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Short Communication

Strategies for mitigating risk posed by biotin interference on clinical immunoassays

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ABSTRACT

Recently, biotin use as an oral supplement has increased significantly among the general population. Biotin is a water soluble B-vitamin and is marketed to improve the cosmetic appearance of hair, skin, and nails. In addition, high-dose biotin (> 5 mg/day) is prescribed to treat inborn errors of metabolism and multiple sclerosis. Many commercial immunoassays employ the high affinity interaction between biotin and streptavidin, a protein purified from bacteria, as part of the analyte capture mechanism. As such, these immunoassays are subject to this interference. The list of affected immunoassays is vendor specific but includes tests for troponin, serum and urine Beta hCG, thyroid function, and tumor markers. The interference can be positive or negative in nature depending on the immunoassay. To address this issue, patients are recommended to abstain from taking biotin supplements for 48 h, and laboratorians and clinicians must be familiar with the potential for biotin interference in performed lab tests. Here we describe strategies to treat high biotin specimens and make them suitable for testing; and detail a number of approaches used successfully by our laboratory to educate patients, doctors, and other healthcare professionals about this interference and to mitigate the posed patient safety risk.

Biotin (also known as vitamin H, B7, or coenzyme R) is a water soluble, B-complex vitamin found in all cells of the body but at elevated levels in tissues with high energy demand such as the brain, pancreas, skeletal muscle, heart, and kidney [1]. Biotin is a cofactor for mitochondrial and cytoplasmic carboxylation reactions involved in energy metabolism, amino acid catabolism, and fatty acid synthesis. Rich dietary sources of biotin include some organ meats, egg yolks, yeast, and milk. Biotin is also found in multi-vitamin supplements. In Western populations, biotin intake from food or multi-vitamins is estimated to be 35–70 μg/day, meeting the Institute of Medicine adequate intake (AI) of 30 μg biotin/day for adults [2]. As a result, biotin deficiency is rare outside of metabolic diseases such as biotinidase deficiency- where the body is unable to recycle biotin [1]. In these cases, doses of 10–30 mg/day are often used. Doses of 300 mg/day are an emerging therapy for progressive multiple sclerosis and other demyelinating diseases [3].

Interestingly, biotin therapy is also marketed as an aid for improving hair, skin, and nail quality. High doses up to 10 mg (333 times the AI) can now be found in over-the counter nutritional supplements. While biotin supplementation may improve pathological hair and nail syndromes (eg. uncombable hair syndrome and brittle nail syndrome) [4], to date, no study has shown the beneficial effect of biotin in improving hair and nail health in otherwise healthy individuals. Nevertheless, consumer interest in biotin supplementation continues to grow as established by increasing internet searches for “biotin” + “hair” over the last decade [5], and a recent prevalence study demonstrating that biotin supplementation may be common in outpatients [6].

Many clinical immunoassays use the interaction between biotin and streptavidin as part of their assay architecture to measure different analytes. Biotin-streptavidin assay architecture is widely used in automated immunoassays from Roche Diagnostics, Ortho Clinical Diagnostics, Beckman Coulter, and Siemens Healthineers. As a result, high-dose biotin can interfere with a broad range of diagnostic tests generating erroneous results and endangering patient safety [7,8]. In the United States, among 374 methods performed by 8 popular immunoassay analyzers, 221 use biotin-streptavidin architecture and 97 are at high-risk for biotin interference [9]. Assay susceptibility to biotin interference varies, and can result in falsely high or low results depending on the design [7,10,11]. In general, homogenous assays give false positive results, whereas non-competitive (sandwich) assays give false negative results. Due to the wide range of tests involved, biotin-interference can for example lead to misdiagnosis of infectious diseases,

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Table 1
Analytical and educational strategies to mitigate the effects posed by biotin interference on clinical immunoassays.

Clinical laboratories	Healthcare professionals	Patients
Biotin unaffected platform	Result comments	Requisition information
Streptavidin particles	Newsletters/memos	Posters and displays
Linearity of dilution	Presentations	Email reminders
	Website information	Website information

failure to recognize tumor recurrence, failure to diagnose or recognize acute myocardial infarctions or congestive heart failure, failure to detect pregnancy, resulting in inaccurate titration of medication dose, and/or unnecessary invasive follow-up procedures including surgery. Unfortunately, these situations are more likely to occur because patients taking high-dose biotin for cosmetic reasons may not report it to their physician and high-dose prescription biotin prepared by compounding pharmacies may not be sufficiently detailed in the medical record [12,13]. Although the potential for biotin to interfere with lab tests has been known for years, patients taking high-dose biotin were rarely encountered until high doses became available over-the-counter within the past five years. The striking increase in case reports of biotin interference reflects biotin's emerging role in multiple sclerosis [3] and has put focus on the prevalence of supplementation [6].

