Interference and Point-of-Care Testing Devices

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Director of Clinical Chemistry, Special Chemistry/Toxicology and POCT
Learning Objectives

• Identify common interferences affecting POC testing
• Describe cases where interfering substances affected patient care.
• Describe solutions to mitigate the impact of interfering substances on POC testing.
POCT Device Formats

**Definition:** POCT is defined as testing at or near the site of patient care
POCT Device Formats

Examples:
- Disposable
- Handheld
- Portable
- Transportable
- Benchtop
- Monitoring
POCT Device Formats

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- Disposable
- Handheld
- Portable
- Transportable
- Benchtop
- Monitoring

Being FDA approved as a POCT device does not mean it is not susceptible to interfering substances!!!
Total Testing Process: Difference Phases

Total Testing Process: Lab testing occurs over three critical phases:

Pre-Analytical
Total Testing Process: Difference Phases

**Total Testing Process**: Lab testing occurs over three critical phases:

- Pre-Analytical
- Analytical
Total Testing Process: Difference Phases

**Total Testing Process:** Lab testing occurs over three critical phases:

- Pre-Analytical
- Analytical
- Post-Analytical
Total Testing Process: Difference Phases

Total Testing Process: Lab testing occurs over three critical phases:

- Pre-Analytical
- Analytical
- Post-Analytical

TREATMENT
Total Testing Process: Sources of Error

Errors in the Pre-Analytical Phase: Most frequent source of errors (up to 70%). Incorrect

Components:
- Patient preparation
- Sample collection
- Transportation
- Accessioning
- Processing

Pre-Analytical | Analytical | Post-Analytical | TREATMENT
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Sources of Error:
- Incorrect patient ID
- Mislabling of specimens
- Hemolysis
- Wrong specimen type
- Improper specimen collection
- Interfering substances

Pre-Analytical | Analytical | Post-Analytical | TREATMENT
Total Testing Process: Sources of Error

Errors in the Analytical Phase: Infrequent in laboratory tests, however may be higher in POCT due to non-lab trained personnel operating devices.

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Testing

Pre-Analytical | Analytical | Post-Analytical

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Testing
- QC/calibration
- Operator error
- Bad reagents

TREATMENT
# Total Testing Process: Sources of Error

**Errors in the Post-Analytical Phase:** Second most common among laboratory-based results.

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<tr>
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<th>Post-Analytical</th>
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</thead>
<tbody>
<tr>
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<td>Testing</td>
<td>Results interpretation</td>
<td>Entry to LIS/EMR</td>
</tr>
<tr>
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<td>Contacting providers</td>
</tr>
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<td>Transportation</td>
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### Sources of Error

<table>
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<td>Hemolysis</td>
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UC Davis Health Department of Pathology and Laboratory Medicine
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- Sample collection
- Transportation
- Accessioning
- Processing

### Sources of Error
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- Improper specimen collection
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### Components
- Pre-Analytical
- Analytical
- Post-Analytical

### Sources of Error
- QC/calibration
- Operator error
- Bad reagents
- Misinterpretation of results
- IT problems

### Treatment
- Results interpretation
- Entry to LIS/EMR
- Contacting providers
- Sample archiving

UCDavis Health
Department of Pathology and Laboratory Medicine
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- Hemolysis
- Wrong specimen type
- Improper specimen collection
- Interfering substances
- QC/calibration
- Operator error
- Bad reagents
- Misinterpretation of results
- IT problems

What is the significance of testing error in POCT?
Glucose Meter Paradigm to Highlight the Role of Testing Errors
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>12,000 glucose meter errors are reported to the FDA each year – highest number of adverse events for any in vitro diagnostic device.
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Most of these reported errors are due to erroneous results from interfering substances and operator error.
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Glucose Meter Paradigm to Highlight the Role of Testing Errors

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Common Confounding Factors for Glucose Meters

Anemia and polycythemia causes falsely high or falsely low results respectively.
Hematocrit Effects on BGMS Measurements

