Medical and Dietary Guidelines for PKU

“Reaching New Heights”

National PKU Alliance Conference
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DISCLAIMER

• Kathleen Huntington has no financial conflicts of interest to disclose.

• Cary Harding has received research grants and consulting fees from BioMarin Corp. for the development of novel PKU treatments.
Thanks to
Amy Cunningham, MS LDN RD
Tulane Hayward Genetics Center
& GMDI/SERC PKU Workgroup

for sharing slides and information pertaining to the recommendations on PKU nutritional management and nutrition guideline development process.
ABOUT THOSE PKU GUIDELINES
ARE YOU----
• The programs listed are provided for reference purposes only. They were current when produced, but are no longer maintained and may now be outdated.

• Due to the cumulative nature of medical research, some of the information in this statement is likely to be out of date. For more current information on this and other health topics, please visit MedlinePlus, a service of the U.S. National Library of Medicine, National Institutes of Health
Metabolic control is necessary across the lifespan

Maintain PHE level of 120-360 umol/L through 12 years of age; \(120 \text{ – } 600 \text{ umol/L after 12 years of age}\)

Uniform policies for removal of financial barriers to acquisition of medical foods & modified low protein foods

Since 2000, 12 states passed medical food legislation out of the 39 total that have passed this legislation
- PHE levels below 360 umol/L should be achieved at least 3 months before conception; maintain PHE level of 120-360 during pregnancy.

- Research on non dietary alternatives to tx of PKU strongly encouraged.
Alphabet Soup

◆ AHRQ
   ✧ Agency for Health Research and Quality

◆ NIH
   ✧ Eunice Shriver National Institute of Child Health & Human Development
   ✧ Office of Rare Diseases Research Center
   ✧ Office of Dietary Supplements

◆ ACMG
   ✧ American College of Medical Genetics

◆ GMDI-SERC
   ✧ Genetic Metabolic Dietitians International (GMDI)
   ✧ Southeast Regional Genetics Collaborative (SERC)
AHRQ Report: PKU and Adjuvant Therapy

(pharmacological agent that modifies the effect of other agents)

- **AHRQ** - Evidence-based literature review
  - Determine blood PHE levels that optimize cognitive development
  - Compare effectiveness of traditional dietary treatment alone – with dietary treatment plus adjuvant therapy of sapropterin or LNAA across the lifespan

◆ **Analytic Framework—**
  ◇ Primary target health outcome: maintenance of cognition

Kuvan, first pharmacologic agent, approved in 2007 by the FDA for treatment of PAH

Large Neutral Amino Acids (LNAA)
- LNAAAs compete with PHE for transport across the blood brain barrier and the gut
2012 AHRQ Report: PKU and Adjuvant Therapy

Key Findings ---

- The treatment target of 120 - 360 umol/L for blood PHE supported in the AHRQ meta analysis

- Pre-conception dietary control and maintenance PHE levels between 120 - 360 umol/L during pregnancy most effective for optimum Maternal PKU outcome

(more studies are needed with larger # of participants)
2012 AHRQ Report: PKU and Adjuvant Therapy

✧ Negative cognitive effects accumulate over a long time period.

✧ Concurrent measurements of PHE are poor predictors of cognitive effect.
2012 AHRQ Report: PKU and Adjuvant Therapy

Key Findings for Kuvan

*Strength of evidence: moderate*

demonstrating that Kuvan lowers PHE levels in responsive individuals in the short term

*Strength of evidence: low*

For Kuvan effects on cognitive outcomes based on evidence from randomized control trials & meta analysis of relationship of PHE and IQ

*Strength of evidence: insufficient*

for Kuvan’s effect on PHE tolerance, quality of life, ability to liberalize diet and nutritional outcomes
2012 AHRQ Report: PKU and Adjuvant Therapy

Key Findings – L Neutral Amino Acids

**Strength of evidence: insufficient**

to indicate that LNAAs could be a viable treatment option for reducing PHE levels or increasing PHE tolerance

