example of protein-free diets for enteral nutrition in a 3.5-kg neonate. These diets must be checked for all micronutrients and vitamins and supplemented in order to provide normal requirements for a newborn

Nutrient	Amount	Energy (Kcal)	Prot (g)	Fat (g)	CHO (g)	Na (mEq)	K (mEq)	Ca (mg)	Pi (mg)
Maltodextrin	92 g	344			86				
Oil	13 ml	117		13					
NaCl	0.75 g					12.75			
KCl	0.65 g						8.6		
Calcium gluc.	4.5 g							405	
Phosphorus	—								250
Water sufficient for a total volume of 500 ml									
Total	500 ml	460	0	13	86	13	9	400	250
Total energy provision (%)			0	25	75				

Calcium gluc, calcium gluconate; CHO, glucose and glucose polymers; Pi, inorganic phosphate; Prot, proteins.
120 ml/kg/day of this enteral solution provide (kg/day): 110 Kcal, 3 mmol Na^+, 2 mmol K^+, 97 mg Ca^{++}, 60 mg P^{--}.
This solution can be used in association with the parenteral solution described in Table 1 (see also text page). At first, nutrition is given at a low rate – for instance, 10 ml/3 h and increased every 3–6 h until the full fluid requirement is met. Simultaneously, the parenteral infusion rate is decreased reciprocally.
To avoid preparing sophisticated diets, some commercially available protein-free powders provide glucose and lipids, as well as minerals vitamins and micronutrients in adequate ratios for newborn nutrition (80056 Mead-Johnson, Energy-vit SHS).

natural protein and amino acid intakes are adjusted to growth and to specific biochemical controls.

Severely affected patients

These neonates with severe ketoacidosis present with intracellular dehydration that is often underestimated. In this situation, aggressive rehydration with hypotonic fluids and alkanization may cause or exacerbate pre-existing cerebral oedema. Therefore, overhydration is proscribed and rehydration should be planned over a 48-h period, with fluid infusion less than 3 l/m2/day. The repair fluid should contain an average concentration of 70–85 mmol/l of Na^+ (4–5 g/l of NaCl) and 30–40 mmol/l of K^+ (2–3 g/l of KCl) and 5% glucose.

Acidosis can be partially corrected with i.v. bicarbonate, especially if it does not improve with the first measures of toxin removal. However, it should be stressed that aggressive therapy with repeated boluses of i.v. bicarbonate may induce

Table 3. Example of a rehydration infusion for a neonate with severe ketoacidosis due to branched chain organic aciduria. Minerals, micronutrients and vitamins must be added to provide normal requirements for a newborn

	Vol ml	Na mEq	K mEq	Ca mg	Pi mg	CHO g	Energy Kcal
Glucose (10%)	500					50	200
NaCl (sufficient for)		72					
KCl (sufficient for)			35				
Phosphate (sufficient for)					200		
Ca-Gluc (10%)	30			270			
Water (sufficient for a total volume of 1000 ml							
Total	1000	72	35	267	270	50	200
Total/24 hours	630	45	22	168	170	31	126

Calcium-gluc, calcium-gluconate; CHO, glucose and glucose polymers; Pi, inorganic phosphate; Prot, proteins.
NaCl, KCl solutions have to be added in volume sufficient to meet 70–85 mmol/l of Na^+ and 30–40 mEq/l of K^+, taking in account that other drugs (such as antibiotics or salt-phosphate) may contain significant amount of Na^+.
Rehydration is planned over a 48-h period. The daily volume covers the individual water requirement and half of the weight loss. For a 3.5 kg new-born who has lost 12% of his birth weight, it means 120 ml/kg/d for daily water requirement plus 210 ml for half the weight loss (=630 ml/day). This solution provides 180 ml/kg/d of water, 13 mEq/kg/d of Na^+, 6.3 mEq/kg/d of K^+, 48 mg/kg/d of both calcium and phosphate.

hypernatremia, cerebral oedema, and even cerebral haemorrhage [13–15]. In order to compensate for bicarbonate consumption, sodium bicarbonate may be substituted for one-quarter to one-half of the sodium requirements during the first 6–12 hours of rehydration. To prevent precipitation with calcium, the bicarbonate solution should be connected to the infusion line with an Y connector.

These supportive cares are applied in parallel with a toxin removal procedure that besides the dialysis of the toxic organic acids should compensate for some hydro-electrolytic imbalance and would allow nutritional support.

