Shannon Whitney:

Good afternoon, and welcome to today's webinar, Pre-Analytical Errors: An Overview and Approach to Prevention. I'm Shannon Whitney and I'll be your moderator for today's event. We are delighted to bring you the LabLeader's webinar series presented by AACC and supported by a generous grant from LabLeaders. This program is accredited for ACCENT Continuing Education Credit. I'd like to point out that depending on remaining time, this webinar will conclude with the Q&A session. You can submit your questions at any time during the webinar through the Q&A dialogue box, which is in the bottom right-hand corner of your screen. However, the questions will not be answered until the Q&A portion of our program.

Please note that there is a Q&A dialogue box as well as a chat dialogue box. To ensure that your questions are received and included, please only submit them through the Q&A box. In order to make sure that the dialogue box is open, please confirm that the Q&A box is visible on the right-hand side of your screen. If it's not, simply click the Q&A icon from the options button in the center of your webinar screen, which will turn the icon blue. The Q&A dialogue box will then become visible. Let's get started. As a global leader in healthcare, Roche Diagnostics has made the promise to empower laboratories and the people within them by providing clinical and strategic insights, support, and solutions from the industry's top innovators through lableaders.com.

Again, thank you for joining us for today's LabLeaders Webinar, Pre-Analytical Errors: An Overview and Approach to Prevention. Our speaker today is Dr. Joe El-Khoury. Dr. El-Khoury is assistant professor of laboratory medicine at Yale University, director of the Clinical Chemistry Laboratory, and co-director of the Clinical Chemistry Fellowship Program at Yale New Haven Health. He is board certified by the American Board of Clinical Chemistry and a fellow of the AACC Academy. His areas of research interests are pre-analytical errors, biomarkers of kidney disease, and liquid chromatography mass spectrometry in the clinical laboratory. Dr. El-Khoury, you may now begin your presentation.

Joe M. El-Khoury, PhD, DABCC, FACC:

02:32 - Thank you, Shannon. I would like to start off by wishing all my American colleagues a happy 4th of July as we head into the holiday tomorrow. I'm very pleased to be starting this discussion on pre-analytical errors. I'd like to start by saying I have no financial disclosures and I decline to receive the honorarium for this talk. For today, we're going to hopefully achieve four goals. One is “Define pre-analytical variation and its contribution to lab errors,” “identify some important guidelines and literature on pre-analytical errors,” and “identify common sources of those errors and how the lab can detect them.” I want to start by saying pre-analytical errors are really difficult to detect by the clinical team.

I've chosen to start with a published case that was recently highlighted in the New England Journal of Medicine in April 2019 issue, where a group of clinicians presented the case of a patient, Mr. P, who's a 68-year-old Hispanic man, who was admitted to the general medicine service two days earlier with a diabetic foot infection. His symptoms showed the foot was hot, red, and quite swollen, with a malodorous toe ulcer that was a necrotic nidus of infection. The foot worsened over the next two days and he was rushed to the OR for a toe amputation. The lactate level was ordered five hours after surgery and it showed a value of 10 millimoles per liter.

04:00 - As reference, the reference interval for the lactate is 0.5 to 2.2, and greater than four is considered critical. A value of 10 is very critical. The lab has notified the resident of the critical result. However, this was puzzling because the patients after receiving antibiotics, LR fluids, and surgery, the value was still high. The patient was not really displaying any symptoms consistent with the elevated lactate. When asked, "How are you feeling?", he would just reply, "I just have a slight headache." Nothing

indicated that the result was reflective of the true picture. Doctors rushed to the room to seek the source of this new lack of tissue perfusion. Their diagnosis was suspected sepsis caused by a foot infection, which was again not concordant with the clinical picture.

They ordered a couple of routine labs, blood gasses, chest X-ray, and a repeat lactate in addition to being given additional fluids and ensuring additional IV antibiotics were being used appropriately. While they were waiting for the results, they started considering other factors. Do amputations cause artifactual lactate elevations? Could Propofol from the OR be the culprit? In the meantime, the lab result for lactate return is 14, so it's even higher. Moreover, what was more puzzling was the CBC, cell blood count, was odd. The patient's leukocytosis has suddenly resolved and now the patient has anemia. They suggested, could it be that the lactate elevation and back pain could be an atypical presentation of an abdominal catastrophe.

05:47 - So they ordered a CT scan of the abdomen because they were essentially running out of other options or diagnostic considerations. This actually demonstrates how complicated the situation can be. It took Mr. P's niece, who's a phlebotomist that has concerns about the technique used by the other phlebotomist and wanted to draw the sample herself. Then the nurse became intrigued by that question and asked, "Could it be the LR?", which is Lactated Ringers. Lactated Ringers are commonly used to replace fluids and electrolytes in patients who have low blood volume or low blood pressure. They contain sodium chloride, sodium lactate, potassium chloride, and calcium chloride in water.

