Improving Children’s Health Through Better Laboratory Testing

Wednesday, February 27, 2019
Luncheon Briefing: 11:30 am – 12:30 pm
Room HC-8, The Capitol
Improving Children’s Health Through Better Laboratory Testing

Moderator:
- Dr. David Koch

Speakers:
- Dr. Dennis Dietzen
- Dr. Patrick Mason
- Dr. Hubert Vesper

Dennis J. Dietzen, PhD, DABCC, FAACC
Immediate Past President, AACC
Professor of Pediatrics and Pathology
Washington University School of Medicine
Medical Director, Lab Services
St. Louis Children’s Hospital
What is a Reference Interval?

Age
Gestational Age
Developmental Age
Genetics
Weight
Birth-weight
Ethnicity
Geography
Diet
Drugs
Season
Posture
Method
Equipment
How do we use Pediatric Reference Intervals?

<table>
<thead>
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<tbody>
<tr>
<td>Sodium</td>
<td>135 - 145 mmol/L</td>
<td>136</td>
<td>139</td>
<td>136</td>
<td>137</td>
<td>141</td>
<td>136</td>
<td>136</td>
<td>138</td>
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<tr>
<td>Potassium, pl</td>
<td>3.3 - 4.9 mmol/L</td>
<td>2.9 (L)</td>
<td>2.7 (L)</td>
<td>3.2 (L)</td>
<td>3.0 (L)</td>
<td>3.7</td>
<td>4.2</td>
<td>4.9</td>
<td>3.9</td>
<td>5.1 (H)</td>
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<td>CO2</td>
<td>20 - 30 mmol/L</td>
<td>23</td>
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<td>22</td>
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<td>27</td>
<td>27</td>
<td>26</td>
<td>25</td>
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<tr>
<td>BUN</td>
<td>9 - 18 mg/dL</td>
<td>5 (L)</td>
<td>5 (L)</td>
<td>5 (L)</td>
<td>7 (L)</td>
<td>8 (L)</td>
<td>12</td>
<td>13</td>
<td>12</td>
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<tr>
<td>Glucose</td>
<td>70 - 199 mg/dL</td>
<td>120</td>
<td>97</td>
<td>108</td>
<td>145</td>
<td>131</td>
<td>119</td>
<td>98</td>
<td>128</td>
<td>94</td>
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<tr>
<td>Creatinine</td>
<td>0.40 - 1.00 mg/dL</td>
<td>0.38 (L)</td>
<td>0.44</td>
<td>0.33 (L)</td>
<td>0.34 (L)</td>
<td>0.30 (L)</td>
<td>0.32 (L)</td>
<td>0.35 (L)</td>
<td>0.38 (L)</td>
<td>0.37 (L)</td>
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<tr>
<td>Calcium</td>
<td>8.5 - 10.3 mg/dL</td>
<td>9.0</td>
<td>8.7</td>
<td>8.4 (L)</td>
<td>8.7</td>
<td>9.1</td>
<td>9.0</td>
<td>9.5</td>
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<td>9.1</td>
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<td>Chloride</td>
<td>100 - 114 mmol/L</td>
<td>105</td>
<td>108</td>
<td>109</td>
<td>108</td>
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<td>105</td>
<td>104</td>
<td>104</td>
<td>106</td>
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<tr>
<td>Anion Gap</td>
<td>2 - 15 mmol/L</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>5</td>
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</table>
How do we use Pediatric Reference Intervals?

