A Multicenter Evaluation of a Point-of-Care Blood Glucose Meter System in Critically Ill Patients

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Background: Our purpose was to evaluate the performance of the ACCU-CHEK® Inform II blood glucose monitoring system (Roche Diagnostics GmbH) compared with the perchloric acid hexokinase (PCA-HK) comparator method on the cobas® 6000 analyzer (Roche Diagnostics International Ltd) in critically ill patients.

Methods: Overall, 476 arterial (376 pediatric/adult, 100 neonate), 375 venous, and 100 neonatal heel-stick whole-blood samples were collected and evaluated from critical care settings at 10 US hospitals, including the emergency department, medical and surgical intensive care units (ICUs), and neonatal and pediatric ICUs. The ACCU-CHEK Inform II system was evaluated at 2 cutoff boundaries: boundary 1 was ≥95% of results within ±12 mg/dL of the reference (samples with blood glucose <75 mg/dL) or ±12% of the reference (glucose ≥75 mg/dL), and boundary 2 was ≥98% of results within ±15 mg/dL or ±15% of the reference. Clinical performance was assessed by evaluating sample data using Parkes error grid, Monte Carlo simulation, and sensitivity and specificity analyses to estimate clinical accuracy and implications for insulin dosing when using the ACCU-CHEK Inform II system.

Results: Proportions of results within evaluation boundaries 1 and 2, respectively, were 96% and 98% for venous samples, 94% and 97% for pediatric and adult arterial samples, 84% and 98% for neonatal arterial samples, and 96% and 100% for neonatal heel-stick samples. Clinical evaluation demonstrated high specificity and sensitivity, with low risk of potential insulin-dosing errors.

Conclusions: The ACCU-CHEK Inform II system demonstrated clinically acceptable performance against the PCA-HK reference method for blood glucose monitoring in a diverse population of critically ill patients in US care settings.
INTRODUCTION

Stress-induced hyperglycemia is commonly observed in critically ill patients and may be experienced by up to 90% of patients in intensive care units (ICUs), including those without a history of diabetes mellitus (1–5).

The landmark Leuven trials (6, 7) suggested that strict glycemic control via intensive insulin therapy could reduce morbidity and mortality in critically ill patients, prompting intensive therapy strategies to achieve normoglycemia in ICU settings (8, 9). However, intensive insulin therapy can increase the risk of hypoglycemia in critically ill patients, which carries an independent risk of increased morbidity and mortality and is associated with significantly extended ICU stays (8, 10). Hypoglycemia is thus considered the primary obstacle to achieving tight blood glucose control in critically ill patients (11).

Accurate monitoring of blood glucose is a key aspect of critical care, in which early clinical signs and symptoms of both hypo- and hyperglycemia can be difficult to identify given the sedation of patients who are critically ill. Intermittent, capillary-based measurement is labor intensive, and large glucose fluctuations may go unnoticed between readings (2, 5, 12, 13). A sampling strategy of hourly testing is costly, increases the workload of ICU nurses, and the multiple blood samples required can be detrimental to effective critical care (4, 5, 13–16). Capillary measurement is potentially compromised by poor peripheral circulation, intravenous pressor administration, acute decompensated heart failure, sepsis, acute blood loss, and diabetic ketoacidosis, all of which are common in patients who are critically ill (17–20). Waiting for laboratory results is especially problematic for pediatric and neonate patients, who have lower blood glucose targets and higher insulin sensitivity, compared with adults, that predispose these patients to hypoglycemia and necessitate close scrutiny (4).

