Acute Illness Protocol for Organic Acidemias
Methylmalonic Acidemia and Propionic Acidemia

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Abstract: Inborn errors of metabolism (IEM) are genetic disorders that disrupt enzyme activity, cellular transport, or energy production. They are individually rare, but collectively have an incidence of 1:1000. Most patients with IEMs are followed by a physician with expertise in Biochemical Genetics (Metabolism), but may present outside of this setting. Because IEMs can present acutely with life-threatening crises that require specific interventions, it is critical for the emergency medicine physicians, pediatricians, internists, and critical care physicians as well as biochemical geneticists to be familiar with the initial assessment and management of patients with these disorders. Appropriate early care can be lifesaving. This protocol is not designed to replace the expert consultation of a biochemical geneticist but rather to improve early care and increase the level of comfort of the acute care physician with initial management of organic acidemias until specialty consultation is obtained.

Key Words: inborn errors of metabolism, methylmalonic acidemia, propionic acidemia

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SUMMARY OF THE PROTOCOL

Methylmalonic (MMA) and propionic acidemia (PA) are genetic defects in the metabolism of organic acids derived from the degradation of isoleucine, valine, methionine, threonine, odd-chain fatty acids, and cholesterol side chains. Both MMA and PA can present acutely with increased anion gap metabolic acidosis, ketosis, elevated lactate, hyperammonemia, hypoglycemia, pancreatitis, and thrombocytopenia. Acute neurological symptoms are common and can range from mild encephalopathy to metabolic strokes involving the basal ganglia. Propionic acidemia can additionally present with cardiomyopathy and QT prolongation. Chronic complications of both diseases include failure to thrive, developmental delay, movement disorder, deafness, and optic atrophy. Methylmalonic acidemia is also associated with progressive renal tubular disease. Metabolic decompensations can be provoked by illness (commonly infections), fasting, excess protein intake, and treatment noncompliance. Early identification and management of a metabolic decompensation is critical to prevent adverse outcomes. The cornerstone of acute management of both conditions is protein restriction, provision of increased nonprotein calories, appropriate correction of base deficit, carnitine supplementation, and identification and treatment of underlying trigger(s). A suggested management algorithm for patients with PA and MMA who present with acute decompensations is summarized in Figure 1.

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BACKGROUND

Methylmalonic (MMA) and propionic acidemia (PA) are genetic defects in the metabolism of organic acids deriving from the degradation of isoleucine, valine, methionine, threonine, odd-chain fatty acids, and cholesterol side chains (Fig. 2).

The accumulating toxic organic acids disrupt additional metabolic pathways, resulting in increased anion gap metabolic acidosis, ketosis/ketonuria, hyperammonemia, elevated lactate, hypoglycemia, and thrombocytopenia. Pancreatitis is another potential complication for both disorders.[1] Propionic acidemia can also present with cardiomyopathy and QT prolongation.[2,3] Chronic complications of both disorders include failure to thrive, developmental delay, movement disorder,[4] deafness, optic nerve atrophy,[5] and metabolic strokes.[6–9] Methylmalonic acidemia is associated with progressive renal tubular disease.[10] It is important to keep in mind that in neonates, signs and symptoms of PA and MMA are often nonspecific and may include irritability, change in tone, and hyperventilation. Common symptoms and signs of PA and MMA are summarized in Table 1.

Patients with MMA and PA are managed with a low-protein diet that is often supplemented with special amino acid–based medical food devoid of the offending amino acids valine, isoleucine, threonine, and methionine.[11] Patients may require chronic enteral medications like sodium or potassium citrate or sodium bicarbonate to maintain adequate bicarbonate levels. Moreover, supplemental carnitine is typically required (25–100 mg/kg per day in 3 divided doses) to address secondary carnitine deficiency.[11] In addition, patients with some forms of MMA may be prescribed vitamin B12 supplements, as a cofactor for the deficient enzyme.

Metabolic decompensation in PA and MMA can be triggered by illness, fasting, excess protein (either exogenous or endogenous such as GI bleeding, menstruation, etc.), and treatment noncompliance.[12,13] Important laboratory tests that are used to guide clinical care are listed in Table 2.

