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Special Report

Identifying and Eliminating Laboratory Contamination by Topical Testosterone Therapeutics

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Many prescription and over-the-counter drugs are available as topical formulations. Contamination of clinical laboratory workspaces by topical drugs may increase the risk of potential interference with diagnostic testing. An example of localized workspace contamination attributed to a topical hormonal drug (testosterone, T) is presented to highlight significant challenges in identifying and resolving this potential problem. Investigation included precision studies, instrument service and parts replacement, instrument replacement, airflow analysis, environmental dust sampling, and the development of customized methods for workspace monitoring and cleaning. Laboratory policies and procedures were also revised to minimize future risk.

Clinical laboratories are required to conduct quality control (QC)[4] procedures under regulations associated with the Clinical Laboratory Improvement Amendments of 1988. When an unexplained QC failure occurs, investigations into the potential causes of such an occurrence are initiated. The present report describes an investigation into analytical imprecision (QC failure) for testosterone (T) on a subset of automated immunoanalyzers. T assays were removed from clinical testing on affected instruments during the entire investigation. Increased amounts of T were identified on surfaces and dust within a localized workspace setting. After excluding multiple potential sources of contamination, the source of T was attributed to use of prescribed topical T therapy. A multifaceted approach of precision studies, airflow analyses, environmental sampling, cleaning, and revision of laboratory policies and procedures led to a resolution of potential analytical interferences. This workup was conducted amidst a scarcity of published literature describing how laboratories can identify, investigate, and resolve environmental contamination of clinical laboratory instruments. As such, we provide a detailed report of how our laboratory navigated this challenging endeavor because it may be helpful to future evaluations in other settings.

Identification of Analytical Interference

Unexplained high QC results ("fliers") for the T assay were observed after installation of several immunoanalyzers (cobas e602; Roche Diagnostics). A representative T flier (>9 SD) observed during a precision study on one of the affected instruments in the course of our investigation is shown in Fig. 1. These instruments were installed in an area approximately 5–10 meters from where prior E170 immunoanalyzers (Roche Diagnostics; previously used for T analysis) were located. Repeat studies demonstrated QC fliers on e602 modules located on the same cobas 8000 system (Roche Diagnostics). No erroneous patient results were identified during this investigation. T testing on this cobas 8000 system was discontinued, however, during the entirety of our workup. Similar QC issues were not observed with other assays on these instruments (chosen to reflect multiple assay methodologies).

The initial phase of our workup consisted of instrument inspection, proactive service with parts replacement, numerous rounds of repeat precision studies, and ultimately instrument replacement. Despite this extensive troubleshooting, rare T fliers were still observed. T "divers" (unexplained low QC results) were never observed.

Several findings became apparent during our investigation. First, the rare and episodic nature of fliers (every few hundred replicates) meant that the workup required an extremely high number of replicates in precision stud-

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Data on T content in HYAL powders was previously presented at the 2017 AACC Annual Meeting in San Diego, CA [La'ulu SL, Turner DR, Zupan E, Genzen JR (08/01/2017; Poster A-272). Testosterone content in hyaluronidase powder: evaluation of commercially-available sources for the pretreatment of viscous body fluid specimens.]
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[4] Nonstandard abbreviations: QC, quality control; T, testosterone; IPA, isopropyl alcohol; PPE, personal protective equipment; Ru, ruthenium; HYAL, hyaluronidase.

