In SARS-CoV-2, small steps but big wins

Karen Titus

December 2020—By its very nature, the global pandemic has forced laboratories to look far and wide, to bring binoculars, in essence, to their views of supply chains, testing platforms, personnel, and the like.

As COVID-19 churns on, some labs are looking through a tinier lens as well. These labs aren't trading their binoculars for a jeweler's loupe, exactly, but they have found small and significant success stories closer to home.

Like so many others, Erin Graf, PhD, D(ABMM), has confronted a spinning roulette wheel since the pandemic's start. In a talk she gave in an AMP webinar in October (she also spoke with CAP TODAY in a follow-up interview), Dr. Graf, director of microbiology, Mayo Clinic in Arizona, posted a vibrantly colored wheel titled, "Which supply chain issue will impact us this week?" Each segment contained a phrase familiar to everyone in 2020, ranging from "swabs" and "sheep blood agar" to "pipette tips" and "chlamydia and gonorrhea tests."

As she surveys these continuous claims on her attention, Dr. Graf says, "I think none of us could have ever thought that COVID would have an impact on all these arms of the testing that we do."

But if supply chain issues have been present almost from day one, so was an intriguing question from a colleague, which has unfolded into a heartening story.

Dr. Graf's institution went live with a laboratory-developed test for SARS-CoV-2 on March 10. "It feels like years ago," she says. "Decades ago." The very next day, a transplant surgeon stopped by, in what was another pandemic-related first. "I don't know about you, but I've never had that happen before," she says. She begins her story almost like a-priest-walks-into-a-bar joke: "So a transplant surgeon comes to our lab. . . ."

Dr. Erin Graf at Mayo Clinic in Arizona, where the laboratory's SARS-CoV-2 testing has been critical to the transplantation workflow. [Photo by Peter Pallagi]

He questioned them in detail, asking, among other things, about the test's sensitivity and specificity, batch size, and when batches were being run. The question behind the question, as Dr. Graf puts it, was his wanting to understand

the lab's turnaround time for the test.

At the time, the laboratory was advertising a 24-hour TAT for all types of samples, including for the solid organ transplant groups, though that promise had a whiff of best-guess estimate about it, as Dr. Graf recalls. The test and EUA paperwork had been launched swiftly. "We really didn't know how fast we were going to be able to do it."

Her transplant colleagues, in the meantime, were absorbing freshly issued COVID-19 recommendations from the American Society of Transplantation, including one that required a negative SARS-CoV-2 swab from the patient prior to transplant. "That makes perfect sense," Dr. Graf says, noting that it would be unwise to immunosuppress anyone who is infected with the virus, regardless of whether they're symptomatic.

In the event that the patient tests positive, the organs could potentially be used for someone else. But that switch has to happen quickly. "When these organs are removed, every minute matters," she says. So when the Abbott m2000 SARS-CoV-2 assay received its EUA, in mid-March, it promised an alluring six- to eight-hour run time. "We immediately brought that in and said goodbye to our LDT."

The assay pared down the TAT, as they hoped, but samples still had to be run in batches. And the lower TAT, averaging 18 hours, still wasn't good enough.

When Cepheid received EUA for its rapid test a few days later, on March 20, Dr. Graf and her colleagues—who were already running a GeneXpert system—thought, *Oh, it's going to be the answer to all our problems*, she recalls. Calls to the company quickly disabused them of that dream, however. They were told in no uncertain terms, "Nope—not even a chance of getting any allocation at that point in time," says Dr. Graf. "We were kind of heartbroken."

Unless one is named Heathcliff, it's possible to move on from heartbreak. That was true for Dr. Graf and her colleagues, who quickly—on March 25—decided to forge ahead on a different path.

The laboratory was doing high-volume outpatient specimen testing at the time, and the 24-hour TAT was fine for people visiting the drive-through collection sites. So the lab started its 21-specimen hold procedure, holding back a pool of samples that were not considered high priority but would still meet the 24-hour mark. When a transplant sample arrived, that run would be prioritized, shaving the TAT to six hours.

"We were doing this around the clock," Dr. Graf says.

And then, finally, dawn broke. "After repeated pleas with the vendor, we were able to get a tiny allocation" of Cepheid's rapid test, starting April 21. The 60 tests a week would cover transplant needs, she says, noting, "We screen a lot more than we transplant." With that, the TAT dropped to under one hour, enabling patients to move straight to surgery.