Patients with a severe course of the disease may be managed with liver transplant (often with combined kidney transplant in MMA).[14] Although liver transplant significantly decreases levels of circulating organic acids in PA and MMA and makes systemic acidosis less common, organic acid levels in the central nervous system may remain elevated. Therefore, there is continued risk of metabolic stroke even after transplant. However, liver transplantation largely eliminates acute episodes of metabolic acidosis.[15,16]

MANAGEMENT

Diet

In a significant metabolic decompensation, exogenous protein should initially be discontinued. If enteral feeds are tolerated, then a protein-free formula can be used by mouth or nasogastric/gastrostomy tubes (NGT/G-tube) ([eg, Duocal (Nutricia, Schiphol, The Netherlands), Prophree (Abbott, Chicago, IL), or Maltodextrin-based formula)]. Generally, protein should not be withheld entirely for more than 48 hours because this may result in catabolism of endogenous protein and a further increase in organic acid and ammonia levels. When a patient is receiving decreased protein,

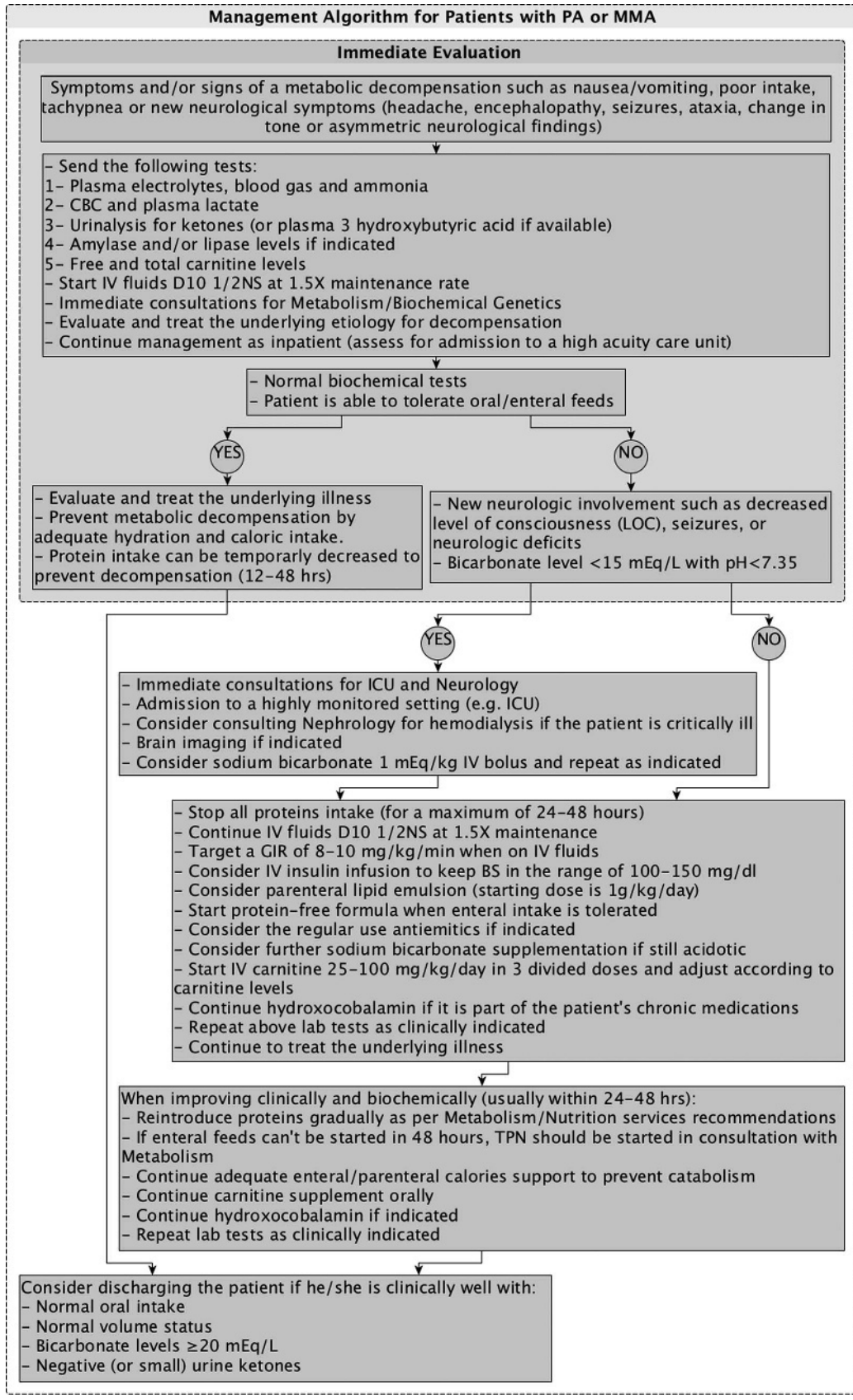

FIGURE 1. Management algorithm for patients with PA or MMA during acute decompensation.

