Assessment of latest LFT guidelines from American College of Gastroenterology

Gus Koerbin
Focus on ALT

• Review
  – AACB current recommendations
  – RI (examples)
  – Bias
    – Clinical Significance
      • BMI

• AGC Guidelines

• Response to these guidelines
What is our current recommendation?

The AACB has recommended harmonised ALT reference intervals?

**Alanine Transaminase (no pyridoxal-5-phosphate)**

Male: 5 – 40 U/L  
Female: 5 – 35 U/L
ALT – A variety of reference intervals

<table>
<thead>
<tr>
<th>ALT</th>
<th>Level</th>
<th>LRL (U/L)</th>
<th>URL (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORIP Nordic countries (M)</td>
<td>2a) Biological Variation direct</td>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>(F)</td>
<td></td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>NHANES – USA (M) (F)</td>
<td>2a) Biological Variation direct</td>
<td>8</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>SIQAG (M) (F)</td>
<td>3) Professional Recommendation</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>ARQAG (M &amp; F)</td>
<td>3) Professional Recommendation</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>SONIC (M) (F)</td>
<td>2a) Biological Variation indirect</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>ALFRED – Blood donors (M)</td>
<td>2a) Biological Variation direct</td>
<td>12</td>
<td>52</td>
</tr>
<tr>
<td>(F)</td>
<td></td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>Aussie Normals (M) (F)</td>
<td>2a) Biological Variation direct</td>
<td>10</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>AACB (M) (F)</td>
<td>2a,3) BV indirect &amp; Profession</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>35</td>
</tr>
</tbody>
</table>

Adapted from AACB presentations by Tate J, Sikaris K
ALT reference ranges: who is normal?

E Kearney
Department of Clinical Biochemistry, East Kent Hospital NHS Trust, Margate CT9 4AN

A number of our primary care users raised concerns that the reference ranges quoted for ALT (male <41 IU/L, female <31 IU/L) were too low, as they have a large number of slightly raised levels.

The data was transformed with natural logs, which then gave a normal distribution (mean + 1.96 SD, male <71 IU/L (n=3493) female <50 IU/L (n=4398)).

The data was further truncated at 3SD. This gave a normal distribution with lower reference limits (mean + 1.96 SD male <66 IU/L (n=3464): female <46 IU/L (n=4358)).

These reference ranges truly reflect the local population. However, as liver disease can exist even within the reference range, the validity of any range for ALT is questionable.
Analytical bias may prevent harmonisation.

Bias in a laboratory sense is a testing error that causes a systematic favoring of some outcome over others.

Consequence: could prevent a reasonable and objective consideration of a clinical situation.
Bias

Westmead (OCD Vitros)
Difference with and without P5P activation
(Courtesy T Yen)

Patients

Bias samples

Non P-5-P

Average

Difference (%) P5P – no P5P

0% 20% 40% 60% 80% 100%

0 20 40 60 80 100

Average

-20% -10% 0% 10% 20% 30% 40% 50%

0 50 100 150 200 250 300 350

Patients

Non P-5-P

P-5-P

Bias samples
Bias

Bland – Altman analysis of ALT bias.
- Assays using P-5-P activation
- Assays not using P-5-P activation

Liquid serum chemistry

Example RI only

Not sorted by method type
Reference Interval: Clinically Significant

• **Use of reference interval**
  – Discussion with experienced clinicians

• **Confirmation of validity**
  – With clinical colleagues using the test to manage patients

• **Lack of consultation and acceptance**
  – Ignore reference interval
  – Use outdated or obsolete guidelines
Effect of BMI on Reference Intervals

<table>
<thead>
<tr>
<th>Status</th>
<th>UNL for serum ALT levels (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt; 25 kg/m² and nondiabetics (n=859)</td>
<td>37.5</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m² (n=875)</td>
<td>37.85</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m² (n=1053)</td>
<td>59</td>
</tr>
</tbody>
</table>

**The Upper Normal Limit of Serum Alanine Aminotransferase in Golestan Province, Northeast Iran**

Raika Jamali MD*, Akrum Pourshams MD**, Sedighe Amini MD**, Mohammad-Reza Deyhim MSc**, Hoori Rezvan PhD**, Reza Malekzadeh MD*
ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries

Paul Y. Kwo, MD, FACC, FAASLD\textsuperscript{1}, Stanley M. Cohen, MD, FACC, FAASLD\textsuperscript{2} and Joseph K. Lim, MD, FACC, FAASLD\textsuperscript{3}

A true healthy normal ALT level in prospectively studied populations without identifiable risk factors for liver disease ranges from 29 to 33 IU/l for males and 19 to 25 IU/l for females, and levels above this should be assessed by physicians.