Effective bedside point-of-care testing (POCT) would enable more rapid, frequent, and less invasive blood glucose monitoring in a near-continuous way, facilitate insulin dose adjustments for tighter glycemic control, and mitigate hyperglycemia and hypoglycemia in patients who are critically ill (15). Portable blood glucose meters have evolved from the self-monitoring devices designed for people with diabetes in the home setting to more complex prescription-based blood glucose monitoring systems that are used for bedside testing in various healthcare settings, including ICUs (21, 22). The ACCU-CHEK® Inform II blood glucose monitoring system (Roche Diagnostics GmbH) is an in vitro diagnostic POCT device that is

IMPACT STATEMENT

This study investigated the use of the ACCU-CHEK® Inform II system for point-of-care (POC) glucose monitoring in a large population of critically ill adult, pediatric, and neonatal patients in US hospital settings. Performance was evaluated against a higher-order perchloric acid hexokinase method (linked to isotope dilution GC-MS), and the clinical implications of using the system were assessed via Parkes error grid, Monte Carlo simulation, and sensitivity and specificity analyses. The ACCU-CHEK Inform II system demonstrated clinically acceptable performance and high sensitivity and specificity, with low risk of insulin-dosing error, furthering insight into the use of POC glucose monitoring devices in critical care.
intended for the bedside quantitative measurement of glucose concentrations in venous, arterial, neonatal heel-stick, or capillary whole-blood samples and that features blood glucose monitoring, data management, and wireless transmission of data to a facility’s internal data management system. ACCU-CHEK Inform II has been cleared by the US Food and Drug Administration (FDA) for use in POCT settings but has yet to be cleared for testing in patients who are critically ill. This study aimed to evaluate the analytic and clinical performance of the ACCU-CHEK Inform II system in patients who are critically ill.

MATERIALS AND METHODS

Study Design

This multicenter performance evaluation of the ACCU-CHEK Inform II system (the ACCU-CHEK system) in patients who were critically ill was conducted using venous, arterial, and neonatal heel-stick whole-blood samples from 10 US hospitals. The accuracy of the ACCU-CHEK system was determined by method comparison against a perchloric acid hexokinase (PCA-HK) comparator method on the cobas® 6000 analyzer (Roche Diagnostics International Ltd). PCA-HK was selected as the high-order reference comparator because the assay quickly arrests glycolysis to release intracellular glucose and exhibits few analytic interferences. It is directly linked to the higher-order isotope dilution GC-MS method by calibration (23).

Performance of the system in neonates was evaluated in a separate study, using venous blood samples from adult donors that were modified to contain high hematocrit and low glucose concentrations, mimicking the matrix properties of neonatal blood.

A clinical evaluation was performed by separate analyses to estimate the clinical implications, in terms of insulin dose adjustment, of differences between the ACCU-CHEK system and PCA-HK results.

The study was conducted in accordance with the Declaration of Helsinki of 1975 (revised 2013). Patients or their legally authorized representatives provided written informed consent for participation, and the study was approved by the relevant Institutional Review Board (see the online Data Supplement).

Patients

Patients (both diabetic and nondiabetic) were included if their medical status required treatment in an ICU or was considered critical by a physician if treated in another unit (non-ICU critical status was determined according to local criteria). Patients were categorized by age as adult (≥22 years), pediatric (29 days to 21 years), or neonate (birth to 28 days).

Participants’ medications (within the 24-h period before sample collection and regardless of administration route) and diagnoses (at inpatient discharge) were compared with those of both patients who were critically ill and those in the general ward; patients were identified using real-world data (RWD) from >700 US hospitals, obtained from the Premier Healthcare Database, a deidentified patient database compliant with the Health Insurance Portability and Accountability Act. RWD critical care settings included ICU, pediatric ICU, and emergency departments; all other encounters were classified as general ward. The 100 most frequent medications and most commonly occurring diagnoses from the RWD were compared with those of participants in each of the 3 patient groups, provided at least 4 patients shared the same medication or diagnosis.

Sample Collection

Venous, arterial, and neonatal heel-stick whole blood samples were collected at 10 US hospitals, including 1 emergency department, 6 medical
ICUs, 5 surgical ICUs, 3 pediatric ICUs, and 4 neonatal ICUs. Capillary finger-stick specimens were not included. Sample testing was designed to mimic routine patient testing, and only 1 sample (regardless of type) was obtained from each patient (approximately 0.5 mL from neonates and pediatric patients, 1 mL from adults). Residual samples were used when possible. Using the same blood sample for both the system and comparator method testing usually required the use of an additional intermediate container (generally an Eppendorf tube) from which the system was dosed and PCA-HK samples prepared.