Total parenteral nutrition (TPN) is the method of choice to provide an efficient nutrition in regards to the high risk of gastric intolerance in these severely affected newborns. The TPN solution described in Table 1 is suitable for the first 48 hours. Then, protein must be added using a commercially available amino acid-solution (Table 4). Initially, the amino acids are introduced in an amount sufficient to meet the minimal daily requirements, and then titrated according to biochemical checks. The method is safe if the amino acid solution is evenly distributed over the whole day [16,17]. As soon as the digestive route is available, the switch from parenteral to enteral nutrition is scheduled over a 4 to 5-day period (Table 5).

Additional therapies

- Owing to its well-known anabolic effect, insulin is used to treat severe catabolism. However, to attain this goal, dehydration and acidosis must have been corrected. High infusion doses (0.2–0.3 IU/kg/h) used in association with high-glucose provision by a TPN may be useful [18,19]. During this process, insulin doses are frequently adapted to glycaemia. Sustained normalization of blood glucose levels allows insulin withdrawal. This situation is, in fact, an indirect biological marker of effective anabolism.
- As a rule, L-carnitine supplementation compensates for urinary losses and allows some urinary detoxification in the form of acyl-carnitines [20] (Table 6).
- As soon as the diagnosis of isovaleric aciduria is suspected on its peculiar, sweety odour, L-glycine supplement (250 mg/kg/day) can be added. It allows efficient detoxification in the form of isovaleryl-glycine.
- Specific vitamins must be systematically tested in each case of potentially vitamin-dependent disorders (Table 6).

Specific approaches in primary hyperlactacidaemia

- Whatever the enzymatic defect involved, newborns affected with primary hyperlactacidaemia may present with acute ketoacidosis. They require a rehydration schedule similar to that described for BCOA (Table 3). Usually, this treatment is sufficient to reduce hyperlactacidaemia to levels that do not lead to severe

Table 4. Example of a low-protein solution for parenteral nutrition in a 3.5-kg neonate. Minerals, micronutrients and vitamins must be added to these solution to provide normal requirements for a newborn

Nutrient	Amount	Energy (Kcal)	Proteins (g)	Fat (g)	CHO (g)	Na (mEq)	K (mEq)	Ca (mg)	Pi (mg)
Amino acids 6.53%	28 ml	7	1.8						
Glucose 30%	240 ml	288			72				
Intralipids 20%	50 ml	90		10					
NaCl (sufficient for)						13			
Kcl (sufficient for)							10		
Phosphate (sufficient for)									200
Calcium gluc. 10%	30 ml							270	
Water (sufficient for a total volume of 500 ml)									
Total	500 ml	385	1.8	10		13	10	270	200
Total energy provision (%)			1.8	23	75				

Calcium gluc, calcium gluconate; CHO, glucose and glucose polymers; Pi, inorganic phosphate.
NaCl and KCl solutions have to be added in volumes sufficient to meet 2 g/l (34 mmol/l) of Na^+ and 1.5 g/l (20 mmol/l) of K^+, taking in account that other drugs (such as antibiotics or phosphate-salt) may contain significant amount of Na^+.
Calculation based on commercially available i.v. amino acid solution (Vaminolact; Pharmacia) containing 9.3 g/l of total nitrogen, and 65.3 g/l aminoacids; 28 ml provides 200 mg leucine, 103 mg valine, 89 mg isoleucine, 37 mg methionine, and 103 mg threonine.
According to daily growth and biochemical results, amino acid mixture can be increased to meet the minimal daily requirements (see also text page).

metabolic acidosis. In some cases, sustained hyperlactacidaemia is due to high glucose infusion and can be reduced by using 5–2.5% glucose i.v. solution.

- Thus, none of these patients require any toxin-removal procedures.
- A normal diet for age can be instituted as soon as clinical and metabolic status allow nutrition.
- Dichloroacetate or dichloropropionate (50 mg/kg/day in one or two i.v. doses), inhibitors of pyruvate dehydrogenase (PDH) kinase, can be an effective means to lower lactate accumulation in both PDH and respiratory chain disorders [21].
- Vitamin responsiveness must be systematically tested (Table 6). Some multiple carboxylase defects may present with similar signs and are highly responsive to biotin. Theoretically, some PDH deficiency could be responsive to thiamine. In addition, L-carnitine may be of benefit since these patients may have secondary carnitine deficiency.