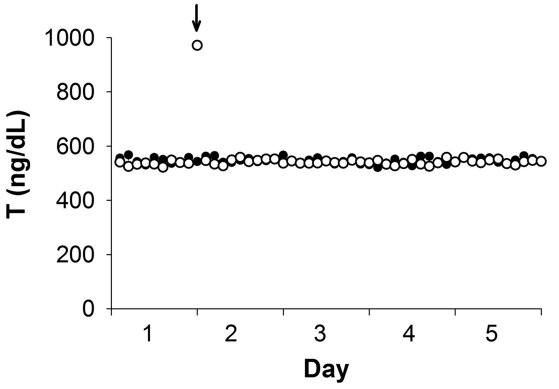

Fig. 1. Representative precision study with QC "flier."
Results from a 5-day precision study for T on a Roche e602 immunoanalyzer [n = 10 aliquots per day, run on both measuring cell 1 (•) and measuring cell 2 (○); note many overlapping data points]. Material used was human AB serum from male donors (Corning). Unexpected QC flier observed (marked by arrow). Summary statistics (all data): mean ± SD, 547.8 ± 44.0 ng/dL (19.0 ± 1.5 nmol/L); %CV, 8.0. Summary statistics (flier excluded): mean ± SD, 543.5 ± 10.5 ng/dL (18.9 ± 0.4 nmol/L); %CV, 1.9.

ies to determine whether interventions might be effective in eliminating potential analytical problems. Second, there was no clear definition of what magnitude of increased results might be considered acceptable or unacceptable. In a practical sense, any results >3 SD from the mean in precision studies were considered potential fliers, although the observed T fliers were usually higher than this and did not require statistical assessment beyond their obvious inappropriateness (e.g., Fig. 1). Third, the T imprecision was identified on a cluster of instruments in 1 general location in the laboratory. To assist in our workup, T assays were also installed on immunoanalyzers from multiple vendors located away from the affected instruments. Precision data [e.g., 100 replicates, intraday with human male serum (Corning; from VWR)] showed acceptable overall %CVs versus alternative methods [%CVs: e601 (Roche Diagnostics), 2.6%; UniCel DxI 800 (Beckman-Coulter), 2.1%; ARCHITECT $i2000_{SR}$ (Abbott), 2.4%; Centaur XP (Siemens), 10.1%; LIAISON XL (DiaSorin), 9.9%; LC-MS/MS, 2.1%; e602 in affected area, 2.2%]. This result suggested that the affected e602 instruments could achieve acceptable analytical precision for T, if a root cause for rare interferences was identified and definitively remediated.

Environmental Sampling

To further investigate a potential cause for the T fliers, dust samples ("bunnies") were collected from underneath or near affected instruments. These samples were incubated in Roche universal diluent and then filtered to remove particulate matter. The diluent was subsequently analyzed for T concentrations by 2 T immunoassays (cobas e602 and ARCHITECT $i2000_{SR}$) and by an LC-MS/MS assay for T. Samples from locations far from the instruments were also included. Increased concentrations of T were observed in many (but not all) of the dust-incubated diluent samples (see Supplement 1 for representative examples in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol65/issue1). It should be noted that universal diluent is not approved by the vendor for use as a diluent in T assays for clinical testing purposes. Indeed, a matrix effect was observed when comparing T results between e602 and the $i2000_{SR}$ and LC-MS/MS T assays (see Supplement 1 in the online Data Supplement). Regardless, the magnitude of results between specimens was concordant, irrespective of the testing platform used to determine T concentration in environmental samples.

The environmental sampling collection procedure was refined after reviewing a 1980s report regarding environmental wipe sampling of estradiol *(1)* and available descriptions of wipe sampling *(2)* and surface monitoring *(3)* techniques for a variety of other substances. The goal was to establish a relatively standardized method of environmental collection, such that one could reliably (*a*) infer relative concentration differences in T between samples (to localize T contamination in the workspace), (*b*) detect T in nondust collections on smooth surfaces, and (*c*) verify removal of T when effective cleaning procedures had been established. The environmental sampling procedure that was developed used isopropyl alcohol (IPA) wipes and was as follows. Wearing gloves, 99.9% IPA wipes (6″ × 5″; MG Chemicals) were used to sample approximately 1 ft^2 surfaces. Sampling consisted of 4 passes over an area, folding wipes between each pass. Wipes were placed into 50-mL conical tubes (Corning), with gloves changed between sampling. Wipe-containing tubes were left open in a separate area to evaporate residual IPA. Five milliliters of universal diluent was added to the tubes, which were capped, vortexed, and held for 2 h at room temperature before repeat vortex. Wipes were transferred into open 50-mL Luer Lok plastic syringes (McKesson), plungers were replaced, and the fluid was gently expulsed through drip filters (Thermo Fisher Scientific) into aliquot tubes. Fluid was then analyzed for T with e602 instruments.

