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Chronic management and health supervision of individuals with propionic acidemia

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ABSTRACT

Propionic acidemia is a relatively rare inborn error of metabolism. Individuals with propionic acidemia often have life-threatening episodes of hyperammonemia and metabolic acidosis, as well as intellectual disability. There are many reports of additional problems, including poor growth, stroke-like episodes of the basal ganglia, seizures, cardiomyopathy, long QTc syndrome, immune defects, pancreatitis and optic neuropathy; however, there is little information about the incidence of these problems in this rare disease. Additionally, there are no clear guidelines for medical or surgical management of individuals with propionic acidemia. Through a comprehensive and systematic review of the current medical literature and survey of expert opinion, we have developed practice guidelines for the chronic management of individuals with propionic acidemia, including dietary therapy, use of medications, laboratory monitoring, chronic health supervision, use of gastrostomy tubes and liver transplantation.

1. Introduction

Any clinician providing care for individuals with Propionic Acidemia (PA) understands that there are myriad subacute and chronic problems involving both somatic and neurologic systems that can develop in children and adults with this disorder. PA is relatively infrequent and, as such, even large metabolic centers may care for only a handful of individuals. There has been little in the way of collaborative efforts toward developing a better understanding about the natural history of PA. Much that we know about the problems seen throughout the lifetime of these individuals comes principally from case reports and anecdotal experience. The precious few larger studies that are available are limited by a lack of uniformity in data collection, differences in approach/treatment among centers and the retrospective nature of the studies [1,2]. Consequently, while we have a pretty good idea of what problems may occur, we do not understand much, if anything, about how often they occur and what factors may be precipitating or preventive of these chronic problems. In an effort to improve the care of individuals with PA and also improve knowledge about the natural history of this disorder, Children's National Medical Center in Washington, D.C. convened a group of healthcare providers, researchers and parents to develop practice guidelines. The recommendations contained within this document come from an exhaustive review of all published English-language articles related to chronic health problems in PA, bolstered by and filtered through expert opinion and rigorous review and honest, Socratic debate. Articles were obtained from Pubmed searches in late 2010 using a variety of terms (organic acidemia, organic aciduria, propionic acidemia, propionic aciduria, propionic acidopathy, ketotic hyperglycinemia, propionate, propionic acid, hyperglycinemia, ketotic hyperglycinemia, organic acidemia, propionic acidemia) and filtered for those pertaining to propionic acidemia; additionally, the references list from the articles retrieved through Pubmed were reviewed to identify additional, relevant publications. Details about the process of guideline development can be found in the accompanying publication in this issue. During this process participants acknowledged the countervailing tension between ensuring that no problem is overlooked and excessive monitoring for a problem that occurs only infrequently. The recommendations below are sorted by system and problem and are intended as a

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guideline that should be tailored, as appropriate, to the individual with PA.

2. Nutrition and laboratory monitoring

2.1. Laboratory correlates of nutrition

Nutrition management, in particular protein restriction, is a primary cornerstone to treatment of patients with PA. Although special metabolic formulas have been demonstrated to improve growth [3], there is little evidence to guide decisions about the diet, particularly the amount of protein provided, and no clear laboratory parameters that are associated with good metabolic control or risk of decompensation. There is some evidence that there are certain laboratory values that correlate with risk of acute decompensation or nutrition status. Serum propionic acid has been shown to correlate with blood ammonia levels [4, 5]; however serum propionic acid is not clinically available in the United States. Elevated plasma glycine levels have been demonstrated to correlate with good acid base balance [6] and glycine is also negatively correlated with caloric intake [3]. Neither protein intake nor plasma glutamine has been shown to correlate with ammonia levels (as it does in urea cycle disorders) [3, 6, 7]. Increased levels of branched-chain amino acids have been shown to correlate with hyperammonemia, and this has been interpreted as being indicative of a catabolic state [7]. Low levels of branched-chain amino acids have been reported in individuals with PA and are likely due to dietary over-restriction [8]. Additionally, urinary excretion of methylcitric acid has been demonstrated to correlate with hyperammonemia [7]; however when the elevation in methylcitric acid occurs relative to ammonia is not established. Given that accurate quantitation of urine methylcitric acid is not widely available, its utility in acute management is currently limited. With regard to serum ammonia levels, clinician and parent experience suggests that certain individuals have ammonia levels that are chronically elevated and that elevated levels can occur in the absence of clinical findings. Although there is no evidence that chronic, low-level hyperammonemia presages acute decompensation or poor metabolic control, we would advocate for regular monitoring of serum ammonia and making a decision about the relevance of elevations based upon the clinical situation, growth, amino acid profile, and diet prescription. Propionylcarnitine has not been demonstrated to correlate with severity or level of control and it is our experience that it does not.