Neurological distress with hyperammonaemia

The presentation is mostly due to primary urea cycle defects. These neonates have an acute neurological deterioration with vasomotor instability, apnoeas, and fits. Biologically, they have respiratory alkalosis, and plasma ammonia levels greater than 400 μmol/l and often very much higher. All other routine laboratory tests are normal, especially, they do not have ketonuria.

As a general rule, treatment schedule is similar to the previous group. However, these UCD newborns have very poor outlook. Even with the most aggressive treatment, the majority of the survivors will be handicapped [12,22]. Those treated prospectively do better, but there may still be significant complications [23,24]. Thus, careful consideration should be taken before starting hopeless treatment.

Some late diagnosed organic acidurias may have similar presentation with huge hyperammonaemia without ketoacidosis. However, this does not change the urgent management and unfortunately the poor prognosis.

Toxin removal procedure and nutritional support

Haemofiltration or haemodiafiltration should be started without delay. Alternatively, peritoneal dialysis can be used but this is a less effective method for reducing hyperammonaemia. Parenteral high-energy, protein-free nutrition must be initiated at once, keeping in mind that some neonates require water volumes restriction if

Table 5. Example of switching a total parenteral nutrition to an enteral diet in a neonate (weight 3.5 kg)

	Vol (ml)	Prot (g)	Fat (g)	CHO (g)	Energy (Kcal)
First step					
Parenteral nutrition					
Glucose (30%)	165	—	—	50	200
Intralipids (20%)	10	—	2	—	18
Enteral nutrition					
Human milk	300	3.9	10.5	20.4	192
Total	475	3.9	12.5	70.4	410
Water (ml/kg per day)	135				
Total energy provision (%)		3.8	27.5	68	
Second step					
Parenteral nutrition					
Glucose (30%)	100	—	—	30	120
Enteral nutrition					
Human milk	300	3.9	10.5	20.4	192
Maltodextrin (30%)	85	—	—	24	96
Oil	2	—	2	—	18
Total	487	3.9	12.5	74	426
Water (ml/kg per day)	140				
Total energy provision (%)		3.6	26	69	

Vol, volume; Prot, protein; CHO, carbohydrates. This diet must be checked for minerals, nutrients, and vitamins and supplemented in order to cover normal requirements for a newborn. Commercially available protein-free powders (80056 Mead-Johnson, Energy-vit SHS) can be substituted for glucose polymers and oil (see also Table 3).
The first step is to progressively reach the desired amount of protein using human milk or infant formula. In this example, the relatively high protein intake is due to a presumed normalization of the specific biochemical controls during the previous period of TPN. Next, calories are slowly added using glucose polymer and lipids. Addition of an amino acid mixture, if necessary, is the last step, because it increases the osmolarity and can induce diarrhoea.

there are signs of cerebral oedema (Table 2). Once blood ammonia levels have decreased (<150 µmol/L), i.v. amino acids must be added (Table 4). The daily amount is progressively increased according to blood ammonia checks. Progressive enteral nutrition is initiated as soon as the blood ammonia levels have stabilized and the baby has regular daily weight gain (Table 5).

Additional therapies

- In emergency, a first group of compounds that allow nitrogen excretion through alternative pathways must be used: Sodium benzoate (500 mg/kg/day) by i.v. route and sodium phenylbutyrate (600 mg /kg/day) either orally or by i.v. route if available [25,26].
- Supplementation with L-arginine is recommended at 300 mg/kg/day by i.v. route before the diagnosis is known and will be later adjusted according to the defect involved [27].
- L-carnitine supplementation (Table 6) may benefit to these patients, especially, during sodium benzoate therapy [28].

Hypoglycaemia

Whatever the cause of hypoglycaemia, the emergency is to correct blood glucose level with an acute glucose administration (0.5–1 g/kg) followed by a permanent i.v. or oral glucose supply. 120 ml/kg/d of a 8% glucose solution (with appropriate electrolytes) cover the normal glucose requirement for a neonate (5–7 mg/kg/min). Thereafter, observation of patient progress under glucose provision is useful for both diagnostic and therapeutic approach. Four main situations can be encountered as follows.

Table 6. Cofactors used in various metabolic disorders

Cofactors (doses) mg/d	Disorders
Biotin (10–20)	Propionic aciduria Multiple carboxylase deficiency Hyperlactacidaemia (PC)
Carnitine (50–100 po, 400 i.v.)	Branched-chain organic aciduria Primary hyperammonaemia Hyperlactacidaemia
(100 po, i.v.)	Fatty-oxidation defects
Cobalamin, Vitamin B12 (1–2)	Methylmalonic aciduria
Folinic acid (10–40)	Folinic-responsive seizures
Pyridoxine, vitamin B6 (50–100)	Pyridoxine-responsive seizures
Riboflavin, vitamin B2 (20–40)	Glutaric aciduria Fatty-oxidation defects
Thiamin, vitamin B1 (10–50)	Maple syrup urine disease Hyperlactacidaemia (PDH)

PC, pyruvate-carboxylase deficiency; PDH, pyruvate-dehydrogenase deficiency.