- Optimal target population should be identified
- Treatment goals should be identified
- Mechanism of how LNAAs would work should be clarified.
Evidence: NIH

PKU State of the Science

**Purpose:** Reevaluate 2000 Consensus recommendations in light of new treatment knowledge and technology

Workgroups

- Diet control and management
- Pharmacologic interventions
- PKU and pregnancy
- Long-term cognitive outcomes and follow-up across the lifespan
- Molecular testing, new technologies, epidemiologic considerations (NBS)
Conclusions re Diet Issues

1. Most serious neurocognitive complications are preventable with current dietary treatment practices.
   - Potential for subtle physical, cognitive, and behavioral consequences despite well-controlled PKU.

2. Dietary management control best at 120-360 µmol/L.

3. Best outcomes for maternal PKU—PHE level 120-360 µmol/L before and during pregnancy.

4. Don’t panic about PKU management.
Conclusions re Diet Issues (cont’d)

5. LNAA not indicated for pregnancy or use with children.

6. GMP containing products can be an alternative to PHE-free amino acid mixtures as a med protein source; be aware of the PHE content.

7. Kuvan – gaps in being able to predict a response, ½ of affected with PKU will have minimal or no response.
2012 PKU State-of-the-Science Conference

- the process preceding
- the conference itself
- the identification of a research agenda

Facilitated the development of clinical practice nutrition management recommendations by GMDI and diagnostic and management guidelines by ACMG
**GMDI** – Recommendations for the Nutrition Management of Phenylalanine Hydroxylase Deficiency

**ACMG** – Phenylalanine Hydroxylase Deficiency Diagnosis and Management Guideline
[http://www.nature.com/gim/journal/vaop/ncurrent/abs/gim2013157a.html](http://www.nature.com/gim/journal/vaop/ncurrent/abs/gim2013157a.html)
Recommendations for the Nutrition Management of Phenylalanine Hydroxylase Deficiency

http://www.nature.com/gim/journal/vaop/ncurrent/abs/gim2013179a.html

✧ Genetic Metabolic Dietitians International
✧ Southeast Regional NBS & Genetics Collaborative
✧ Dietitians from NIH Diet Control & Mgmnt & Maternal PKU Workgroups
Monitoring of nutritional and clinical markers
Prevention of nutrient deficiencies
Choice of appropriate medical foods
Compliance strategies
Integration of adjuvant therapies
Treatment during pregnancy
Providing access to care

Areas of Investigation for Nutrition Management
Recommendation: Prevention of Nutritional Deficiencies

- Provide the same nutrients intakes as everyone else EXCEPT for PHE, TYR and Protein

- Assess need for vitamin/mineral supplementation depending on medical protein option(s) or if therapy adherence is in question

- Monitor nutritional status
Monitoring of nutritional and clinical markers

Domain Measures:
- Infants (0–1 yr)
- Children (1-7 yrs)
- Adolescents (8-18 yrs)
- Adults (8-18 yrs)
- Pregnancy & Post Partum

Clinical Assessment:
- Weight, Height, weight for length
- Prealbumin
- Complete Blood Count
- Albumin
- Ferritin
- Vitamin D
- Comprehensive Metabolic Panel
- Select Vitamins & Minerals Levels
- DEXA Scan

Most important for individuals who are unable to adhere to the diet.
Recommendation: Monitoring of nutritional and clinical markers

◆ Monitor PHE level more frequently during times of anabolism: infancy, childhood and pregnancy

Monitor blood PHE at consistent time during the day – i.e. 2-3 hours after eating
Recommendation: Ensure Access to Medical and Modified Low Protein Foods (aka Medical Foods)

Low protein modified foods --

1. Provide calories with negligible protein content
   
   A. Supply < 50 - 75 mg PHE/100 grams weight of product

2. Prevent catabolism and thereby elevation of PHE level

3. Normalize the eating experience

Third party reimbursement not universal despite cost saving advantages
Recommendation:
Develop Individual Nutrition Strategies for Management of Individuals with PAH Deficiency

Individualize dietary treatment to meet nutritional needs on or off Kuvan in terms of --
◆ PHE allowance,
◆ medical protein,
◆ modified low protein foods
◆ vitamin and mineral supplementation.

