Molecular Genetics and Metabolism xxx (2011) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Conference Proceedings

Acute management of propionic acidemia

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ARTICLE INFO

Available online xxxx

Keywords:
Propionic acidemia
Inborn error of metabolism
Organic acidemia
Treatment
Acute management

ABSTRACT

Propionic acidemia or aciduria is an intoxication-type disorder of organic metabolism. Patients deteriorate in times of increased metabolic demand and subsequent catabolism. Metabolic decompensation can manifest with lethargy, vomiting, coma and death if not appropriately treated. On January 28–30, 2011 in Washington, D.C., Children's National Medical Center hosted a group of clinicians, scientists and parental group representatives to design recommendations for acute management of individuals with propionic acidemia. Although many of the recommendations are geared toward the previously undiagnosed neonate, the recommendations for a severely metabolically decompensated individual are applicable to any known patient as well. Initial management is critical for prevention of morbidity and mortality. The following manuscript provides recommendations for initial treatment and evaluation, a discussion of issues concerning transport to a metabolic center (if patient presents to a non-metabolic center), acceleration of management and preparation for discharge.

1. Introduction

Propionic acidemia (PA, OMIM #606054) is one of the intoxication type organic acidemias [1, 2] which often present in the neonatal period with lethargy, poor feeding, and vomiting and can progress to coma if not identified and treated appropriately. In addition, individuals known to have PA can also present with acute metabolic decompensation requiring similar therapy. Patients with related intoxication type organic acidemias present in a similar way, respond to many of the same interventions, and have similar outcomes, if not treated [2].

In regions where expanded newborn screening panels are available, patients with PA can be identified by an elevated propionylcarnitine (C3). While many of these individuals are detected in a presymptomatic state, the rapidity of onset of symptoms and the time necessary to process newborn screening samples mean that a number will be symptomatic before results are available. Early identification, evaluation, and treatment of a metabolically unstable patient with PA are important to improve survival and reduce morbidity [2].

Individuals, known to have PA, develop worsening metabolic acidosis in the presence of physiological stress from increased catabolism during episodes of fever, infection, vomiting, trauma, and psychological or physiological stress. At these times, individuals are thought to have higher metabolic rates than they can tolerate and they require prompt therapy (similar to that used in new onset patients) to mitigate complications, morbidity, and mortality [3].

The following sections are therapeutic recommendations for acute interventions in undiagnosed and known cases of PA. These recommendations are based on discussions from the 2011 PA consensus conference hosted by Children's National Medical Center in Washington, D.C. by a panel of metabolic specialists, metabolic dietitians, other physicians, and family representatives and incorporate the most recent available literature. Much of the presented therapeutic interventions are expert opinion based on clinical experience and literature review. The goals of these recommendations include

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1096-7192/$ – see front matter
doi:10.1016/j.ymgme.2011.09.026

standardizing the treatment protocols used for patients with PA using the best data available, and providing a resource to not only metabolic physicians, but also physicians who may come in contact with undiagnosed and diagnosed individuals with PA.

Despite acute management protocols being available from other sources (e.g. the New England Consortium of Metabolic Programs and by the British Inherited Metabolic Disease Group), these recommendations are meant to be an update to present protocols and

2.1Recommendations for initial care and interventions in a symptomatic known or suspected PA patient (these steps can occur at or prior to transfer to a metabolic center)

2.1.1 Stabilization, if Critically Ill

1. Intubate and ventilate, if necessary
2. Place intravenous lines. Do not use right intrajugular or one of the two femoral sites (these will be needed for large bore dialysis or central catheters), if necessary. An intraosseus and nasogastric tube are preferred, if unable to access other venous sites, selection of which alternative should be done according to clinician judgment.
3. Add vasopressors to maintain blood pressure, as necessary.
4. Normal saline fluid bolus can be given if necessary. Avoid over hydration and do not delay reversal of catabolism to give normal saline bolus.
5. Draw laboratory studies outlined in **TABLE 2**; do not discard any blood left over after running the testing. (If the presenting institution cannot run the recommended labs, transfer the previously drawn date and time labeled blood samples with the patient).

2.1.2 Reversal of Catabolism

1. STOP all sources of protein (enteral and parenteral nutrition)
2. Give non-protein calories in the form of intravenous fluids (10% dextrose, or higher if appropriate, with electrolytes) at 120-150 mL/kg/ day, 1.5 times maintenance, or a goal of 6-8 mg glucose /kg/min. If intralipids are available, they may be started as needed at 3 g/kg/day to provide additional calories. DO NOT STOP calorie delivery in the acute stage for any reason (e.g. medications, addition required fluid bolus or hyperglycemia).

2.1.3 Other interventions to be done at the presenting institution

1. Start antibiotics (after blood cultures are drawn).
2. If neonate and newborn screen results are not known, call newborn screening laboratory to check for results or expedite their processing (normal results do not rule out metabolic disease).
3. Arrange transport to a metabolic center as soon as there are concerns for metabolic disease or decompensation