2.2. Nutritional recommendations

Given the current lack of appropriate nutrition-based studies, recommendations for dietary prescriptions are provided based on clinical and laboratory assessment. Protein is restricted in the diet to provide limited amounts of isoleucine, methionine, threonine, valine and odd chain fatty acids and the further supplemented with a medical food to provide additional amino acids without the offending amino acids. The individual's medical food ensures they are consuming not only adequate protein but also supplies vitamins, minerals, and fats to supplement the restricted diet. Of note is the variation of different brands of formula, which should be considered in the determining of an appropriate medical food. Current guidelines are available and recommend 1.5 to 3.5 g protein/kg body weight/day, depending on the age [9, 10]. However, the distribution of natural and medical food varies based on clinical judgment. Protein should at least meet established dietary needs [11], and the amount should be individualized based upon growth velocity and laboratory results, such as plasma amino acid levels and measures of protein nutrition. When necessary, total parenteral nutrition can be used safely, provided the amount of protein provided is not excessive [12, 13].

Currently, nutritional management guidelines are being formulated by a group of metabolic dietitians and should be available by early 2012. Thus far, it has been shown that protein intake does not correlate with blood ammonia levels [3] and asserted that elevated branched-chain amino acids correlate with hyperammonemia and reflect catabolism [7]. In addition, it is our personal observation that most episodes of acute decompensation occur with acute illnesses during which protein and caloric intake is decreased and metabolic need is increased (such as intercurrent infections, see guidelines regarding nutrition during acute illnesses in the accompanying paper). We therefore assert that catabolism is the major reason for acute decompensation. In chronic dietary management, individuals with PA should be provided with a diet using a special metabolic food combined with restriction of propiogenic amino acids and odd chain fats. Experience has shown that levels of protein intake modestly above the recommended daily allowance (RDA) are well-tolerated and can provide a buffer against catabolism.

Regular monitoring of growth, along with measures of protein nutrition, such as albumin and prealbumin, are indicated to ensure the diet is providing adequate calories, basic nutrients and protein. In addition, routine monitoring of fasting plasma amino acid levels (i.e. 3–4 h after consumption of food/formula) should be done to assess the balance of protein (in the form of free amino acids) from metabolic formula and dietary protein from regular formula and/or food. In addition, it would seem that elevated levels of glycine are desirable as they are indicative of replete nutritional status [6]. Lastly medical nutrition therapy should be individualized with addition laboratory monitoring as necessary to ensure these specialized diets are providing adequate vitamins, minerals and essential fats. This process should be done by a metabolic registered dietitian.

- Recommended Nutrition Assessments at Routine Outpatient Visits (every 6 months minimally in an established patient)
  - Albumin
  - Ammonia
  - Plasma amino acids (fasting 3–4 h)
  - Prealbumin
- Optional Nutrition Assessments
  - Plasma propionylcarnitine (i.e. quantitative acylcarnitine profile)
  - Urine methylcitric acid
  - Other general measures of nutrition as needed, based upon history, dietary intake and growth, such as calcium, 25-hydroxyvitamin D, Complete Blood Count (CBC), essential fatty acids, etc.
- Diet history should be reviewed at each visit and adjustments should be made to maintain:
  - Normal growth velocity for weight (assessed at least monthly in infants, and less frequently as children get older and the normal rate of growth velocity slows)
  - Normal levels of serum albumin and prealbumin
  - Normal levels of plasma isoleucine, methionine, threonine and valine.
  - Normal to elevated levels of plasma glycine

3. Neurologic sequellae

3.1. Intellect and development

There is a wide range of IQ/developmental outcomes in individuals with PA and conflicting data regarding risk factors to predict developmental outcome. IQ has been reported to range from normal to severe-profound intellectual disability [2, 14, 15]. In one study of 20 individuals (11 early presentation and 9 late presentation), all early-presenters had IQ<60 and many late-presenters had normal IQ [14]; however, another study of 17 individuals (12 early presentation and 5 late presentation), some early-presenters had normal motor development and the late-presenters are reported to have more neuromotor and psychiatric problems [15]. This latter study is limited by a lack of IQ/DQ scores or other objective measures in the publication. A study of six individuals found that all had hypotonia and mild-moderate intellectual disability [16]. It has been asserted that early motor repertoire may

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directly correlate with neurological outcome [17]. There is limited information on which factors – such as acute decompensation, ammonia levels, diet, etc. – are important for neurological outcome. Based upon this limited information, it seems that individuals with PA have the potential for relatively normal IQ and intellectual outcome which emphasizes the need for concerted efforts to ensure adequate nutrition, minimize the risk of acute decompensation, treat episodes of acute decompensation quickly and aggressively [Chapman et al. in this issue] and provide early therapy services to improve early neuromotor function.

