Introduction of automatically generated comment in clinical biochemistry: an audit of technical effectiveness

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Laboratories in the UK have seen a large increase in the number of tests requested since the introduction of the new General Medical Services contract in 2004. This increase is in addition to the underlying steady increase observed over the past few decades. However, a steep increase was not unexpected, as specific clinical biochemistry assays are mentioned specifically in the contract.[1, 2]

The clinical biochemistry laboratory in Ipswich analyses approximately 3.5 million tests per annum and has seen an increase in workload of approximately 45% since 2004. The increase in requests has also been associated with an increase in the requesting of more specialised tests. Despite these increases, staffing levels have remained relatively static; thus, productivity per staff member has increased year on year. In addition, quality expectations are increasing with each update of Clinical Pathology Accreditation (UK) standards.

This study considers the implications of this workload increase on the ability to apply specific technical input and investigates the implications for performance of the high-density lipoprotein (HDL)-cholesterol (HDL-C) assay, where sample pretreatment may be necessary prior to assay.

The laboratory determined HDL-C concentration using a method that employs an anti-human β-lipoprotein antibody that binds to non-HDL lipoproteins and allows the quantification of HDL-C by the presence of a cholesterol esterase and cholesterol oxidase/peroxidase (CHE and CHO/POD) enzyme chromogen system (Olympus Life and Material Science Europa, Lismeehan, Co. Clare, Ireland) on an Olympus AU600 or more recently an Olympus AU2700 analyser.

Triglycerides were determined using a glycerol phosphate oxidase phenol-aminophenazone method (GPO-PAP; Olympus) on either an Olympus AU600 or AU2700 analyser, as above. The manufacturer recommends that specimens for HDL-C determination be diluted with saline (no dilution factor stated) when the triglyceride concentration is >11.3 mmol/L (>1000 mg/dL). Previously, this laboratory did not dilute such specimens, and informal discussion with colleagues elsewhere indicated that the authors were not alone in this respect.

The need for dilution was evaluated and showed that the majority of undiluted HDL-C specimens would produce lower results when triglyceride concentration was >11.3 mmol/L.[3] As a result, the standard operating procedure (SOP) was amended to indicate that all HDL-C requests with a triglyceride concentration >11.3 mmol/L should be diluted with normal saline (one part serum plus two parts normal saline). Subsequently, a rule-based comment was implemented using the laboratory information system (LIS) to alert the biomedical scientist staff that a sample required dilution with saline due to triglyceride concentration >11.3 mmol/L.

It was decided to carry out an audit to evaluate the technical effectiveness of this change to the SOP and the introduction of the automatically generated comment by the LIS.

The laboratory specimen number and triglyceride concentration for all HDL-C requests received from 1 May 2003 to 6 July 2006 with a triglyceride concentration >11.3 mmol/L were obtained from the LIS. The pre- and post-dilution HDL-C concentrations were obtained manually from the LIS audit trail to verify that dilution had been performed. Depending on request date, the specimens were assigned to the following period groups: no laboratory policy (dilution not performed), evaluation (different dilutions evaluated but undiluted concentrations reported), SOP (all appropriate specimens diluted) and LIS-generated comment (rule-based alert to indicate the need for dilution).

There were 18, 10, 17 and 25 requests for HDL-C where the triglyceride concentration was >11.3 mmol/L in the no laboratory policy, evaluation, SOP and LIS-generated comment periods, respectively. No specimens were diluted in the no laboratory policy and SOP periods; however, 21 out of the 25 specimens received during the LIS-generated comment period were diluted. To date, there has been no follow up of the four specimens that were not diluted during the LIS-generated comment period. Once validated, such specimens are usually assumed to be analytically correct when being validated clinically.

This audit shows that merely incorporating a change in practice in an SOP is insufficient in a modern laboratory with a high throughput of samples. This was not unexpected due to the relative infrequency of hypertriglyceridaemia >11.3 mmol/L (70 specimens with triglycerides >11.3 mmol/L had HDL-C requested during the 38-month audit) and the significant increase in the total number of tests analysed per staff member. However, the LIS is capable of automatically alerting the biomedical staff to the fact that significant hypertriglyceridaemia exists and that the specimen requires dilution, irrespective of frequency and workload.

The present study demonstrates that use of a LIS is a more effective means of changing practice than amendment to an SOP and manual identification of the required specimens. It is possible that the use of middleware (software that sits strategically between analytical instruments and the LIS) may improve the figures yet further by triggering specimen dilution without the need for human intervention.