2.3 Acceleration of care in a severely decompensated patient with known or suspected PA (only in a metabolic center)

2.3.2 Acceleration of care at a metabolic center

1. Laboratory: Repeat laboratories in **Table 2** upon arrival stat. Collect confirmatory laboratories (acylcarnitine profile, urine organic acids, and plasma amino acids) if they have not been collected previously and are not available for immediate analysis and resulting.
2. Continue reversal of catabolism with at least 10% dextrose containing fluids and possibly intralipids to aim for maximum energy intake for age and weight.
3. Consider starting an insulin drip (0.01 units/kg/hour). Increase dextrose amount if hypoglycemic at this dose, do not decrease dextrose delivery rate or amount.
4. Arrange for and consider initiation of hemodialysis, hemofiltration of extracorpeal membrane oxygenation driven filtration (ECMO). This is particularly important in patients with ammonia >300 micromoles/L, extreme acidosis/electrolyte imbalance, coma, dilated pupils, poor neurological findings, deterioration, failure to improve, or increased respiratory rate. Do not use peritoneal dialysis. Continue this intervention for at least 24 hours and then as clinical findings dictate. This may be stopped when acidosis is corrected, ammonia is less than 200 mcmol/L, and a small amount of protein has been reintroduced and tolerated. Leave the catheters in place for at least 24 hours (and avoid using them for IVF and medications as this can render them unusable for dialysis) in case re-initiation is necessary.
5. In an undiagnosed patient, if hyperammonia is present, consideration may be given to starting sodium benzoate/sodium phenylacetate (at same doses as urea cycle defects and/or N-carbamylglutate (dosing in **Table 3**). Sodium benzoate/ sodium phenylacetate should be stopped once the diagnosis of PA has been made In known patients, N-carbamylglutate may be started for hyperammonia for treatment or as a bridge to hemodialysis during transport or while awaiting initiation of hemodialysis.
6. Intravenous carnitine boluses 100 mg/kg/dose 3-4 times daily should be given if appropriate urine output is appropriate (or hemofiltration ongoing).
7. Follow ammonia, electrolytes and blood gases at regular intervals. The frequency is dictated by the patient's condition and the speed at which results can be obtained.
8. Protein should be reintroduced within 24-36 hours of initiation of therapy (some will require sooner if protein deficiency is cause of decompensation). Protein must be reintroduced even if patient on hemodialysis or ECMO.

Fig. 1. Complete recommendations for the acute management of a suspected or known patient with PA.

Please cite this article as: K.A. Chapman, et al., Acute management of propionic acidemia, Mol. Genet. Metab. (2011), doi:10.1016/j.ymgme.2011.09.026

9. Consider sedation, ventilation, and chemical paralysis if aggressive management is necessary. If available, continuous EEG is helpful to monitor progress.
10. Packed red blood cell transfuse as necessary based on age, clinical condition and physician discretion.

2.4 Transition from acute to chronic management: Discharge planning

1. Establishment of home metabolic nutrition support regimen
2. Gastrostomy tube (G-tube) or nasogastric tube (NG tube) placement for enteral feeding
3. Carnitine transitioned to oral medication (Recommend 200 mg/kg per dose twice daily), taking amount of carnitine from metabolic formula into account.
4. Instructions for a "gut flora control" regimen and prevention of constipation
5. Screening studies including echocardiogram, electrocardiogram (EKG), hearing screen, optic fields (if cerebral edema), dilated ophthalmologic exam,
6. Involvement of physical therapy and occupational therapy (as soon as possible) and referral to early intervention (in the neonates)
7. Parental training needed prior to discharge (**Table 4**)

Fig. 1 (*continued*).

provide a standard protocol that can be used to be the basis for clinical studies in PA in patients at multiple institutions in multiple regions and countries. Additionally, this protocol may be useful for education of metabolic physicians and for use by critical care, emergency and primary care medical professionals who will be the initial caregivers for these patients.

The initial section focuses on identifying unknown patients at risk for having PA. The next sections describe recommendations for acute management and are divided into several sections. All recommendations are listed in Fig. 1. The first section reviews the interventions that may be done outside a metabolic center prior to transport to a metabolic center or at presentation to the emergency room at a metabolic center (Section 2.1). The following section reviews important aspects of transport of metabolic patients (Section 2.2). Once transferred to a metabolic center, acute maximum treatment is outlined (Section 2.3) followed by a review of the transition of care required to prepare patients for discharge (Section 2.4). The final section reviews some considerations for home management of a known patient with PA and decision making approaches to initiate hospitalization (Section 3).

1.1. Recognition of possible patients with PA and initiation of therapies in potential and symptomatic known patients with PA

When a healthcare provider is presented with a neonate or infant with poor feeding, vomiting, altered consciousness or acidosis, inborn errors of metabolism should be included in the differential diagnosis. In the United States, newborn screening identifying an elevation in propionylcarnitine (C3) may be a useful first hint of disease. In several European countries and much of the world, newborn screening does not include C3, so presymptomatic identification is much rarer. Infants may present with a spectrum of intoxication symptoms (Table 1) and closely resemble septic patients. Consequently we recommend that ANY infant less than 4 weeks old undergoing a sepsis work up who does not have a documented negative newborn screening result have a metabolic disease work-up as well (Table 2). Early onset neonatal sepsis can be seen in 1 of 1000 live births [4]. The incidence and identification of an inherited metabolic disorder by newborn screening is about 0.2 to 1.5 of 1000 live births depending on the population [5,6,7].

Once the possibility of metabolic disease is raised (via newborn screen or in a sick infant with findings concerning for symptomatic disease), if the patient is not currently at a metabolic center, the supervising physician needs to immediately contact the metabolic center with whom they have a relationship. In many cases of infantile presentations, the exact metabolic disease is not always clear in the

Table 1
List of concerning laboratory, physical exam findings and history seen in symptomatic patients with metabolic disorders, especially propionic acidemia, which require additional evaluations. Patients who are considered to have symptomatic metabolic decompensation if they have any one of the following.

History
Not feeding well (including not finishing bottles)
Vomiting
Heavy breathing
Poor suck
Concern based on clinical judgment
Physical exam findings (*based on gestational appropriate exam*)
Absence of proper perfusion (prolonged capillary refill)
Abnormal movements including bicycling
Abnormal tone
Seizure(s)
Low body temperature
Laboratory abnormalities
Anion gap (without potassium) >15
pH<7.3
Urine ketones (in an infant greater than trace or child greater than small)
Elevation of lactic acid
Neutropenia or thrombocytopenia

Table 2
Laboratory testing that should be done in any patient suspected of having an intoxication type metabolic disorder at presentation as well as in any patient with known propionic acidemia at time of metabolic decompensation.