Environmental sampling demonstrated increases in T predominantly within a 5-m area near the affected instrument (Fig. 2). Samples near this area—but on opposite sides of an automation track—did not show increased T (Fig. 2; black circles). One additional increased

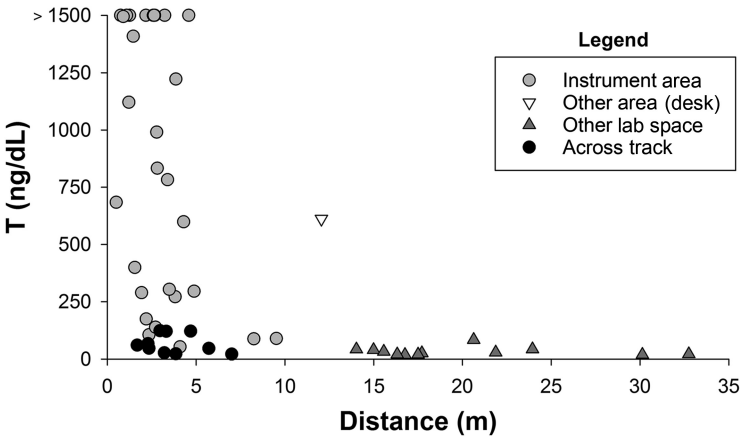

Fig. 2. Testosterone (T) content in environmental samples.

T dissolved from either dust samples or environmental IPA wipes incubated in universal diluent and plotted versus distance from the involved instruments. General location of specimen is indicated by symbol shape (see legend).

T sample was observed on a computer desk away from the laboratory (Fig. 2; downward triangle).

Given the evidence demonstrating T in environmental samples near these instruments, the goal was to (*a*) understand the potential mechanism(s) for instrument contamination and (*b*) to identify and remediate the potential source. While it seemed unlikely that microscopic airborne particles could contaminate distant open specimen tubes and lead to the magnitude of fliers observed, the possibility of instrument contamination by either (*a*) dust contamination of instrument pipettors, mixing cells, or reaction cells (with smaller relative volumes) or (*b*) direct and/or indirect transfer (i.e., by hand) to instrument surfaces or disposables was a primary concern. The possibility of direct and/or indirect transfer is discussed later in the context of personal protective equipment (PPE).

Instrument Airflow

Instrument airflow is typically only considered during installation requirements to prevent overheating. We have not identified published literature regarding how airflow might contribute to analytical performance in the context of environmental contamination. Most automated chemistry and immunoanalyzers typically have fans that draw airflow out of or into the instrument. A comparative study across multiple instruments was therefore conducted to characterize instrument airflow and better understand the potential risk of analytical interference due to environmental contamination across platforms.

With a Digi-Sense (Model 20250-16; NIST-traceable) hot wire anemometer from Davis Instruments, airflow was measured at 11 predefined locations (20-s measurements, performed in duplicate on each of 5 days) on 8 different analyzers (Fig. 3, A–D; see Supplement 2 in the online Data Supplement for exact measurement locations). From these data, instruments could be divided into those with relatively "defined" air intake locations [e.g., UniCel DxI, ARCHITECT *ci*8200 (Abbott), Centaur XP, Immulite 2000 XPi (Siemens), LIAISON XL] and those that draw air into the instrument through "any" open location [e.g., E170, e602, VITROS ECi (Ortho)]. Because the E170 and e602 have similar external architecture, the locations of measured positions exactly matched between those two instruments. Through this method, it was demonstrated that inward airflow is greater on the e602 versus the E170 instruments (Fig. 3A; $P < 0.05$, n = 10 of 11 positions). Particulate or aerosolized matter from any source (e.g., cleaning with compressed air, vacuums without high-efficiency particulate air filters, construction debris, movement of furniture, lyophilized reagents, specimen aerosols, etc.) can be drawn into analytical instruments depending on their unique airflow characteristics and/or whether air intake locations have filters. Manufacturers should consider engineering design controls that minimize the potential for instrument contamination.

