estimates—serves as a reminder of the greater HCV disease burden in the veteran population. Given the high HCV infection prevalence, full adoption of birth cohort screening may reveal substantial numbers of veterans with previously unknown HCV infection.

Lisa I. Backus, MD, PhD
Pamela S. Belperio, PharmD
Timothy P. Loomis, PhD
Gale H. Yip, BA
Larry A. Mole, PharmD

Author Affiliations: Population Health/Office of Public Health, Palo Alto, California (Backus, Belperio, Loomis, Yip, Mole); Veterans Health Administration, Palo Alto, California (Backus); Veterans Health Administration Greater Los Angeles, Los Angeles, California (Belperio).

Corresponding Author: Lisa I. Backus, MD, PhD, Office of Public Health/Population Health, 3801 Miranda Ave, Mail Code #132, Palo Alto, CA 94304 (lisa.backus@va.gov).


Conflict of Interest Disclosures: None reported.


Reference Laboratory Values for Digoxin Following Publication of Digitalis Investigation Group (DIG) Trial Data
The translation of new findings into clinical practice is an ongoing challenge for physicians and health systems. The definition of a reference range for serum digoxin concentration (SDC) in patients with heart failure provides an example in which published data have not been incorporated into laboratory practice, which as a result may have an adverse impact on clinical care.

Specifically, in a post hoc analysis from the Digitalis Investigation Group (DIG) heart failure trial, higher mean SDCs were associated with increased mortality; the optimal therapeutic range for clinical benefit among men with a left ventricular ejection fraction of less than 45% was 0.5 to 0.8 ng/mL. A second analysis indicated that SDCs of 1.2 ng/mL or higher may be harmful in women. (To convert digoxin to nanomoles per liter, multiply by 1.281.) In light of these studies, we sought to determine the current practice of reporting SDCs in hospital-based chemical laboratory analyses.

Methods | A brief written survey (with telephone follow-up) (eSupplement) was sent to chemistry laboratory directors at hospitals listed in the top 50 for cardiovascular medicine reported by US News and World Report2 and an additional 50 from the top 100 hospitals rated by Thomson-Reuters (now Truven Health Analytics)4 in 2012. The study was approved by the Saint Louis University institutional review board, St Louis, Missouri.

Results | A total of 60 surveys were completed and returned for analysis (a 60% response rate). Respondents were 27 laboratory directors or assistant directors, 21 supervisors, 11 technicians, and 1 laboratory medicine fellow. Five different commercial assays were used; in the year prior to the survey, 5 laboratories changed their commercial assay citing upgrades in equipment or laboratory processes. No laboratory reported a change in the SDC reference range.

Most respondents defined a therapeutic reference range as 0.8 to 2.0 ng/mL (Figure 1); 56 of 60 report SDCs of 2.0 ng/mL or greater as being within the normal range.

A total of 41 laboratories reported the mean SDC evaluated over a period of up to 1 year, most commonly over the prior month (18 of 41). Nearly half (19 of 41) reported mean concentrations of 1.0 ng/mL or greater (Figure 2). A subset (13 of 41) reported on the proportion of SDCs higher than various thresholds; a significant number reported levels of 1.5 ng/mL or higher (Figure 2). When asked if SDC correlated with clinical efficacy, most respondents answered “don’t know” or “no” (76%); of the sites that answered in the affirmative (24%), only 1 site used a reference range with an upper limit lower than 1.0 ng/mL, whereas 8 listed a range up to 2 ng/mL, 1 each listed 1.5 ng/mL and 1.0 ng/mL, and 2 respondents did not provide a range.
Discussion | In an early but influential study that helped establish the therapeutic range for digoxin, Smith et al reported digoxin toxicity based on electrocardiographic (ECG) manifestations. In the 0.80 to 2.4 ng/mL range, patients without evidence of ECG changes were considered to have nontoxic levels. Subsequently, data from the DIG trial suggested that SDCs lower than 0.9 ng/mL are associated with therapeutic benefit and values higher than 1.2 ng/mL may be harmful. This observation has been incorporated into practice guidelines.

Of note, we obtained only a cross-sectional overview of SDCs detected in hospital-based chemical laboratory analyses and have no data on whether the levels were appropriately timed relative to dose. Furthermore, most data correlating concentrations to outcomes were generated from the DIG trial in heart failure, which excluded patients with atrial fibrillation at baseline; however, the 2 conditions often coexist. There is also no empirical evidence to suggest a therapeutic benefit of digoxin in atrial fibrillation at concentrations beyond those established for heart failure.