◆ Consume medical protein throughout the day for optimal metabolic control
Classification of Medical Food per Macronutrient Content & Patient Age

<table>
<thead>
<tr>
<th>Classification</th>
<th>Nutrient Profile</th>
<th>Forms *Suitable for Age</th>
</tr>
</thead>
</table>
| AA, Carb, Fat Vits & Minrls | Most complete  
   ✦ *High to Medium* | Powder  
   *Infants, Kids, Adults* |
| AA, Carb, Vits & Minrls | Most Vits & Minerals, no fat  
   ✦ *Medium to Low*    | Powder, ready-to-drink  
   *Kids, Adults*       |
| AA                     | Few or no Vits & Minerals  
   ✦ *Low*              | Powder, capsules, tablets  
   *Adults*            |
| Glycomacropeptide      | Variable depends on option, contains PHE  
   ✦ Variable           | Powder, ready-to-drink, bars, pudding  
   *Kids, Adults*      |
| LNAAs                  | Variable depends on option,  
   ✦ *Low*              | Powder, tablets  
   *Adults*            |
Dietary PHE
Blood PHE level determines the amount of dietary PHE intake

- **Infants**
  - Recommend:
    - Breast Milk and/or Infant Formula

- **Children, Adolescents and Adults**
  - Vegetables, fruits, grain based foods

- Wide range for PHE intake – influenced by PAH deficiency, patient age, growth rate, BH4 response, etc.
Recommendation: Track PHE Intake By Preferred Method

- **Exchange/Equivalent Method**
  - 1 exchange = 15 mg of PHE

- **Protein Counting Method**

- **European Method**
  - Fruits are free
  - Vegetables & low protein medical foods are free if supplies either < 50 or 75 mg of PHE per 100 gram weight of food
Recommendation: Consider Kuvan use on a case by case basis for pregnant women who have difficulty adhering to diet depending on PAH mutation, cofactor treatment may enhance enzyme function--

- Helps to lower PHE levels for non adherent individuals without further diet restriction

- May allow liberalization of dietary PHE and therefore less dependency on medical foods while still maintaining PHE level within treatment range
Recommendation: Consider LNAAs for adults not able to adhere to dietary treatment options

**LNAAs** supply 25-30% of protein needs, balance from intact protein sources.

- Difficult to monitor positive effects of LNAA, PHE level remains high
- Not for young children or pregnant women, adults only
Timeline

2010
GMDI/SERC PKU Workgroup Formed

2011
AHRQ Review of Literature
NIH Work Groups Reviews
ODS Conference

2012
AHRQ Report
NIH State of the Science Conference
IEM Survey
ACMG/GMDI Consensus Meeting
Delphi 1

2013
* ACMG Guidelines
* GMDI-SERC Recommendations
NPKUA Grant

2014
Nominal Group Delphi 2
GMDI-SERC Guidelines
# Nutrition Guideline Development Cycle

The following disorders were selected by the workgroups for initial guideline development:

<table>
<thead>
<tr>
<th>Workgroup</th>
<th>Disorder(s)</th>
<th>Planned Release</th>
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</thead>
<tbody>
<tr>
<td>Amino Acidemias</td>
<td>Maple Syrup Urine Disease (MSUD)</td>
<td>Available Now</td>
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<tr>
<td></td>
<td>Phenylketonuria (PKU)</td>
<td>Fall 2013 (NIH Base Recommendations)</td>
</tr>
<tr>
<td></td>
<td>Phenylketonuria (PKU)</td>
<td>Fall 2014 (Full DNDF Model Guidelines)</td>
</tr>
<tr>
<td>Organic Acidemias</td>
<td>Propionic Acidemia (PROP)</td>
<td>Spring 2015</td>
</tr>
<tr>
<td>Fatty Acid Oxidation Disorders</td>
<td>VLCAD</td>
<td>2015</td>
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<td></td>
<td>MCAD</td>
<td>2015</td>
</tr>
<tr>
<td>Urea Cycle Disorders</td>
<td>Citrullinemia (CIT)</td>
<td>2016</td>
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<tr>
<td></td>
<td>Argininosuccinic aciduria (ASA)</td>
<td>2016</td>
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<tr>
<td></td>
<td>Argininemia (ARG)</td>
<td>2016</td>
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PKU Management