- Measures to Maximize Intellectual-Developmental Outcome
  - Early initiation of physical, occupational and speech therapy services, to continue throughout childhood
  - Optimize nutrition
  - Avoid acute metabolic decompensation
  - Treat episodes of metabolic decompensation swiftly and aggressively

3.2. Basal ganglia stroke-like episodes

Stroke-like or metabolic infarctions of the basal ganglia are known to occur in individuals with PA but the frequency and incidence has not been established [1]. These stroke-like episodes of the basal ganglia may manifest as extra-pyramidal movement disorders, hemiplegia, altered mental status and death [18]. The episodes do not appear to be caused by thrombi or hemorrhage. Some series have reported no resultant focal neurologic deficits [16], while others report that it can occur frequently and is seen in both early-onset and late-onset presentation [14, 2]. While these episodes may occur in conjunction with acute metabolic decompensations, they may also occur independently of biochemical evidence of generalized metabolic decompensations [19, 20]. The preponderance of evidence does support the clinical importance of stroke like episodes. There are no factors that have been definitively established as precipitating or preventing these stroke-like episodes. Measures should be taken to ensure that inability to feed or protect the airway during a stroke-like episode does not result in an acute, generalized metabolic decompensation or other problems.

- Management of stroke-like episodes
  - Ensure adequate fluid and caloric intake during the episode
  - Symptomatic treatment of focal neurological deficits and altered mental status (supportive care primarily)

3.3. Cerebellar hemorrhage

There are a handful of cases of neonatal cerebellar hemorrhage reported, but all infants had been hemodynamically unstable and this has not been reported in older children. This complication is most likely related to treatment complications or hemodynamic instability secondary to hyperammonemia or acidosis and not a direct consequence of abnormal propionate metabolism [21, 22].

3.4. Seizures

Seizures appear to occur in about half of individuals with PA [2, 23]. In one series, 9/15 children had pathologic EEG epileptiform discharges. The epileptiform electrical activity sometimes preceded clinical seizures; however, all 9 eventually developed seizures. The most common type of seizure was generalized tonic–clonic but absence and myoclonic were also observed. The development of seizures did not correlate with early-onset vs. late-onset disease, episodes of decompensation or neurological outcome [23]. Given the high incidence of seizures and that abnormal EEG seems to be a good predictor of the ultimate development of seizures, periodic EEG studies may be warranted.

- Evaluation for seizures
  - EEG at diagnosis and then yearly
  - Referral to child neurology if epileptiform activity detected

3.5. Magnetic resonance imaging and spectroscopy (MRI/MRS) abnormalities

Imaging abnormalities are commonly found and include progressive basal ganglia changes, cerebral volume loss and signal abnormalities in the caudate and putamen [24, 25]. Four of five children (who were well at the time of the study) had elevated lactate peaks on MRS [26]. At this time however, routine screening MRI/MRS in the absence of changes in neurological behavior is probably not necessary as they are not known to correlate with outcome, prognosis or therapeutic management. Future refinements in MRS may provide useful biomarkers of disease that can be used in management.

4. Cardiac sequellae

4.1. Cardiomyopathy

The occurrence of cardiomyopathy appears frequently, in about one-quarter to one-third of patients. In one study, 6/19 had "features of cardiomyopathy" (although convincing echocardiographic or pathologic evidence was presented for only 5/19). One of the five had spontaneous resolution of the cardiomyopathy. Cardiomyopathy did not seem to respond to carnitine supplementation [27]. A more recent study found dilated cardiomyopathy in 6/26 cases; two of these resolved after orthotopic liver transplant [28]. Both hypertrophic [29] and dilated forms of cardiomyopathy have been reported [28, 30]. Presentation has been reported from 10 months of age to adulthood and is typically *not* associated with acute, generalized metabolic decompensation. Symptoms may include shortness of breath or emesis and many are tachycardiac at presentation. Rapid progression to ventricular fibrillation or other uncontrollable cardiac rhythm can occur and result in death [29, 30]. A single case was found to have very low levels of cardiac muscle carnitine, despite having had normal levels of plasma carnitine [29]. Proposed etiologies for cardiomyopathy include muscle carnitine depletion and abnormal oxidative phosphorylation; however, convincing evidence regarding the cause does not exist at this time. Given the high incidence and life-threatening nature of the cardiomyopathy in PA, echocardiography should be monitored regularly in individuals and shortness of breath, tachycardia or symptoms of cardiomyopathy should prompt echocardiographic evaluation.