Venous/arterial blood gas
Glucose
Electrolytes (including calcium)
Blood urea nitrogen
Creatine
Liver transaminases
Bilirubin
Total protein
Alkaline phosphatase
Blood Culture
Complete blood count
Urine ketones (healthy infants should not have any)
Anion gap ($[Na^+]-([Cl^-]+[HCO_3^-])$) with abnormal >15
Lactate
Ammonia
Lipase (if symptoms indicate)
Urine organic acids (obtained within 2 h of presentation by any method of collection)
Plasma amino acids
Acylcarnitine profile
Save a blood sample for DNA and DNA testing (if genotype is not known)

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initial hours and thus laboratory testing available at a metabolic center (often in real time) allows additional information that leads to appropriate management. In a similar way, if a known patient with PA presents to an acute care setting, not at a metabolic center the supervising physician should arrange transport to a metabolic center and contact the managing metabolic team.

If an infant is identified by newborn screening with elevated propionylcarnitine (C3), then a portion of the work up focuses on identifying whether the child is symptomatic, has a false positive newborn screen or is presymptomatic (Fig. 2). In addition, elevated C3 is the marker for not only PA, but also methylmalonic aciduria (acidemia) and disorders of vitamin B12 transport and biosynthesis. Consequently, these disorders must also be considered. In a symptomatic individual in whom PA is known or highly suspected, treatment should be initiated immediately, in consultation with a metabolic specialist. Treatment of patients with confirmed PA who are in the midst of metabolic decompensation follows a similar treatment protocol. Moreover many beneficial interventions can be begun prior to transport to a metabolic center.

Occasionally an individual with PA (previously diagnosed or undiagnosed) will present to acute care with findings of cardiomyopathy, pancreatitis or movement disorder instead of metabolic acidosis [8,9,10,11] and so consideration of PA as a possibility and recognition of this presentation in the absence of metabolic acidosis is important for appropriate therapy.

2. Recommendations for acute management

The complete recommendations for acute management are listed in Fig. 1. The following sections provide a discussion for each section of the recommendations. They are divided into initial care and stabilization of a sick patient with known or suspected PA which can be done at a metabolic center or a non-metabolic center, recommendations for transport of a sick PA patient, acute aggressive interventions offered at a metabolic center, recommendations for de-acceleration of care and preparation for discharge. Section 3 focuses on special issues during episodes of increased metabolic demand (e.g. menses, illness, fever) in known patients.

2.1. Discussion of recommendations for initial care and interventions in a symptomatic known or suspected PA patient (these steps can occur at or prior to transfer to a metabolic center)

2.1.1. Stabilization, if critically ill

The following recommendation section focuses on stabilization of the patient according to basic life support or ABC (or now CAB) guidelines [12,13] and with obtaining vital signs as with any critically ill patient. Not all patients will require all the following steps.

1. Intubate and ventilate, if necessary and if respiratory fatigue is developing.
2. Place intravenous lines. Do not use right intrajugular or one of the two femoral sites (these will be needed for large bore dialysis or central catheters), if necessary. An intraosseus and nasogastric tube are preferred, if unable to access other venous sites, selection of which alternative should be done according to clinician judgment.
3. Add vasopressors to maintain blood pressure, as necessary.
4. Normal saline fluid bolus can be given if necessary (but if hemodynamically stable, reversal of catabolism as outlined below in Section 2.1.2 is preferred). Avoid over hydration and do not delay reversal of catabolism in order to give a normal saline bolus.
5. Draw laboratory studies outlined in Table 2; do not discard any blood left over after running the testing. (In some cases, if the presenting institution cannot run the recommended labs, transfer the previously drawn date and time labeled blood samples with the patient).

Intravenous access is an important element of this initial therapy (step 2). However, from the committee's experience, there are several cases in which all easily accessible sites for hemodialysis or extracorporeal membrane oxygenation (ECMO) were compromised at the time of presentation and when these more aggressive therapies were attempted to be initiated there was a significant delay. As a result, we are recommending using intraosseus access prior to use of the right intrajugular or one of the two femoral veins.

While there is no evidence that fluid boluses increase cerebral edema, but caution must be used since over-hydration and fluid overload can delay recovery due to second and third spacings. Moreover, the mainstay in therapy for PA is reversal of catabolism which is discussed in the next section.

2.1.2. Reversal of catabolism

Catabolism in PA increases metabolic toxins and stress making reversal of catabolism an essential step to reverse metabolic decompensation [3]. The next set of recommendations focus on reversal of catabolism, which should be initiated as soon as possible. Moreover, this process in many cases can correct acidosis without the addition of buffers.

1. STOP all sources of protein (enteral and parenteral nutrition) temporarily (see nutritional management).
2. Give non-protein calories in the form of intravenous fluids (10% dextrose, or higher if appropriate, with electrolytes) at 120–150 mL/kg/day, 1.5 times maintenance, or a goal of 6–8 mg glucose/kg/min. If intralipids are available, they may be started as needed at 3 g/kg/day to provide additional calories. DO NOT STOP calorie delivery in the acute stage for any reason (e.g. medications, addition required fluid bolus, or hyperglycemia) as this can precipitate hypoglycemia and catabolism which will further worsen the patient's condition.

Reversal of catabolism is the mainstay of most interventions in an acutely ill individual with PA [3]. This corrects acidosis more effectively than buffers; however sometimes hemofiltration is required (discussed in Section 2.3.2 item 4). The goal of 6–8 mg of dextrose/kg/min is based on the amount of glucose required to reverse catabolism in children with glycogen storage disease 1A [14] and it is unclear whether this is adequate for PA. Fluid recommendations are standard for age. Using a 10% dextrose solution at 120–150 mL/kg/day (or 1.5 times maintenance) often can provide this level of glucose delivery [1, 15, 16]. Many individuals who are critically ill will require higher calories which can be delivered by increased dextrose concentrations or by intralipids, requiring