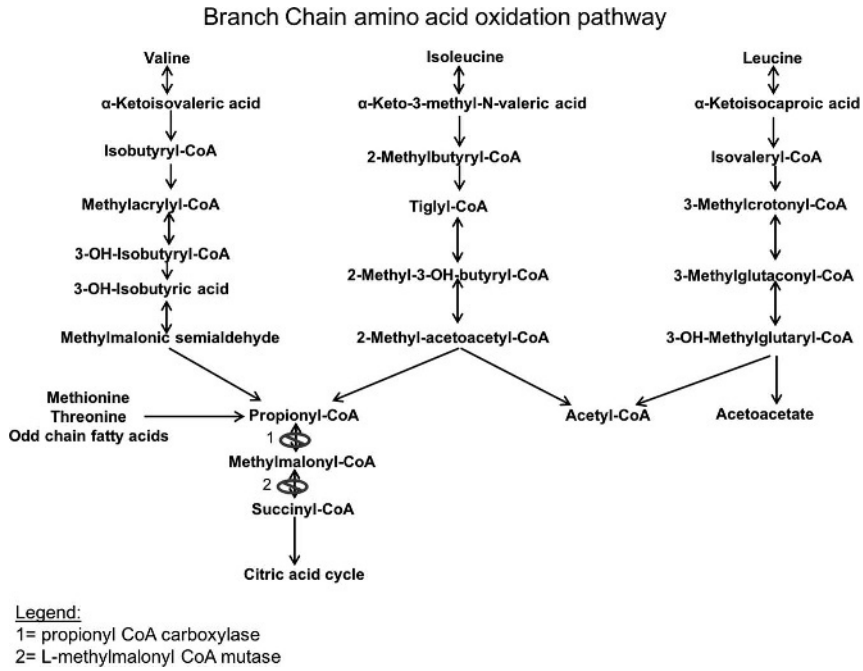

FIGURE 2. Branch chain/threonine/methionine metabolic pathways.

amino acid–based metabolic formula devoid of valine, isoleucine, methionine, and threonine [eg, Propimex (Abbott, Chicago, IL)] can be supplemented to increase total protein (nitrogen) intake while limiting offending amino acids.[11]

In addition to diet composition, total daily calories should be increased during a metabolic decompensation to promote an anabolic state (ideally 20%–25% increase above maintenance).[11,17]

Patients with MMA and PA are also prone to anorexia and commonly need a temporary or permanent method for enteral feeding. When clinically appropriate, tube feeding should be used. Common antiemitics can be used safely to treat nausea and vomiting as indicated.

Intravenous Fluids

In a metabolic decompensation, intravenous (IV) dextrose-containing fluids should be used to increase calories and to promote insulin release and anabolism.[11,17] Generally, IV D10-containing fluid at 1.5 times maintenance rate is used to provide a glucose infusion rate of 8 to 10 mg/kg per minute. Higher glucose infusion rate may be required if there is no clinical response. If blood glucose is greater than 150 mg/dL, IV insulin infusion (begins at 0.01 units/kg per hour and titrated according to blood sugar levels) can be instituted to promote anabolism. Blood glucose should be maintained between 100 and 150 mg/dL. To provide additional calories, IV intralipid can also be initiated at a starting dose of 1 to 2 g/kg per day; serum triglyceride levels should be monitored on this therapy.

Patients with MMA and PA can be volume depleted on presentation and may need additional fluid resuscitation (in conjunction with the dextrose-containing fluid) using crystalloids as per the emergency department/intensive care unit protocols. It should be noted that patients with PA can have cardiac dysfunction, which can make them prone to developing heart failure due to aggressive volume resuscitation. In addition, chronic renal disease is a feature of MMA and should be taken into consideration when determining fluid resuscitation.

Medications

Sodium Bicarbonate

Low bicarbonate levels should be corrected aggressively. The goal for immediate management is to have bicarbonate levels greater than 15 mmol/L, although maintaining a level greater than 18 to 20 mmol/L is desired beyond the hyperacute stage. Sodium bicarbonate can be given as a 1 mEq/kg IV bolus and repeated as necessary. As usual, interpretation and treatment of bicarbonate levels should also take into account blood pH.