Potential Sources of Testosterone Contamination

One potential nonpharmaceutical cause of T contamination might be reagent spillage. The Roche Testosterone II assay reagent 2 includes a T-peptide-ruthenium (Ru) complex *(4)*. Reagent spillage and/or splatter might theoretically result in environmental contamination in close

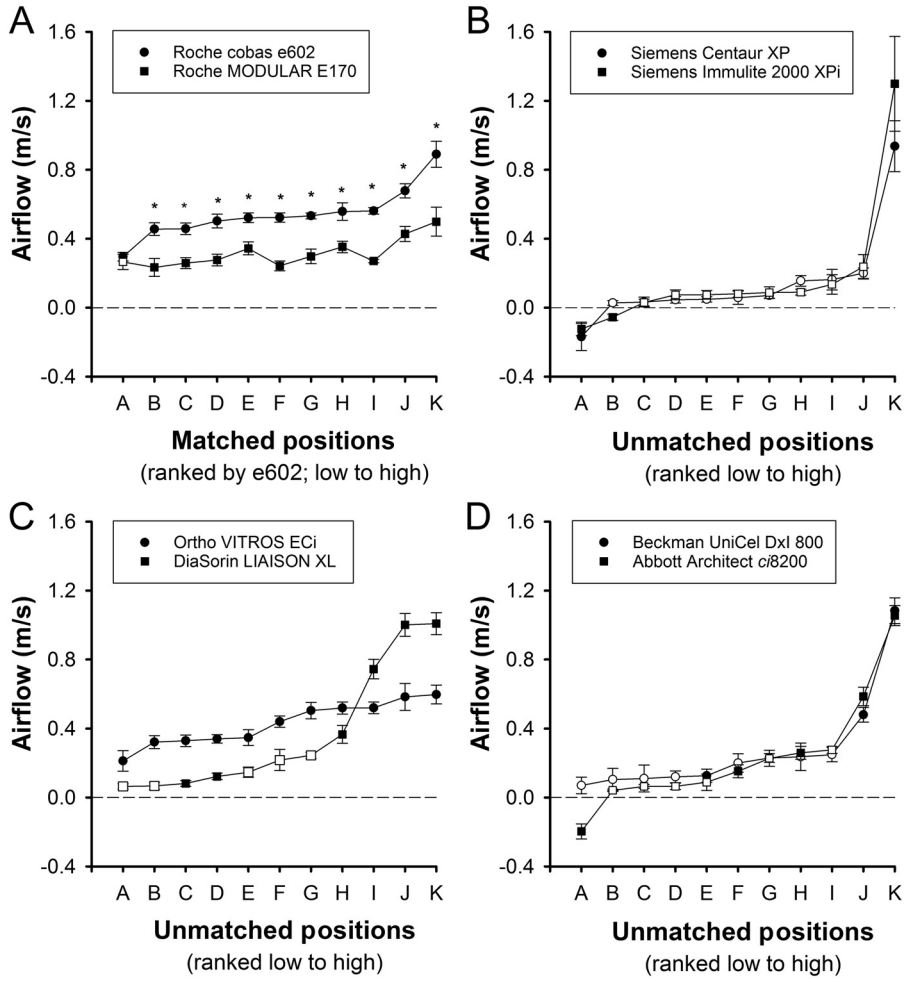

Fig. 3. Instrument airflow studies.

Instrument airflow (positive = inward) at 11 exterior positions on 8 analyzers [(A), Roche cobas e602 and MODULAR E170; (B), Siemens Centaur XP and Immulite 2000 XPi; (C), Ortho VITROS ECi and DiaSorin LIAISON XL; (D), Beckman UniCel DxI 800 and Abbott ARCHITECT *ci*8200].

Location of measurement positions are shown in the online Data Supplement. Since cobas e602 and MODULAR E170 have similar external design, measurement positions across designated letters for (A) are "matched" to the same position across both instruments, thus permitting statistical comparisons ($*P < 0.05$). All other points across instruments (B–D) are "unmatched." (A–D), Closed symbols (black) indicate definitive inward or outward airflow (verified by 2 observers); open symbols (white) indicated inconclusive airflow direction; fan vents for outward airflow were not measured.

proximity to instruments. Additional dust specimens were tested, however, for Ru content by an in-house inductively coupled plasma mass spectrometry method. Increases in Ru were not observed in dust with increased T (versus "control" dust from distant locations; data not shown). Additionally, the T-peptide-Ru complex would not be expected to have the same mass-to-charge ratio as T measured on our LC-MS/MS assay. Reagent spillage was therefore excluded as a potential source of T.