It's not usually an issue if you draw a patient who has Lactated Ringer fluids being used as long as you follow appropriate protocol and either discard a tube of blood if you're collecting from the central line or draw from the opposing arm. In this case, the fact that the patient had LR and that the wrong phlebotomy technique was used caused this value to be wrong. When the new labs were drawn from the opposing arm, the labs were normal. It's important to mention that in this case, they note that it was a nurse and I would argue even possibly the phlebotomist themselves and not the 8 MDs at a prestigious hospital who formulated the pivotal hypothesis in a confusing situation.

This is a clear example of a pre-analytical error that can lead down diagnostic dilemmas that are costly in terms of the procedures that are performed and extremely inconvenient to the patient. I really appreciate this case because it just showed as one example of how clinicians start thinking about these pathways that may not be relevant to the patient's case. At what point do we just stop and say, "Is something wrong with the lab result?" This brings us to the need to look at the total testing process. What happens when a patient orders a result or when a physician orders a result after seeing a patient? What really are pre-analytical errors?

Looking at this diagram, anything that happens from the moment the physician orders the test all the way up to the sample being analyzed is what we call the pre-analytical steps. Also, often referred to in some guidelines as pre-examination steps. From ordering the test, to patient preparation, to samples being drawn, transported, delivered, and then processed in the lab, all of these are opportunities that something can go wrong with the sample before it even gets to us. Basically, one way to look at the analytical errors is often it's things that the lab gets blamed for that they have little to do with to begin with.

That said, there is the argument to be made that some of these processes like sample processing often occur in the lab, but the bigger issue here is that up to 75% of all errors occur before the specimen even gets to the lab. Then what should we be doing? This is where I'd like to refer to some of the guidelines and literature that's out there. Starting with ISO 15189, which is the International Standards Organization, they have a guideline that is specifically geared towards medical laboratories, which are requirements for quality incompetence. In 2007, it's shown here on the left of the table, section 5.4, they had a small section describing what should be done for pre-examination procedures.

But in their revision in 2012, they basically broke that up into specific sections, giving advice to laboratories to give specific information for patients and users, specific instructions for pre-collection, collection activities, and then handling preparation and storage requirements. The guidelines have taken significantly further to provide further guidance for laboratories. This is essential and just goes to show how big this problem is and the attention it's receiving even at the level of developing guidelines. In a nutshell, one of the most important things I took from those guidelines is the requirement for labs to develop quality indicators. QIs can measure how well an organization meets the needs and requirements of users and the quality of all operational processes.

10:27 The labs, as they noted in the guidelines, should establish and periodically review QIs to monitor and evaluate the performance throughout the whole testing process, pre, intra, and post-examination. In a nutshell, this really is reflective of the spirit of, if you can't measure it, you can't improve it. Some of the things that are suggested, and I give an example here shown in the gray box, is looking at things we probably already measured in the lab and maybe not review regularly and maybe some do. But one example here is the percentage of number samples lost or not received divided by the total number of samples in the lab. It's important to look at the two different components of the QI. One is the numerator, which is something we define related to the pre-analytical process.

Two is the denominator, which has to be something that we can normalize too, so we can compare hospitals to each other. It's important to say that the IFCC has taken an initiative and established a work group. That's the Laboratory Errors and Patient Safety work group that have defined specific quality indicators for every phase of testing. They have further expanded that and harmonized that up to 35 for just the pre-analytical phase alone, in addition to prioritizing those QIs. For some labs, they may not be amenable to adopt all of these QIs, but at least having specific QIs in each section that we think are required for labs to monitor is the spirit of this. This is clearly receiving attention at the international level as well. Getting into then, "What are the sources of pre-analytical errors?"

I grouped them here into four major buckets. First is order entry, then it's patient preparation, specimen collection, and processing transportation and storage as one. What we will be doing next is spending some time on common sources of errors for each of these phases of testing and then talking about some possible solutions. We'll be using specific examples from the literature. To begin, we'll look at order entry. The most common causes of errors in order entry are tests with similar names, duplicate orders, transcription entry orders, and verbal orders being misinterpreted. This is especially true if you have physicians who are not entering their own orders for tests and if they're relaying this information to other healthcare providers who may not be as proficient.

What are some possible solutions to addressing these issues? For similar test names, redesigning the requisitions if you use paper requisitions or this computerized physician order entry system with explanatory footnotes. We're going to look at a couple of examples on how to deal with those. Duplicate ordering, by building rules to detect duplicate orders in your LIS or lab information system, you can make sure that no test is ordered more than it's needed in the appropriate time frame. We'll also talk about a couple of examples there. Transcription entry errors, you need to make sure that the computer entry is verified against written orders. Verbal orders being misinterpreted can be addressed by requiring physicians to enter their own orders.