Sample Size: 60
Hematocrit Range: 19 - 60%
Glucose Range: 90 - 296 mg/dL

Note: Bias = BGMS – Plasma Glucose

\[ y = -0.9465x + 30.951 \]
\[ R^2 = 0.4171 \]
Common Confounding Factors for Glucose Meters
Common Confounding Factors for Glucose Meters

Oxidizing and reducing substances interfere with electrochemical sensors causing falsely high or low results.
Drug Interferents (Oxidizing Substances)

The role of drug interferences in critical care BGMS accuracy

Tran NK, et al. *J Burn Care Res* 2014;35:72-79
**CASE EXAMPLE: ASCORBIC ACID INTERFERENCE**

**History:** Patient is a 21 y/o woman with 90% TBSA burns from MVA.

**Blood Glucose (mg/dL)**

- Started Ascorbic Acid (66 mg/kg/hr)
- Stopped Ascorbic Acid
CASE EXAMPLE: ASCORBIC ACID INTERFERENCE

Blood Glucose (mg/dL) vs. Time Following Admission (Hours)

- Started Ascorbic Acid (66 mg/kg/hr)
- Stopped Ascorbic Acid

BGMS B
PLASMA GLUCOSE (Lab)
CASE EXAMPLE: ASCORBIC ACID INTERFERENCE

Started Ascorbic Acid (66 mg/kg/hr)

Stopped Ascorbic Acid
Common Confounding Factors for Glucose Meters
Common Confounding Factors for Glucose Meters

Specimen temp alters biosensor enzyme kinetics. Hypotension/shock affect capillary specimens.
Common Confounding Factors for Glucose Meters

Some glucose meters cannot differentiate between certain non-glucose sugars (e.g., maltose, galactose)
Non-Glucose Sugar Interferences

- Icodextrin is a dialysis drug. It is metabolized by the body to maltose. In some glucose biosensors, maltose is indistinguishable from glucose.
Abstract and Introduction

Abstract

Maltose, a disaccharide composed of two glucose molecules, is used in a number of biological preparations as a stabilizing agent or osmolality regulator. Icodextrin, which is converted to maltose, is present in a peritoneal dialysis solution. Galactose and xylose are found in some foods, herbs, and dietary supplements; they are also used in diagnostic tests. When some blood glucose monitoring systems are used—specifically, those that use test strips based on glucose oxidase chemistry—it can interfere with the test results. This article discusses the interference of maltose, icodextrin, galactose, or xylose with blood glucose monitoring systems.
Maltose Related Deaths

<table>
<thead>
<tr>
<th></th>
<th>BGMS A</th>
<th>BGMS B</th>
<th>BGMS C</th>
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<tbody>
<tr>
<td>Timeframe</td>
<td>1997-14</td>
<td>2013-14</td>
<td>2007-11</td>
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<tr>
<td>Adverse Events</td>
<td>28 (13)</td>
<td>5 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>(Deaths)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erroneous Results</td>
<td>557</td>
<td>168</td>
<td>15</td>
</tr>
<tr>
<td>Non-Clinical Event</td>
<td>387</td>
<td>59</td>
<td>21</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1094</td>
<td>232</td>
<td>36</td>
</tr>
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</table>

Continuous Glucose Monitors?

- Similar sensor designs so susceptible to similar interferences (will vary based on manufacturer).
- CGM based on interstitial fluid measurements and not plasma or whole blood.
- Potential for many other sources of interferences.
- CGM does not fall under CLIA and most devices compared against obsolete or poor reference methods such as the YSI.
- Use WITH caution!
INTERFERENCES IN WHOLE BLOOD ANALYSIS

- Air Contamination
- Delayed Testing
- Hemodilution/Hemoconcentration
- Hemolysis
INTERFERENCES IN WHOLE BLOOD ANALYSIS

Air Contamination

Delayed Testing

Hemodilution/Hemoconcentration

Hemolysis
Air Contamination of Blood Specimens

**Background:** Anesthesia reports “impossible venous blood gas values” in one patient where end tidal CO2 was greater than the venous blood gas (VBG).
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- POC Venous Blood Gas: pH = 7.54, pCO2 = 17.5, pO2 = 168.5
- POC VBG#2: pH = 7.56, pCO2 = 12.7, pO2 = 165.9
- End tidal CO2 = 28
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Blood Gas Laboratory identified “air bubbles” in syringe
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- Lab Venous Blood Gas: pH 7.54, pCO2 = 19.2, pO2 = 161.5
- Air bubbles can quickly (<5 mins) cause the specimen to equilibrate atmospheric air (1 atm = 760 mmHg = 0.21 x 760 = 150 mmHg for pO2!!!)
INTERFERENCES IN BLOOD GAS ANALYSIS

