Mon, 23 h9.00 - Laboratory Reference Intervals: Global Initiatives and Harmonization Challenges

HARMONISATION OF LABORATORY REFERENCE INTERVALS: THE AUSTRALIAN EXPERIENCE

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Introduction

Harmonisation of reference intervals (RIs) refers to use of the same or common RI across different platforms and/or assays for a specified analyte. It occurs optimally where there is sound calibration traceability and evidence from a between-method comparison shows that bias would not prevent use of a common RI. The concept of harmonised RIs is a pragmatic approach to the use of RIs within a country that aims to reduce the unwarranted variation in RIs between laboratories hence enabling similar interpretation of laboratory results across Australia.

Methods

An evidence-based harmonisation process has been developed and incorporates a checklist approach to assess: 1) common laboratory usage and assay calibration traceability; 2) method differences (bias study); 3) evidence for selection of a common RI by searching the literature, lab surveys, local RI studies, and manufacturers' product information, data mining, and determining an acceptable bias goal; and 4) clinical implications of the RI (flagging rates). Validation of RIs by local laboratories can be by a simple validation using 20 normal subjects, or mining your laboratory's existing data. Surveillance of RI uptake is through the Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP).

Results

Harmonisation workshops are held annually in Australia to discuss, select and agree upon common chemistry RIs. Harmonised RIs have been selected so far for 18 analytes in adults, nine analytes in children and five for pregnancy. The common RIs that have been selected compare well with those from the recently conducted Aussie Normals study but are slightly wider as there is greater measurement variance when an interval is determined for eight manufacturers' platforms. Surveillance by the RCPAQAP indicates a constantly increasing implementation of the common RIs within Australia and New Zealand.

Conclusions

Harmonisation of RIs is a continuing project in Australia and New Zealand that is being led through the profession, namely the Australasian Association of Clinical Biochemists and RCPA. Harmonisation aims to create uniform interpretation of results and prevent misdiagnosis caused by a greater variation in RI than in the measurement result.

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CLOSING THE GAPS IN PEDIATRIC REFERENCE INTERVALS: THE CALIPER AND CHMS INITIATIVES

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Clinical laboratory reference intervals provide valuable information to medical practitioners in their interpretation of quantitative laboratory test results, and therefore are critical in the assessment of patient health and in clinical decision-making. The reference interval serves as a health-associated benchmark with which to compare an individual test result. Unfortunately, critical gaps currently exist in accurate and up-to-date pediatric reference intervals for accurate interpretation of laboratory tests performed in children and adolescents. These critical gaps in the available laboratory reference intervals have the clear potential of contributing to erroneous diagnosis or misdiagnosis of many diseases. To address these important gaps, several initiatives have begun internationally by a number of bodies including the KiGGS initiative in Germany, the Aussie Normals in Australia, the AACC-National Children Study in USA, the NORICHILD Initiative in Scandinavia, and the CALIPER and CHMS studies in Canada. In the current presentation, I will review the recent worldwide initiatives in pediatric reference intervals, and discuss the concept and feasibility of common reference intervals. I will also discuss the recently published CALIPER and CHMS reference interval databases. CALIPER (www.caliperdatabase.ca) has recently developed age and gender specific pediatric reference intervals for a larger number of assays, based on a large and diverse healthy children cohort. The CALIPER database is based on a multiethnic population examining the influence of ethnicity on laboratory reference intervals. Thus the database has proved to be of global benefit and is being adopted by hospital laboratories worldwide.

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GLOBAL PROJECT TO DETERMINE REFERENCE INTERVALS IN HARMONIZATION

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Objectives:
From 2011, the IFCC Committee on Reference Intervals and Decision Limits (C-RIDL) coordinated the global multicenter study on reference values (RVs) with participation from 19 countries across 5 continents. The primary objective was to explore a rational protocol for conducting the reference interval (RI) study applicable to any country. It included evaluation of statistical theories described in the IFCC/CLSI guideline by actually conducting the study on a large scale. The issues addressed were (1) number of samples required, (2) rationale for secondary exclusion, (3) how to examine the need for partitioning RVs, (4) selection between parametric and nonparametric methods. The second objective was to investigate the feasibility of sharing the RIs in common in consideration of ethnicity/regionality based-on this first worldwide study ever conducted.

Methods:
To ensure harmonization a pragmatic approach was used to recruit subjects who considered themselves to be healthy for this study. Inclusion criteria that were not too strict with respect to personal habits, BMI and medication were developed and used through consensus. This pragmatic policy facilitated the recruitment process, but entailed the need for secondary action to exclude subjects with common conditions such as metabolic syndrome, inflammations, and excessive exercise. It was empirically done through the use of the latent abnormal values exclusion (LAVE) method. For validating the common use of RIs, a serum panel for aligning RVs across the countries by all-pairwise regression-line analyses was utilized. Value assignment of the serum panel was performed to make each country's RIs traceable to reference measurement procedures for standardized analytes.

Results:
In each country most volunteers who enrolled had profiles of apparently healthy subjects with low percentage of them being under regular medication. Interim analyses of RVs for 50 major analytes from 12 countries consisting of 13,400 healthy volunteers were performed. As expected, the LAVE method led to obvious changes in RIs for nutritional, inflammatory and muscle markers, such as TG, ALT, GGT, CRP, LDH and CK. This implies that there is a need for secondary exclusion to cope with latent abnormalities which occur no matter how carefully volunteers are selected. In contrast, the LAVE procedure was unnecessary for other analytes whose values are rarely abnormal among the healthy. To assess the need for partitioning RIs, simple stratification and testing differences between subgroups was occasionally not appropriate and the multivariate judgement was required to avoid mutually confounding influences of sex, age, and BMI. For the final decision to partition by a given factor, the ANOVA-based SD ratio (SDR) was found useful as a guide. The validity of the parametric method was confirmed by the presence of analyte-specific distribution patterns and invariably successful Gaussian transformation using the modified Box-Cox formula in all countries. A better performance of the parametric method was shown by generally narrower 90% confidence intervals (CIs) of RI limits and successful exclusion of tailing values which remained even after applying the LAVE method. Regarding the sample size, our target of 250 for each sex was found acceptable with narrower 90% CI than using a smaller size of 100. Unacceptably large between-country differences in two third of analytes were observed after alignment of RVs

Conclusion:
Our collaborative experience has shown that the task of deriving RIs has several complicated aspects, the output of which depends on the design of the study and the manner in which it is implemented. Dataset generated from this study is available for validation as well as the software. RIs for one third of analytes without appreciable between-country differences can be shared worldwide, but should be preferably done after RVs from 7 other countries become available for a more comprehensible analyses.