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Result (mcmol/L)</th>
<th>Reference Range (mcmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylalanine</td>
<td>68</td>
<td>35-90</td>
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<tr>
<td>Tyrosine</td>
<td>49</td>
<td>25-85</td>
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<tr>
<td>Isoleucine</td>
<td>89 HIGH</td>
<td>15-75</td>
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<tr>
<td>Leucine</td>
<td>121</td>
<td>40-150</td>
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<tr>
<td>Valine</td>
<td>281</td>
<td>85-325</td>
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<tr>
<td>Alpha-Isoleucine</td>
<td>0</td>
<td>0-2</td>
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<tr>
<td>Threonine</td>
<td>206 HIGH</td>
<td>40-200</td>
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<tr>
<td>Serine</td>
<td>191</td>
<td>90-200</td>
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<tr>
<td>Glycine</td>
<td>163</td>
<td>125-300</td>
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<tr>
<td>Methionine</td>
<td>48</td>
<td>10-50</td>
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<tr>
<td>Homocysteine</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Cystathionine</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cystine</td>
<td>8 LOW</td>
<td>10-50</td>
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<tr>
<td>Glutamine</td>
<td>705</td>
<td>475-750</td>
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<tr>
<td>Glutamic Acid</td>
<td>177 HIGH</td>
<td>60-130</td>
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<tr>
<td>Citrulline</td>
<td>50 HIGH</td>
<td>10-40</td>
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<td>Argininosuccinic Acid</td>
<td>0</td>
<td>0</td>
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<td>Arginine</td>
<td>73</td>
<td>70-160</td>
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<tr>
<td>Ornithine</td>
<td>45</td>
<td>30-200</td>
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<tr>
<td>Homocitrulline</td>
<td>2</td>
<td>0-2</td>
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<tr>
<td>Alanine</td>
<td>302</td>
<td>150-400</td>
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<tr>
<td>Hydroxyproline</td>
<td>19</td>
<td>0-50</td>
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<tr>
<td>Proline</td>
<td>317 HIGH</td>
<td>110-230</td>
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<tr>
<td>Lysine</td>
<td>215 HIGH</td>
<td>85-205</td>
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<tr>
<td>a-Amino Adipic Acid</td>
<td>1</td>
<td>0-5</td>
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<tr>
<td>B-Amino Isobutyric Acid</td>
<td>7 HIGH</td>
<td>0-5</td>
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<tr>
<td>B-Alanine</td>
<td>3</td>
<td>0-20</td>
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<tr>
<td>Sarcosine</td>
<td>3</td>
<td>0-5</td>
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<tr>
<td>Gamma-Amino Butyric Acid</td>
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<tr>
<td>Histidine</td>
<td>16</td>
<td>25-100</td>
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<tr>
<td>Carnosine</td>
<td>0</td>
<td>0-2</td>
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<tr>
<td>a-Amino Butyric Acid</td>
<td>20</td>
<td>0-50</td>
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</tbody>
</table>
What Happens if we don’t have Accurate Pediatric Reference Intervals?
Why are Pediatric Reference Intervals so hard to build?

Bins: Age + Gender

9 bins x 120 individuals = 1080 “Healthy Volunteers”
What do we need to build better Pediatric Reference Intervals?

• A large cohort of “healthy” children from birth through adulthood.
• Cohort with maximal gender, geographic, and ethnic diversity
• Associated physical data (e.g., height, weight, diet, sexual development)
• Sample collection infrastructure
• Sample processing and storage infrastructure
• Sample analysis infrastructure
• Data analysis infrastructure
Parting Thoughts about Pediatric Reference Intervals

- Reference intervals are key to medical decision making.
- Reference intervals depend on geography, gender, diet, season, time of day…..
- Accurate reference intervals require large numbers of healthy participants.
- Pediatric reference intervals must account for rapid growth and development.
- There are large gaps and mistakes in current pediatric reference intervals.
- Recent progress has been promising.
- Much more to do…………. 
Thank you!
Importance of Pediatric Reference Intervals – Clinical Cases

Patrick Mason, MD, PhD
Regional Medical Director
Quest Diagnostics
Children are not Little Adults
Location of the Thyroid Gland
Regulation of Thyroid Hormones

- **HOMEOGONASIS DISTURBED**
  - Decreased T₃, T₄ concentration in blood or low body temperature

- **HOMEOGYASIS RESTORED**
  - Increased T₃ and T₄ concentration in the blood

- Hypothalamus releases TRH
- Anterior pituitary releases TSH
- Thyroid follicles release T₃ and T₄
Thyroid Abnormalities – In Adults

- **Hypothyroid (Low)**
  - Tired
  - Weight gain
  - Constipation
  - Dry skin
  - Brittle hair
  - Cold intolerance
  - See high or normal TSH and low T4

- **Hyperthyroid (High)**
  - Tired but trouble sleeping
  - Weight loss
  - Loose and frequent stools
  - Increased sweating
  - Heat intolerance
  - Often high T4 and low TSH
Thyroid in Babies