Method Comparison

Quantitative analyses were performed to compare blood glucose measurement between the ACCU-CHEK system and the PCA-HK reference method on the cobas 6000 analyzer, with all results electronically captured using WinCAEv, a data capture software compliant with CFR 21 Part 11. Each sample was used to dose the system and to prepare 2 aliquots for PCA-HK determination. Each PCA-HK aliquot was run separately in triplicate, and results were averaged. An outlier analysis was performed on the PCA-HK results to detect gross statistical outliers resulting from preanalytic technique and for which supportive alternative data from a blood gas instrument were required.

The accuracy of the ACCU-CHEK system was evaluated against the following criteria: (a) ≥95% of results within either ±12 mg/dL of the reference method (samples with <75 mg/dL blood glucose) or ±12% of the reference method (samples with ≥75 mg/dL blood glucose) and (b) ≥98% of results within ±15 mg/dL or ±15% of the reference method (21).

Contrived Sample Study

Venous samples from 13 adult donors (≥22 years), with and without diabetes, were contrived to produce 8 different samples with normal or high hematocrit and low glucose target concentrations, to result in 104 samples in total. Target hematocrit concentrations were 40% (normal) and 65% (high; both n = 52), and glucose concentrations ranged from 10 mg/dL to 58 mg/dL in the group with normal hematocrit concentration and 10 mg/dL to 53 mg/dL in the group with high hematocrit concentration. Within these ranges, 22 and 23 of the samples had a glucose concentration <25 mg/dL in the normal and high hematocrit concentration groups, respectively. For each sample, ACCU-CHEK system dosing and PCA-HK test specifications were the same as for the main accuracy study, and PCA-HK tests had to be processed within 5 min of dosing the system. Results for both systems were compared and evaluated against the same specifications as the main accuracy study.

Assessment of Clinical Interferences

Potential interferences with the functioning of the ACCU-CHEK system were identified from participant medications and clinical diagnoses. A workflow algorithm was used to statistically determine whether further evaluation of any medication or diagnosis given within 24 h before blood sampling was required. Medications were assessed by in vitro bench studies, and endogenous substances associated with diagnoses were investigated for potential interference. Bench interference studies were conducted outside of this performance evaluation study. These interference studies followed CLSI EP7-A2 and A3 and CLSI EP37 guidelines. Those identified interferences are listed within the “Limitations” section of the ACCU-CHEK Inform II test strip package insert (20).

Clinical Performance Analyses

The following analyses were performed as theoretical estimates of the effects of clinical adjustments in insulin dosing, based on differences
between the ACCU-CHEK system and PCA-HK results.

**Parkes error grid.** A Parkes error grid analysis was constructed to assess the clinical risk associated with any differences between blood glucose results obtained from the system and the PCA-HK test. The error grid specifies 5 zones corresponding to level of risk, from none (A) to dangerous (E) (24). Analysis was performed on the paired ACCU-CHEK system/comparator method values to position all results within these zones.

**Monte Carlo simulation.** A Monte Carlo simulation analysis, as described by DuBois et al. (25), was performed to evaluate the influence of bias and precision of the ACCU-CHEK system results on the risk of potential insulin-dosing error in patients who were critically ill, using an insulin sliding scale. The scale is applied only in pediatric and adult patients; therefore, neonatal samples were excluded from this analysis. For 747 evaluable samples, blood glucose measurements obtained using the PCA-HK reference method were classified according to 13 insulin-dosing classes as defined by DuBois et al. (25). Multiple “cells” were created, reflecting discrete combinations of percentage of CV (%CV) and percentage of bias (%bias), to create total analytic error (TAE) values incorporating both imprecision and bias. To each PCA-HK-measured glucose concentration value (reference), a concentration-specific TAE was added comprising the reference plus %bias plus a randomly selected value from a normal distribution with a mean of zero and variance equal to (%CV \times \text{reference} / 100)^2. A proportion of misclassified samples was identified in which a difference of a minimum of 2 dosing classes was observed between the insulin-dosing class of the true blood measurement value and the class assigned after adding the randomly generated TAE. Data were presented as contour plots to visually represent the anticipated probability that the ACCU-CHEK system would generate a result associated with a minimum of insulin-dosing error classes, at the combinations of imprecision and bias (TAE values) added to the measurements of the reference method. The contour lines delimit areas within the 2-dimensional space within which predefined misclassification probabilities are not exceeded. A predefined limit for total allowable error of \pm 20 mg/dL (\pm 20%) of the comparator method (for insulin-dosing errors of \pm 2 classes) was selected, based on a similar previous study (25), and contour lines were created at values 0.05%, 0.1%, 0.2%, 0.5%, 1%, 2%, 5%, 10%, and 20%. The proportion of %bias estimates (100 \times [\text{test} - \text{reference}]) observed in the clinical study at an imprecision of the average CV (3.25%) located inside specific contour lines was estimated.