- Evaluation for cardiomyopathy
  - Echocardiogram at presentation and yearly afterwards to evaluate for cardiomyopathy
  - Echocardiogram as needed to evaluate shortness of breath, tachycardia or other signs and symptoms of cardiac failure

4.2. Long QTc

In a longitudinal, prospective study of 10 individuals with PA, 70% were found to have prolonged QTc (QTc >440 ms). This was observed in young children as well as adolescents and adults, but was not seen in infants. Rhythm disturbances were found on 24-hour Holter monitoring in 20%. Biochemical correlates were not established but hypotheses regarding the etiology of these cardiac conduction defects included cardiac muscle carnitine deficiency, toxic substrates and impaired oxidative phosphorylation [31]. The frequency of severe morbidity from arrhythmias is not well established although possible deaths have been reported [31]. There is a case report of a teenager presenting with syncope and collapse [32], as well as another case detected incidentally after having been referred to cardiology to be evaluated for cardiomyopathy [33]. Although the exact cause of Long QTc is not known, the incidence of this, as well as that of other rhythm disturbances, seems remarkably high and given the risk of sudden death from long QTc and other cardiac conduction abnormalities, regular screening with electrocardiography and 24-hour Holter

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monitoring is warranted. Treatment for long QTc in PA patients is similar to that utilized in non-PA patients.

- Screening for Long QTc and Other Cardiac Conduction Defects
  - ECG yearly
  - 24-hour Holter yearly
  - ECG and 24-hour Holter for syncope, fainting or other signs and symptoms of Long QTc

5. Immune defects

Nearly all published information on immune defects in PA comes from single case reports. A retrospective study of 38 patients suggested that there was an increased incidence of viral and bacterial infections [34]; however it is limited by the absence of laboratory data to support immune dysfunction and also by the fact that there was not an effort to compare with a reasonable control group (control group with hypotonia, port-a-caths, etc.). Other case reports have demonstrated pancytopenia at diagnosis [35–37] that appears to be due to bone marrow suppression. One study reported autopsy finding of depletion of T-cell and B-cell dependent areas of lymph nodes and low IgG, with normal IgM and IgA [35]. There is also a report of myelodysplastic syndrome in association with neutropenia [38]. It is our impression that many newborns with PA will have neutropenia and occasionally pancytopenia at diagnosis, but that this usually resolves without the need for granulocyte colony stimulating factor (G-CSF). We have not observed significant issues with chronic neutropenia or pancytopenia outside the newborn period. We would therefore recommend performing a complete blood count at diagnosis to assess for neutropenia and pancytopenia, followed by appropriate precautions to minimize the risk of infection and expectant management and judicious use of G-CSF. Patients with inborn errors of metabolism do *not* have a higher incidence of complications from vaccination [39], and therefore a full vaccination course and influenza vaccine are recommended. Appropriate fever management and fluids are recommended with vaccination.

- Recommendations for immune defects
  - CBC with differential at diagnosis annually, and as needed to follow abnormalities
  - If neutropenia present, institute infection control precautions (isolation, gown and glove, etc.), as indicated by hospital policy
  - Expectant management with judicious use of colony stimulating factors only in cases where neutropenia is not resolving or there is evidence of bacterial infection with neutropenia

6. Pancreatitis

Single episodes of acute pancreatitis have been reported [40], as well as recurrent acute pancreatitis [41, 42]. Elevations in lipase and amylase with radiographic evidence of pancreatic inflammation have been reported. The signs and symptoms of acute pancreatitis in PA have not been documented to be different from that in individuals without PA, and include stomach pain, anorexia and vomiting with amylase and lipase elevations in blood. Episodes have been associated with acidosis but it seems that the acidosis could be secondary to the pancreatitis and not the primary event that causes pancreatitis. Hyperammonemia has not been reported in association with acute pancreatitis in PA. The pathogenesis of pancreatitis in PA is unclear; some have postulated that it is due to a high-fat, low protein diet [42]. Supportive care for pancreatitis has been employed successfully. There is no documentation of chronic pancreatitis resulting in pancreatic endocrine or exocrine dysfunction.