Guideline priorities

The guideline panels’ priority of lowering the ALT cut-offs is not to miss cases where disease is present
Table 2. Summary of studies proposing ULN for ALT and or AST levels

<table>
<thead>
<tr>
<th>Author /Year</th>
<th>Proposed ALT ULN (male)</th>
<th>Proposed ALT ULN (female)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuschwander-Tetri et al. (13)</td>
<td>401U/L</td>
<td>401U/L</td>
<td>Gender not specified, not derived from data</td>
</tr>
<tr>
<td>Pithon et al. (18)</td>
<td>42 U/L for males with BMI&lt;23 and 66 U/L if BMI&gt;23</td>
<td>51 U/L for females with BMI&lt;23 and 441 U/L if BMI&gt;23</td>
<td>Derived from reference population with HCV</td>
</tr>
<tr>
<td>Prati et al. (24)</td>
<td>301U/L</td>
<td>191U/L</td>
<td>Derived from reference population</td>
</tr>
<tr>
<td>Lee et al. (25)</td>
<td>331U/L</td>
<td>251U/L</td>
<td>All had normal liver biopsies</td>
</tr>
<tr>
<td>Ruhl and Everhart (26)</td>
<td>291U/L</td>
<td>221U/L</td>
<td>Derived from NHANES</td>
</tr>
<tr>
<td>Wright et al. (34)</td>
<td>331U/L</td>
<td></td>
<td>Gender not specified</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ULN, upper limit of normal.

- **Aussie Normals** [Exclusions (Prati et al) Glucose >5.8, Cholesterol >5.7, Triglycerides > 2.26, BMI >23]

  Male URL n=58: 33 U/L (ACG: 33 U/L)

  Female URL n=95: 28 U/L (ACG: 25 U/L)

American liver guidelines and cut-offs for 'normal' ALT: a potential for overdiagnosis
Mauro Panteghini, Khosrow Adeli, Ferruccio Ceriotti, Sverre Sandberg, Andrea Rita Horvath

The first problem is the analytical variation among commercial assays measuring ALT.

- The mentioned guidelines recommend the use of universal cut-offs for ALT without considering any differences between laboratory assays.
In spite of the availability of a reference measurement system (RMS) for standardizing ALT

- Current evidence: ALT is still measured by methods that give quite differing values.
- Assay performance varies considerably within users of instruments from the same manufacturer.
- For measuring aminotransferases, almost all manufacturers still market assays with or without the addition of pyridoxal-5-phosphate (P-5G-P), and declare:

  “both are traceable to the RMS”

BUT.....it is impossible to calibrate procedures for aminotransferases that do not incorporate P-5G-P using a procedure that does.

• This is immediately evident when looking at the CALIPER data.
## Caliper

### Alanine Aminotransferase

#### Without Piridoxal Phosphate [ALT]

<table>
<thead>
<tr>
<th>Age</th>
<th>Female Reference Interval</th>
<th>Male Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower Limit</td>
<td>Upper Limit</td>
</tr>
<tr>
<td>13 - &lt; 19 yrs (with P5P)</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>13 - &lt; 19 yrs (without P5P)</td>
<td>8</td>
<td>22</td>
</tr>
</tbody>
</table>
Missed diagnosis vs overdiagnosis

“Due to inappropriate application of the laboratory-related concepts, there is a danger that a universally recommended URL for ALT will flag a large number of subjects in whom the ALT testing will potentially generate overdiagnosis with unnecessary further investigations and health care costs”
Flagging Rates

- **Males (n=274):**
  - Guideline recommended cut-offs are 29 and 33 U/L
  - Flagging rates in hospital population at >29 U/L: 42%; at >33 U/L: 30%
  - Flagging rates in healthy volunteers at >29 U/L: 41.5%; at 33 U/L: 28%

- **Females (n=668):**
  - Guideline recommended cut-offs are 22 and 25 U/L
  - Flagging rates in hospital population at >22 U/L: 37%; at >25 U/L: 27.5%
  - Flagging rates in healthy volunteers at >22 U/L: 34%; at >25 U/L: 24%

*The ALT flagging rates were established on a small but representative sample of adults. NB: our patient population is not ideal for such checks as we are a tertiary centre. Outpatient or GP data would be more powerful, although we also checked flagging rates on over 200 healthy volunteers and the flagging rates are very similar.*

Supplied by R. Horvarth
Non alcoholic fatty liver disease (NAFLD)

• No outcome data on patients screened vs. not screened by ALT for NAFLD.
• In such cases, obesity is the underlying pathophysiology needing intervention.
• Recent guideline by the National Institute for Health and Care Excellence (NICE) in the UK does not consider a similar screening scenario for NAFLD,
  – and its evidence summary is helpful in demonstrating that there is hardly any or very weak evidence to support the use of ALT as a screening tool for this clinical condition.
Adequate consultation?

• In the American guideline panels no laboratory professionals were involved to offer specialist advice on the critical appraisal of the evidence on ALT URLs published in the literature.

• The NICE guideline involved a laboratory expert in its panel and their conclusions and recommendations related to the clinical utility of ALT significantly differ.
Panteghini conclusions

• Strongly believe that only a multidisciplinary approach helps focussing guideline panels on important laboratory-related items that can influence the implementation of recommendations and subsequent health care outcomes.

• The issues raised clearly highlight the critical need for laboratory expertise when drafting clinical guidelines involving the use of laboratory tests.
What to do now?

- Review the AACB current recommendations?
- More Consultation?
  - Laboratory
    - Endorsement
      - Methodologies; P-5-P?
  - Clinical
    - BMI partitioning recommendations?
- Discussion (Prof. Rita Horvarth)