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Filling in the gaps with non-standard body fluids ☆

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ABSTRACT

Objectives: Body fluid specimens other than serum, plasma or urine are generally not validated by manufacturers, but analysis of these non-standard fluids can be important for clinical diagnosis and management. Laboratories, therefore, rely on the published literature to better understand the validation and implementation of such tests. This study utilized a data-driven approach to determine the clinical reportable range for 11 analytes, evaluated a total bilirubin assay, and assessed interferences from hemolysis, icterus, and lipemia in non-standard fluids.

Design and methods: Historical measurements in non-standard body fluids run on a Beckman Coulter DxC800 were used to optimize population-specific clinical reportable ranges for albumin, amylase, creatinine, glucose, lactate dehydrogenase, lipase, total bilirubin, total cholesterol, total protein, triglyceride and urea nitrogen run on the Beckman Coulter AU680. For these 11 analytes, interference studies were performed by spiking hemolysate, bilirubin, or Intralipid® into abnormal serous fluids. Precision, accuracy, linearity, and stability of total bilirubin in non-standard fluids was evaluated on the Beckman Coulter AU680 analyzer.

Results: The historical non-standard fluid results indicated that in order to report a numeric result, 4 assays required no dilution, 5 assays required onboard dilutions and 2 assays required both onboard and manual dilutions. The AU680 total bilirubin assay is suitable for clinical testing of non-standard fluids. Interference studies revealed that of the 11 total AU680 analyte measurements on non-standard fluids, lipemia affected 1, icterus affected 3, and hemolysis affected 5.

Conclusions: Chemistry analytes measured on the AU680 demonstrate acceptable analytical performance for non-standard fluids. Common endogenous interference from lipemia, icterus, and hemolysis (LIH) are observed and flagging rules based on LIH indices were developed to help improve the clinical interpretation of results.

1. Introduction

Analysis of abnormally accumulated body fluids is used to diagnose and manage the pathological conditions underlying their formation. To date, most commercial chemistry assays are only FDA-approved for serum, plasma, and urine, with a few exceptions for cerebrospinal and pleural fluids such as glucose, lactate and pH. Individual clinical laboratories interested in

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offering non-standard fluids testing must, therefore, complete extensive studies to evaluate assay performance characteristics with alternative fluid types. For some laboratories, attaining regulatory compliance has impeded or ceased the implementation of this important clinical testing service. In particular, laboratory accreditation agencies, such as the College of American Pathologists, regard analysis of these abnormal body fluids as a laboratory-developed test and require validation of accuracy, precision, analytical sensitivity, analytical specificity, interferences, and reportable ranges [1]. Furthermore, demonstration of clinical claims and commutability between non-standard fluids and FDA-cleared specimen types is needed.

To improve resource utilization in meeting these complex regulatory requirements, laboratories can limit their testing menu of non-standard fluid analytes to those with clinical significance [2,3]. For example, Light's criteria includes measurement of total protein and lactate dehydrogenase in pleural effusions to differentiate transudate and exudate. These two types of effusions have distinct analyte profiles: transudates form as an ultrafiltrate caused by imbalance of hydrostatic or oncotic pressure and exudates form due to local inflammation leading to increased capillary permeability or impaired lymphatic fluid reabsorption. Clinical management of these pathological fluid accumulation depends on correct classification. Similarly, albumin concentrations in serum are compared to albumin concentrations in peritoneal effusions, known as serum ascites albumin gradient (commonly referred to as “SAAG”), to differentiate clinical conditions related to changes in portal hypertension. Many other analytes have also demonstrated clinical utility, albeit less general, such as cholesterol and triglyceride for chylothorax and pseudochylothorax, amylase and lipase for pancreatitis, creatinine and urea nitrogen for urinary leakage, glucose for parapneumonic or malignant effusions, and total bilirubin for detection of biliary leaks.

Validating non-standard fluids for chemistry testing is challenging and requires strategic planning. The limited published studies on non-standard fluid validation have provided useful, but incomplete, practical guidelines for clinical laboratories to design and complete their own validations [4–6]. In the present study, our objective was to address some of these literature gaps. Specifically, we established a data-driven approach to determine the clinical reportable range for non-standard fluid analytes, evaluated the total bilirubin assay for non-standard fluids, and assessed interferences from hemolysis, icterus, and lipemia on the performance of 11 non-standard fluid analytes measured on the Beckman Coulter AU680 chemistry analyzer.

2. Materials and methods

2.1. Specimens, instrument and chemistry assays

This quality improvement project, conducted at the University of Washington Medical Center (UWMC, Seattle, WA), was granted an exemption by the UW Medicine institutional review board. Residual ascites, pelvic, pericardial, and pleural fluids submitted to UWMC for testing were used to evaluate the performance characteristics of 11 Beckman Coulter AU680 serum chemistry assays for non-standard fluids. The 11 assays were: albumin, amylase, bilirubin (total), cholesterol (total), creatinine, glucose, lactate dehydrogenase, lipase, total protein, triglyceride, and urea nitrogen. Specific test parameters were programed for each assay in order to define different onboard dilution factors for non-standard fluids relative to serum. The remaining test parameters (ie. – sample volume, reaction monitoring, associated calibration curve or enzyme blank, etc.) programmed for non-standard fluids were configured identically to the specific test parameters recommended by the manufacturer for serum except that “other-1″ was designated for specimen type. All non-standard fluid specimens were stored at 4 °C and utilized within 2 months of collection. Prior to analysis on the Beckman Coulter AU680 chemistry analyzer, all specimens were visually inspected and filtered through a 200–300 μmol filter (Fisher Scientific, No. 1,138,750) or centrifuged at 4500*g* for 10 min to remove large debris.

2.2. Laboratory data and clinical reportable range

Historical results for the 11 non-standard fluid analytes generated between January 1st, 2013 and December 31st, 2014 using the Beckman Coulter DxC800 were retrieved from the laboratory information system (Sunquest, Version 7.1). Prior to analysis, these results were de-identified after excluding specimens submitted without a description or for proficiency testing. The AU680 onboard dilution factor (0, 2, 3, 5, or 10; manufacturer recommends less than 5-fold) and pre-defined manual dilution factor (0, 2, 3, 11, or 51) for each analyte were selected to include the majority of historical results.

2.3. Total bilirubin

The performance characteristics for all 11 AU680 assays for non-standard fluids were evaluated, but only total bilirubin is described here (information on remaining AU680 assays can be found in Lin et al. [5]). Intraday and interday precision studies were performed using 2 ascites and 2 pleural fluids, with low and high bilirubin concentrations collected from 4 different individuals. Each non-standard fluid specimen was analyzed 20 consecutive times to obtain the intraday precision and 4 consecutive times per day for 5 consecutive days to obtain the interday precision. To define the lower limit of blank, the mean plus 3 SD was calculated from 20 consecutive measurements of a 0.9% saline solution. For the analytical measurement range, Verichem Bilirubin Standards A (0.565 mg/dL) and F (28.4 mg/dL) were diluted into an ascites fluid