Starting with tests with similar names, I'd like to share with you a success story from Seattle Children's Hospital where they had an issue with inappropriate ordering of 1,25-dihydroxyvitamin D. When they did a study, they noticed that 66% of 1,25-dihydroxyvitamin D orders were mistake. In fact, in these cases 25-hydroxyvitamin D was the intended test. To intervene, they decided to send every care provider who ordered 1,25-dihydroxyvitamin D the communication from the lab that recommends 25-hydroxyvitamin

D for the assessment of vitamin D status. They also gave the provider the option of proceeding as intended or changing their order to 25 and canceling the 1,25.

14:46 - It's nice because the communications that I outlined here from their publication is basically a very nice letter that they provide saying, "For this patient, we did the study. You ordered 1,25 for this patient. We did a study that showed 50% of these orders were inappropriately ordered by accident, and this is why 25-hydroxyvitamin D is the most useful test. Then how would you like us to proceed?" That really notified the physicians that that could be ordered by mistake. Then monitoring the number of orders they were receiving before and after the implementation, they noticed a significant drop, 58% after seven months of 1,25-dihydroxyvitamin D tests were canceled and modified to 25-hydroxyvitamin D, which is shown in the white bars in the graph.

You also notice an arrow there right after October which indicates privilege implemented. Now, as you can imagine, when you start sending letters to every physician ordering this test, the physicians who most commonly order the test are going to get [inaudible 00:15:57], because essentially, you're asking people who know what they're doing, who constantly order a test, and you're bothering them with this email and they don't feel the need to justify it. What they ended up implementing is privileging endocrinologists so that they don't get the letter and their orders are automatically honored. But this is one example of a manual intervention that can be done for tests with small volumes.

However, if you have large volume tests that you need to address, of course, it would not be feasible to implement such a system. Then you'd have to look at trying to make changes within your LIS or your computer physician order entry system, which basically in this case, I'm showing an example of a notification that pops up on the order entry system. When a physician tries to order B type natriuretic peptide, so BNP. In fact, the recommendation has been changed for a while to switch to NT-proBNP instead of BNP ordering because it has longer stability. We have this pop-up that would basically populate if somebody tries to order BNP to direct them to the appropriate order.

This can be used in a variety of ways for several tests, where you can essentially guide individuals to the appropriate order or allow them to proceed. It would be up to you. You can choose it to be a soft stop as they would call it, if you're allowing them to proceed. As you notice, you have on the right side under web links an opportunity to include links to additional footnotes or explanations. This is a really useful tool to educate and to provide guidance on best ordering practices. In addition, creating test algorithms would help in making sure that the appropriate follow-up is done to the right test. In the case of thyroid testing, for example, if someone orders TSH, then it should be appropriately reflexed based on the result, the free T4 or total T3 or in some cases thyroid peroxidase antibodies.

These are examples of how you can implement some approaches, whether it's reflex testing to computerized physician order entry systems to help make sure that the correct tests are not only ordered but also followed-up on appropriately. Looking at the second component of that, which was order entry, how do we reduce duplicate orders? Reviewing the literature, Cleveland Clinic implemented a clinical decision support tool that they used to block unnecessary duplicate test orders through their CPOE. This list included 1,200 tests that should not be ordered more than once on the same day.

What they noticed is over a two-year period, they were able to cancel 11,790 duplicate tests that resulted in a cost saving of $183,586, not to mention unnecessary blood drawn for tests that weren't really needed. One important conclusion from that study is that hard stop alerts that I just mentioned briefly, which basically do not allow a clinician to proceed with a test, are significantly more effective than smart alerts, 92% versus 42%. It's actually smart or I should say soft alerts which basically allow the clinician to continue with the original order as intended, which is not that unexpected. Moving on to the second source of errors, looking at patient preparation, really looking at diet, exercise and posture, and collection timing.

Solutions for these include fasting or restricting diet if necessary. For exercise and posture, normal activities preferred, delay testing that is affected by hospitalization until discharge. I'll mention why that is important in a bit. Collection timing, optimizing collection for therapeutic drug monitoring and diurnal variation, and also communicating well and documenting drug administration accurately with respect to the specimen collection. I would also add that it's very important that the lab receives collection timing and not simply accept the sample and put your receipt time as your collection time, as can be done in certain laboratories as well.

20:25 - All of these are important factors. Just to look at a few examples of things that can affect testing and related to patient preparation, I pulled out all the examples I could find from a textbook. As expected, there's really a lot from physiologic variables, diet, and lifestyle. All should be a consideration for certain tests, which is why it becomes really important also to make sure we delay certain tests until discharge, because patients also experience significant changes in concentrations from going from lying to standing and back. This is just a small list of analytes that change significantly from lying to standing. You have a concentrating effect due to fluid shifts from blood to the extra fluid tissues.