- Umbilical hernia
- Large tongue
- Poor feeding
- Coarse facial features
- Low muscle tone
- Hearing loss
- May cause Severe growth failure
- Mental retardation – many parts of the world it’s the leading cause of preventable mental retardation

All symptoms can be prevented with early diagnosis and treatment
Case One

• You are called by State newborn screening about one day old full term baby’s state screen
  • T4 15 mcg/dL (adult normal – 4.8-10.4 mcg/dL)
  • TSH 40 miU/L (adult normal - 0.4-4.5 mIU/L)
• Should you treat the baby?
• What should be done next?
Newborn Screening

• US programs initially screen for T4 with TSH secondary screen
• Screen by 3-5 days most reliable
• Blood spots on day 1 elevated due to physiologic neonatal TSH surge.
  • Early discharge increase false positives to 5:1
Thyroid Hormone in the Infants

- Term TSH
- Premature TSH
- Term T4
- Premature T4
Diagnosis???

Premature testing with elevation secondary to newborn surge
Case Two

- Called to the newborn nursery to evaluate a baby
- Past history was significant for
  - 25 year old mother who just delivered her first child
  - No prenatal issues or concerns noted
  - Physical examination showed a baby with normal vital signs
  - Physical examination was unremarkable except……..
    - The child had a normal penis but no testicles were noted on examination.
Evaluation of the baby?

- Hormonal evaluation showed low levels of testosterone at 1 week of age.
- Parents want to know if their child was a boy or girl
- What do you tell them?
Bipotential Gonads and Ducts

- Virilization- “Becoming a boy”
  - Begins around 7 weeks done by 13 weeks
- If SRY found on Y chromosome then gonads become testicles.
  - Testicles make
    - AMH which causes regression of Mullerian structures
    - Testosterone preserves Wolffian structures
Testosterone levels – throughout life
Laboratory follow up

- Baby’s testosterone levels at 8 weeks were 250 ng/dL
- Ultrasound showed presence of testicles
- Surgery will bring testicles into the boys scrotum.
Thank you!
Expertise at CDC to generate better pediatric reference intervals

Hubert W. Vesper, PhD
Director, Clinical Standardization Programs
Division of Laboratory Sciences
**Problem:** Pediatric reference intervals used by laboratories are very inconsistent

Pediatric reference intervals describe biomarker levels in healthy children.

Pediatric reference intervals are not sufficiently consistent and accurate to reliably diagnose and treat children in a cost-effective manner.

![Graph showing upper level of normal for thyroid stimulating hormones in children less than 1 week old used in 3 labs.](image)
Solutions: Common pediatric reference intervals

- Created using well-characterized children
- Measured with reliable and accurate laboratory tests
CDC Environmental Health Laboratory together with Division of Health and Nutrition Examination Surveys has a good track record in developing and applying highly accurate and reliable laboratory tests in well-characterized pediatric populations.
CDC NHANES data on iron-status indicators help health care providers identifying iron deficiency in children

Iron-status biomarker levels in children

Prevalence of iron deficiency in children

CDC NHANES data on vitamin D help health care providers identifying children with vitamin D deficiency at risk for rickets.

Vitamin D concentrations in children

Prevalence of vitamin D deficiency in children

CDC creates data that are widely used by health care providers and clinical laboratories

- CDC reference intervals are broadly accepted by clinical laboratories and physicians

More reference intervals in children at all stages of development are needed
National Health and Nutrition Examination Survey (NHANES): most comprehensive health information on children and adults in the U.S.

Clinical Reference Laboratory: highly specific and accurate laboratory tests for chronic disease biomarkers

Accurate and reliable laboratory data suitable to establish pediatric reference intervals for laboratories and health care providers.
NHANES provides data on over 30 health and disease biomarkers in children and adolescents

Examples:
• Hormones
• Lipids
• Iron Status

More biomarker measurements are needed
CDC Environmental Health Laboratory together with NCHS’s Division of Health and Nutrition Examination Surveys

- conduct the only survey highly suitable to collect appropriate specimens and data from children in the U.S. population
- have highly accurate and reliable laboratory tests that generate data applicable to all clinical laboratories and health care providers
Questions?