**Clinical sensitivity and specificity.** A stratified clinical sensitivity and specificity analysis was conducted to determine whether the ACCU-CHEK system is sufficient for intervention and therapeutic purposes at blood glucose concentrations at medical decision limits. Measurements from the system and PCA-HK methods were stratified into blood glucose categories associated with the glycemic range tested, at 10-mg/dL intervals between 50 and 150 mg/dL, and frequency distributions were determined. Paired results from the 2 methods were sorted into the 13 insulin-dosing classes (25) and cross-tabulated to show patterns of association. Sensitivity within each insulin-dosing class was calculated based on the fraction of the system results within \pm 1 of the results from the comparator method category, and the false-negative percentage was calculated as 100% \times (1 - \text{sensitivity}). Specificity within each ACCU-CHEK system category was calculated based on the fraction of system results within \pm 1 category compared with the PCA-HK comparator; the false-positive percentage was calculated as 100% \times (1 - \text{specificity}).
Statistical Analyses

All statistical analyses were performed using SAS software (version 9.4; SAS Institute). Regression analyses were performed using SAS (version 9.4) and R (version 3.4.0; R Foundation for Statistical Computing) software. The main R package used for analysis is package mcr (version 1.2.1).

RESULTS

A total of 954 patients were enrolled in the study and provided a total of 993 samples: 387 venous (375 evaluable), 481 arterial (476 evaluable), 100 neonatal heel-stick samples, and 25 samples were excluded. Patient demographics and clinical characteristics are presented in Table 1; 551 (58%) patients were male, 669 (70%) were White, and 796 (83%) were non-Hispanic/Latino. A total of 743 medications and 1612 diagnoses were represented, and 97 of the 100 top medications observed in RWD from Adult Critical Care departments were encountered in the data set.

The percentages of overlap between the 100 most common RWD medications and those

| Characteristic                  | Patients providing venous samples (n = 378), n (%) | Patients providing arterial samples (n = 476), n (%) | Patients providing neonatal heel-stick samples (n = 100), n (%) | Total patients (N = 954), n (%) |
|--------------------------------|--------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------|-------------------------------|
| Male                           | 220 (58)                                        | 284 (60)                                        | 47 (47)                                                        | 551 (58)                      |
| Age group                      |                                                  |                                                  |                                                               |                               |
| 0–28 days                      | 2 (<1)                                          | 100 (21)                                       | 100 (100)                                                     | 202 (21)                      |
| 29 days–21 years               | 51 (13)                                         | 51 (11)                                        | 0                                                             | 102 (11)                      |
| ≥22 years                      | 325 (86)                                        | 325 (68)                                       | 0                                                             | 650 (68)                      |
| Race                           |                                                  |                                                  |                                                               |                               |
| American Indian/Alaska Native  | 2 (<1)                                          | 9 (2)                                           | 0                                                             | 11 (1)                        |
| Asian                          | 7 (2)                                           | 16 (3)                                         | 0                                                             | 23 (2)                        |
| Black/African American         | 80 (21)                                         | 63 (13)                                        | 36 (36)                                                       | 179 (19)                      |
| Native Hawaiian/Pacific Islander| 0                                              | 1 (<1)                                         | 0                                                             | 1 (<1)                        |
| White                          | 267 (71)                                        | 340 (71)                                       | 62 (62)                                                       | 669 (70)                      |
| Other                          | 15 (4)                                          | 36 (8)                                         | 2 (2)                                                         | 53 (6)                        |
| >1 race                        | 1 (<1)                                          | 0                                              | 0                                                             | 1 (<1)                        |
| Not reported/unknown           | 6 (2)                                           | 11 (2)                                         | 0                                                             | 17 (2)                        |
| Ethnicity                      |                                                  |                                                  |                                                               |                               |
| Hispanic/Latino                | 91 (24)                                         | 52 (11)                                        | 3 (3)                                                         | 146 (15)                      |
| Non-Hispanic/Latino            | 286 (76)                                        | 413 (87)                                       | 97 (97)                                                       | 796 (83)                      |
| Not reported/unknown           | 1 (<1)                                          | 11 (2)                                         | 0                                                             | 12 (1)                        |
| Diabetic status, n\(^a\)       | 375                                             | 951                                             |                                                               |                               |
| Diabetic                       | 88 (23)                                         | 98 (21)                                        | 0                                                             | 186 (20)                      |
| Nondiabetic                    | 282 (75)                                        | 374 (79)                                       | 100 (100)                                                     | 756 (79)                      |
| Unknown                        | 5 (1)                                           | 4 (<1)                                         | 0                                                             | 9 (<1)                        |