Importantly, we talked about all the factors that can affect a patient when you're preparing them, especially diet. ISO 15189:2012 had specific instructions that I found really helpful and would be nice to give to patients. For example, imagine if you gave something like this blue card that had information that is important to know for a specific test, where you tell them you need to be awake specifically two hours before the blood is taken, you must not do any exercise. Also, you are specific in terms of what food they should eat and how long they should abstain. You say, you must not eat or drink anything during the 8 to 10 hours before your sample is taken. Then you add, you may drink water.

This is an important concept or an important point because a lot of people don't agree on what fasting is. Fasting means different things for certain people, especially if you think of some religions that consider fasting not drinking water. We really need to be clear about what we're asking of our patients so that they don't show up dehydrated and then we can't collect blood and I've seen that happen as well. Moving on to specimen collection, a lot more can go wrong here. As you can see there's at least eight points listed. Looking from patient identification, which is critical, to using the wrong needle size, to selecting the right tube or drawing it in the right order. Long use of a tourniquet can be a problem for certain tests.

Fist clenching as well, specimen clotting, urine stability for certain analytes, and inappropriate tube filling, especially for coag testing. Possible solutions for all of these, we're looking at using two identifiers as a start for correct appropriate patient identification. I would also add you need to be careful about your workflow, because I've seen in some hospitals, nurses or physician assistants who do the blood collections, sometimes phlebotomist, they basically print all the labels for all the patients they're going to collect that morning, put them with the tubes in a basket, and walk into all of the patients they're seeing having all of these labels with them that are for different patients.

That clearly opens up an opportunity to make a mistake and take the wrong label and put it on the wrong tube, even after you've confirmed with the first tube that the patient is who you're expecting to draw. It's very important that we look at workflow and try to make sure that only labels that are needed for a particular patient are in the room with that patient when the blood's collected. Ideally, you'd have a label printer close to that room or a mobile station that allows you to print onsite. As far as needle sizes go, 21 to 23-gauge size needles are typical to reduce the likelihood of that being an issue. Tube type, again, collecting the appropriate tube in the right order.

Limiting tourniquet time to one minute, encouraging patients to rest arm, and mixing tubes immediately by gentle inversion, and providing preservatives and collection devices for certain urine tests who need that. As far as inappropriate tube filling, again, ensuring that tubes are more than three quarters full. In

the case of our patient who we saw that the issue ended up being wrong, like phlebotomy technique, you need to either draw a discard tube if you're drawing from an IV line or collect from the opposing arm. Moving to the last phase, we're looking at processing, transportation, and storage.

The common sources of error there are pocketing samples or delayed processing, recentrifugation, outpatient clinic delayed processing, exposure of tubes to the environment, and add-on tests are important to look at. Starting with the first one, so delayed processing, we really need to make sure all the samples are centrifuged and aliquoted promptly. Recentrifugation is a big issue because that essentially reopens up the gel even if you're using gel barrier tubes and allows cellular content to leak to plasma or serum. Recentrifugation also causes more hemolysis. What you're essentially doing is allowing more cells to lyse and leak back into the plasma or serum.

25:54 - What we need to do if we have to spin for any reason, such as the plasma looking cloudy or the serum having another cloudy or lipemic issue, you have to take the plasma or serum off the cells or the gel and recentrifuge that portion separately, but you should never recentrifuge the primary tube. As for outpatient clinic delayed processing, we really need to provide centrifuges for the samples to be processed on collection sites. That is especially important. The samples are being transported for over two to three hours from different health centers to the main lab where they're being tested. You can have a lot of issues, especially when the weather changes, and you have analytes, even as simple as potassium in the outreach can change dramatically in cold weather.

So, if you're seeing any issues with analytes that are sensitive to that, that would be one area you need to look closely at and try to justify the purchase of these equipment for tube administration. As far as exposure of the tubes to the environment, again, it's very important to protect and insulate the samples during transportation and that becomes less of an issue if you're processing onsite. But for some samples, you still need to freeze, refrigerate, et cetera. So, you need to follow appropriate storage transitions and transportation. For add-on testing, we really need to make sure all the analytes that we're reporting results on have a validated stability period under the conditions in which we store samples in the lab. So, that way any follow up testing is done is also high accuracy, high quality.

So, this essentially concludes the discussion on the sources of error. Now, next, we're going to look at how we detect pre-analytical errors in the lab. I'll start off with this one case that is commonly seen and I also see that commonly in textbooks and I've seen it in my lab where you have a purple-top EDTA microtainer collected from a patient and after phlebotomy staff realized they needed to collect the gel barrier tube instead of the purple-top tube. So, the purple-top microtainer was then pushed into a gel barrier tube and sent to the lab. When staff was contacted about this issue, they did not understand when called to cancel the specimen and they claimed that the specimen was indeed in a gel tube.