- Air Contamination
- Delayed Testing
- Hemodilution/Hemoconcentration
- Hemolysis
Specimen Processing Delays and Lactate

Pre-Analytical
• Transportation delays

Analysis should be performed within 20 to 30 minutes—Faster is better!
Specimen Processing Delays and Lactate

Pre-Analytical
• Transportation delays

Specimen Processing Delays and Lactate

**Pre-Analytical**
- Transportation delays
- Inadequate inhibition of glycolysis

If delays are expected, using a grey top tube may be appropriate, however it may take up to 15 minutes to achieve inhibition!
Specimen Processing Delays and Lactate

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Specimen Processing Delays and Lactate

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Fig. 1. Effectiveness of F/OX in samples from patients with leukocytosis. Samples were evaluated from three patients with increased neutrophil counts due to granulocyte colony-stimulating factor, and a fourth patient with a carcinoma-associated leukemoid reaction. EDTA-anticoagulated whole blood was stored at room temperature with (closed symbols) and without F/OX (open symbols). Neutrophil counts were 51.7 (Φ), 52.5 (○), 27.1 (□), and 23(△) × 10⁹/L.
Specimen Processing Delays and Lactate

Pre-Analytical
- Transportation delays
- Inadequate inhibition of glycolysis
- Specimens not placed on ice

False elevations of lactate could be mitigated by placing samples on ice. Iced samples exhibit similar results to those tested immediately at up to 6 hours.
Specimen Processing Delays and Lactate

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INTERFERENCES IN WHOLE BLOOD ANALYSIS

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Contemporary Hemoglobinometric Techniques

- Spectrophotometric (Non-Cyanohemoglobin)

- Measurement of hemoglobin is based on the absorption spectra
- Oxy- and deoxyhemoglobin exhibit different absorption in the red to IR wavelengths.
- Measurement based on Beer’s Law ($A = elc$).
- Some methods require lysis and reacting with non-cyanide-based reagents.
Contemporary Hemoglobinometric Techniques

Conductance (Impedance)

- Red blood cell membranes are not conductive.
Contemporary Hemoglobinometric Techniques

Conductance (Impedance)

Electrode

• Red blood cell membranes are not conductive.

![Diagram showing relationship between resistance, hematocrit, and red blood cells.](image)
Contemporary Hemoglobinometric Techniques

Conductance (Impedance)

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• The number of red blood cells is proportional to the change in conductance and conforms to Ohm’s Law ($V = IR$)
Contemporary Hemoglobinometric Techniques

Conductance (Impedance)

Electrode

• Red blood cell membranes are not conductive.

• The number of red blood cells is proportional to the change in conductance and conforms to Ohm’s Law ($V = IR$)

• Conductance-based methods measure hematocrit. The hematocrit can then be used to calculate hemoglobin based on a conversion factor (estimated hemoglobin = hematocrit / 3.4)*
Contemporary Hemoglobinometric Techniques

Conductance (Impedance)

Electrode

VS.
Case Study 2: Hemoconcentration

**Background:** Patient with suspected Ebola Virus symptoms admitted for evaluation. Isolation protocols were in effect.
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Inadequate mixing may result in artificial changes in total hemoglobin measurements.
Contemporary Hemoglobinometric Techniques

Conductance (Impendence)

- Plasma protein content contributes to hematocrit measurements for conductance-based systems.
Contemporary Hemoglobinometric Techniques

Conductance (Impedence) $\bullet =$ Plasma Protein

Electrode

Low Resistance from low plasma protein concentration!