Table 7. Example of a high-carbohydrate solution for a 3.5 kg baby affected with fatty acid-oxidation defect

Nutrient	Amount (ml)	Energy (Kcal)	CHO (g)	Na (mEq)	K (mEq)	Ca (mg)	Pi (mg)
Glucose 30%	240	288		72			
NaCl (sufficient for)					10		
KCl (sufficient for)						8	
Phosphate (sufficient for)							200
Calcium gluc. 10%	30					270	
Water sufficient for a total volume of 500 ml							
Total	500	288	72	10	8	270	200
Total energy provision (%)			100				

Calcium gluc, calcium gluconate; CHO, glucose and glucose polymers; Pi, inorganic phosphate; Prot, proteins. NaCl and KCl solutions have to be added in volumes sufficient to meet the requirements according to the cardiac status and, taking in account that other drugs (such as antibiotics or phosphate-salt) may contain significant amount of Na^+. For 120 ml/kg/day this parenteral solution provides (kg/day): 82 Kcal, 2.4 mmol of Na^+, 2 mmol K^+, 65 mg Ca^{++}, 48 mg P^{--} and, 12 mg/kg/day of glucose.

Hypoglycaemia and/or cardiac failure

Fatty-acid-oxidation defects can be suspected in newborns who present with fasting hypoglycaemia variously associated with lethargy, hepatomegaly and liver failure, cardiomyopathy or cardiac dysrhythmia [29]. Alternatively, wathever the blood glucose level, they may present with acute deterioration suggesting cardiac collapse or missed sudden death. Biologically, there is no ketoacidosis, blood ammonia level can be high, and they have high blood creatine kinase and uric acid levels. This severe condition, that may require resuscitation, is due to severe energy deprivation. In order to prevent further deterioration a high-glucose provision must be substituted for the standard previously described infusion.

- At first, an i.v. solution providing 10–12 mg/kg per min of glucose is necessary (110–120 ml/kg/day of a 15% dextrose solution). The fluid volume and sodium provision must be adapted to the cardiac status (Table 7). Once acute problems are resolved, continuous enteral feeding is progressively started with a low-fat and high-glucose diet that otherwise provides the normal amount of protein for age. Assessment is based upon plasma free fatty acids that should be maintained below 0.1 mmol/l.

- In order to further block the lipolysis, continuous i.v. insulin infusion can be added with doses adapted to glycaemia. If hyperammonaemia, due to N-acetylglutamate synthetase inhibition by acyl-CoA does not resolve with i.v. glucose, treatment with carbamyl-glutamate (50 mg/kg/day in four divided doses) could be an additional treatment. L-carnitine supplementation (100 mg/kg/day) compensates for urinary losses. Theoretically, some patients affected with generalized fatty-oxidation defect can be riboflavin responsive (Table 6).

Hypoglycaemia and/or liver failure

In situations during which, despite blood glucose correction, liver failure remains obvious, three disorders require urgent and specific treatment: galactosaemia, hereditary fructose intolerance, and tyrosinaemia type I.

- As soon as these disorders are considered, galactose, fructose and protein must be excluded from the diet with normal intakes of all other nutriments. If liver failure improves within the following 24–48-h period, the diagnosis of galactosaemia is likely and protein can be reintroduced. Nowadays, hereditary fructose intolerance is a rare disorder during this newborn period, since fructose is largely excluded from the diet.
- Conversely, if liver failure does not improve, tyrosinaemia type I is a potential diagnosis. However, tyrosinaemia type 1 rarely (if ever) starts before the third week of life. Conversely, many acquired disorders such as sepsis and severe neonatal hepatitis (congenital herpes) may elicit liver failure with unspecific hypoglycaemia, hyperlactacidaemia and even hyperammonaemia secondary to liver damage. At last, a few neonates with hereditary respiratory chain disorder can present severe liver failure [30]. At that point, whatever the final diagnosis, it is safe to introduce a low-protein diet (1–1.5 g/kg/d) and, to sustain exclusion of galactose and fructose since these nutriments have some hepatotoxicity. When, tyrosinaemia type I is confirmed, NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) treatment must be initiated.