Of course, there's a couple of issues here. One may be related to the staff's understanding of what the tubes are and what they contain. Of course, the purple-top contains potassium EDTA. Whereas the gel barrier tube, if it's serum or plasma, it would be lithium heparin, which usually is what we use for testing complete metabolic panels and basic metabolic panels. Whereas the purple-top EDTA is not appropriate because that A has potassium as a counterion. So, your potassium is going to be sky high, usually above 15. The calcium is going to be less than two usually because EDTA itself chelates metals including calcium.

29:00 - So, this is how we detect it on our end and we are certain of what we see and then can report this back to the phlebotomist, but it's also an issue when you have samples that are drawn out of order and if EDTA is drawn first and then you draw your other tubes, you can have contamination that could cause less of an effect, but you'll see these changes where potassium would be slightly higher than usual and calcium slightly lower. It's important to look at these things when considering the factors that could

affect this patient. So, other types of errors. So, we have erroneous flags, things that can flag on the instrument for being wrong or not right. Critical error flags are things that flag simply too high or too low.

Delta checks are things that would flag based on criteria that we build or rules that we build in our either middleware or lab information system to look at a patient's previous history and compare that with their current history. We'll get into that more in a little bit. Hemolysis index is the fourth one that we use to look for typically hemolysis which indicates either inappropriate transportation or inappropriate collection. So, starting with critical error flags, an example I will use which is relevant for our patient that we started with, Mr. P, is we use flags to detect IV contamination. So, if you get a critical sodium less than 120, the rules basically are you can do this manually or you could do this by having the process automated.

But typically, chloride is also looked at. If it's less than 100 and potassium, if it's greater than 5.5, this indicates a likelihood of an IV contamination. Basically, this could be a patient who has potassium being infused and their other analytes are diluted as a result of inappropriate collection. Same goes for the second step, which is glucose greater than 800 and creatinine less than 0.6. Again, this is flagging on the instrument as critical, so we have to stop and take action anyway. So, then we investigate, "Could this be an IV contamination while we are doing that?" Creatinine at less than 0.6 indicates, again, dilution.

Finally, if a patient has a saline infusion that basically causes this issue, sodium would be really high, potassium would be really low, and that is an indication that this could be IV contamination. So, again, it's important to say at this point that we do not cancel results without contacting the clinical team and asking them if they've drawn this from an IV line and if they suspect that these results are concordant with the clinical picture. So, we leave the decision to them, but we do notify them as we're giving them the critical result that this could be IV contamination. If they say yes, then of course we remove it from the patient's chart. This is an example of a quality indicator plan.

32:09 - So, we do monitor this regularly and I'm showing you an example of a plan we developed here, where I'm reviewing these quarterly to look at changing rates in IV contamination. What's nice is now we have a good system to track these and I'm showing you what our IV contamination report looks like from January up to May here, which was the last one I reviewed. As you can see, our total so far for the year is 336. This is again only starting since January and so on. We're averaging about 70 IV contamination as we detect them by the current methods. One more thing I want to add is we can actually drill down to a great level of detail into which unit we're seeing this.

In this case, I chose specifically the North Pavilion, which is one unit. You can see in May for unit NP 10, we're seeing a lot of redraws related to IV contamination. So, this is an opportunity to ask, "What's going on? Why is this happening? Do you have someone who's new, who potentially needs to be training on this?" So that's really where the utility of this report comes in. The question that we asked then is, "What is normal though? So how do we know if numbers we're seeing are normal compared to others?" So, there's not really great literature on this, but I found the recent article in Clinical Laboratory News by Dr. Jaime Noguez who looked at the University Hospital of Case Western Reserve. They saw similar contamination was causing 5% of all test cancellations in their lab.

33:51 - Now that includes IV contamination and other sources of contamination, but roughly, they were seeing around 1,500 specimens a year, which would put us close to that or slightly below that based on our current detection mechanism. But this just goes to show that it's important not only to monitor a QI, it's also important to have a baseline and comparator and why we really need to have a system eventually that would allow us to compare the QIs that we develop to other labs. So, looking at delta checks, again, very useful for detecting if there's been a patient identification issue. Sometimes also an IV contamination can be detected this way. The way it works is it looks at a patient's previous result and compares it to the patient's present result. The only limitation of this is that it requires patient history.

So, a patient who shows up new, you won't be able to really apply this tool for, but also, it doesn't necessarily apply to a lot of analytes. So, it has to be an analyte that is known to change only minimally within a certain time period. So, having defined acceptable time periods and ranges is very important to get this flagging appropriately. Then finally, as far as the tools go, we're looking at the hemolysis index, which is a commonly used index on many automated analyzers. It is used to indicate cell lysis, but also, it's helpful to detect interferences on analytical instruments. So, in our world, the pre-analytical errors, it's actually useful to let us know if there's improper sample collection or transportation.