- Plasma protein content contributes to hematocrit measurements for conductance-based systems.
- Conductance-based systems assumes a relatively fixed protein concentration. Therefore, during hemodilution, hematocrit may be falsely lower and causing an underestimation of total hemoglobin.
Contemporary Hemoglobinometric Techniques

Conductance (Impendence) \(=\) Plasma Protein

- Plasma protein content contributes to hematocrit measurements for conductance-based systems.
- Conductance-based systems assumes a relatively fixed protein concentration. Therefore, during hemodilution, hematocrit may be falsely lower and causing an underestimation of total hemoglobin.
- **UCDMC Study**: Comparison of a handheld blood gas analyzer using conductance-based measurement of hemoglobin versus a benchtop blood gas analyzer using a spectrophotometric-based method for hemoglobinometry.
Clinical Impact of Hemodilution for Point-of-Care Hemoglobin Measurements

- Sixty patients requiring cardiac surgery were evaluated.
- Paired specimens were tested using a handheld POC analyzer and spectrophotometric methods through the core laboratory.
- Mean (SD) bias was -1.4 (1.1) g/dL, P = 0.011.
- Based on core laboratory results 12 patients would have received unnecessary transfusions.
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$219 \times 12 = $2,628 POTENTIALLY WASTED
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**Background:** FDA MAUDE database reports a case (03P76-25) of a neonatal patient with discrepant point-of-care (POC) hemoglobin values compared to the laboratory. The POC device used a conductance-based method of hemoglobin measurement, while the laboratory used a spectrophotometric method.
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- Transfusion was stopped halfway after the laboratory reported a hematocrit of 40% and hemoglobin of 11.7 g/dL.
- Post-transfusion POC and lab hematocrit values were 45 and 50% respectively.
Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry

Device #1 Hb (g/dL) vs. Central Laboratory Hb (g/dL)

y = 0.5092x + 4.0176

R² = 0.5253
Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry

\[ y = 0.5249x + 3.9443 \]
\[ R^2 = 0.5407 \]
Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry

\[ y = 0.9345x + 0.4057 \]

\[ R^2 = 0.9205 \]
Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry

Notes: Reference Method = Beckman LH hematology analyzer
Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry

Median (IQR) Bias: 0.78 (0.78) g/dL
P < 0.001
N = 50

Notes: Reference Method = Beckman LH hematology analyzer
Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry

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Median (IQR) Bias: 0.73 (0.60) g/dL
P < 0.001
N = 50
Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry

Notes: Reference Method = Beckman LH hematology analyzer

Median (IQR) Bias: 0.22 (0.20) g/dL
P = 0.510
N = 50
Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry

Serial Testing Performance at 7 and 8 g/dL
- Serial testing revealed significant analytical bias between spectrophotometry vs. conductance-based measurements.

Notes: *** P<0.001, Central Lab = Spectrophotometric Method, n = 20 patients
Analytical Performance of Optical vs. Conductance-Based Hemoglobinometry

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### Manufacturer and User Facility Device Experience (MAUDE) Database Summary

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<tr>
<th></th>
<th>Device 1</th>
<th>Device 2</th>
<th>Device 3</th>
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<td>2011-2016</td>
<td>2011-2016</td>
<td>2014-2016*</td>
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<tr>
<td><strong>Erroneous Results</strong></td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Improper Transfusions</strong></td>
<td>5</td>
<td>0</td>
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INTERFERENCES IN WHOLE BLOOD ANALYSIS

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- Delayed Testing
- Hemodilution/Hemoconcentration
- Hemolysis
INTERFERENCES IN WHOLE BLOOD ANALYSIS

- Air Contamination
- Delayed Testing
- Hemodilution/Hemoconcentration
- Hemolysis
- Pseudohyperkalemia
INTERFERENCES IN WHOLE BLOOD ANALYSIS

- Air Contamination
- Delayed Testing
- Hemodilution/Hemoconcentration
- Hemolysis

Pseudohyperkalemia
“Pseudonormokalemia”
INTERFERENCES IN WHOLE BLOOD ANALYSIS

- Air Contamination
- Delayed Testing
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No current FDA approved integrated solutions for detecting hemolysis at the point-of-care

