Change in Albumin Methodology (June 2015)

As of Tuesday 2nd June 2015 the two laboratories in the Canterbury region, Canterbury Health Laboratories (CHL) and Canterbury Southern Community Laboratories (CSCL) will be changing albumin assays, with the introduction of a more accurate and specific method. This is part of a national (and global) effort to harmonize assays and reference intervals to bring greater consistency between laboratories.

KEY MESSAGES

• The new method is more specific, resulting in a more accurate measure of albumin.

• Results will be on average lower by 4-5 g/L. Greater differences may be seen in patients with low (<30g/L) albumin levels. (e.g. on average 6-8 g/L for dialysis and ICU patients)

• A new reference interval for serum albumin will apply.

• A note will be appended to albumin results regarding new method and reference intervals.

• A new formula will be applied for calculation of corrected calcium. Corrected calcium results should not change on average.

• This change has already occurred in Auckland, Wellington and Waikato, together with other centres in Australia and globally.

Current status of albumin measurement

The most common methods for measuring albumin are dye binding methods and antibody-based (immunochemical) methods.

• **Dye-binding** (‘colorimetric’) methods measure albumin concentration by binding to a dye, and are in wide use. There are two main dyes used:
  - **Bromcresol green (BCG)**, traditionally the main one used previously in New Zealand.
  - **Bromcresol purple (BCP)**, which is increasingly used internationally. Laboratories in Auckland, Wellington and other regions have already changed to the BCP method.

• **Immunochemical** methods are most sensitive and useful for detecting low albumin concentrations (e.g. for albumin:creatinine ratio in detecting microalbuminuria). This is the most accurate method but is too expensive for routine use.

Changes in dye binding method

• BCG lacks specificity towards albumin and reacts with other serum proteins, especially alpha-1 and alpha-2 globulins, causing significant overestimation of albumin. Studies show a mean bias of +1 to +5 g/L compared with ‘gold standard’ (immunochemical) methods. This difference is most marked at low albumin levels (<30g/L). 1-5

• BCP is more specific for albumin, hence more accurate. 1,3,5 Some reports questioned the performance of BCP in haemodialysis patients, as BCP can under-estimate albumin due to cross-
reactivity with a uraemic toxin. However the cross-reactivity is seen in only a small proportion of the patients and overall BCP is still superior for haemodialysis patients.  

- Nearly 40% of laboratories in Australia, and 54% of accredited laboratories in US are using BCP.

Clinical impact of the new BCP albumin assay

- **Reference interval**
  - BCP results will be on average lower by 4-5 g/L and a new reference interval will be implemented.
  - See table 1 for new reference intervals, which will apply in Canterbury.

- **Corrected calcium results**
  - Corrected (adjusted) calcium concentrations are calculated to compensate for albumin concentration, allowing a single reference interval to be used irrespective of albumin level.
  - Several formulae are available and these equations are dependent on the calcium and albumin methods used.
  - A new formula will apply for BCP albumin, by James et al 2008.  
    - **New formula**: \( [\text{Ca adjusted}] = [\text{Ca actual}] + 0.012 \times (39.9 - \text{[albumin]}) \)
  - Results from our laboratory suggest that corrected calcium results using the new formula will not change on average, although there may be changes in some patients.

- **Globulin results**
  - Globulin is a calculated value (Globulin = total protein – serum albumin)
  - With lower albumin results, the calculated globulin result will be higher than previously.

- **In haemodialysis patients**
  - BCP can underestimate albumin in a small proportion of patients due to the presence of a uraemic toxin (carboxy-methyl-propyl-furanpropanoic acid, or CMPF).
  - However, in general, overestimation by BCG in these patients is more significant problem and BCP albumin results are still more accurate overall in this patient group, especially in the low range of most clinical importance.

- **Multiple myeloma staging**
  - International staging system for MM does not specify a preferred method for albumin determination.
  - Different stages based on β2 microglobulin levels and albumin >35 g/L or <35 g/L
  - Australasian Working Party on Standardized Reporting of Protein Electrophoresis recommends using BCP (or capillary zone electrophoresis) to measure serum albumin but BCG is still acceptable.

- **In cirrhotic patients**
  - More than 40 years ago, in Child’s classification, serum albumin was measured by a colour reaction that shows poor specificity for albumin. The reference interval at the time was 46 to 67 g/L, which is considerably higher than that used at present.
  - Therefore the cut off of 35 g/L used for Child-Pugh score at the time was considered significantly low, but the same cut off is currently being used worldwide even though the analytical method has improved and reference interval is much lower.
  - It is recognised that some clinicians prefer the alternative MELD score, which does not include serum albumin.

- **Other clinical situations**
  - Measurement of albumin in urine (albumin:creatinine ratio), and in CSF, will still be performed using an immunochemical method and will not change.
  - Other fluids (e.g. ascitic fluid): lower albumin levels may be seen with the new BCP method, but the difference should be small as these fluids would contain less interfering proteins (alpha-1 and alpha-2 globulins).
Figures and tables

Figure 1. Comparison between two dye-binding methods (BCG and BCP) and immunoassay (gold standard). BCG consistently over-reads serum albumin and more markedly at lower concentrations. 3

Table 1. Albumin reference intervals (g/L)

<table>
<thead>
<tr>
<th>Age</th>
<th>Old RI</th>
<th>New RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 days</td>
<td>30-45</td>
<td>28-41</td>
</tr>
<tr>
<td>&gt;14d - 1 yr</td>
<td>30-45</td>
<td>28-45</td>
</tr>
<tr>
<td>&gt;1 yr - 8 yr</td>
<td>35-50</td>
<td>35-45</td>
</tr>
<tr>
<td>&gt;8 yr - 15 yr</td>
<td>35-50</td>
<td>37-47</td>
</tr>
<tr>
<td>&gt;15 yr - adult</td>
<td>35-50</td>
<td>34-48</td>
</tr>
</tbody>
</table>

For reference only (will be available in Test Manager)

<table>
<thead>
<tr>
<th>Pregnancy - trimester</th>
<th>New RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-14 wks</td>
<td>33-45</td>
</tr>
<tr>
<td>&gt;14-28 wks</td>
<td>27-37</td>
</tr>
<tr>
<td>&gt;28-42 wks</td>
<td>25-35</td>
</tr>
</tbody>
</table>

Globulin reference intervals (reported by CSCL only) will be simplified into fewer age partitions and be about 5 g/L higher than previously. (eg current adult reference interval is 18-36 g/L)

Table 2. Globulin reference intervals (g/L)

<table>
<thead>
<tr>
<th>Age</th>
<th>New RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 m</td>
<td>&gt;16</td>
</tr>
<tr>
<td>&gt;3m – 1 yr</td>
<td>&gt;18</td>
</tr>
<tr>
<td>&gt;1 – 4 yr</td>
<td>22-35</td>
</tr>
<tr>
<td>&gt;4 yrs</td>
<td>25-41</td>
</tr>
</tbody>
</table>

In-house new method (Albumin BCP) and between method (Albumin BCG vs BCP) evaluation data are available for review on request.
References