\(^a\) Venous samples from 3 patients were not evaluable for diabetic status.
received by participants in adult critical care, the adult general ward, pediatric critical care, and the pediatric general ward were 97%, 95%, 74%, and 64%, respectively. There was 100% diagnosis overlap of the system organ classes in all wards. For individual conditions, the percentages for overlap in adult critical care, the adult general ward, pediatric critical care, and the pediatric general ward were 84%, 83%, 35%, and 55%, respectively.

### Accuracy of the ACCU-CHEK Inform II System

Accuracy results for the ACCU-CHEK Inform II system by sample type and by blood glucose concentration category (<75 mg/dL and ≥75 mg/dL) are shown in Table 2 and Table 3, respectively. The outlier analysis of the duplicate PCA-HK test results necessitated removal of 6 results that were clearly due to a preanalytic error in the preparation of the corresponding aliquot. For the 375 evaluable venous samples, 96% were within ±12 mg/dL or ±12% of the comparator method, and 98% were within ±15 mg/dL or ±15% of the reference method, and 97% were within ±15 mg/dL or ±15% (Table 2). When the 376 pediatric and adult arterial samples were reanalyzed separately, 94% were within ±12 mg/dL or ±12%, and 97% were within ±15 mg/dL or ±15% of the reference method (Table 2); for the 100 neonatal arterial samples, 84% were within ±12 mg/dL or ±12%, and 98% were within ±15 mg/dL or ±15% of the reference method (Table 2).

### Accuracy of the ACCU-CHEK Inform II System in Contrived Samples

All samples tested, regardless of hematocrit or glucose concentration, met the acceptance criteria of ±12 mg/dL or ±12%, and no significant trends were observed in the bias for different glucose concentrations. The biases between the system and the comparator method averaged −0.2 mg/dL for the 65% hematocrit samples (mimicking neonatal blood) and −1.7 mg/dL for the 40% hematocrit samples (Supplemental Fig. 1).

### Clinical Performance Analyses

**Parkes error grid.** Figure 1 shows the Parkes error grid associated with the ACCU-CHEK system:
99.5% of the results fell within zone A, corresponding to clinically accurate measurements associated with no risk. The remaining results were within zone B, indicating slight risk (3 results) and zone C, indicating moderate risk (1 result). No results fell within zones D and E (significant risk and dangerous results, respectively).

