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Developing optimized automated rule sets for reporting hemolysis, icterus and lipemia based on *a priori* outcomes analysis

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ABSTRACT

Background: There is limited information about the effects of instituting CLSI Document C56A recommended workflows for the automated detection of hemolysis, lipemia and icterus (HIL) in different clinical laboratories and patient populations. We describe a process to develop and tailor automated reporting rules that are appropriate for the local laboratory population.
Methods: Automated decision algorithms were generated and applied to 2 high volume labs serving community and hospital populations. Proposed rules were applied to the datasets offline to predict the outcomes, and then were further optimized prior to implementation.
Results: Introduction of automated serum indices decreased HIL flagging compared to manual flagging. Hemolysis flagging was the greatest in all 3 patient populations, and was successfully reduced for LD, CK and AST by optimized rules that incorporated both the H-index result and the analyte result. Changes in flagging rates were also patient population specific, particularly for icterus which was a problem in hospitalized populations but not in the community. Overall, concordance between manual and automated flagging methods was very low in both laboratories.
Conclusions: We demonstrate that flagging algorithms may not be universally transferable due to lab specific and population specific factors and demonstrate the benefits of local, *a priori* testing of algorithms prior to implementation.

1. Introduction

Hemolysis, icterus and lipemia (HIL) interferences are common pre-analytical sources of error in the clinical laboratory [1–4]. Determination of HIL interferences has traditionally been done by manual visual grading by technologists; however, this process is highly subjective and variable [5–7]. Serum indices are a semi-quantitative measurement of HIL interference, using spectrophotometric measurement and mathematical correction to determine the level of interference. Serum indices are less subjective than manual grading, can be automated, and negligibly impact turnaround times [8].

CLSI document C56A provides guidance on the use of serum indices for measurement of HIL interference [1]. It recommends selection of assay specific HIL cut-offs, above which HIL interferences will affect results, and development of algorithms to deal with samples exceeding the HIL cut-offs (*e.g.*, cancelation, report with comment). HIL cut-off selection and algorithm design is left to the discretion of each laboratory.

Although serum indices have been available for several years, there is limited information about their implementation in clinical laboratories, either for selection of assay specific HIL cut-offs or development of algorithms. One study has looked at retrospective development and implementation of algorithms for processing HIL interferences [6]. The authors investigated the changes to HIL flagging after switching from visual inspection to automated indices and found large increases in flagging for all 3 interferences. Test specific flagging rates were not included so it is uncertain if the flagging increases were seen across many tests or dominated by a few interference prone assays. It is also unknown if increased flagging would be seen in other patient populations (community *vs.* hospital). The large increase in flagging suggests that flagging analysis prior to implementation may be necessary in order to minimize the impact of introducing automated serum indices on lab workflow and provide adequate notification to physicians of the anticipated changes to reporting.

We outline a process to develop and test an HIL algorithm with the overall goal of producing a process that can identify specimens with interference levels relevant to the tests ordered; alert technologists to the

Abbreviations: HIL, Hemolysis, icterus, lipemia; CLSI, Clinical Laboratory Standards Institute; LIS, Laboratory information system.

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interference if intervention is required; provide interpretive information to physicians about specimens with interference; cancel the least number of tests; and avoid adverse effects caused by failure to report results with HIL interference.

2. Materials and methods

2.1. Ethics

This project is classified as quality assurance in nature by our institutional Co-joint Health Research Ethics Board and is granted exempt status for research ethics review.

2.2. Demographics

Data from 2 high-volume community labs and one group of hospital labs were analyzed in this study (Table 1). Lab A is a high volume lab in Ontario, Canada with 3 locations serving western, central and eastern Ontario. Labs B1 and B2 serve the same city in Alberta, Canada. Lab B1 is a centralized, high volume laboratory serving the community population while Lab B2 is a combination of 5 urban hospital labs serving different sub-populations. Labs B1 and B2 were analyzed separately because of the differences in population served, instrumentation and test menus.

2.3. Lab inclusion rationale

2.3.1. Patient population

No data is currently available comparing the application of identical HIL algorithms to different patient populations (e.g. hospital *vs.* community, community *vs.* community). To address this, 2 community labs (Labs A and B1) and one hospital lab (Lab B2) were included in the present study.