Goal: optimum cognitive outcome as well as a happy and healthy individual
Change Ahead
New Acts to Follow
◆ Individualize nutritional and treatment recommendations to maintain appropriate PHE levels throughout the lifespan

◆ Medical protein intake should be distributed throughout the day for optimal nutritional benefit and metabolic control

◆ Track PHE intake using preferred method

◆ If response to Kuvan, Individualize adjuvant therapy based on the degree of response and adjust overall recommendations and menu choices accordingly

What To Do ?!

Monitor PHE level --
Metabolic control is necessary across the lifespan

Maintain PHE level of 120-360 umol/L through 12 years of age; 120 – 600 umol/L after 12 years of age

Uniform policies for removal of financial barriers to acquisition of medical foods & modified low protein foods

Since 2000, 12 states passed medical food legislation out of the 39 total that have passed this legislation
Research Agenda Identified

- Outcome measures & endpoints for PKU
- Pathophysiology of PKU
- Therapy response
- Issues of treatment access thru healthcare coverage, social supports
- Genotyping issues
- Clinical trial design
- Resources and technology design

Research design for PKU and other IEM *not* a trivial matter – Patient population is small and dispersed.
◆ AHRQ

✦ Agency for Health Research and Quality

AHRQ is the research arm of the US Dept of Health and Human services on the topic of health care quality, costs, outcomes and patient safety

– sister agency of NIH that focuses on biomedical research
The SE Newborn Screening and Genetics Collaborative (SERC) convened a group of national experts in metabolic nutrition.

The workgroup developed a multi-step process for guideline development.
2012 AHRQ Report: PKU and Adjuvant Therapy

**AHRQ** - Evidence-based literature review of 5 databases

- Did not address dietary restriction as the sole treatment for PKU as its effectiveness has been shown in numerous studies and considered standard of care.

**Analytic Framework**—

- Primary target health outcome: maintenance of cognition

Examined 2 adjuvant treatments for PKU

- Effectiveness of FDA approved Kuvan® (aka BH4 or Sapropterin dihydrochloride) plus dietary intervention vs diet alone

- Effectiveness of Large Neutral Amino Acids (LNAAs) considered nutritional supplements not subject to FDA approval with dietary intervention vs diet alone

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Guideline Template

- Background
  - Definition
  - Incidence
  - Pre-symptomatic detection
  - Genetics
  - Confirmatory testing
- Biochemical Basis
  - Rationale for treatment
  - Biochemical pathway
- Nutrition Assessment
  - Signs and Symptoms
  - Laboratory Findings
- Nutrition Problem Identification
  - Common Diagnoses using NCP language
- Nutrition Management
  - Initial
  - Follow-up
  - Pregnancy
  - Special Circumstances
- Education
  - Patient Goals
  - Patient Resource
  - Provider Resources
- Monitoring and Evaluation
  - Biomarkers to follow
  - Health benefits
  - Harms (side effects, risks)
- Barriers to Implementation
- Areas for Future Research
- References
Published Guidelines

- Published on GMDI and SERC websites
- Transparent evidence base
  - Links to literature reviewed, strength of evidence, reasons for articles excluded
- Evidence summary supporting conclusions for each recommendation
- Links to tables cited
- Nutrition management “Tool Kit” – practical guide for clinical practice – how to implement recommendations
- Electronic portal – public and GMDI member access, allows interactive links and updating
Coming Soon
2014 Published Guidelines

Electronic portal – public and GMDI member access, allows interactive links and updating
GMDI – Recommendations for the Nutrition Management of Phenylalanine Hydroxylase Deficiency
http://www.nature.com/gim/journal/vaop/ncurrent/abs/gim2013179a.html