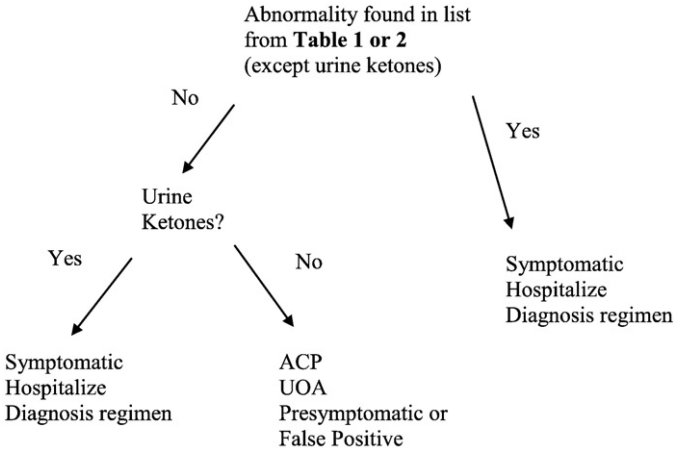

Fig. 2. Quick diagnostic pathway for propionic acidemia used to evaluate a sick neonate or a neonate with an elevated propionylcarnitine (C3) on newborn screening.

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more centrally placed lines. Studies are ongoing to better determine the metabolic needs in patients with PA.

Patients with the related disorder methylmalonic acidemia are known to have a mildly lower resting metabolic energy expenditure (REE) than age matched controls [17]. Moreover, REE increases with increased metabolic demand, though how this would apply to PA is unknown [18].

Once the reversal-of-catabolism interventions begin, vital signs, urine ketones, ammonia, and venous or arterial blood gases are used to follow progression. Urine ketones should be checked with every void. Vital signs and blood gases should be analyzed as per institutional procedure for a critically ill child. If the patient is not at a metabolic center, repeat ammonia, comprehensive metabolic panel, glucose and venous or arterial blood gas 30–60 min prior to arrival of transport team so that results are available upon transport. As catabolism reverses, laboratory results can look worse due to a wash out effect so contact with metabolic specialists is helpful.

2.1.3. Other interventions to be done at the presenting institution

1. Start antibiotics (after blood cultures are drawn).
2. If neonate and newborn screen results are not known, call newborn screening laboratory to check for results or expedite their processing (normal results do not rule out metabolic disease).
3. Arrange transport to a metabolic center as soon as there are concerns for metabolic disease or decompensation (since there is a risk of swift life threatening complications which will require aggressive therapies and laboratories that are only available at such an institution).

Most neonates who have PA or similar disorders and are symptomatic have features also seen in individuals with sepsis. This may not be the case if presenting with a positive newborn screen with elevated propionylcarnitine (C3). Estimates of bacterial causes for decompensation and sepsis at presentation in PA patients are as high as 85% [19,20,21,22] and so antibiotics are recommended for any decompensated individual with known or suspected PA, pending results from diagnostic evaluation for infection.

2.2. Transport to a metabolic center and transport teams

Every medical institution (hospital or clinic) should have identified and recognized a metabolic center to which a patient may be transferred if it is not a metabolic center itself. Every metabolic center should have a reliable and prepared transport service which can transport critically ill or metabolically unstable patients to their institution.

Transport teams who transport metabolic patients should always carry the intravenous form of sodium benzoate/sodium phenylacetate (Ammunol®), 10% dextrose with 77 mEq/L sodium chloride intravenous fluids, insulin (to create insulin drips), and N-carbamylglutamate (Carbaglu®) (if available) in addition to their usual medications, to any possible metabolic transport [23,24].

2.3. Acceleration of care in a severely decompensated patient with known or suspected PA (only in a metabolic center)

2.3.1. Metabolic center requirements

A metabolic center should have a recognized team which treats and evaluates infants (and children) presenting with findings concerning metabolic disease or with metabolic decompensation in known patients with inborn errors. The metabolic physician should be the primary decision maker in terms of interventions, in conjunction with critical care attending physicians, once a metabolic disease diagnosis is probable or known. This team must also include critical care nursing, metabolic dietitians, biochemical and chemistry laboratory staff, pharmacy, renal physicians and dialysis staff, surgeons and extracorpeal membrane oxygenation (ECMO) staff.

2.3.2. Acceleration of care at a metabolic center

Not all patients with PA who are ill will require accelerated care. Some will stabilize with reversal of catabolism alone. Most symptomatic infants will require some level of accelerated care. Clinical judgment is useful at this stage.

1. Laboratory: Repeat laboratories in Table 2 upon arrival stat since management decisions will be based on these laboratories. Also collect confirmatory laboratories (acylcarnitine profile, urine organic acids, and plasma amino acids) if they have not been collected previously and are not available for immediate analysis and resulting.
2. Continue reversal of catabolism with at least 10% dextrose containing fluids and possibly intralipids to aim for maximum energy intake for age and weight that previously started.
3. Consider starting an insulin drip (0.01 units/kg/h). Increase dextrose amount if hypoglycemic at this dose, *do not* decrease dextrose delivery rate or amount.
4. Arrange for and consider initiation of hemodialysis, hemofiltration of extracorpeal membrane oxygenation driven filtration (ECMO). This is particularly important in patients with ammonia >300 μmol/L, extreme acidosis/electrolyte imbalance, coma, dilated pupils, poor neurological findings, deterioration, failure to improve, or increased respiratory rate. Do not use peritoneal dialysis. Continue this intervention for at least 24 h and then as clinical findings dictate. This may be stopped when acidosis is corrected, ammonia is less than 200 mcmol/L, and a small amount of protein has been reintroduced and tolerated. Leave the catheters in place for at least 24 h (and avoid using them for IVF and medications as this can render them unusable for dialysis) in case re-initiation is necessary.
5. In an undiagnosed patient, if hyperammonia is present, consideration may be given to starting sodium benzoate/sodium phenylacetate (at same doses as urea cycle defects) and/or N-carbamylglutate (dosing in Table 3). This intervention can be started during transport to a metabolic center. Sodium benzoate/sodium phenylacetate can be stopped once the diagnosis of PA has been made. In known patients, N-carbamylglutate may be started for hyperammonia for treatment or as a bridge to hemodialysis during transport or while awaiting initiation of hemodialysis.
6. Intravenous carnitine boluses 100 mg/kg/dose 3–4 times daily (300–400 mg/kg/day) should be given. Urine output should be appropriate prior to dosing (or hemofiltration be ongoing).
7. Ammonia, electrolyte and blood gases need to be followed at regular intervals during this acceleration of management stage. The frequency is dictated by the patient's condition and the speed at which results can be obtained.
8. Protein should be reintroduced as early as possible, preferably within 24–36 h of initiation of therapy (some will require sooner if protein deficiency is cause of decompensation). Protein must be reintroduced even if patient on hemodialysis or ECMO. An early task in management is the placement of a nasogastric or nasojejunal tube in anticipation of this.
9. Consider sedation, ventilation, and chemical paralysis if aggressive management is necessary. If available, continuous EEG is helpful to monitor progress. If available some of the newer modalities for measuring central nervous system oxygen consumption or metabolism are appropriate.
10. Packed red blood cell transfuse as necessary based on age, clinical condition, frequent blood sampling, and physician discretion.