**Monte Carlo simulation.** The 2-dimensional space defined by %CV (x-axis) and %bias (y-axis), where %CV reflects the normal distribution of ACCU-CHEK system measurements associated with each reference value and %bias is the fraction of each true glucose concentration (as measured by the comparator method), is shown in Fig. 2. The contour plots displaying the probability of misclassification at a minimum of 2 insulin-dosing classes are also shown. The proportions of true bias values for misclassification probabilities at a minimum of 2 insulin-dosing classes are presented in Supplemental Table 1. Of 747 sample results included, 18 fell outside the total allowable error of ±20% (±20 mg/dL) of the comparator method (error rates) for insulin-dosing errors of ±2 classes, which represents 2.4% of samples (Supplemental Fig. 2).

**Clinical sensitivity and specificity.** The stratified clinical sensitivity and specificity analysis demonstrated that the ACCU-CHEK system has high sensitivity and specificity across the glycemic range tested (50–400 mg/dL) (Table 4).

**DISCUSSION**

Our performance evaluation of the ACCU-CHEK Inform II blood glucose monitoring system compared with a PCA-HK comparator method in patients who were critically ill established several key findings. Results for all venous and neonatal heel-stick samples met the predefined evaluation criteria, demonstrating that the ACCU-CHEK system had analytic accuracy equivalent to the PCA-
HK comparator method for these samples from patients who were critically ill. Pooled arterial samples, however, did not meet the evaluation criteria, and further analysis revealed that this result was due to the contribution from neonatal arterial samples, for which only 84% of results were within \( \pm 12 \) mg/dL or \( \pm 12\% \) of the reference method. The outcome for the neonatal sample group, however, was successful at the outer criterion of \( \pm 15 \) mg/dL or \( \pm 15\% \) of the comparator method, for which 98% of results qualified, and the observation that all results were within \( \pm 20 \) mg/dL or \( \pm 20\% \) provides further reassurance.

Our study was designed to mirror a similar investigation of a point-of-care glucose monitoring system that is FDA-approved for hospital use, including in patients who are critically ill, in a study by DuBois et al. (25). That study also utilized Parkes error, Monte Carlo, and sensitivity and specificity statistical analyses to evaluate the clinical accuracy of the glucose monitoring system in a large and diverse population of patients who were critically ill and demonstrated that the combined statistical analyses provided an effective clinical assessment. Our study was not a head-to-head comparison but was distinct in 2 aspects: whereas DuBois et al. (25) report results for patients aged 2 months to 99 years, we differentiated among adult, pediatric, and neonatal subgroups and reported separate venous and arterial sample concentrations.

**Fig. 1.** Parkes error grid for the ACCU-CHEK Inform II system (pediatric/adult arterial and venous samples, \( n = 750 \); 750 of 751 samples qualified for analysis). The error grid specifies 5 zones corresponding to different levels of risk, from none (A) to dangerous (E) (24). Analyses performed on the paired ACCU-CHEK system or PCA-HK positioned all results within these zones. The triangle denotes results outside the safest zone (A). One sample with glucose concentration (comparator measurement) of 563.64 mg/dL was excluded because it exceeds the maximum permissible for inclusion (550 mg/dL).
and neonatal sample results. In addition, our supplementary contrived sample study adds insight into the performance of the ACCU-CHEK system in this subgroup. These differences complicate comparisons between the 2 studies, with implications for conclusions about the overall performance of the ACCU-CHEK system in patients who are critically ill.

When we removed neonatal arterial samples from the main overall analysis, combined pediatric and adult sample results remained outside the predefined ±12 mg/dL or ±12% evaluation criteria. However, all results for samples at the lowest glucose levels (<75 mg/dL) were within ±12 mg/dL. The reason for the lower performance of the system in neonatal arterial samples is unclear; result variability among study centers may have had an impact on performance estimates, but sample numbers are too small to evaluate this possibility. An exploratory investigation was conducted into the underlying cause, which examined potential correlations with parameters such as age, environmental variables, and interfering substances. The proportion of results outside the ±12 mg/dL or ±12% boundary was larger for samples from younger and extreme preterm babies and in those receiving caffeine citrate, which is commonly administered to preterm babies with immature
Table 4. Stratified clinical sensitivity and specificity analysis for the ACCU-CHEK Inform II system.\(^a\)