- Recommendations for evaluation and management of acute pancreatitis
  - Vomiting, anorexia, abdominal pain and unexplained acidosis should prompt evaluation for pancreatitis, to include serum amylase and lipase measurements
  - Episodes of acute pancreatitis in PA should be managed like any other case of acute pancreatitis (i.e. fluids, judicial short term bowel rest, jejunal feeds, pain management)
  - When necessary, total parenteral nutrition can be used safely, provided the amount of protein provided is not excessive (at or near the RDA for patient's age) [12,13].
  - Intravenous carnitine at 200–300 mg/kg/day to maintain propionylcarnitine excretion.

7. Optic neuropathy

Optic atrophy has been reported in PA. A prospective study of six individuals (3 male; 3 female) ages 2–10 years found that all males had moderate-severe, bilateral, symmetric optic nerve atrophy. No correlation was found between optic atrophy progression and metabolic control. Additionally, there did not seem to be any correlation between degree of developmental delay/neurologic impairment and optic atrophy [43]. There is also a report of optic atrophy resulting in acute visual loss in an adult female [44]. It seems that the incidence of visual loss due to optic atrophy could be quite high, but the studies are small. There is also some suggestion that the risk increases with age but the cause is not evident. Based upon this, regular, dilated ophthalmologic evaluation is indicated for assessment and treatment of vision loss.

- Recommendations for evaluation and management of optic atrophy
  - Annual examination by an ophthalmologist to include visual acuity as well as visual examination of the anterior chamber and dilated evaluation of the fundus
  - Treatment of decreased visual acuity, as indicated

8. Ancillary treatments

8.1. Carnitine

Increased excretion of acylcarnitines in the urine has been documented to result in low levels of plasma carnitine [45, 46]. Plasma levels of acylcarnitines and free carnitine inversely correlate with hyperammonemia and the administration of carnitine supplementation has been demonstrated to improve the urine excretion of acylcarnitines [7, 47, 48]. In the absence of carnitine supplementation, low levels of free carnitine and elevated levels of acylcarnitines have been documented in muscle [47] and low levels of free carnitine have been documented in the heart of a child who died of cardiomyopathy, despite carnitine supplementation and normal levels of free carnitine in blood and muscle [29]. The side effects of oral carnitine supplementation are few and include transient nausea and vomiting, abdominal cramps, diarrhea and fishy body odor, particularly during hot weather. It is the authors' observation that high doses of carnitine can be useful in individuals with both acute hyperammonemia and acidosis as well as in the chronic management of individuals with recurrent episodes of acute decompensation. Dosing of carnitine should take into account the carnitine provided by the individual's medical food. Some formulas contain a large amount of carnitine (for example 60 mg/g protein equivalent in Propimex-2 manufactured by Abbot) whereas others have very little. In summary, oral or IV carnitine supplementation is generally safe and well-tolerated. It assists in the excretion of acylcarnitines (propionylcarnitine) which has been documented to improve hyperammonemia. There is conflicting evidence on the correlation of plasma/muscle/heart levels, thus the role of monitoring plasma levels would seem to be restricted to ensuring compliance with therapy; supranormal levels of free and total carnitine are well-tolerated and are NOT a reason to decrease carnitine supplementation.

- Recommendations for carnitine supplementation
  - 200–300 mg L-carnitine/kg body weight/day divided 2–3 times per day
  - For acute hyperammonemia and recurrent metabolic decompensations, doses on the high end of the range (300 mg/kg/day) may be helpful and may be administered intravenously.

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- Free and total plasma carnitine analysis at metabolic checkup visits and as indicated to monitor therapy compliance.

8.2. Biotin

There is conflicting evidence as to whether biotin can improve isoleucine metabolism and reduce propionate production [49, 50] and there is no evidence that biotin is useful in either the acute or chronic setting. It is the experience of the authors that in the majority of individuals with PA, neither a clinical nor a biochemical response occurs with biotin supplementation. Even at high doses, biotin has no evident side-effects.