There are several strategies by which clinical laboratories can eliminate or limit the effect of biotin on immunoassay test results and ultimate risk to the patients (Table 1). 1) Samples suspected of containing biotin can be tested on a platform unaffected by biotin interference. This requires access to an alternative and unaffected assay platform. This may not be feasible due to distance to the referral laboratory, which could inappropriately increase turn-around-time (TAT). Any increase in result reporting TAT would need to be communicated to the requesting clinician. Furthermore, not all manufacturers report biotin interference thresholds in package inserts, which makes it hard to determine if a test is susceptible to biotin interference [9]. 2) Samples suspected of biotin interference could be pre-treated with streptavidin particles to remove biotin [14]. Although this procedure is effective, it requires laboratories to validate or verify that assay performance has not been influenced by the pre-treatment step in order to produce reportable results. 3) Samples suspected of containing biotin may be diluted with a validated assay diluent to reduce the interference prior to testing, provided the analyte level is not diluted below the limit of quantification of the assay or diluting the samples does not interfere with the assay principle [15]. For example, dilution cannot be performed for assays such as free T4 because it affects the equilibrium between the bound and unbound fraction of the analyte.

At Calgary Laboratory Services (CLS), most of our immunoassays are vulnerable to biotin interference. To mitigate this patient safety risk, we have put into place a number of strategies to educate our fellow laboratorians and clients (eg. healthcare professionals and patients) about biotin's effects. Before being implemented, these approaches were summarized in a "*Biotin Interference Communication Plan*" developed by a committee of clinical biochemists and operational staff at CLS and approved by a provincial working group. As part of this plan, we raised awareness of biotin interference via laboratory grand rounds and in-service presentations at various sites. We also created workarounds for two high-value tests susceptible to biotin interference: serum Beta hCG and high-sensitivity cardiac troponin T. For both tests, we identified backup platforms within in our existing laboratories that were unaffected by biotin and developed procedures to direct candidate specimens for rapid testing on these platforms (Fig. 1).

To educate healthcare professionals a number of approaches were used. 1) A chartable comment "*Biotin taken in doses > 1 mg/day may interfere*" was auto-appended as the first read comment to all tests affected by biotin. 2) Memos were distributed across the province describing the importance of biotin interference with the following recommendation: "*Biotin oral supplements may interfere with lab tests. CLS recommends all patients discontinue Biotin supplements for 48 hours prior to specimen collection*". Peak biotin concentration in plasma occurs 1–3 h post dose [1], and although pharmacokinetic studies suggest 8 h is

