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Measurement of Serum Immunoglobulins: A National Survey of Practice

A. Beverland, T. Cronin, K. Khalib, M. Keogan

Department of Immunology, Beaumont Hospital, Dublin, Ireland.

Abstract

Aim

To survey how serum immunoglobulins (IgG, IgA, IgM) are measured and reported across public hospitals in Ireland.

Methods

We developed a seven-point questionnaire to elicit the methodology, reporting and reference intervals of serum immunoglobulins. It was distributed electronically by email to sixteen laboratory managers of Irish public hospitals.

Results

A total of twelve questionnaires were completed. The test method was the same in each laboratory, whilst the analyser and source of the reference intervals varied. In some institutions, the reference interval differed within the adult age population and for sex. The IgG parameter contained the highest spread of results. The lower reference limit ranged 5.4-8.0 g/L, with a standard deviation of 0.81, and the upper reference limit ranged 14.9-18.2 g/L (SD 1.04).

Conclusion

Considerable variation exists in the reference intervals of serum immunoglobulins within different Irish public hospitals. This has important implications for users of the test, patients and referral patterns.

Introduction

The measurement of serum immunoglobulins provides an assessment of the humoral immune system. The test comprises of three out of the five circulating immunoglobulins – IgA, IgG and IgM.

Low immunoglobulin states may indicate immunodeficiency, and abnormalities may constitute diagnostic criteria.

The international consensus on the diagnosis of Common Variable Immunodeficiency (CVID) include a serum IgG result as two standard deviations below the age-related mean[1], with most reference intervals defined as two standard deviations above and below the age adjusted mean. Other proposed CVID definitions specifically denote an IgG below 5 g/L (in adults)[2].

Meanwhile, high levels of immunoglobulins may be polyclonal or monoclonal, and can be associated with liver disease, chronic inflammatory conditions and haematological disorders[3].

In our institution, we are frequently referred patients from different geographical regions for further assessment of immunodeficiency due to an immunoglobulin result falling below the reference interval in the laboratory where the sample was tested. However, there are significant differences in serum immunoglobulin reference intervals used across different laboratories.

As a result, we sought to investigate the measurement and reporting of serum immunoglobulins across public hospitals in Ireland.

Methods

We developed a seven-point questionnaire that was designed to elicit; test methodology, reporting, and reference intervals of serum immunoglobulins (*link*). It was distributed electronically by email to sixteen laboratory managers of Irish public hospitals where serum immunoglobulin testing was performed. A follow up email was sent two weeks later, and specific targeting of responses was subsequently performed to non-responders. Simple descriptive statistics were used to analyse the data, including range and standard deviation.

Results

A total of twelve out of sixteen questionnaires were completed. All laboratories used the same test method (immunoturbimetry) and reported in the same units (g/L). In 9 out of 12 cases, serum immunoglobulins were performed in a biochemistry laboratory, whilst the remainder (*n*=3) were conducted in an immunology laboratory.

Three different diagnostic platforms (Abbott, Beckman-Coulter, and Roche) were used to perform serum immunoglobulin measurement. In three laboratories a serum protein electrophoresis was automatically performed alongside an immunoglobulin request. The most common source of the reference interval was the manufacturer's instructions for use (IFU) (*n*=9), followed by in-house validation (*n*=3), and then external laboratory (*n*=2).

Ten institutions indicated age specific reference intervals for paediatric age groups. In five laboratories different age specific reference intervals were also used within the adult population for IgA and in one laboratory for IgM. In two laboratories, reference intervals also differed according to sex in the adult population.

The surveyed adult reference interval for IgG had the highest spread of results. The lower reference limit (LRL) ranged 5.4-8.0 g/L, with a standard deviation (SD) of 0.81, and the upper reference limit (URL) ranged 14.9-18.2 g/L (SD 1.04). IgM had the lowest spread, with the LRL between 0.22-0.5 g/L (SD 0.09) and URL 1.8-2.9 g/L. For IgA, the LRL ranged from 0.61-0.9 g/L (SD 0.07), with the URL between 2.8-6.45 g/L (0.71).

Reference intervals were similar from laboratories using the same analyser, whilst those derived from in-house validation tended to have narrower reference intervals (*Figure 1*).