- Recommendations for biotin supplementation
  - May consider biotin 5 mg daily
  - If no reduction in plasma propionylcarnitine discontinue biotin

8.3. Laxative agents

A prospective study of four children, ages 4–15 years, demonstrated that the intestinal laxative, Senokot® (5–10 ml) daily (8.8 mg/5 ml) resulted in a significant decrease in blood ammonia, a decrease in the urine excretion of propionylglycine and an increase in the ratio of free: total carnitine [51]. It would therefore seem that regular use of a laxative would be a useful adjunct to other established therapies. Although studies have not been done, the use of centrally acting pro-motility agents (like metoclopramide) requires care in patients already at risk for basal ganglia and central movement disorders.

- Recommendations for pro-motility agents
  - Daily use of laxative at age/weight-appropriate doses

8.4. Intestinal bactericidal therapy

The effect of metronidazole was studied in four children and there was a reduction of both plasma and urine propionate metabolites. No clinical improvement was reported or analyzed and changes in ammonia levels were not evaluated. The dose utilized was 20 mg metronidazole/kg body weight/day orally divided t.i.d. for 5 days followed by 10 mg metronidazole/kg body weight/day orally divided t.i.d. [52]. This study reflects biochemical improvement but there are no studies that evaluate the clinical efficacy of metronidazole in improving clinical outcome, reducing ammonia levels or reducing episodes of acute metabolic decompensation, though given that propionate correlated with ammonia levels [5], one might infer that this would be helpful. There is an assertion that metronidazole reduces unnecessary dietary adjustments [15] but data proving this or improved outcome is not provided. Metronidazole toxicity creates dystonia as a side-effect which should be considered in dosing and in evaluation of movement changes in a PA patient.

- Recommendations for bactericidal therapy
  - Metronidazole 10–20 mg/kg/day divided t.i.d. may be considered in individuals refractory to other standard interventions. A variety of schedules have been used but the most common is one week on drug with three weeks off.

8.5. Sodium benzoate

There is no published evidence that benzoate has clinical usefulness in the treatment of PA. Given that certain studies have found that higher glycine levels are indicative of good metabolic control [6] there is limited theoretical evidence for its usefulness as well. Its use as a nitrogen scavenger may also have some utility. This is balanced against the consumption of CoA elements which bind to benzoate. If used, it is recommended that patients also be placed on carnitine.

- Recommendation for sodium benzoate
  - There is no evidence that would support a role for benzoate in acute or chronic treatment
  - In difficult to control chronic hyperammonemia, a dose of 250 mg/kg (similar to that used in urea cycle disorders) per day divided into 3 doses can be considered. Phenylbutyrate and the glycerol-phenylbutyrate conjugates have not been evaluated in PA.

8.6. Carglumic acid

Although there is evidence that Carbaglu® (carglumic acid) may be useful in the management of acute hyperammonemia [Chapman et al. this journal], to date there are no studies that assess chronic use of Carbaglu® in PA.

- Recommendation for Carbaglu® (carglumic acid)
  - There is no current published evidence for its use in chronic management, although ongoing studies suggest a utility for PA associated chronic hyperammonemia.

8.7. Growth hormone

In a study of three children with PA, two had blunted growth hormone with arginine or clonidine stimulation. Growth hormone therapy (alone or in combination with alanine supplementation) improved lean body mass and linear growth and increased protein tolerance [53]. However, a number of children in the study were found to be in negative nitrogen balance which suggests that simply increasing protein and/or calories may have led to these improvements, since poor nutrition could have been the reason for the deficient growth hormone stimulation. One of the two children with PA died during the course of the study and one had recurrent pancreatitis. The authors themselves seem to question whether improved attention to nitrogen balance would have led to similar improvements. It is our expert opinion that careful attention to ensuring adequate protein and caloric intake results in normal growth and that the role for growth hormone in PA is limited.

- Recommendations for growth hormone
  - Low levels of growth hormone/IGF1 should prompt careful assessment of nutritional parameters listed above in the “Nutrition and Laboratory Monitoring” section; only if these items are normal should growth hormone treatment be considered.

8.8. Gastrostomy tubes/buttons

Although there are no studies in PA comparing outcomes of individuals with and without gastrostomy tubes/buttons, it is the expert opinion of the group that these devices improve care. The ability to have immediate enteral access, particularly in individuals who may have anorexia or vomiting for medications, formula and fluids seems of benefit for chronic or sub-acute management in both the home setting and in hospital. Gastrostomy tubes have proven effective in reducing hospitalizations in other inborn errors of metabolism [54]. PA does not increase the risk of gastrostomy tube placement in the experts' experience. It is our opinion that both parents and healthcare providers find these to be helpful in the chronic management of PA.