Hypoglycaemia with hepatomegaly

These neonates maintain normal blood glucose levels under permanent glucose provision and, have permanent hepatomegaly with cytolysis but no liver failure. Glycogen storage diseases type I and type III, and fructose-1,6-biphosphatase are likely. As soon as biological values have return to normal, a continuous enteral feeding is substituted for glucose infusion. At first, a milk-based, lactose-free, sucrose-free formula enriched with maltodextrin is used. The total amount of glucose should allow an average glucose provision of 10–12 mg/kg/min. This is easily reached using a normal energy intake, in which 50–60% of energy is supplied by glucose. This diet is later adapted to the correct diagnosis.

Recurrent intractable hypoglycaemia

- Despite permanent glucose provision, neonatal hyperinsulinism presents with recurrent intractable hypoglycaemia without ketoacidosis. The newborn requires a continuous high-glucose provision that exceeds the capacity of the peripheral i.v. route and continuous enteral feeding. Thus, central venous catheterization in emergency is quite unavoidable in meeting the excessive glucose requirement.
- In case of persistent hypoglycaemia, continuous i.v. or subcutaneous glucagon administration (0.1–0.2 mg/kg per day) can be instituted.

At last, many metabolic disorders may revealed with non-specific neurological signs such as lethargy, hypotonia and seizures. They do not require specific treatment in emergency except for pyridoxine (50 mg), biotin (10 mg), and folinic acid (10–40 mg/day) that must be systematically tested, when seizures are the preponderant or revealing sign. In addition, by the end of the first month, familial hypomagnesaemia with secondary hypocalcaemia may present with intractable seizures that requires elemental magnesium supplementation (50 mg/kg/d).

Appendix: Medicine cited in this chapter

- L Carnitine: 100–400 mg/kg/d, i.v. route 100 mg/kg/d, per oral route
- Dichloroacetate/dichloropropionate: 50 mg/kg/d, i.v./oral routes, in one to two divided doses
- Sodium benzoate: 500 mg/kg/d in acute management of UCD, by i.v. route

- Sodium phenylbutyrate: 600 mg/kg/d in acute management of UCD, by i.v. route if available/ oral
- L-arginine: 300 mg/kg/d in acute management of yet unspecified UCD, by i.v. route
- Carbamyl-glutamate: 50 mg/kg/d, by oral route, in four divided doses
- NTBC: 1 to 2 mg/kg/d, by oral route, in two divided doses
- L-glycine: 250 mg/kg/d, by oral route, in two to four divided doses
- Magnesium sulfate: 50 mg/kg/d (elemental magnesium), by oral route