Spillage of QC material could be excluded as a potential cause of contamination because our laboratory uses multianalyte QC material and no similar increases in other analytes were observed in environmental sampling. While spillage of T calibrators could lead to environmental contamination, the amount of lyophilized T in a calibrator bottle (at or above the upper limit of the analytical measuring range upon reconstitution) would not be expected to create the extent of contamination observed in

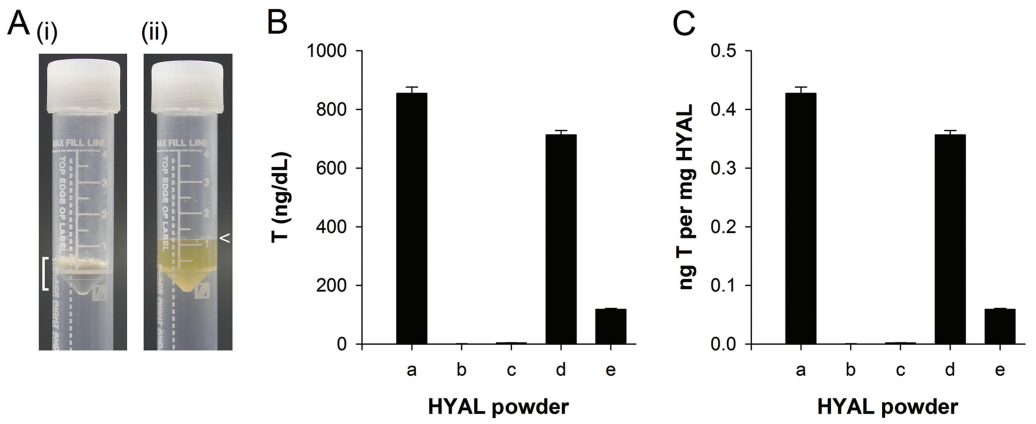

Fig. 4. Hyaluronidase (HYAL) studies.

(A), HYAL dissolved in human AB serum. Photos illustrate 21 mg of HYAL powder [bovine type I-S (Sigma Aldrich, #H3506)] before [(*i*), left; see bracket] and after [(*ii*), right] being dissolved in a human serum pool at a concentration of 20 mg HYAL per mL serum. "<" indicates top of fluid line. Baseline T concentration (pre-HYAL) in the serum pool was 396 ng/dL, whereas concentration in the solution with dissolved HYAL (right) was 1240 ng/dL. (B–C), T content in HYAL powders. Five commercial sources of HYAL were used to create 20 mg/dL HYAL aliquots (n = 5, each source) dissolved in Roche universal diluent. Sources were as follows: a, bovine type I-S (Sigma Aldrich, #H3506); b, bovine (VWR/MP Biomedicals, #IC1007490); c, ovine type V (Sigma Aldrich, #H6254); d, ovine (VWR/MP Biomedicals, IC151272.5); e, ovine type II (Sigma Aldrich, #H2126). T was measured by LC-MS/MS. (B), Results displayed as T concentration (ng/dL) in the HYAL aliquot. (C), Results normalized to HYAL concentration (ng T per mg HYAL powder). All results are mean ± SD.

any of the following: our environmental sampling, the distribution of T found in locations that are frequently touched (e.g., keyboards, computer mice, desktops), the isolated increase on a desk surface outside the laboratory (Fig. 2; downward triangle) that is not involved in handling calibrator materials nor performing analytical testing.