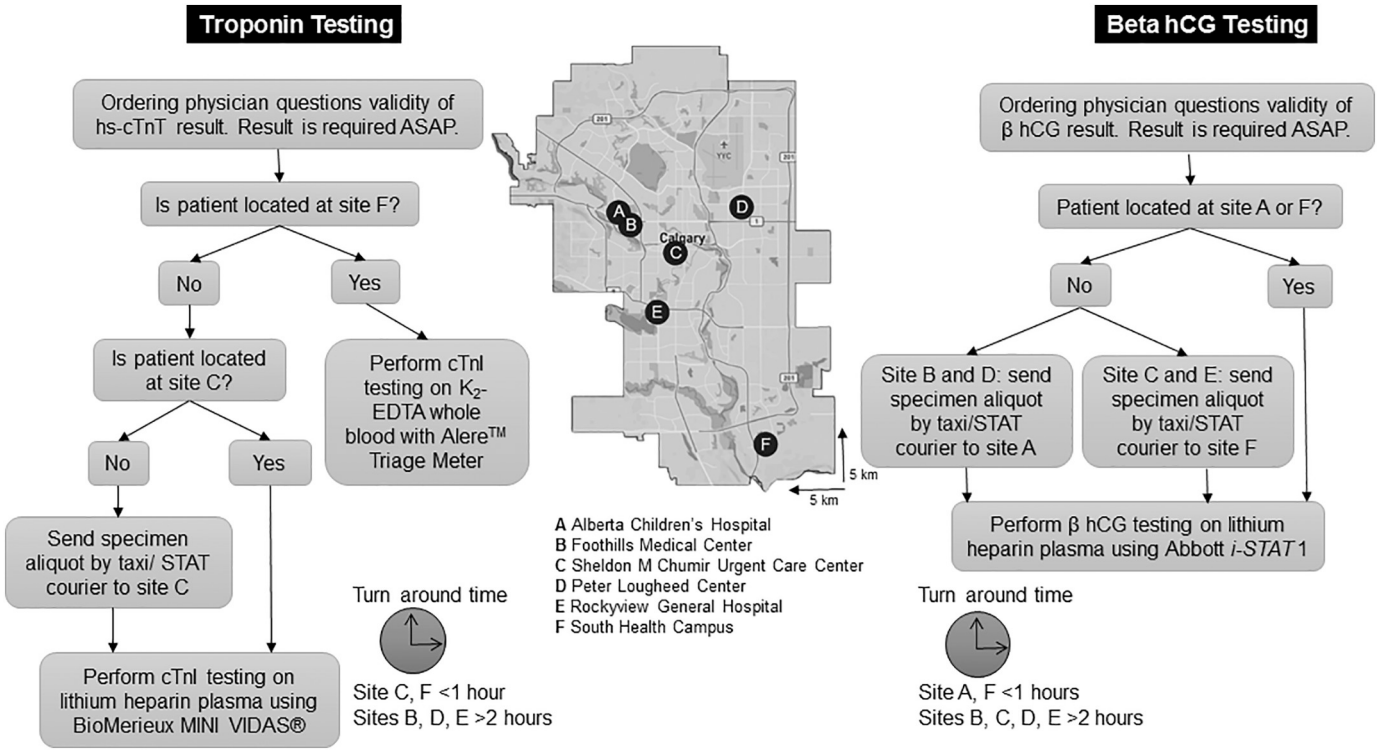

Fig. 1. Specimen handling workflows for samples with suspected biotin interference collected for high sensitivity cardiac troponin T (hs-cTnT) or serum Beta hCG testing in the Calgary Zone of Alberta Health Services. The Calgary Zone serves a population of 1.4 million.

required to clear the interference from 5 to 10 mg/day doses [16], our recommendation of abstaining from biotin supplementation for 48 h is based on recommendations from the American Thyroid Association in order to minimize the possibility of an interference [17]. However, it should be noted that the withholding time required to prevent biotin interference is dependent on the dose [1], assay tolerance [9–11], and patient specific factors (eg. pediatric patients [18], kidney function [19]). 3) Presentations to specialist physician groups who may be unduly affected by biotin interferences (eg. endocrinologists) were made at regular quarterly meetings. 4) Finally, a link to further information on biotin interference was added to our laboratory's website section for Medical Professionals.

In order to educate patients on the effect of biotin on lab tests, the following measures were put in place. 1) A phrase was added to all community and acute care requisitions: "*Biotin oral supplements may interfere with lab tests. CLS recommends all patients discontinue Biotin supplements for 48 hours prior to specimen collection. If your Health Care Provider recommended you take Biotin, contact them for further guidance.*" 2) Information on biotin supplements and our recommendations appear on our website under the "Patients & Visitor Guide" Tab. 3) The *Patient Appointment Line FAQ*, online patient appointment booking system, and confirmation and reminder emails all contain the phrase "*Notice: Biotin supplements may interfere with lab tests. CLS recommends all patients discontinue Biotin supplementation for 48 hours prior to specimen collection. Refer to FAQ.*" 4) A script outlining the above information was developed for laboratory staff upon patient inquiry to the laboratory call center. 5) Finally, the effects of high-dose biotin on lab tests are noted on closed-circuit TV monitors and posters at specimen collection sites; and these posters are displayed at physician offices, emergency departments, and urgent care centers.

In summary, although high-dose biotin can produce false test results, the laboratory can make several relatively simple changes to reduce the incidence of biotin interference. We are a relatively large laboratory with an annual volume of about 25 million chemistry tests. When our "*Biotin Interference Communication Plan*" was first put in place 22 months ago, the laboratory call center received at least two biotin-related calls per day from both clinicians and patients. Currently, we receive two such calls per month. To date, no adverse effects of biotin on our immunoassay tests have come to our attention. As such, we believe the best approach for dealing with the effects of biotin interference is to raise awareness among the medical community and the patient population.

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