| PCA-HK reference glucose category, mg/dL | Inform II glucose category | < 40 | 40–80 | 81–90 | 91–110 | 111–130 | 131–150 | 151–175 | 176–200 | 201–250 | 251–300 | 301–350 | 351–400 | > 400 | Total | Sensitivity | FN,\(^b\) | % |
|------------------------------------------|---------------------------|------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|------|-------------|       | --- | --- |
| < 40                                     |                           | 2    | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 2    | 1           | 0     |     |     |
| 40–80                                    |                           | 1    | 23    | 4     | 0     | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 28   | 1           | 0     |     |     |
| 81–90                                    |                           | 0    | 9     | 22    | 1     | 1      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 34   | 0.97        | 2.94  |     |     |
| 91–110                                    |                           | 0    | 2     | 27    | 125   | 12     | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 166  | 0.99        | 1.2   |     |     |
| 111–130                                   |                           | 0    | 0     | 0     | 26    | 116    | 13     | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 155  | 1           | 0     |     |     |
| 131–150                                   |                           | 0    | 0     | 0     | 0     | 35     | 74     | 9      | 0      | 0      | 0      | 0      | 0      | 0      | 118  | 1           | 0     |     |     |
| 151–175                                   |                           | 0    | 0     | 0     | 0     | 0     | 35     | 57     | 8      | 0      | 0      | 0      | 0      | 0      | 100  | 1           | 0     |     |     |
| 176–200                                   |                           | 0    | 0     | 0     | 0     | 0     | 14     | 41     | 7      | 0      | 0      | 0      | 0      | 0      | 62   | 1           | 0     |     |     |
| 201–250                                   |                           | 0    | 0     | 0     | 0     | 0     | 0     | 5      | 39     | 1      | 0      | 0      | 0      | 0      | 45   | 1           | 0     |     |     |
| 251–300                                   |                           | 0    | 0     | 0     | 0     | 0     | 0     | 2      | 19     | 1      | 0      | 0      | 0      | 0      | 22   | 1           | 0     |     |     |
| 301–350                                   |                           | 0    | 0     | 0     | 0     | 0     | 0     | 3      | 4      | 3      | 0      | 0      | 0      | 0      | 10   | 1           | 0     |     |     |
| 351–400                                   |                           | 0    | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 1      | 1      | 1      | 1      | 0      | 2    | 1           | 0     |     |     |
| > 400                                     |                           | 0    | 0     | 0     | 0     | 0     | 0     | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 7    | 1           | 0     |     |     |
| Total                                     |                           | 3    | 33    | 53    | 154   | 164    | 122    | 80     | 54     | 48     | 23     | 6      | 4      | 7      | 751  |             |       |     |     |
| Specificity                               |                           | 1    | 0.94  | 1     | 1     | 0.99   | 1      | 1      | 1      | 1      | 1      | 1      | 1      | 1      |       |       | 1           |     |     |     |
| FP, %                                     |                           | 0    | 6.06  | 0     | 0     | 0.61   | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      |       |       | 6           |     |     |     |

\(^a\)Only evaluable subjects without deviations were used for this analysis (excluding neonatal samples). The following subjects with deviations were excluded: 1511, 3001–3006, 3201, 5008, and 5010. The green boxes depict values where the comparator method and the ACCU-CHEK Inform II system agree within 1 insulin dose category or disagree when > 1 dosing category. The yellow boxes depict values where the 2 methods disagree by > 1 or < 1 dosing category.

\(^b\)FN, false negative; FP, false positive.
pulmonary function. Because of the small size of the patient population, it was not possible to determine any clear association.

When examined alongside neonatal arterial sample data for the similar FDA-approved point-of-care system by DuBois et al. (25), our findings appear in a positive light. Because these were not head-to-head studies of the same sample set, data comparison is limited and can generate only cautious and preliminary observations. For the point-of-care system in current use, results at the lowest glucose levels (<75 mg/dL) were within 10 mg/dL of the reference, for samples ≥75 mg/dL, 63% of results were within 10%, and 92% were within 15% of the reference (26). For the ACCU-CHEK system, these percentages are higher (65% and 98%, respectively), with 81% of results within 12% of the reference.