Continuation of reversal of catabolism with calories [14] throughout the acceleration phase is necessary since it is important to decrease the source of excess toxic intermediates from cannibalism of tissues. In some cases more aggressive removal of toxins will be required and

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Table 3
Nitrogen scavenger medications for hyperammonemia and their doses used in Urea Cycle defects and initially in propionic acidemia.

Medication	Carbaglu	Sodium phenylacetate and sodium benzoate[a]	Sodium phenylacetate	Sodium benzoate
0 to 20 kg	100 mg/kg divided every 6 h	2.5 mL/kg (before dilution)	250 mg/kg Loading[b] Maintenance[c]	250 mg/kg Loading[b] Maintenance[c]
> 20 kg	2.2 g/m^2 divided every 6 h	55 mL/m^2 (before dilution)	5.5 g/m^2 Loading[b] Maintenance[c]	5.5 g/m^2 Loading[b] Maintenance[c]

[a] Sodium phenylacetate/Sodium Benzoate must be diluted with sterile dextrose injection 10% before administration.
[b] Over 90 to 120 min.
[c] Over 24 h.

hemofiltration is useful for this intervention. The physician should balance the risk of delays in hemofiltration versus its inherent risks carefully. Time becomes an important factor and significant delay in toxin removal will adversely impact outcome. Given the near certainty of neurological damage from extensive exposure to metabolic toxins in the acutely ill patient a heavier weight should be given to early hemofiltration.

In addition to the typical laboratories, often a prealbumin and albumin are useful to determine dietary protein state and will be helpful for dietary management decisions.

Insulin drip to drive calories into the cell and reverse catabolism has been used in patients with Maple Syrup Urine Disease [25, 26]. With PA, one-tenth the dose of insulin in diabetic ketoacidosis is used [27]. Even with this precaution, care must be given to the maintenance of blood glucose levels and increased calories in the form of dextrose, may be necessary to maintain blood glucose levels in the normal range. Do not decrease insulin drip rate if hypoglycemic, increase dextrose delivery instead until reversal of catabolism is obtained, then wean insulin as usual. For older previously diagnosed patients, ruling out insulin resistant diabetes is helpful.

Many patients in a severe metabolic crisis not only present with metabolic ketoacidosis, but also with hyperammonemia. Ammonia can reach extremely high levels, approaching those found in individuals with urea cycle defects. The increased ammonia seen in PA is often attributed to a secondary urea cycle defect in which propionic acid or its metabolites are hypothesized to inhibit N-acetylglutamate synthetase or carbamoyl phosphate synthase I activity (the first step in the urea cycle) [28]. Elevated ammonia levels parallel levels of propionic acid and are a good indicator of metabolic decompensation [29], although there are some individuals with PA who have elevated ammonia levels even in the “well” state.

Some very ill individuals with PA require hemodialysis, hemofiltration, or ECMO to remove acid load and/or ammonia. In some acutely ill infants, the diagnosis may not be clear at presentation and they can also benefit from hemofiltration. Rate of hemofiltration is important for prompt removal of toxins [30]. Data from urea cycle disorders indicate that it is not only the level of hyperammonemia, but more importantly the length of time the ammonia is elevated that dictates outcomes. Thus swift and aggressive treatment of hyperammonemia (and acidosis) is important. Peritoneal dialysis is not recommended based on low filtration rates, delays in gut access, and infection risk. Propionic acid and other organic acids are dialyzable and with ammonia the removal is mainly dependent on the flow rate of the dialysis system. Pre-planning with the dialysis team to maximize flow rates and clearance is an important task for any metabolic center.

Some individuals require re-institution of dialysis, thus we recommend not removing or using dialysis catheters for at least 24 h after initial completion of hemofiltration or ECMO so that the catheters may be reused, if necessary. Many patients are transitioned to hemofiltration from hemodialysis to provide ongoing toxin removal (albeit at a slower rate) and hemofiltration is used in milder patients in whom the hemodynamic stability risks of hemodialysis outweigh the benefit of a high flow system.

In the acute phase of a not yet diagnosed metabolic patient with hyperammonemia, urea cycle disorders are a possibility. In these cases it is useful to start the nitrogen scavengers, intravenous sodium benzoate/sodium phenylacetate (Ammunol®) or oral N-carbamylglutamate (Carbaglu®) in transport and continue as part of initial management. However, there are theoretical concerns about the usage of sodium benzoate and sodium phenylbutyrate in PA. Sodium benzoate can isolate CoA moieties [31] preventing their availability. Low glutamate and glutamine levels are typically found in hyperammonemia due to PA, related to a number of biochemical abnormalities, including oxaloacteate depletion, functional deficiency of α-ketoglutarate and decreased N-acetylglutamate synthesis [32]. Sodium phenylbutyrate may exacerbate these abnormalities by causing further glutamine depletion. For these reasons, nitrogen scavengers (especially phenylbutyrate) should be stopped once a diagnosis of PA is made in a patient with acute hyperammonemia; hemodialysis/filtration and N-carbamylglutamate are the treatments of choice. Another consideration in compromised urea cycle function is the availability of citrulline and arginine. Monitoring of plasma amino acids should indicate if supplementation is needed. If so then doses similar to urea cycle management should be used acutely (250 mg/kg/day).