As laboratory workload and complexity continue to increase, automated systems will need to be implemented in order to maintain or even improve quality, and analytical platforms increasingly employ IT solutions such as automated dilutions[4] and simple automatic repeat and cascade reflex testing.[5] However, the technical issue raised is more complex because the quality of one result depends on the concentration of a second analyte. Accordingly, few if any analytical platforms available currently can deal with this issue.

The situation described here is similar to the analytical issues with indirect sodium electrodes and high total protein[6] or triglyceride concentrations. These are relevant to

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most laboratories and thus others should evaluate their technical service.

Systems such as middleware and LIS are perfect for overcoming such technical problems as they allow laboratories to approach a given problem in a timely, consistent and standardised fashion. Thus, once the appropriate programming is in place, analytical problems that occur several times a day are dealt with in the same appropriate way as are those that occur only monthly or even less frequently.

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Detection of HCV antibody-negative donations: Saudi experience with nucleic acid testing

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Currently, the risk of contracting hepatitis C virus (HCV) or human immunodeficiency virus (HIV) in the blood transfusion setting is very low. The sensitivity of donor screening using serological tests and donor selection practices ensures that transfused blood is an extremely safe product. However, there is a small residual risk of infection from individuals who test serologically negative during the so-called window period or from immunosilent infectious donors.

In 1999, the European authorities required all plasma for fractionation to be tested for HCV RNA, which led many European blood services to implement HCV nucleic acid amplification testing (NAT) in small pools. Subsequently, the UK and other European countries implemented HCV NAT as a release criterion for all blood components (including platelets). In the USA, the American Association of Blood Banks (AABB) recommended mandatory screening for blood donors from March 1999.[1]

Jarvis *et al*.[2] reviewed the yield of serologically negative, nucleic acid-positive window-period donations and described lower than expected detection rates following NAT for antibody-negative HCV and HIV-1 donations. They suggest that the donor health assessment questionnaire has improved the safety of the blood supply greatly, hence the low rates of detectable infection.[2] Similar results have been obtained in Canada.[3]

The prevalence of HCV antibodies in Saudi blood donors is estimated at 0.6–1%.[4] However, results suggest that the majority of blood donors who are anti-HCV-positive by the screening method are negative by recombinant immunoblot assay (RIBA).[5] Blood donors who attend the authors' hospital mainly comprise male National Guard soldiers. Prior to donation, donors undergo strict selection criteria as laid down by the AABB.

Currently, all blood donations in the authors' hospital are tested for HCV and HIV-1 using the Abbott Architect serology screening platform and also by NAT, with HCV and HIV NAT implemented in April 2006.

The present short study describes the NAT methodology used in the Saudi National Guard Health Affairs programme and describes the first NAT-positive, seronegative HCV case.

All blood units were tested routinely for HBV, hepatitis C virus (HCV), HIV, syphilis and human T-lymphotropic virus (HTLV) by serology. Sera with a signal-to-cut-off ratio (S/CO) ≥1.0 were considered reactive, whereas sera with a S/CO <1 were considered non-reactive. All initial reactive specimens were retested in duplicate.

A plasma preparation tube (K3 EDTA, Greiner Bio-One, Germany) was collected from each donor who demonstrated HCV and HIV seronegative results and submitted for NAT testing. A minipool of 24 donors was prepared by mixing equal quantities of plasma from seronegative donors. Positive primary pool results were resolved in four secondary pools of six donors. If a secondary pool proved to be positive then all six pool samples were tested individually.

Nucleic acid was extracted from a 1 mL plasma pool using the AmpliPrep total nucleic acid isolation kit and the Cobas AmpliPrep instrument (Roche Molecular System, Branchburg, NJ, USA). An internal control was added to each pool specimen in order to monitor the extraction and amplification efficiency. Following the manufacturer's recommendation, a 50 µL sample of the extracted nucleic acid was mixed with an equal volume of the Cobas AmpliScreen HCV (version 2.0)/HIV-1 (version 1.5) reagents to amplify and detect HCV/HIV RNA. The final amplified products for both targets and the internal controls were determined by measuring colorimetric absorbance at a wavelength of 660 nm using the Cobas Amplicor analyser (Roche).

Total HCV nucleic acid (RNA) was extracted from 1050 µL patient plasma using the Cobas AmpliPrep instrument and the Cobas TaqMan HCV test kit (Roche), following the

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