So, anytime we see an increased hemolysis, it usually indicates there's a different issue at hand that we need to look at. One example I'll use related to that is my own story, which I also reported or talked about for AACC lab stories. Basically, we were approached by nurses from the neonatal intensive care unit who were concerned about an increased level of test cancellations due to hemolysis. This was an interesting problem, because when we asked them what happened and what changed recently in your process that would've indicated that, they mentioned that recently our blood collection device manufacturer recently updated the pediatric tubes for lithium heparin. They were a different tube shape and size, and the collection technique was very different than what they were used to.

So, they suspected that essentially this was an issue with the tube itself. The collection related to that too was causing hemolysis. So, our blood collection device manufacturer came onsite, provided multiple educational sessions on appropriate collection techniques. However, this had no impact on what the nurses were seeing. So, they kept complaining, concerned. All these canceled tests on NICU patients is definitely not something that we wanted to see. So, this is when we were brought in and trying to figure this out. In speaking with the blood collection device manufacturer, they suggested that it could be also related to the pneumatic tube system.

Now, of course, in speaking with the nurses, they were convinced it has to be the tube because that's the only thing that changed. Since that changed, we were having issues. The pneumatic tube system itself hadn't changed in the process. So, we decided we're going to test this. So, we need to figure out which one is the cause. So, the quality indicator we were going to look at, just to use this as an exercise, is the percentage of the number of samples that were hemolyzed in the NICU over the total number of samples that were collected in the NICU. Now it's important for me to mention this, that this data was not routinely collected in my lab at the time and the LIS did not offer an option to specifically look at hemolysis in the NICU.

So, we have to do the study manually. So, the way we collected our baseline data to see if this was a problem to begin with, the samples were tubed to the lab as they normally are. The NICU samples were received between 4:00 AM and 7:00 AM, which is the majority of our samples, were centrifuged and evaluated manually for any hemolysis for eight days. We also looked at the results from those tubes to see if there were any tests that were canceled on them. So, out of a total of 150 samples that were processed from the NICU, we had about 61% that were shown to have visible hemolysis by inspection. However, 11.3% of those tests were canceled because they exceeded our hemolysis cutoff. So, how do we know if this is a big issue?

I mean, clearly, we're relying on the nurses initially to guide our inspection of this process, and I reached out to the literature and came across other findings. So, I'm just going to skip this part due to time. Basically, I was fortunate that I found the study that was done at the Mayo Clinic and recently reported in the American Journal of Clinical Pathology on rates of hemolysis in the NICU. Specifically, they were looking at it for a different reason. They were trying to figure out if they can lower it by adjusting the lipid cycling that was done in the NICU. So, what they reported at baseline was really helpful for us because they had a 6.4% hemolysis rate that dropped to 3.5% post-intervention and education phase. So, they're seeing around 3.5% test cancellation.

So, this tells us that the rate we were currently seeing is at least four times higher than this. So, something needed to be done. So, given what we had at the time, we decided that we needed to look at what the truth of the source was. Well, the hypothesis here was if it was a collection, samples should be hemolyzed before transportation. If it was transportation samples, it would only be hemolyzed after transportation. So, the one way we could look at this is if we essentially just spun the sample and walked it to the lab and looked for hemolysis to see if there's any difference versus what we've established at baseline.

So, we set up a processor and a centrifuge in the NICU for five days and lithium heparin with gel samples were centrifuged in the NICU and walked over to the lab to rule out any issues related to transportation. What we found was 27% of the samples were hemolyzed and no samples were canceled based on the samples that were basically spun and walked over to the lab. So, what that tells us is that there's really no issue with the nurses' collection technique. This seems to be more related now to the new tube. It could be centrifugation and transportation.

So, we really focused then on the pneumatic tube system. We're like, "Okay, the new tube is smaller in size and shape? So could it be that the new tube was bouncing more within the pneumatic tube system than the older tube?" So, we decided we're going to add a foam insert that allows us to just put one tube in there and it would hold it snugly in, so it would prevent it from bouncing all over the canister. So, these specific yellow tube carriers were purchased just for the NICU and we have six of them that are still in use today. The added foam has basically been a big help. So, what we did was we redid the study after adding the foam to see if the problem is resolved, if they continue to collect in the NICU, but sent the samples using these canisters.

So, what we found was when we redid the study that we had a higher hemolysis rate, which was just on visual observation, but none of the tests were canceled. So, what that tells us is there is some hemolysis that's happening still due to transportation, but it's not significant enough now to cause a concern. None of the tests were crossing our thresholds and none of the results were being canceled based on this study. Then a couple of months later, we followed up with the nurses and they confirmed that the problem has been resolved, at least from their perception since going live with this intervention. So, it was a happy story all over.