TABLE 1. Symptoms and Signs of Patients With PA and MMA During Acute Decompensations

Body System/Process	Symptoms and/or Signs*
Metabolic	Increased anion gap metabolic acidosis, ketosis/ketonuria, hyperammonemia, lactic acidosis, hypoglycemia
Neurological	Headache, psychiatric symptoms, encephalopathy, seizures, ataxia, change in tone, hyperkinetic movement disorder, rarely asymmetric neurological deficits like hemiparesis
Gastrointestinal	Nausea and vomiting, pancreatitis, dysmotility
Respiratory	Hyperventilation (Kussmaul respiration) secondary to acidosis
Hematological	Bleeding diathesis from thrombocytopenia, rarely anemia, neutropenia or pancytopenia, can occur. Neonatal intracranial hemorrhage can rarely occur
Cardiovascular (PA)	Prolonged QT, cardiomyopathy
Renal (MMA)	Renal insufficiency and failure

*Close relatives of affected individuals know the signs of decompensation in their relatives, and it is important to listen to their insight.

TABLE 2. Laboratory Tests and Investigations that can Guide Clinical Care During Acute Metabolic Decompensations*

Laboratory Tests	Comments
Chemistry panel for bicarbonate level, anion gap, and blood glucose	To evaluate the degree of acidosis and hypoglycemia if present
Venous blood gas for pH, bicarbonate, and PCO2	To assess the severity of metabolic acidosis
Plasma ammonia (STAT)†	To be collected from a free-flowing sample, without tourniquet, placed immediately on ice, and analyzed ASAP (typically within 15 minutes)
Urine ketones	Always abnormal in the neonate. In the older child or adult, ketosis may indicate metabolic instability, particularly if present in the fed state
Serum lactate	Can be elevated in hypovolemia
Serum amylase and lipase	Pancreatitis may result as a complication of metabolic decompensation
Plasma-free and total carnitine levels	To guide dosing of carnitine supplementation
Plasma amino acid levels	To determine protein nutritional status and glycine levels
Quantitative urine organic acid levels and/or plasma MMA‡	To monitor burden of organic acid
Complete blood count with differential	Assess for thrombocytopenia and/or pancytopenia
Electrocardiogram	Assess for QT prolongation
Chest x-ray (in posterioranterior and lateral)	To evaluate for cardiomegaly
Infectious work-up (cultures, chest x-ray, urinalysis, etc)	To assess for the underlying etiology
Neuroimaging	To evaluate for metabolic basal ganglia stroke if the patient develops neurological deficits or coma

*Sending laboratory tests should be guided by the clinical presentation of the patient. This is not an exhaustive list and some of the tests listed here may not be indicated.

†To convert from μmol/L to μg/dL, multiply by 1.8 (eg, an ammonia level of 100 μmol/L is equivalent to 100 × 1.8 = 180 μg/dL). Normal ammonia level is 15 to 35 μmol/L in an older child or adult; less than 110 μmol/L in a neonate. Range for normal values can be different based on the local laboratory.

‡Unlike in the urea cycle disorders, plasma glutamine may be normal or paradoxically decreased in the context of hyperammonemia in PA and MMA and should not be used as a measure of ammonia burden.

After the acute correction, the remainder of the base deficit should be corrected gradually to avoid overcorrection that may result in central nervous system acidosis. Typically, the goal is half-correction in the first 24 hours. The following formula can be used to calculate mmol of base to provide for half correction[18]:

[Desired bicarbonate level (mmol/L) − current bicarbonate level (mmol/L)] × [volume of distribution (0.7 in neonate; 0.6 in older child and adult) × body weight (kg)] × [0.5].

For the gradual correction of base deficit, intermittent enteral dosing of sodium bicarbonate, sodium citrate, or potassium citrate may be used. Alternatively, acetate or bicarbonate can be added to IV fluids in measured amounts.

L-Carnitine (Levo-carnitine)

L-Carnitine should be provided during metabolic decompensation to address secondary carnitine deficiency (carnitine conjugates with organic acids precursors to allow for urinary excretion of the organic acid-carnitine complexes).[11] If acute carnitine levels are not available, then treatment with 100 mg/kg per day (divided in 3 doses) of IV carnitine should be considered.[19] When the patient is clinically stable, the IV dose can be transitioned to enteral form. Although 1:1 conversion between IV and enteral carnitine is often used, the IV formulation is more bioavailable and can be reduced by 30% to 40% from the oral dose. Once carnitine levels are available, the dose can be titrated to maintain *free* carnitine levels within the normal range.