Pseudohyperkalemia
“Pseudonormokalemia”
Biotin: The “Snake Oil” of 2018?
The FDA Warns that Biotin May Interfere with Lab Tests: FDA Safety Communication

Product:

Many lab tests use biotin technology due to its ability to bond with specific proteins which can be measured to detect certain health conditions. For example, biotin is used in hormone tests and tests for markers of cardiac health like troponin. Biotin, also known as vitamin B7, is a water-soluble vitamin often found in multi-vitamins, prenatal vitamins, and dietary supplements marketed for hair, skin, and nail growth.
Biotin and Cardiac Troponin Testing
1,443 Gen 5 troponin T samples tested (0-hour, n = 797; 3-hour, n=646) from 850 patients.

*There was a statistically significant difference between 0-hour and 3-hour biotin concentrations (p<0.001; paired Wilcoxon rank sum test).
Estimating the Probability of Biotin Interference

• 1,443 Gen 5 troponin T samples tested (0-hour, n = 797; 3-hour, n=646) from 850 patients.

• Biotin not detectable in 471 (59%) and 399 (62%) 3-hour samples.

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• Biotin not detectable in 471 (59%) and 399 (62%) 3-hour samples.

• Only one 0-hour sample and one 3-hour sample had biotin >20 ng/mL (0.13% [95% CI: 0-0.7%]).

*There was a statistically significant difference between 0-hour and 3-hour biotin concentrations (p<0.001; paired Wilcoxon rank sum test).
Estimating the Probability of Biotin Interference

Intended-use population (patients presenting to US emergency departments with suspected AMI)

- Biotin concentration: ≤20 ng/mL
  Lower confidence limit: 99.3%
  Upper confidence limit: 0.7%

- Biotin concentration: >20 to ≤100 ng/mL

Non-AMI prevalence: 85%
AMI prevalence: 15%

- 0-hour TnT Gen 5 result
  <19.00 or >45.24 ng/L: 75%
  ≥19.00 to ≤45.24 ng/L: 25%

Likelihood of false-negative
0-hour TnT Gen 5 result
due to biotin interference: 0.026%

Mumma B, et al. AACC Poster Presentation 2018
Estimating the Probability of Biotin Interference

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**Likelihood of false-negative 0-hour TnT Gen 5 result due to biotin interference**: 0.026%
UC Davis Cardiac Troponin Patients

Adult ED Patients with Unknown Biotin Status: 540
Average Plasma Biotin: 1.15 (0.97) ng/mL

Specimens collected as part of clinical validation
Gen 5 TnT Biotin Interference Threshold is 20 ng/mL

Biotin quantified by GC-TOF-MS

UC Davis Cardiac Troponin Patients

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BIOTIN IS LESS LIKELY TO BE A PROBLEM IN CARDIAC TROPONIN TESTING AND IS POPULATION SPECIFIC!
Biotin and Urine Pregnancy Testing
Biotin Interference with Urine Pregnancy Tests

- Recent studies show some point-of-care urine pregnancy tests were affected by biotin.
- Biotin is cleared by the kidneys.
- In this study, the QuickVue urine pregnancy test exhibited interference as low as 6 microgram/mL of urine biotin!

Best POCT Practices for Mitigating Interfering Substances
POCT Best Practices for Interferences

- **Education:** The laboratory must be the leader in educating providers and patients of potential test interferences. Go to grand rounds, build partnerships, and provide multi-modality means to disseminate knowledge.
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• **Surveillance:** Know your population! Collect data and determine if your local population may be at risk for certain interferences (e.g., biotin, vitamin C, etc). MAUDE database is also helpful!
POCT Best Practices for Interferences

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- **Electronic Early-Warning Systems**: Leverage electronic solutions. Ordering of susceptible tests could flag both on the provider and laboratory side certain substances are identified.
Conclusions

• Interfering substances are out there and impact POC testing as much as traditional lab testing!
• Interferences in common POC devices such as glucose meters have resulted in injury and death.
• Interferences in whole blood analysis have resulted in inappropriate treatment decisions.
• Medications and supplements may also affect POC immunoassays such as urine pregnancy tests.
• Education and awareness is critical to minimizing errors associated with interfering substances.
Questions?