Carnitine conjugates with propionic acid which improves its disposal and promotes transfer out of the mitochondrial so it can be excreted in the urine. Individuals with PA are at increased risk of secondary deficiencies of carnitine and so carnitine can be used to scavenge propionyl groups as well as replace if deficient [33,34,35,36,37]. Initial studies of carnitine in PA dosed it as an intermittent oral dose and continuous dosing [38]. We are recommending bolus intravenous dosing [36]. In part, we recommend this approach in the absence of evidence of superiority of one approach versus another. In addition, bolus dosing allows for other intravenous interventions in an individual with limited intravenous access. Bolus intravenous dosing versus continuous intravenous dosing in an acutely ill individual with PA should be an area of future studies.

Anecdotal evidence of worsening acidosis in the presence of increased carnitine delivery is present. In theory this would be due to release (so called washout) of new propionyl carnitine groups from the muscle where the propionic acid could be sequestered. However, delivery of carnitine to the kidneys and liver following carnitine supplementation is much faster than that to the muscle. This concern of worsening acidosis due to increased propionylcarnitine dumping from the muscles is unlikely to cause whole system acidosis in light of these kinetics [39].

Ventilation, sedation, and paralyzation, as well as, pain control are useful in the first 24 h of a critically ill child's management. Unfortunately, with these interventions, the opportunity to conduct a neurological exam is lost. On the other hand, sedation and paralyzation significantly decrease baseline metabolic needs and, in theory, can help rapid reversal of catabolism. Using this idea, if a patient develops seizures, consider placing him/her in a pentobarbital coma with 24 hour EEG monitoring. Therapeutic coma in the presence of seizures decreases metabolic demand and assists in stabilizing the metabolic state of a severely catabolic individual. Also because of loss of neurological exam, if a patient is sedated and paralyzed, start 24 hour EEG for monitoring (if available). Most metabolically unstable patients have a slowing of normal wave forms and metabolic improvement often correlates with improvement of sleep-wake forms on EEG. In addition, seizures increase central nervous system metabolism placing the brain at further risk for cellular death or damage.

Protein should be reintroduced within 24–36 h of initiation of therapy to prevent worsening catabolism from protein deficiency. This should begin with essential amino acids which can be provided as a sole supplement enterally or as a component of TPN/PPN. Use of a propionic acidemia formula with reduced isoleucine, methionine, threonine, valine and odd chain fatty acids enterally allows a more

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aggressive restitution of essential amino acids and nutrients and should be considered in initial therapy. This protein should fulfill at least the essential amino acid requirements [40] and be based (if available) on quantitative amino acid levels, aiming to promote metabolic stability. Nutrition support may be delivered by TPN/PPN or enterally (through nasogastric or nasojejunal tube) even when on other management and dialysis [41–44]. This aggressive approach to use the gut is often counter to most intensive care unit policies but the critical role in the reduction of catabolism and prevention of production of metabolic toxins warrants this exception. Introduction of protein should not decrease calorie delivery but enhance it. Since for the most part these are term infants or known patients who tolerated full feeds, there is no need to slowly increase volume delivery, instead start at full volumes as tolerated and as long as acute pancreatitis has been ruled out.

Due to endogenous and exogenous causes many patients with PA will become anemic. Some children will require blood transfusions. In addition, maintenance of blood pressure can be a challenge in an acutely ill individual with PA from many causes (i.e. infection, metabolic acidosis, etc.) and vasopressors in this phase of therapy is useful.

There are no recommendations for an acute gut cleanout to remove propionic acid producing bacteria (source of about 30% of body propionic acid) since neonates are not yet significantly colonized and a majority of known patients are on a "gut" regimen to decrease bacterial produced propionic acid (Please see Discharge Planning 2.4 item 4 and the Chronic Health Monitoring paper for greater details about these approaches for older previously diagnosed patients) [45, 46].

2.4. Transition from acute to chronic management: discharge planning

Upon metabolic stabilization, patients require transition and deceleration of the therapies to those that can be continued as a home regimen.

1. Establishment of home metabolic nutrition support regimen
2. Gastrostomy tube (G-tube) or nasogastric tube (NG tube) placement for enteral feeding and medication administration
3. Carnitine transitioned to oral medication (recommend 200 mg/kg per dose twice daily), taking amount of carnitine from metabolic formula into account.
4. Instructions for a "gut flora control" regimen and prevention of constipation
5. Screening studies including echocardiogram, electrocardiogram (EKG), hearing screen, optic fields (if cerebral edema), dilated ophthalmologic exam,
6. Involvement of physical therapy and occupational therapy (as soon as possible) and referral to early intervention (in the neonates)
7. Parental training needed prior to discharge (Table 4).

Table 4 includes recommended discharge instructions and is designed specifically for the newly diagnosed PA patient, but can be modified for a known inborn error patient according to their needs.

One of the long term major challenges in PA is nutritional support. Medical nutrition therapy (MNT) is individualized according to differences in needs at different life stages and situations, as well as in different individuals [15]. Individual recipes with combinations of complete (natural) protein and incomplete (synthetic) protein are used in order to limit nutritional precursors to the endogenous production of toxic metabolites. MNT goals for patients are calculated and adjusted based on individual response to the limitation of offending amino acids (isoleucine, valine, methionine, and threonine); while still meeting daily age appropriate goals to support growth and development in children and health maintenance in adults. For discharge, every patient should be transitioned to a realistic metabolic home feeding regimen and schedule. This is done under the direction of a dietitian with special training in metabolic disorders. More detailed recommendations are provided in the subsequent consensus document focused on the chronic management of individuals with PA.