2.3.2. Effect on existing methods to detect HIL interference

Only one study investigating one lab has been published describing the effects of switching from manual grading to automated serum indices. To determine if the same effects are seen in other labs making this transition, data from 2 labs were included (Labs A and B2).

No data is available to determine if the index cut-offs and algorithms need to be periodically evaluated and revised or if they can be left alone indefinitely. In this study, Lab B1 was included to evaluate this question, as it was re-evaluating its automated serum index rules as it changed its analyzers from Roche Modular P/E to Roche Cobas c701/e602. Cut-off changes were observed for some tests because of methodology changes (*e.g.* calcium from o-cresolphenol to NM-BAPTA) or because Roche stated different HIL cut-offs for the same test run on different analyzers (*e.g.* TBIL c701 I index = 90, c501 I-index = 1000). In addition, there was interest in determining if the algorithm could be modified to cancel fewer tests, as the lab had experienced some calls about too many tests being canceled.

2.4. Measurement of serum indices

All instruments used in this study were from Roche Diagnostics (Laval, QC) (Table 1) and used the same serum index measurement principle [9]. To confirm that serum index values were consistent among analyzers within each lab, several specimens representing a range of HIL values were split and analyzed across all analyzers within each lab. All results were within 10%.

2.5. Tests included in the analysis

Serum indices were collected on a combined 80 tests between the 3 labs (see Supplemental Table S1 for test abbreviations and methodologies). HIL flagging rates were not available if the lab did not perform the test or if it was performed on an instrument that was not collecting serum indices.

2.6. Selection of HIL cut-offs and decision algorithm development

2.6.1. Desired outcomes and assumptions

Five objectives were used to guide cut-off selection and algorithm development: identify specimens with interference levels relevant to the tests ordered; alert technologists to the presence of interference when intervention is required; aid physicians with interpretation of test results from samples with interference; cancel the least number of tests; and avoid adverse effects caused by failure to report results with HIL interference.

The algorithm was also designed to reduce manual technologist interventions as much as possible. The effect of introducing the algorithm was determined by assessing sample flagging and cancelation rates in 2 different laboratories, serving 3 different populations. This allowed for assessment of lab specific and population specific factors requiring refinement of the algorithms with the ultimate goal of reporting more results with better interpretive information to physicians. By performing this analysis *a priori*, the impact on laboratory workflows could be determined and the process refined prior to implementation.

2.6.2. HIL cut-off selection

Selection of test-specific HIL cut-offs is discussed in Section 3.1.

2.6.3. Rule sets

The 3 sets of comment and cancelation rules assayed in this study are baseline rules (the existing HIL flagging process in place in each lab), proposed rules (automated HIL indices with test specific comment and cancelation cut-offs chosen using manufacturers' package inserts, information from literature [10], and CLSI guideline C56A [1]); and optimized rules (use of alternative cut-offs or interference clearing strategies to increase the number of reportable results). Five or more flags under proposed rules were used as the trigger for consideration of an optimized rule for any test.

The general process used to develop and refine the serum index rule sets is illustrated in Supplemental Fig. S1. Specific details about the 3

Table 1
Key demographics of Labs A, B1 and B2.

Patient population	Lab A	Lab B1	Lab B2
	Community	Community	Hospital
Average # of tests per day during data collection period	77,319	22,713	15,381
# of chemistry tests on menu	55	45	47
# of days data collected	7 (Nov 28–Dec 4, 2011)	14 (Oct 16–30, 2013)	21 (Jan 13–Feb 3, 2014)
Total number of tests performed during data collection period	541,236	317,986	323,018
Total number of tubes analyzed during data collection period	66,668	48,245	48,460
Instrumentation	Roche Modular P and E170	Roche c701 and e602	Roche c501 and e601
Location where rule sets are applied	In house developed LIS IBM AS400	Roche Cobas IT Middleware	Roche Cobas IT Middleware
LIS	In house developed LIS IBM AS400	Cerner Millennium	Cerner Millennium