We previously showed that despite a secular decline in the use of digoxin, admissions for toxicity have not declined in parallel. As such, the persistence of a broad reference range for digoxin, a drug with a well-documented narrow therapeutic window, is a cause for concern. Based on our survey findings and a clear evidence base, we recommend the adoption of a redefined reference range for digoxin by chemical laboratory analyses with an upper limit no greater than 0.9 ng/mL and a change in laboratory reporting processes.

Paul J. Hauptman, MD
Patrick McCann, MD
Jorge M. Ramirez Romero, MD
Mary Mayo, PhD

Author Affiliations: Division of Cardiology, Saint Louis University School of Medicine, St Louis, Missouri (Hauptman, McCann); Department of Medicine, Saint Louis University School of Medicine, St Louis, Missouri (Hauptman, McCann, Romero); Department of Pathology, Saint Louis University School of Medicine, St Louis, Missouri (Mayo).

Corresponding Author: Paul J. Hauptman, MD, Department of Medicine, Saint Louis University Hospital, 3635 Vista Ave, St Louis, MO 63110 (hauptmpj@slu.edu).

Published Online: June 24, 2013.

Author Contributions: All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hauptman.

Acquisition of data: All authors.

Analysis and interpretation of data: Hauptman and McCann.

Drafting of the manuscript: Hauptman, McCann, and Ramirez Romero.

Critical revision of the manuscript for important intellectual content: Hauptman, McCann, and Mayo.

Statistical analysis: Hauptman, McCann, and Ramirez Romero.

Administrative, technical, and material support: Hauptman, McCann, and Mayo.

Study supervision: Hauptman.

Conflict of Interest Disclosures: Dr Hauptman received an honorarium for his participation in a CME event titled “Digoxin Toxicity: Awareness, Recognition, and Treatment,” sponsored by BTG International Inc (released August 21, 2012, and available at http://theheart.medscape.org/viewarticle/767832 (sign-up required)).

Correction: This article was corrected online on June 26, 2013, to add a text citation for the eSupplement.


A Prospective Study of Nighttime Vital Sign Monitoring Frequency and Risk of Clinical Deterioration

The routine practice of collecting vital signs every 4 hours in hospitalized ward patients has been perpetuated since as early as 1893, but little evidence supports this tradition. Although vital signs can be indicative of impending clinical deterioration, routine nighttime vital sign monitoring adds to the already fragmented sleep of inpatients. Sleep disruptions are prevalent among ward patients and are associated with several negative health outcomes, including elevated blood pressure and delirium. Overnight vital sign checks not only are an especially bothersome disrupter but also can deplete crucial health care resources. Track and trigger systems, such as the Modified Early Warning Score (MEWS), have been used to identify high-risk patients for critical interventions. The present study investigated whether the MEWS could identify low-risk patients who might forgo overnight vital sign monitoring.

Methods | We conducted a prospective cohort study of consecutive adult inpatients at a 550-bed academic institution between November 4, 2008, and August 31, 2011. All vital signs were extracted from the electronic medical record (Epic; Epic Systems Corporation), and a MEWS was calculated for each data set obtained on the general floors, with forward imputation used for incomplete sets. The MEWS most closely preceding 11 PM each evening was used to stratify patients. The number of nighttime (11 PM to 6 AM) disruptions for vital sign monitoring and the occurrence of adverse events, defined as intensive care unit transfers or cardiac arrests in the next 24 hours (11 PM to 11 PM), were compared across all MEWS categories.

Results | In total, 54,096 patients were included in the study, accounting for 182,828 patient-days on the wards and 1699 adverse events. The patient sample was 43.0% male and had a median age of 56 years (interquartile range, 40-68 years). The median evening MEWS was 2 (interquartile range, 1-2). The adverse event rate increased with higher evening MEWS, from a rate of 5.0 per 1000 patient-days (when the MEWS was ≤1) to 157.3 per 1000 patient-days (when the MEWS was ≥7) (P = .003 for trend) (Figure). However, the frequency of vital sign disruptions was unchanged, with a median of 2 vital sign checks per patient per night and at least 1 disruption from vital sign collection 99.3% of the nights regardless of MEWS category. Almost half of all nighttime vital sign disruptions (45.0%) occurred in patients with a MEWS of 1 or less.

Discussion | To our knowledge, this is the first study to critically examine the practice of vital sign collection on medical wards. Our study found that overnight vital signs are collected frequently among ward patients regardless of their risk of clinical deterioration. The evening MEWS identified a low-risk subset of patients who had significantly fewer adverse events but had overnight vital signs taken at a similar rate as high-risk patients. This suggests that the nighttime frequency of vital sign monitoring for low-risk medical inpatients might be reduced. Such a reduction could have dramatic benefits to patient sleep, considering that vital sign checks have been shown to be the environmental factor most disruptive to patient sleep. In addition to being linked to negative health outcomes and patient distress during inpatient care,