So, in summary, we talked about pre-analytical variation as a major source of laboratory error. We discussed several possible sources of error that really need to be looked at when considering pre-analytical errors. Then to help detect these errors, we have several tools at our disposals from error flags, surgical results, delta checks, and serum indices, but it is vital that every lab establishes their own quality indicators and you monitor them regularly. Hopefully, you have access to some literature that can help you give you guidance in terms of where you should be.

That's been my primary resource, but it's also important to think about pre-analytical errors as a team effort because you really cannot resolve or have successful interventions without working with the entire patient care team because many of these issues, again, are happening outside of the laboratory. So, it's crucial that we collaborate with our nursing partners, even in this case, engineering who helped us design the new canister with the new insert and get everybody on board so we can provide solutions that would address those issues. Before I sum up, I just want to say basically we looked at a case where we had one patient that had a pre-analytical error and that's typically how these errors show up.

The last case I presented, my laboratory looked at specifically having an entire section or a unit having issues. That also happens where you have to really dig deep and see what the common thread is and try to address it. So, pre-analytical errors can show up in a variety of ways. Some can impact a single patient, others can impact a bigger section. With that, I would like to recommend one specific book if you're really interested in following up on the subject. Donald Young has a really amazing pre-analytical

variables and biological variation chapter in Tietz, but the last resource on the bottom there is the effect of pre-analytical variables on clinical laboratory tests.

I resort to that anytime I have issues I'm looking at. It's really, really well done and summarizes literature in the field by analyte. Not only that, you can look at if you're suspecting I'm seeing an increase in potassium, you can go to the potassium page and look at, "Okay, what causes increases?" It lists everything and references the studies that are associated with it. So, that has been really my go-to book when it comes to troubleshooting some of these issues that I would like to recommend to you. At this point in time, I'm happy to take any additional questions you have.

Shannon Whitney:

Thank you so much Dr. El-Khoury for sharing such a wonderful presentation with us. We would like to remind everyone that you can ask a question via the Q&A dialogue box in the right-hand panel of the screen. But before we begin the Q&A, we'd like to take just a moment to do a quick poll about today's program. So, on a scale of 0 to 10, how likely are you to recommend this webinar program to your friend or colleague? We'd greatly appreciate it if you could take just a second to enter your response on the right side of your screen.

LabLeaders and AACC strive to continue to bring you the relevant and actionable insights to empower laboratory professionals. So, while those responses come in, I can see we have some questions lined up already. So, we'll go ahead and get started with our Q&A. So, Dr. El-Khoury, our first question is, who oversees the implementation of new testing algorithms at your institution and are your ordering physicians involved?

Joe M. El-Khoury, PhD, DABCC, FACC:

Thank you. So, for the TSH example, I mentioned all of these initiatives are driven by a lab formulary committee. In some hospitals, those can be called test utilization committees and it's essential to have physician involvement in the group. We actually have a very senior physician in the hospital who runs those meetings, co-chairing them with a senior figure here in laboratory medicine as well.

All of the suggestions I mentioned on putting in duplicate ordering, actually duplicate orders, was one of the first projects that the committee undertook when it was established in 2014 and then has moved on to establishing algorithms for testing, eliminating outdated tests. So, all of that's through the lab formulary committee. Definitely, this is not something that I would recommend going alone. It's really a lab medicine and a clinical team effort.

Shannon Whitney:

Wonderful, thank you. Our next question is in your neonatal ICU hemolysis study, what cutoff did you use for calling a sample hemolyzed?

Joe M. El-Khoury, PhD, DABCC, FACC:

So, as I mentioned, there were two components here. One was visual, so that was very subjective in terms of looking at and inspecting the sample before running it. So, that really was on visual observation. The second component, so the test cancellations were variable by the tests. So, some tests have low cutoffs like potassiums are cut off at 85. AFD has a higher cutoff. I believe it's at 150. So, it's basically based on the tests that were canceled, that is a result of the individual cutoff that we have established for each test.

Shannon Whitney:

Thank you. The next question is why is it unacceptable to recentrifuge tubes?

Joe M. El-Khoury, PhD, DABCC, FACC:

So, I'll start by saying excellent question. I start by saying that this is something that the manufacturer does not recommend. To be clear, I'm saying it is unacceptable to recentrifuge primary tubes. So, if you want to recentrifuge a plasma sample or a serum sample, you should take it off the gel or cells then recentrifuge. The reasons are two. One is when you recentrifuge, you're causing more hemolysis, so you're putting more pressure on the cells. They're going to lice and they're going to leak their contents into plasma or serum. Two, when you centrifuge, that gel barrier reopens up.