The story could end there, but doesn't. With SARS-CoV-2 testing the topic of the year, word of the transplant program's success soon spread through the hospital. "Immediately our phones were ringing off the hook," Dr. Graf says, with colleagues asking, "Why don't we have access to the rapid test?" She understood that desire. "We would have loved to have used it in other settings," she says, "including the ED and for high-risk patients being admitted."

That outpouring led to a meeting between the laboratory and hospital administrative and medical leadership. "We made a strong case for *how* these tests should be used," Dr. Graf says. The decision doesn't rest solely with the laboratory, but it only made sense that transplant should be the use case, she says, given that a positive test directly affects a medical decision. That's different from the logistics-based arguments that were being made—for example, delaying a surgery (absent a patient's COVID-19 status) because of issues related to use of negative-pressure rooms or PPE availability. While that adds other burdens (including for cleaning staff), she acknowledges, it's not a true medical decision.

"Our leaders were in complete agreement with this plan," Dr. Graf says, and they made sure to make that

message clear to the rest of the Mayo practice. “That took the burden off the laboratory” to respond to calls and explain the decision.

The success of this approach has spread beyond the daily screen/transplant workflow at Mayo. As the laboratory was working to reduce its TATs, it also formed a partnership, on April 5, with the Donor Network of Arizona, an organ procurement organization that coordinates transport of donor organs in Arizona and beyond.

Dr. Graf’s laboratory began performing SARS-CoV-2 molecular testing for all donors and recipients; prior to that, the network was sending its testing to a reference lab. “Their turnaround times were just atrocious—way over 24 hours,” Dr. Graf says. Mayo took on the testing and was able to offer results in less than 24 hours, using the Abbott m2000 assay.

But the real impetus for the shift was that the Donor Network had begun requiring bronchoalveolar lavage testing in May, amid mounting evidence that lower respiratory tract sampling is more sensitive than using an NP swab.

The laboratory ran into problems running the BAL specimens on the Abbott instrument, however. Nearly 100 percent of the specimens had issues with internal control inhibition, Dr. Graf reports, even after repeated testing. The samples, coming as they do from deceased patients, are often viscous and contain particulate matter.

So, executing yet another pandemic do-si-do, they ran a pilot study on the Cepheid rapid test—and obtained valid results on 100 percent of specimens. The laboratory wanted to expand rapid test usage outside of Mayo, but in a way that would benefit the hospital, since oftentimes the organs are transplanted there. Another meeting with leadership, another use case pitch—and another show of support from those at the top, who were “in full agreement,” Dr. Graf says.

The impact has been huge. While the hospital is part of the large Mayo network, it’s not particularly big by itself. Nevertheless, it has become the leading transplant center in the country during the pandemic, she says. The Donor Network of Arizona had a historic number of transplants in June (32 donors, 96 organs, 89 lives saved). In July and August combined, there were 46 donors, 146 organs, and 124 lives saved.

In early November, she reports, the institution was still on a record-breaking pace for transplantations. Last year the center was among the top three in the country for number of solid organ transplants; this year, she says, it’s No. 1. And the number has already exceeded those done in 2019.

“We have had no cases of COVID-19 in the immediate post-transplant period,” Dr. Graf says, though she’s not resting easy by any means.

“One of the unanswered questions is, which organs might harbor virus?” she asks. Lungs from a donor who had COVID-19 disease wouldn’t be transplantable, obviously, but other organs might be allowable. For now, organs from COVID-19-positive donors aren’t being transplanted, “but that’s just out of an abundance of caution. I don’t think there’s really good data to say you can’t use those organs at all. You might be able to use the liver, perhaps.”

She also worries about patients who face COVID-19 risks post-transplant. Though the vast majority of patients are extremely cautious, she says, unchecked spread of the disease throughout the country is a variable they can’t control. “It’s just a scary time, as cases climb and climb.”

Rising COVID-19 cases in communities could also threaten to upend transplant surgery, she says. Since these patients often require ICU-level care, “if your ICU beds are filled with COVID cases, you really can’t do a transplant safely unless you’re sure you have that bed available if you need it.”

In the meantime, the system they put in place a while ago continues to work, with no real modifications—possibly another pandemic first. “At least until we run out of tests,” she says.

Another victory was notched at Children’s Hospital of Philadelphia, where Stella Chou, MD, associate professor of pediatrics, University of Pennsylvania Perelman School of Medicine, has been involved in a reconfiguration of the

sickle cell disease transfusion program.