Table 4
List of discharge instructions for a patient newly diagnosed with PA.

Referral to early intervention
Parental training
Preparation of metabolic formula with their home gram scale
G-tube or Nasogastric care
Lessons in giving all medications
1 week supply of all medications
Prescriptions for all these medications and ketosticks (give 2 days prior to discharge so filled by discharge)
List of medications with dosages, times, and reasons for use
Emergency room letter
Several cans of metabolic formula
Paper and electronic copy of diet (list of feeding times)
Emergency contact information for the metabolic physician and clinic
Follow-up appointment time and date in metabolic clinic

Many children with PA are poor oral feeders. They should have a G-tube placed or parental education for nasogastric placement prior to discharge from their initial presentation. G-tubes are useful in home management of a PA patient when ill. In addition, G-tubes can be used to meet daily metabolic nutrition therapy goals when a patient is anorexic as is often seen in patients with PA [47, 48, 37]. They are also useful in the administration of medications which are often unpalatable.

In addition, many patients with PA have gastroesophageal reflux (GERD) and should be aggressively treated with medications to prevent significant vomiting or feeding intolerance that could compromise their metabolic states. GERD in an individual with PA can trigger cyclic vomiting resulting in worsening metabolic control. Equally important is identification that "gagging" or vomiting can be an indication of poor control and metabolic decompensation [49,20].

Approximately 20–30% of whole body propionic acid is derived from gut flora. Control of this flora is an important element of long term therapy. We recommend that most patients be placed on a cyclic bowel "cleanout" regimen with metronidazole [46, 45] in which an individual takes one week of metronidazole at 10–20 mg/kg per day and then has 3 weeks off. Gut therapy is initiated at discharge from the hospital.

Patients and their parents need to be instructed to avoid constipation [50] and should be treated aggressively (at home and throughout a hospital stay). The consensus panel did not typically treat individuals with PA with medications to increase gut motility. However, a study using Senokot indicates that increased motility does improve propionic acid levels [50]. Concerns about the common motility drugs' extrapyramidal side effects, in a group of patients who are known to have extrapyramidal complications were felt to outweigh the benefits if patients could maintain regular bowel movements by other means.

Screening exams prior to discharge include echocardiogram (ECHO), electrocardiography (EKG), hearing screen, ophthalmologic exam, and a full neurology exam. Cardiac complications in PA including cardiomyopathy and arrhythmias should be identified by ECHO and EKG prior to discharge. Hearing screens in neonates are important to identify any hearing loss (especially if neurological symptoms, seizures, or treated with antibiotics). Ophthalmology examination helps identify optic field defects or retinal injury that can occasionally be seen in PA.

Neuroimaging has an important role in the evaluation and monitoring of PA patients. There is ample evidence to suggest that PA is associated with basal ganglia injury, white matter injury and cortical atrophy. Magnetic resonance imaging of the brain may reveal abnormal, mixed signal intensity and restricted diffusion in the bilateral basal ganglia, including the globus pallidus, putamen, and head of the caudate nucleus, and diffuse cortical edema. Studies with 1H Magnetic resonance spectroscopy (MRS) may show elevations of lactate.

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While the early changes may lag radiographically, an MRI after clinical stabilization may be useful for assessment of injury and prognosis. A follow up MRI several months later will help determine permanent changes and further advise prognosis and burden of injury. Newer modalities such as diffusion tensor imaging (DTI) and MRS can identify alterations prior to changes on T1/T2 weighted images and, if available, may be helpful in this regard.

On both computed tomography and magnetic resonance imaging, PA may manifest as diffuse cerebral edema, atrophic changes, and bilateral basal ganglia involvement.

In the first few months of life, nonspecific white-matter changes may be seen, but may resolve on follow up imaging. These transient basal ganglia changes tend to improve with treatment and may prove useful as a monitor for response to therapy. If there is deterioration in mental status or concern for cerebral ischemia emergent imaging may be useful. Use of these modalities must be balanced against the risk of sedation to obtain them.

Table 4 provides a list of discharge instructions for the caregivers of new patients with PA, but it can be modified to fit the needs of known patients with PA. Prior to discharge, patients (depending on their age and intellectual ability) and/or their caregivers should be able to: briefly describe the disorder to relatives, friends, and health care providers, be comfortable with preparation of metabolic formula, be able to track oral intake of protein in foods (for those able to eat solids), be able to follow and administer the timing of feeds and medications, gastronomy (G-tube) or nasogastric tube (NG) care (if applicable), medications (and their timing), as well as know the emergency metabolic clinic contacts and reasons to call or come to the emergency room prior to discharge. Because metabolic formula and medications are not always on local pharmacy's formularies, a supply of medications and formulas as well as prescriptions should be available at least 2 days prior to discharge for new patients or new medications and formulas.

To prevent problems, assurance that the metabolic formula has already arrived or will arrive on the day of discharge at the newly diagnosed patient's home is important. In addition, extra supplies needed to feed should be available. Prior authorization letters of medical necessity for new or changes to prescriptions for metabolic formulas and medications should be submitted for review by the patients' health insurance company as soon as possible. All patients need an updated emergency letter, written metabolic formula recipe and list of medications dosages and times at discharge.

3. Additional acute issues in known PA patients

Stabilization of a known patient with PA who has a metabolic decompensation is similar to that of a new patient. Clinical decision making and aggression of therapy is based on clinical conditions and age should not be a detriment to aggressive therapy. This section focuses on specific issues in individuals with PA prior to their presentation to medical care (the emergency room or other acute care setting).

3.1. Reasons to contact the metabolic specialist

Patients with PA have episodes of increased metabolic demand due to illness, increase psychological stressors, menses, increased physical activity, etc., and many of these episodes can be managed at home with a home or activity specific regimen. However, sometimes admission to the hospital is necessary. The specifics of home regimen are very much dependent on the brittleness of the patient's metabolic state, as well as caregivers and patient's ability and comfort with interventions at home.