- Recommendation for gastrostomy tube/button placement
  - We recommend consideration be given to the placement of a gastrostomy tube, particularly in infants and young children with PA at the time of diagnosis.

8.9. Port-a-caths

There are no studies demonstrating that port-a-caths (totally implantable central venous access devices) improve outcomes in PA. In one study that included two individuals with PA, both had the devices removed; one for a systemic infection and one due to a “pocket infection”. Both ultimately died [55]. It is our experience that there are certain individuals with PA who have poor peripheral venous access and

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frequent illnesses requiring rapid and reliable venous access for diagnostic testing and treatment. It is also our experience that individuals with port-a-caths frequently develop a central line infection which can precipitate an acute metabolic decompensation.

- Recommendation for Port-a-cath placement
  - Placement of a port-a-cath (totally implantable central venous access device) may be considered when unreliable peripheral venous access is significantly compromising patient care but should be balanced by the increased risk of destabilizing infection.

10. Liver transplant

Early reports of liver transplant for PA indicated that overall outcome was not very good, with significant mortality and transplant-related complications. In a report of two individuals who received liver transplant at 7 and 9 years, one had significant complications related to rejection, EBV-induced lymphoproliferative disorder and hepatic artery thrombosis and ultimately died; the other did well [56]. A large cohort was reported with poorer results with regard to two-year survival and developmental outcome [57]. No data is provided regarding the age at transplantation, cognitive status at transplantation or surgical difficulties or anti-rejection medication regimen. More recent studies suggest much lower morbidity and mortality and a much higher success rate with improving acute decompensations and other parameters (cardiomyopathy, development, and biochemical markers). In a multi-site, retrospective study of 12 individuals with PA receiving orthotopic liver transplant (OLT), the one-year survival rate was 72.2%. Clear clinical improvement, including elimination of episodes of hyperammonemia and liberalization of diet (i.e. avoidance of meats but no specific dietary restriction of protein) was seen. It was also asserted that OLT halted or slowed neurological decline and prevented cardiomyopathy [58]. In a report of 3 children with PA who received living related donor transplant, all were surviving (21–59 months) and it is reported that they did not have further episodes of acute decompensation with metabolic acidosis [59]. Auxiliary liver transplant has also been reported in a single 2-year-old girl. She had recurrent metabolic decompensations that prompted the transplant and had normal biochemical parameters, normal growth and no cognitive decline on an unrestricted diet up to 10 years after the procedure [60]. A very recent report of 5 individuals with median follow-up of 7.3 years, all were surviving and had good graft function, though one had experienced a basal ganglia stroke after transplant. Post-transplant development (as evaluated by the Griffiths Mental Developmental Scale) was normal for one, moderately impaired for one and mildly impaired for three [61]. From these reports and our experiences, improved surgical techniques and anti-rejection regimens appears to have resulted in much better outcomes than were initially reported in the 1990s and early 2000s. From the more recent reports, the survival is good (lowest one-year survival was 72%) and it appears that when the new liver is working properly that there are no further episodes of acidosis or hyperammonemia, without dietary restriction of protein. Reports also suggest that further cognitive decline is not seen, and this is our experience as well.

- Recommendations for liver transplantation
  - In individuals with recurrent episodes of hyperammonemia or acidosis that are not adequately controlled with medical therapies outlined above, liver transplant may be considered
  - Recipients of living-related donor livers from carriers (i.e. haploinsufficient livers) seem to have similar results to OLT recipients

11. Anticipating emergency situations

As individuals with PA get older they are more likely to be supervised by individuals who may not be familiar with their condition. As well, it is to be anticipated that an emergency medicine physician may not be familiar with a rare conditions such as PA. In emergency situations it is important for information about PA, including appropriate treatment, to be communicated to healthcare providers. We therefore recommend that the metabolic team provide a letter to the parents/primary caregivers that briefly summarizes the condition and emergency treatment and provides contact information for the metabolic team. Parents can take this letter with them should they need to go to the emergency room. Additionally, we recommend that parents obtain a medical alert bracelet (or necklace, etc.) to ensure that an emergency team has ready access to a diagnosis and information about PA.