Another potential source of T contamination was hyaluronidase (HYAL) powder, which was used for pretreatment of viscous body fluid specimens on a bench near this area. Of note, the HYAL powder used by the laboratory was of bovine testicular origin (Product H3506-1G; Sigma Aldrich) and had a light, flaky characteristic appearance. It is important to note that HYAL pretreatment was not an approved or used protocol in our laboratory for specimens undergoing clinical T analysis. A large amount of HYAL powder added to human serum could increase T concentrations (see Fig. 4A). Variable amounts of T were also found to be present in multiple commercial sources of HYAL powders (Fig. 4, B and C), with T amounts higher in bovine (cow) versus ovine (sheep) sources. Given the theoretical potential for airborne instrument contamination by HYAL powder, HYAL pretreatment was moved to a biosafety level 2 hood outside of the affected space, located more than 17 meters away from involved instrumentation.

Accumulating evidence, however, suggested that HYAL was not the likely source of rare observed T fliers. Along with the large amount of HYAL powder required to significantly increase T concentration in serum specimens (e.g., Fig. 4A), T fliers continued to be observed in precision studies of affected instruments months after HYAL pretreatment was removed, even after multiple rounds of high-efficiency particulate air vacuuming and cleaning of the area and instrumentation. Additionally, other analytes identified in HYAL powder [e.g., vitamin B12 and N-telopeptide (collagen fragments)] were not observed in environmental sampling (data not shown). Out of an abundance of caution, an alternative non–T-containing ovine HYAL for viscous body fluid pretreatment was validated for use in our laboratory.

Other theoretical sources of contamination could relate to specimen collection and handling (by phlebotomists, specimen processors, technicians, and/or technologists), surface contamination of specimens by other male specimens that have increased testosterone, and/or cross-contamination related to automation or instrumentation. Phlebotomy through skin covered with topical steroids has previously been shown to affect laboratory results *(5)*. Touching of skin by a phlebotomist who is using topic steroids may also be expected to have a similar effect. However, T fliers were observed with QC material and commercial pools of human AB serum; therefore, phlebotomy and specimen processing could reasonably be excluded as the cause of interference in the present investigation. Risk of contamination of speci-

mens, reagents, or disposables due to handling by technicians and technologists is addressed below in the workup related to PPE policies and procedures. Carryover (or surface contamination by male specimens with endogenously increased T) could also theoretically lead to erroneous results. However, neither scenario would explain T fliers observed during precision studies using pools of commercially acquired human AB serum, in which each replicate tube contains the same material. Cross-contamination on instrumentation or automation could also lead to erroneous results, but it is not a likely cause for the interference observed in this investigation, as cross-contamination would not be selective for T assays and similar QC fliers were not observed with other tests on these instruments.

Concurrent with the workup above, the laboratory addressed the possibility that use of pharmaceutical T could also result in a focal environmental or instrument contamination. In this context, topical T therapeutics (if present on hands or arms) could be introduced into the workspace through touching or brushing against objects or more generally via normal skin sloughing. If such use of topical therapeutics leads to instrument contamination, then policies and procedures should prevent that possibility to ensure quality patient results. As such, the laboratory management team in collaboration with human resources developed a multistep plan to understand the potential scope of the issue and to establish policies to remove any risk of T contamination going forward. This process involved careful consideration of existing laws regarding employment discrimination and bona fide occupational qualifications, and it protected the health privacy of all parties. Though this process, a policy was developed and successfully implemented such that individuals using topical steroid therapies would not be permitted to work in proximity to instrumentation where corresponding analytes were being measured.

Personal Protective Equipment (PPE)

Decades of laboratory safety practices have focused on the use of PPE to protect employees from bloodborne pathogens such as hepatitis B, hepatitis C, and human immunodeficiency virus. Perhaps only in microbiology and molecular diagnostics has there been a longstanding practice of "protecting the assay" (e.g., cultures or polymerase chain reactions) from exogenous contamination. In the context of topical pharmaceuticals, however, PPE can also be used to protect the instruments, assays, and/or specimens. There is a general lack of recognition that many processes in the laboratory that do not involve patient specimens (e.g., unboxing reagents, loading pipette tips and aliquot tube supply bins, touching "clean" keyboards) have the potential to cross-contaminate these surfaces. Additionally, potential environmental cross-contamination or dispersion of topical steroids through skin sloughing or indirect contact can occur. Indeed, our environmental sampling showed evidence of increased T not just on floors, but also desktops, shelves, instrument handles, and other surfaces that might frequently be touched. Floor contamination suggested that "indirect dispersion" or tracking via footwear might also be present.