Patients and parents of individuals with PA should maintain open communication with their metabolic team and reasons to speak to the team include (but are not limited to):

1. Illness
2. Fever
3. Vomiting (and dehydration)
4. Change in mental status
5. Immunizations
6. Parental concerns
7. Procedures and interventions
8. Other specialists' (or other physicians') recommendations for change in diet
9. Any proposed new medication
10. Any symptom listed on Table 1
11. Change in normal physical activity regimen (e.g. increase or change in exercise levels)
12. Initiation and continuation of menses (in females)
13. Changes in medication administration or feeding schedule due to factors such as traveling away from home

Vomiting, fever, poor or change in oral/enteral intake, dehydration, seizures, or parental concerns are all reasons to instruct patients and their parents to discuss their condition with a metabolic specialist in real time due to the possibility of worsening and increased metabolic demands.

Metabolism specialists (including metabolic dietitians) should be the only individuals to change diet, or recommend intravenous fluid types and amounts. Moreover, patients or their parents should contact their metabolism specialists prior to any planned procedure or diagnostic testing (e.g. MRI) because pre-procedure interventions may be required to prevent catabolism. Basically if in doubt or if a question, instruct patients with PA to contact their metabolic specialists (by their previously established preferred manner).

Immunizations are encouraged in this population and are safe, but prophylactic use of fever control is recommended. Fevers are treated prophyllactically with acetaminophen (ibuprofen contains propionate). There are no data that immunizations and their increased risk of fevers increase hospitalizations in patients with other intoxication type inborn errors [51, 52]. As a result, we recommend every PA patient and their siblings receive the typical childhood immunization schedule. In addition, to prevent hospitalizations and increased metabolic demands from a preventable illness, we recommend that all patients, their caregivers and household members receive the inactivated influenza vaccine annually.

Certain medications are always contraindicated in a patient with PA. These include, mannitol, 5-pentanoic acid, and lactated ringers, and usually include, except under very special individualized circumstances, systemic steroids and valproic acid. If one of these medications is considered, discussion with metabolism specialists is essential to prevent an increased acid load, an increased propionic acid load or increased protein catabolism.

3.2. Times and interventions for increased metabolic demand

Patients with PA will have episodes of increased metabolic demand due to illness and changes in everyday activities (such as increased activity or exercise), particularly those who do not eat orally and rely solely on metabolic formulas to meet their nutritional needs.

The following are interventions to be done at times of increased metabolic demand. (One and two should be done prior to calling the metabolic specialist since they are useful for decision making):

1. Check ketones
2. Capillary refill
3. Ondansetron for vomiting (if known responsive)
4. Prescribed home increased metabolism diet (H-IMD)

Most metabolic centers use urine ketosticks to determine clinical metabolic state at home. Ketones are never elevated in healthy infants. Trace and small ketones are not unusual in children. Moderate to large ketones usually require intervention and often hospitalization.

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Caregivers, patients, and their families should be reminded that ketosticks have expiration dates. Always check the expiration date before using these. Capillary refill times can be taught to anyone and can be useful to evaluating a sick patient over the phone. Many caregivers find home doses of ondansetron useful to treat nausea at home. This medication can prevent hospitalizations in older children improving feeding tolerance, but should only be used under the supervision of and after notification of their metabolic specialist.

3.3. Increased metabolic demand diet (more details will be available in the chronic care and health monitoring section)

Most patients with PA are on a protein restricted diet in which propionic acid precursors are limited [41]. Dietary alterations during times of increased metabolic demand (especially when associated with illness) are varied among institutions and can be called a "sick day diet". Some institutions use a graduated elimination of complete (natural) protein at home, others use a no protein diet only in the hospital. In addition, some limit all natural protein sources, and some just increase calories and fluid amounts for home therapy. Due to confusion on definition, "sick day diet" is not a term that should be used with specific definition—instead we will use the term "increased metabolism diet" (IMD).

Our recommendations for IMD is that it does not restrict amino acids in any way, rather it should focus on increased fluid volume and calories and be individualized for existing co-morbidities in older patients. In some cases if natural protein intake is down, there may be need to increase amino acid delivery in a patient's metabolic enteral feeding. There is no evidence that patients are admitted due to too much protein intake except in very rare cases which are often related to dietary indiscretion instead of increased metabolic demand [19,21]. Patients and their families need to be instructed that they always need to speak to their metabolic specialists (including their metabolic dietitian) before using an IMD at home for specific instructions and follow-up.

The ideal regimen for sickness or increased metabolic demand for another reason (e.g. times of increased activity, menses, etc.) in terms of number of required calories to prevent or treat catabolism is unclear for patients with PA [17, 53]. However, evidence is consistent that increased metabolic demand requires an increase in calorie delivery and ongoing adjustments to protein goals. The minimal amount of calories needed to reverse catabolism is probably different in different individuals, however, a general idea of the needed calories in a patient with PA is an area in need of study.

4. Conclusions

Patients with PA can decompensate during periods of increased metabolic demand. Infants prior to diagnosis can also present in severe metabolic decompensation. Aggressive identification and initiation of therapy are necessary to prevent severe morbidity and mortality. Therefore, reversal of catabolism and removal of toxic compounds are lifesaving measures. Using a similar therapeutic approach across multiple institutions will standardize and allow identification of beneficial interventions initially described in other metabolic diseases and focus the testing of new interventions and therapies, and guide future research. This list of recommendations for acute management in PA patients moves toward the goal of standardization of therapies and allows for clinical studies to improve management by providing a standard of treatment from which all institutions can start to individualize metabolic management.

Acknowledgments

Special thanks to Dr. Brendan Lanpher for his critical review and editing of this manuscript. This publication arises from the project 'E-IMD 2010 12 01' which has received funding from the European Union, in the framework of the Health Programme.

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Please cite this article as: K.A. Chapman, et al., Acute management of propionic acidemia, Mol. Genet. Metab. (2011), doi:10.1016/j.ymgme.2011.09.026