Developmental and environmental considerations in analysis of “Big Data” in pediatrics

Jennifer Goldman MD, MS
ADEPT4
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Disclosures

In the past 12 months, I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or providers of commercial services discussed in this presentation.
Objectives

• Highlight key differences in pediatric exposures as compared to adults
• Discuss factors that may influence the interpretation of big data in pediatrics
• Recognize information that is important when evaluating pediatric drug exposure but is not readily available in big data
Making the link between drug exposure and an adverse reaction
Textbook Drug Exposure

- **Duration of action**
- **Therapeutic Range**
- **AUC**
- **C_{max}**
- **Onset time**
- **t_{max}**

Courtesy Steve Leeder ADEPT 2016
Reality as related to exposure

- Dose 0.5 mg/kg
- Mean AUC differs **14.2-fold** between PM and EM2 groups
- **50-fold** absolute range in AUC values

Reality as related to exposure
Four Vs

• Volume
• Velocity
• Variety
• Variability
Four Vs

• Volume
• Velocity
• Variety
• Variability
Volume

Number of participants or data points
Volume

• Fewer drug exposures in pediatrics

• Fewer ADRs identified/reported
  • ADR hospital admission rate
    • Pediatrics 4.1% (IQR 0.16-5.3%)
    • Adults 6.3% (IQR 3.9-9.0%)
    • Elderly 10.7% (IQR 9.6-13.3%)

• Under recognized?

Four Vs

• Volume
• **Velocity**
• Variety
• Variability
Velocity

Estimation of trends within and between people across time
Antibiotic Exposure By Age

Antibiotic Exposure in Infancy and Risk of Being Overweight in the First 24 Months of Life

Antibiotic Exposure During the First 6 months of Life and Weight Gain During Childhood

Children Experiencing TMP-SMX ADRs

Number of cases of TMP-SMX ADRs in hospitalized children

Outpatient Prescribing of TMP-SMX

Four Vs

- Volume
- Velocity
- Variety
- Variability
Variety

Range of measurement types employed across developmental spectrum
<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkaline Phosphatase</strong></td>
<td>0-3 yrs = 110-320 U/L</td>
</tr>
<tr>
<td></td>
<td>3-10 yrs = 140-400</td>
</tr>
<tr>
<td></td>
<td>10-12 yrs = 140-560</td>
</tr>
<tr>
<td></td>
<td>12-14 yrs = 105-420</td>
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<tr>
<td></td>
<td>14-16 yrs = 70-230</td>
</tr>
<tr>
<td></td>
<td>&gt;16 yrs = 50-130</td>
</tr>
<tr>
<td><strong>Aspartate aminotransferase (AST)</strong></td>
<td>0-1wk = 10-100 U/L</td>
</tr>
<tr>
<td></td>
<td>1wk-2yrs = 20-77 U/L</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 yrs = 12-50 U/L</td>
</tr>
<tr>
<td><strong>Gamma-glutamyl transferase (GGT)</strong></td>
<td>0-3 months: 27-210 U/L</td>
</tr>
<tr>
<td></td>
<td>3 months - 1yr: 10-115</td>
</tr>
<tr>
<td></td>
<td>&gt;1yr: 10-78</td>
</tr>
<tr>
<td><strong>Bilirubin, total</strong></td>
<td>0 - 1 mo: 0.6 - 11.1 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 mo: 0.0 - 1.2 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Critical Value: &gt;20.0 mg/dL</td>
</tr>
<tr>
<td><strong>Protein, serum</strong></td>
<td>0-1day = 4.0-6.8 g/dL</td>
</tr>
<tr>
<td></td>
<td>1day-2mos = 5.4-7.4</td>
</tr>
<tr>
<td></td>
<td>2mos-2yrs = 6.2-8.3</td>
</tr>
<tr>
<td></td>
<td>&gt;2yrs = 6.5-8.3</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>0-2mos = 2.0-5.3 g/dL</td>
</tr>
<tr>
<td></td>
<td>2mos-1yrs = 2.7-5.6 g/dL</td>
</tr>
<tr>
<td></td>
<td>1-12yrs = 2.9-5.1 g/dL</td>
</tr>
<tr>
<td></td>
<td>&gt;12yrs = 3.0-5.1 g/dL</td>
</tr>
</tbody>
</table>
Examples of commonly utilized laboratory tests with age-dependent reference ranges

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Endocrine</th>
<th>Immunology/renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Factors V and IX</td>
<td>• IGF-1</td>
<td>• White blood cell count</td>
</tr>
<tr>
<td>• Hemoglobin</td>
<td>• Follicle-stimulating hormone</td>
<td>• Immunoglobulins (IgA, IgM,</td>
</tr>
<tr>
<td>• Partial thromboplastin time</td>
<td>• Luteinizing hormone</td>
<td>IgG and IgE)</td>
</tr>
<tr>
<td>• Prothrombin time</td>
<td>• Thyroxine</td>
<td>• Complement C3 and C4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Creatinine</td>
</tr>
</tbody>
</table>
Age- and Sex-related Reference Ranges of Alanine Aminotransferase Levels in Children: European Paediatric HCV Network

- 1,293 hepatitis C virus-uninfected children
  - ALT levels peaked between 6 and 18 months of age
  - decreased with increasing age
  - lower in girls compared to boys
  - increased with increasing weight for age (z scores)
A

Centiles for ALT levels in males

B

Centiles for ALT levels in females

Clinical chemistry criteria for drug-induced liver injury

• Increase in alanine aminotransferase (ALT) 5 times above the upper limit of normal or baseline value

• Alkaline phosphatase 2 times above the upper limit of normal

• Combination of ALT 3 times above the upper limit of normal and bilirubin 2 times above the upper limit of normal
Four Vs

• Volume
• Velocity
• Variety
• Variability
Variability

Intra-individual variability and complexity
Variability

- Ontogeny
- Genetic variation

Neonate → Infant → Toddler → Child → Adolescent
Activity-based protein profiling of P450 enzymes

Sadler NC et al. Drug Metab Dispos 2016;44:984-991
Human Transport Proteins for Drugs and Endogenous Substances

Variability

The relative abundance values (A) and (B), and the age-related changes in the relative importance of two transporters T1 (C) and T2 (D) in different age groups.

Elmorsi Y et al. Drug Metab Dispos 2016;44:992-998
Textbook Drug Exposure

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Conclusions

• Changes during human development influence drug exposure (both AUC and types of exposure)
• Development and environment must be considered when using big data in pediatrics
• While many variables important in pediatrics can be captured in large data sets, data related to developmental changes may be overlooked or unavailable