Vitamin B12 (Cobalamin)

In forms of MMA potentially responsive to vitamin B12 supplementation, vitamin B12 should be started (or continued if patient is already receiving it) during a metabolic decompensation. The typical formulation and starting dose is *hydroxocobalamin* 1000 μg intramuscular once daily.

Ammonia Scavengers

Because ammonia levels typically normalize with correction of acidosis, provision of adequate calories, and acute protein restriction, ammonia scavengers are typically not required (and are not considered standard of care) to treat hyperammonemia in PA and MMA. Furthermore, scavengers are acids themselves and may contribute to further intramitochondrial CoA depletion.[20] However, in rare circumstances of refractory or severe hyperammonemia, IV Ammonul and oral ammonia scavengers can be considered.[21]

Ammonul is a combination of sodium phenylacetate and sodium benzoate. Depending on ammonia level, rate of rise of ammonia, and clinical status, a loading dose can be given followed by maintenance dosing. Both loading dose and maintenance dosing (calculated for a 24-hour period) of Ammonul are the same. Dosing depends on body weight and body surface area (BSA) as follows:

- Body weight of 20 kg or less: 250 mg/kg
- Body weight of 20 kg or more: 5.5 g X BSA
  BSA=√(weightXheight/3600)

The Ammonul dose is diluted in 25 cc/kg of D10W. The loading dose is typically given over 1.5 to 2 hours. Slower infusions can be used, for both loading and maintenance, if there is concern for volume overload. For the maintenance phase, additional D10W is typically given to maintain a total fluid intake of 1.5 times maintenance rate.

- Potential adverse effects of Ammonul:
- Nausea — consider premedicating with ondansetron

- Hypernatremia
- Hypokalemia
- Ammonul toxicity: metabolic acidosis, increased anion gap, elevated lactate and ketones, hyperventilation, and hyperthermia.

Maintenance treatment with oral scavengers is typically not required.

Hemodialysis

Hemodialysis is indicated urgently in the following situations[22]:

- An initial ammonia level greater than 500 μmol/L (>700 μg/dL)
- Increasing ammonia level despite adequate calories/nutritional management, correction of acidosis, +/−Ammonul therapy
- Poor clinical status: coma, concern for metabolic stroke
- Significant electrolyte derangements as per usual hemodialysis protocols

If hemodialysis is a potential consideration, the nephrology service should be advised as soon as possible.

Management of Possible Neurologic Complications (Decreased Level of Consciousness, Seizure, or Coma)

If there is concern for metabolic stroke, then standard neurocritical care principles should be followed. Consider neuroimaging, preferably with magnetic resonance imaging.[6,8]

Treatment of the Underlying Etiology

Every effort should be made to identify and treat the underlying illness or metabolic stressor that triggered the decompensation. Infections such as gastritis/gastroenteritis, upper respiratory tract infection/bronchitis and urinary tract infections are common causes for metabolic decompensations (as high as 85% of the cases).[12,13,23] Nonadherence to low-protein diet and medical foods is also common. These conditions should be managed according to the usual protocols and recommendations. Commonly used antibiotics and antiemetics can be used safely in patients with PA and MMA.

Monitoring

1. If the patient with MMA or PA is ill, then strong consideration should be given to monitoring in an intensive care unit setting.
2. Neurological status should be monitored with a frequency indicated by clinical concern.
3. Chemistry panel (including bicarbonate), ammonia levels, +/−blood gas should be repeated based on levels and clinical status. A common initial interval is every 4 hours for 12 to 24 hours.
4. Urine ketones should initially be monitored with every void.
5. Plasma amino acids as clinically indicated to evaluate essential amino acid levels (for nitrogen balance).
6. Plasma free/total carnitine as clinically indicated to monitor plasma levels on carnitine supplementation.

CONCLUSIONS

Propionic acidemia and MMA are severe metabolic disorders with a number of potential life-threatening acute complications. Early recognition of metabolic decompensation and institution of appropriate management is critical to ensure good outcome. The acute care physician is usually the first provider to evaluate the patient with PA or MMA and is in the unique position to improve patient outcome by instituting the appropriate early management while expert opinion from a biochemist geneticist is sought.

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