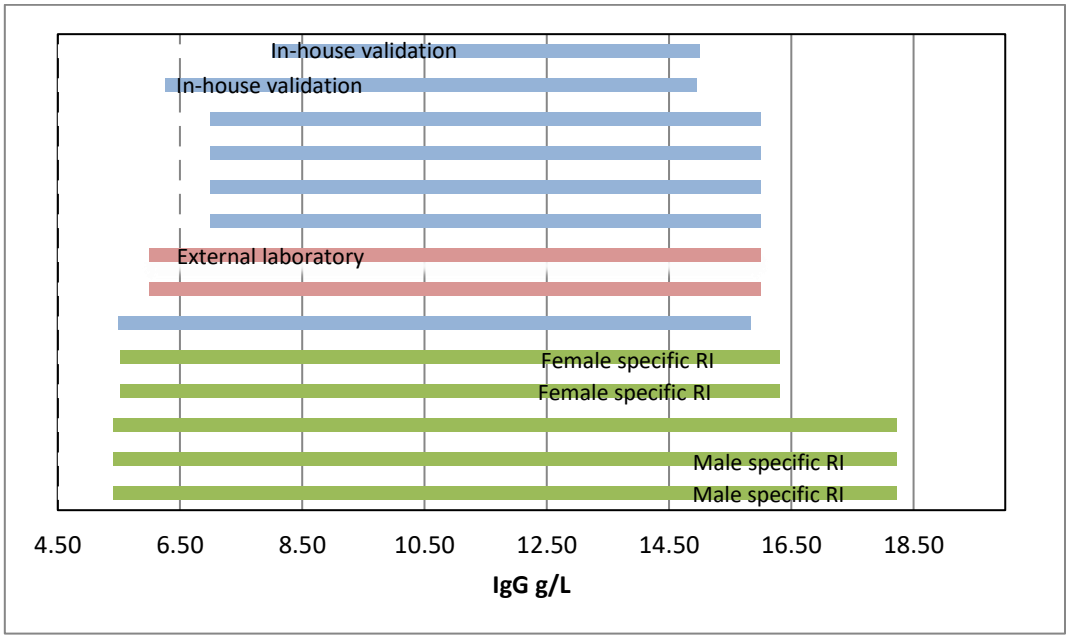

Figure 1. *Graphical distribution of adult IgG reference intervals across surveyed laboratories. The analyser platform is denoted by the colour. Blue = Roche; Red = Beckman-Coulter; Green = Abbott.*

Discussion

Considerable variation exists in the reference intervals of serum immunoglobulins within different Irish public hospitals. This has important implications for users of the test, patients and referral patterns.

The most frequent source for the reference intervals recorded in our survey was from the manufacturer's IFU. Manufacturer's IFU recommend that each laboratory investigate the transferability of the expected values to its own patient population and if necessary determine its own reference interval based upon its particular location and population characteristics[4].

Indeed, clinical laboratories seeking accreditation for compliance with ISO 15189:2012 need to demonstrate that reference intervals communicated to all users of the laboratory service are appropriate for the patient population served and for the measurement systems used[5].

Previously, efforts have been made to standardise immunoglobulin measurement at national levels. The release of 'Certified Reference Material 470', prepared from serum collected from several hundred healthy donors in five European cities, was used as the international standard for fifteen commonly measured plasma proteins, including IgG, IgA, and IgM[6]. These were then used to derive interim reference intervals independent of the system or instrument used[7], with Roche continuing to use these for their reference intervals[4].

Harmonisation of reference intervals, when scientifically appropriate, aims to create uniform interpretation of results and prevent delayed diagnosis and unnecessary investigation caused by a greater variation in reference interval than in the measurement of specimen itself. Whilst there are arguments for harmonisation of immunoglobulin reference intervals in Ireland, efforts may be limited by a current reliance on the different manufacturer's IFU as a source for reference intervals. Nevertheless, European External Quality Assurance (EQA) data has shown low between-manufacturer variances for immunoglobulins (4.8% , 8.1 % & 6.2% for IgG, IgA and IgM respectively.[8]

Indeed, there are examples of successful harmonisation projects within Ireland, including recommendations on standardised reference intervals for ten common clinical chemistry analytes[9] and harmonisation on prostate specific antigen assays to better inform decision making around prostate biopsy[10]. Furthermore, the introduction of the new National Laboratory Information System (MedLIS) presents an opportunity to optimise the reporting of reference intervals across Ireland. Consideration should be given towards using the same source for reference intervals amongst the different laboratories. Additionally, a standard practice should be developed in relation to the testing of serum protein electrophoresis alongside serum immunoglobulin measurement, given the discrepancy in this practice that was identified from this survey.

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Declaration of Conflicts of Interest:
The authors declare no conflicts of interest relating to this work.

Corresponding Author:
Dr Mary Keogan
Department of Immunology,
Beaumont Hospital,
Dublin 9.
E-Mail: mariekeogan@beaumont.ie

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