To address these issues, policies requiring PPE (gloves and lab coats) were revised and enhanced to clarify that no individuals (including operators, staff, management, service personnel, vendors, or medical directors) could enter this technical space without wearing gloves and a lab coat at all times, regardless of activity or purpose. Floor signs were posted around the laboratory, and strict adherence to this policy has been maintained.

Cleaning

The most physically demanding phase of this investigation was developing and implementing a cleaning protocol for the affected laboratory area including instrumentation. This was particularly challenging as (*a*) this is an active workspace with ongoing clinical testing, (*b*) instrumentation is large and bolted to the floors, (*c*) no previously described cleaning procedures effective for T contamination were identified, (*d*) harsh cleaners could not be used on internal and/or external surfaces of complex instrumentation, (*e*) hazardous fumes associated with cleaning would be unacceptable, and (*f*) T is not water soluble.

On nonporous surfaces (e.g., metal shelving), pre- and postenvironmental sampling demonstrated that multiple rounds of soap-and-water cleaning by vigorous scrubbing with Dawn Ultra dish soap (Proctor & Gamble) was effective. This protocol was not effective on rough or porous surfaces, including flooring and black laminated bench tops. Additionally, soaking with soap and water was not a viable option for electronics and analytical instrumentation. Over a dozen home and industrial cleaning solutions were subsequently tested on affected floors. Substantive elimination of T was not observed, however, with any of these alternative cleaners, despite multiple rounds of vigorous scrubbing. Technically, any solvent capable of dissolving T should be effective, although we were unable to identify a nonflammable, noncarcinogenic solvent in the literature that could be safely used in an open laboratory space. One multistep greaser/degreaser formula did remove T from floors, but it was not incorporated into ongoing routine cleaning protocols owing to odor observed during an initial cleaning event.

In the end, all shelves, desks, and instrument surfaces were cleaned. All area floors were stripped and resurfaced. Instrument external surfaces were cleaned with

repetitive 6″ × 8″ 70% IPA wipes (VWR). Equipment cleaned by IPA wipes was unplugged and unpowered to eliminate flammability risk, with wipes immediately placed into water buckets after use. All disposables, keyboards, computer mice, and floor mats in the laboratory area were discarded and replaced.

Postcleaning environmental sampling was conducted, followed by several rounds of focused cleaning and sampling to verify elimination of T. Subsequent interday precision studies (n = 500) on each of the instruments were conducted with no T fliers observed. No unexplained T fliers have been observed after cleaning and resumption of analytical testing. Cleaning protocols and PPE policies have been sustained.

Conclusions

The number and types of spills and contamination events in the clinical laboratory community are unknown and generally not reported. As such, we do not know if this was an isolated incident or something that might be occurring in other settings and laboratories. Clinical laboratory instrument contamination issues are not well described, and decontamination protocols from vendors typically reflect tube, probe, and bath cleansing but not surface cleaning per se. Additionally, processes for effective cleanup of different types of substances are rarely published. Indeed, this investigation involved establishing a monitoring technique and developing a cleaning protocol that would work with different types of surfaces in an open clinical laboratory space.

With pharmaceutical company direct-to-consumer promotion of T replacement therapy and societal propagation of terms such as "low T," a 10-fold increase in transdermal T prescriptions has been observed in the US between 2000 and 2011 *(6, 7)*. The present report described an environmental contamination in our laboratory attributed to direct and/or indirect contact with topical pharmaceutical T. It is possible that similar increases in environmental T may be expected in other workplace and domestic settings around individuals using topical T therapeutics. Additional studies focused on environmental contamination related to topical steroids may therefore be warranted. This is particularly troubling given the difficulty we experienced in effectively cleaning our workspace. Vendors should consider revising package inserts for clinical laboratory assays measuring substances that are frequently administered as topical formulations to include warnings about the risks of instrument contamination by operators.

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