References

1 Burton BK. Inborn errors of metabolism: the clinical diagnosis in early infancy. *Pediatrics* 1987; **79:** 359–369.
2 Saudubray JM, Ogier H, Bonnefont JP, *et al*. Clinical approach to inherited metabolic diseases in the neonatal period: a 20-year survey. *J Inherit Med Dis* 1989; **12**(Suppl 1): 1–17.
3 Saudubray JM, Ogier H, Charpentier C, *et al*. Neonatal management of organic acidurias – Clinical update. *J Inherit Med Dis* 1984; **7**(Suppl 1): 2–9.
4 Donn SM, Swartz RD, Thoene JG. Comparison of exchange transfusion, peritoneal dialysis, and hemodialysis for the treatment of hyperammonemia in an anuric newborn infant. *J Pediatr* 1979; **95:** 67–70.
5 Wendel U, Langenbeck U, Lombeck I, Bremer HJ. Exchange transfusion in acute episodes of maple syrup urine disease: Studies on branched-chain amino and keto acids. *Eur J Pediatr* 1982; **138:** 293–296.
6 Batshaw ML, Brusilow SW. Treatment of hyperammonemic coma caused by inborn errors of urea synthesis. *J Pediatr* 1980; **97:** 893–900.
7 Goertner L, Leupold D, Pohlandt F, Bartmann P. Peritoneal dialysis in the treatment of metabolic crises caused by inherited disorders of organic and amino acid metabolism. *Acta Paediatr Scand* 1989; **78:** 706–711.
8 Sadowski RH, Harmon EH, Jabs K. Acute hemodialysis of infants weighing less than five kilograms. *Kidney Int* 1994; **45:** 903–906.
9 Gouyon JB, Desgres J, Mousson C. Removal of branched-chain amino acids by peritoneal dialysis, continuous arteriovenous hemofiltration, and continuous arteriovenous hemodialysis in rabbits: Implications for maple syrup urine disease treatment. *Pediatr Res* 1994; **35:** 357–361.
10 Jouvet P, Poggi F, Rabier D, *et al*. Continuous venovenous haemodiafiltration in the acute phase of neonatal maple syrup urine disease. *J Inherit Med Dis* 1997; **20:** 463–472.
11 Schaefer F, Straube E, Oh J, Mayatepeck E. Dialysis in neonates with inborn errors of metabolism. *Nephrol Dial Transplant* 1999; **14:** 910–918.
12 Picca S, Dionisi-Vici C, Abeni D, *et al*. Extracorporeal dialysis in neonatal hyperammonemia: modalities and prognostic indicators. *Pediatr Nephrol* 2001; **16:** 862–867.
13 Dave P, Curless R, Steinman L. Cerebellar hemorrhage complicating methylmalonic and propionic acidemia. *Arch Neurol* 1984; **41:** 1293–1296.
14 Surtees R, Leonard JV. Acute metabolic encephalopathy: A review of causes, mechanisms and treatment. *J Inherit Med Dis* 1989; **12**(Suppl 1): 42–54.
15 Orban T, Mpofu C, Blackensee D. Severe CNS bleeding followed by a good clinical outcome in the acute neonatal form of isovaleric aciduria. *J Inherit Metab Dis* 1994; **17:** 755–756.
16 Berry GT, Heidenreich R, Kaplan P, *et al*. Branched-chain amino acid-free parenteral nutrition in the treatment of acute metabolic decompensation in patients with maple syrup urine disease. *N Engl J Med* 1991; **324:** 175–179.
17 Khaler SG, Millington DS, Cederbaum SD, *et al*. Parenteral nutrition in propionic and methylmalonic acidemia. *J Pediatr* 1989; **115:** 235–241.
18 Biggemann B, Zass R, Wendel U. Postoperative metabolic decompensation in maple syrup urine disease is completely prevented by insulin. *J Inherit Med Dis* 1993; **16:** 912–913.
19 Leonard JV, Umpleby AM, Naughten EM, *et al*. Leucine turnover in maple syrup urine disease. *J Inherit Med Dis* 1983; **6**(Suppl 2): 117–118.
20 Chalmers RA, Roe CR, Stacey TE, Hoppel CR. Urinary excretion of L-carnitine and acyl-carnitine by patients with disorders of organic acids metabolism: evidence for secondary insufficiency of L-carnitine. *Pediatr Res* 1984; **18:** 1325–1328.
21 Stacpoole PW, Barnes CL, Hurbanis MD, *et al*. Treatment of congenital lactic acidosis with dichloroacetate. *Curr Top Arch Dis Child* 1997; **77:** 535–541.
22 Msall M, Batshaw ML, Suss R, *et al*. Neurologic outcome in children with inborn errors of urea synthesis. *N Engl J Med* 1984; **310:** 1500–1505.
23 Maestri NE, Hauser ER, Bartholomew R, Brusilow SW. Prospective treatment of urea cycle disorders. *J Pediatr* 1991; **119:** 923–928.
24 Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, physiopathology, and therapy. *Adv Pediatr* 1996; **43:** 127–170.
25 Brusilow SW, Valle DL, Batshaw ML. New pathways of nitrogen excretion in inborn errors of urea synthesis. *Lancet* 1979; **II:** 452–454.
26 Feillet F, Leonard JV. Alternative pathway therapy for urea cycle disorders. *J Inherit Med Dis* 1998; **21**(Suppl 1): 101–111.
27 Brusilow SW. Arginine, an indispensable aminoacid for patients with inborn errors of urea synthesis. *J Clin Invest* 1984; **74:** 2144–2148.
28 Ohtani Y, Ohyanagi K, Yamamoto S, Matsuda I. Secondary carnitine deficiency in hyperammonemic attacks of ornithine transcarbamylase deficiency. *J Pediatr* 1988; **112:** 409–414.
29 Bonnet D, Martin D, de Lonlay P, *et al*. Arrhythmias and conduction defects as presenting symptoms of fatty acid oxidation disorders in children. *Circulation* 1999; **100:** 2248–2253.
30 De Lonlay P, Valnot I, Barrientos A,, *et al*. A mutant mitochondrial respiratory chain assembly protein causes complex III deficiency in patients with tubulopathy and liver failure. *Nature Genetics* 2001; **29:** 57–60.