12. Summary

Having employed expert opinion and critical and comprehensive review of the medical literature, the following should help to guide the care of individuals with PA:

- Recommended Nutrition Assessments at Routine Outpatient Visits (at least every 6 months)
  - Albumin
  - Ammonia
  - Plasma amino acids (fasting 3–4 h)
  - Prealbumin
- Optional Nutrition Assessments
  - Plasma propionylcarnitine (i.e. quantitative acylcarnitine profile)
  - Urine methylcitric acid
  - Other general measures of nutrition as needed, based upon history, dietary intake and growth, such as 25-hydroxyvitamin D, iron, selenium, free fatty acids etc.
- Diet history should be reviewed at each visit and adjustments should be made to maintain:
  - Normal growth velocity for weight (assessed at least monthly in infants, and less frequently as children get older and the normal rate of growth velocity slows)
  - Normal levels of serum albumin and prealbumin
  - Normal levels of plasma isoleucine, methionine, threonine and valine.
  - Normal to elevated levels of plasma glycine
- Measures to Maximize Intellectual-Developmental Outcome
  - Early initiation of physical, occupational and speech therapy services, to continue throughout childhood
  - Optimize nutrition
  - Avoid acute metabolic decompensation
  - Treat episodes of metabolic decompensation swiftly and aggressively
- Management of stroke-like episodes
  - Ensure adequate fluid and caloric intake during the episode
  - Symptomatic treatment of focal neurological deficits and altered mental status
- Evaluation for seizures
  - EEG at diagnosis and then yearly
  - Referral to child neurology if epileptiform activity detected
- Evaluation for cardiomyopathy
  - Yearly echocardiogram to evaluate for cardiomyopathy
  - Echocardiogram to evaluate for shortness of breath, tachycardia or other signs and symptoms of cardiac failure
- Screening for Long QTc and Other Cardiac Conduction Defects
  - ECG yearly
  - 24-hour Holter yearly
  - ECG and 24-hour Holter for syncope, fainting or other signs and symptoms of Long QTc
- Recommendations for immune defects
  - CBC with differential at diagnosis and as needed to follow abnormalities
  - If neutropenia present, institute infection control precautions (isolation, gown and glove, etc.), as indicated by hospital policy

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- Expectant management with judicious use of colony stimulating factors only in cases where neutropenia is not resolving or there is evidence of bacterial infection

- Recommendations for evaluation and management of acute pancreatitis
  - Vomiting, anorexia, abdominal pain and unexplained acidosis should prompt evaluation for pancreatitis, to include serum amylase and lipase measurements
  - Episodes of acute pancreatitis in PA should be managed like any other case of acute pancreatitis
  - When necessary, total parenteral nutrition can be used safely, provided the amount of protein provided is not excessive [12,13].
- Recommendations for evaluation and management of optic atrophy
  - Annual examination by an ophthalmologist to include visual acuity as well as visual examination of the anterior chamber and dilated evaluation of the fundus
  - Treatment of decreased visual acuity, as indicated
- Recommendations for carnitine supplementation
  - 200–300 mg L-carnitine/kg body weight/day divided 2–3 times per day
  - For acute hyperammonemia and recurrent metabolic decompensations, doses on the high end of the range (300 mg/kg/day) may be helpful
  - Free and total plasma carnitine analysis as indicated to monitor therapy
- Recommendations for biotin supplementation
  - May consider biotin 5 mg daily
  - If no reduction in plasma propionylcarnitine discontinue biotin
- Recommendations for pro-motility agents
  - Daily use of pro-motility agent at age/weight-appropriate doses
- Recommendations for bactericidal therapy
  - Metronidazole 10–20 mg/kg/day divided t.i.d. may be considered in individuals refractory to other standard interventions
- Recommendation for sodium benzoate
  - There is no evidence that would support a role for benzoate in acute or chronic treatment
- Recommendation for Carbaglu® (carglumic acid)
  - No evidence for its use in chronic management
- Recommendations for growth hormone
  - Low levels of growth hormone/IGF1 should prompt careful assessment of nutritional parameters listed above in the "Nutrition and Laboratory Monitoring" section; only if these items are normal should growth hormone treatment be considered.
- Recommendation for gastrostomy tube/button placement
  - We recommend consideration be given to the placement of a gastrostomy tube, particularly in infants and young children with propionic acidemia.
- Recommendation for Port-a-cath placement
  - Placement of a port-a-cath (totally implantable central venous access device) may be considered when unreliable peripheral venous access is significantly compromising patient care
- Recommendations for liver transplantation
  - In individuals with recurrent episodes of hyperammonemia or acidosis that are not adequately controlled with medical therapies outlined above, liver transplant may be considered
  - Recipients of living-related donor livers from carriers (i.e. haploinsufficient livers) seem to have similar results to OLT recipients

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