So, meaning that if you think that recentrifugation, you're actually going to allow remixing of the blood and the plasma. So, things that were initially sealed, that could be even small molecules like potassium from cells that were lying underneath will once you reopen up that gel and do recentrifugation, they leak back up. So, it's not recommended by the manufacturer and I wouldn't recommend it without aliquoting the sample.

Shannon Whitney:

Thank you. Our next question is how do you monitor IV contamination, manually or is it automated in LIS?

Joe M. El-Khoury, PhD, DABCC, FACC:

Excellent question. So, we do that right now manually, because like I said, a critical error flag is our trickler. So, when we assign the values that are used in those rules, it's actually the instrument's flagging a critical result and then which would require a manual lookup. I know you can automate that process and it's something we're working on, because we recently went live with new automation. So, we're still building some of the rules and capabilities, but definitely, I would recommend automating that.

Shannon Whitney:

Thank you. The next question is, is there a trend in using automation to detect hemolysis?

Joe M. El-Khoury, PhD, DABCC, FACC:

So at least as far as I know, in chemistry, most labs have moved to automated methods for detection of hemolysis versus manual. Simply because with automated methods, you have better reliability and you can establish more specific cutoffs that allow you to release certain results like potassium or AST that are affected at low levels or even LDH that are affected at low levels versus others that can be affected at moderately or high. So, you're more specific and granular in your separation when you use an automated method versus the old school way, which is doing visual inspection, putting slight, moderate, or severe. So, definitely, in the chemistry world at least, we see a lot more push towards automated hemolysis checks.

In immunology and other labs who don't have maybe an automated analyzer or they're running their samples on one analyzer that doesn't have that capability, then it would be best to at least implement the visual inspection. Of course, it's understandable if you don't have that capability. You might not want to run all your samples through the automation line first and then bring them back to that lab. But for us here, we actually use our automation line as a central processing and receiving. So, all samples do go through that and then go to the other areas where they need to go.

Shannon Whitney:

Wonderful, thank you. The next question is, if a lab does not currently use any delta checks, which analyte would you suggest they start with?

Joe M. El-Khoury, PhD, DABCC, FACC:

So that's a great question. It's something actually we are also in the process of working on as well. Typically, it's best to start by looking at your CMP and BMP, which are the most commonly ordered tests. So, there's plenty of literature out there that I'd be happy to reference, but looking at things like albumin calcium, things that have low intra-individual variability is what delta checks would work well for. But generally, you're better off starting with something like your analytes within your comprehensive metabolic panel like albumin or calcium.

Shannon Whitney:

Great, thank you. We have a situational question here. So, it says falsely elevated potassium [levels] were observed from our satellite phlebotomy stations. We verified that all centrifuges in the satellite labs were acceptable. What other sources of error should I look into?

Joe M. El-Khoury, PhD, DABCC, FACC:

So, it's also interesting with potassium is a big one and I see that often. I would also look at the patient population. So, there are some instances where potassium can be more elevated in patients with thrombocytopenia if you're collecting a serum tube. So, it also depends on what they're collecting. Patients with very high platelets will have really high potassium when you collect serum. Simply because when serum clots, all these high platelets will release potassium a significant amount. So, there's some patient specific issues that could be looked at in addition to, again, patients with leukocytosis also have... I'm sorry, I said thrombocytopenia. I meant thrombocytosis. Leukocytosis would also have issues because you have significantly high white cells.

So, if those aren't processed right away, those can be an issue. Another thing, again, looking at how are they storing the samples before they're shipping them, sometimes if they're refrigerating the samples on site once they collect the samples, are they waiting a significant amount of time to spend or are they spinning them right away? Again, refrigeration, I just want to mention, is bad for potassium. So, that's something I typically look at. Sometimes what I notice with plasma, you do get elevated potassium if the plasma is a little bit cloudy. We noticed that when you respin just the plasma off the cells, that resolves.

So, that's why in some cases, it may be best to look at if you want to switch some of those sites to serum to avoid having that issue, but again, you'd have to double check and make sure they don't normally get a lot of patients who have thrombocytosis. So, potassium is a very complicated issue. Again, I would recommend you also look at the book that I was recommending by Donald Young who has a lot of these resources that could be helpful to look at.

Shannon Whitney:

Thank you so much, Dr. El-Khoury. There are so many questions that have come in. Unfortunately, due to time, we need to wrap up, but we will definitely provide you with those questions after this webinar. So, we would like to, once again, thank you Dr. El-Khoury for providing such an excellent presentation. For those of you in the audience, if you'd like to request a copy of today's slide deck, please visit lableaders.com and select the connect button. We'd also like to thank all of you in the audience for listening to this LabLeader's webinar today and ask that you be sure to mark your calendar for next month's LabLeader's webinar, which will take place on August 7th.

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