Our results from neonatal heel-stick samples met both evaluation requirements, and all of the contrived samples, regardless of hematocrit or glucose concentration, displayed performance vs the comparator method within the expected 12 mg/dL criteria. This suggests that high hematocrit values and low blood glucose concentrations characteristic of neonatal venous samples do not have any negative effect on the performance of the ACCU-CHEK system.

The clinical performance analyses demonstrated the system to be of high clinical sensitivity and specificity. The location of 99.5% of the data points within zone A of the Parkes error grid meets required criteria of >95% for clinical utility (24) and indicates that no patient requiring treatment for hypoglycemia would be misdiagnosed. The Monte Carlo simulation showed that the system has low error rates; with only 2.4% of samples having >20% chance of ≥2 insulindosing errors during treatment. A similar performance with regard to misclassification error rates has been reported for the system in current use in critically ill patients (25). Stratified analyses demonstrated high sensitivity and specificity of the system across the glycemic range tested, including cutoff values for both hypo- and hyperglycemia, which are important to detect in patients who are critically ill.

A study published by Louie et al. (27) demonstrated good performance of the ACCU-CHEK Inform II system when testing remnant arterial and venous whole blood samples from patients who were critically ill, revealing a strong correlation with both hexokinase and hospital laboratory PCA-HK reference methods. We conducted a post hoc analysis of this data set, for comparison with our study data, using the same performance evaluation criteria. In both data sets, all results from arterial samples with blood glucose <75 mg/dL (each n = 21) were within ±12 mg/dL of the PCA-HK result. In our study, 94% of results from samples with blood glucose ≥75 mg/dL were within ±12% of the reference, whereas in the data set from Louie et al., 97% of results qualified. The number of venous samples with blood glucose <75 mg/dL included in the data set from Louie et al. (n = 8) was too small to draw any conclusions, although all results were within the specified reference range.

The findings of Louie et al. (27) provide further support for the clinically acceptable performance of the ACCU-CHEK system for glucose monitoring in patients who are critically ill. Strengths of the current study include its design as a large multicenter study with good diversity, conducted across 10 different hospital critical care units, in patients with a wide range of diagnoses and concomitant medications. The overlap between our study population and RWD from adult ICUs was 97% for medications and 84% for diagnoses, achieving fair representation of the US critical care population.

Limitations of our study include the absence of capillary finger-stick sample data and the paucity of blood samples at low blood glucose concentrations (<75 mg/dL), allowing a few results with large bias to have a disproportionate impact on
performance estimates and causing lower proportions to fall within the 12- or 15-mg/dL criteria. Sampling at both the hypo- and hyperglycemic ends of the glucose concentration spectrum was somewhat hindered because of conscientious clinical management of glycemic control at the sites. Furthermore, the requirement for informed consent before participation precluded access to patients who were sedated, intubated, or on a vasopressor and who may have had unstable glycemic control.

Finally, the clinical evaluation comprised reanalyses of study data and did not involve actual clinical decision-making with respect to the patients included. The Parkes error grid analysis is based on analytic performance and potential insulin mismanagement criteria, and the Monte Carlo analyses are based on simulation data. Treating clinicians were not privy to patients’ blood test results and had no opportunity to utilize them to adjust insulin dosing if necessary. Equally, it was not possible to assess whether any such adjustments would have affected outcomes, which can only be hypothesized based on any differences between subsequent ACCU-CHEK system and PCA-HK results.

**CONCLUSIONS**

The ACCU-CHEK Inform II system demonstrated good performance in comparison to a high-order PCA-HK comparator method for blood glucose monitoring in a large, clinically diverse population of patients who were critically ill in the US care setting. Performance of the ACCU-CHEK system depends on the patient population tested and potential interference from a small number of substances.

**SUPPLEMENTAL MATERIAL**

Supplemental material is available at The Journal of Applied Laboratory Medicine online.

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**Nonstandard Abbreviations:** ICU, intensive care unit; POCT, point-of-care testing; PCA-HK, perchloric acid hexokinase; RWD, real-world data; %CV, percentage of CV; %bias, percentage of bias; TAE, total analytic error

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