Her March memories are of donor drives screeching to a halt as stay-at-home orders took hold. Those who regularly give blood also became reluctant to visit donor centers. “There was a significant shortage of products,” recalls Dr. Chou, a pediatric hematologist who cares for patients with sickle cell disease on an outpatient basis.

At the same time, numerous elective surgeries were being postponed. With surgeons ordering significantly fewer red cell units, Dr. Chou and her colleagues had some breathing room. But not much, since their own patients would still require their regular transfusions. How could they conserve as much blood as possible? Patients typically receive four to six units per exchange, Dr. Chou says, though some patients receive eight or nine units. One even receives 10 every visit.

‘We made the conscious decision . . . that these patients have room to load a little bit of iron over time, just to make sure we have enough blood for everybody.’ Stella Chou, MD

To maneuver around the shortage, Dr. Chou and her colleagues became much more precise in calculating each patient’s needs, based on pretransfusion lab work. Most patients have a goal to maintain their hemoglobin S percentage less than 30 percent before transfusion (though some are slightly higher). “Based on their actual pretransfusion hemoglobin S percentage, we can precisely determine how many red cell units we need to give them. For patients who need to maintain a hemoglobin S percentage of less than 30 percent pretransfusion, we aim to have them leave our unit with a percent S of 12 to 15 percent.”

Before the pandemic, the order would simply be matched to the previous amount. If someone typically received five units, “we just went ahead and ordered five units,” Dr. Chou says.

No longer. “We were very proactive in making sure patients had their labs done at least a full day before the procedure, so we would have those values.” By calculating the fraction of cells remaining post-exchange, Dr. Chou and her colleagues were able to reduce red cell unit utilization by 18 percent.

Dr. Chou wonders aloud if she should add a qualifier to that number—*only* 18 percent—but quickly says, “If people are saving anywhere between 10 to 20 percent of units, it can have a significant impact on the entire population of patients with sickle cell disease or thalassemia who require these antigen-negative units.” She and her colleague plan to publish their results so others can follow suit.

The shortage persists, she notes, which has led to other changes. Rather than have standing orders in the blood bank inventory, as in the past, Dr. Chou and colleagues now must order patient-specific antigen-negative units. “We can’t just order an extra 10 units to have in our blood bank, for instance.” Blood banks have become very tight with their inventories, she says, with shades of just-in-time inventory practices.

The CHOP apheresis team also recognized another opportunity to better manage the blood supply.

For patients who are chronically transfused via red cell exchange, she says, “there’s minimal iron loading in most scenarios,” though, again, there are exceptions—the machine is programmed to increase the hematocrit to a modest degree for some patients with a very low baseline hematocrit pretransfusion.

She and her colleagues have increased the hematocrit slightly in patients who are not iron-overloaded. Someone who has a hematocrit of 30 percent pretransfusion, for example, would be increased to 33 or 34 percent. The body, sensing the higher percentage of hemoglobin and hematocrit, would suppress the endogenous red blood cell production, “which also means we could suppress the hemoglobin S.” Over the course of several transfusions, “you would end up potentially seeing a decreased red cell unit demand,” Dr. Chou says. “Because if we’re suppressing their own erythropoiesis, then their S level will be suppressed.” In subsequent transfusions, less blood is required. “That has seemed to work nicely for many of our patients,” she says, and has contributed to the overall 18 percent reduction.

The approach has had wide support at CHOP. “We made the conscious decision with our hematology colleagues that these patients have room to load a little bit of iron over time, just to make sure we have enough blood for everybody,” Dr. Chou says. “Two of us are hematologists who are trained in transfusion medicine. Our decision-making in doing this was there was very minimal risk to the patient. We were really cautious,” she says. “It took a lot of planning, and just keeping track of our patients more closely.”

Similarly, patients have been responsive when asked to come in earlier for their pretransfusion lab work. Especially early in the pandemic, when the change first went into effect, “nobody had anything else they really had to do,” she laughs.

A whirlwind pace of challenge and change has become the pandemic norm for laboratories.

But so have success stories, Dr. Graf suggests.

“It may feel—this is how I feel— that each day is a hamster wheel of disappointment,” she says. “But recognize your successes. Even the ones that seem so tiny and so small. Because you are the reason your hospital is functioning right now. You are the reason patients are getting the best possible care in this incredibly challenging time.”

She likens laboratory efforts this year to the inventive feats of the MacGyver TV character (original or reboot, depending on your age). “I feel like I’m slapping things together with duct tape and string,” she says. But that’s not necessarily a bad thing, in her view. “Celebrate your creativity.”

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