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Patient Safety Tip of the Week

May 12, 2020 Lab Errors and COVID-19

Yes, we told you we were trying to avoid articles on COVID-19 because you are being deluged with them from all sources. But we were looking to do another column on errors related to lab testing and COVID-19 testing happens to provide a great opportunity for that discussion.

In many of our columns on lab errors (most of which actually originate outside the lab) we've highlighted works done by European researchers Giuseppe Lippi and Mario Plebani. They recently joined with Ana-Maria Simundic to provide an excellent summary of potential errors that may impact COVID-19 testing and management (Lippi 2020).

In the US there has been a push to increase COVID-19 testing to 5 million tests per day and some have recommended we may need up to 20 million tests per day. Lippi et al. point out that the volume pressures and time pressures involved in such testing increase the vulnerabilities of multiple components of the whole process and are prone to errors.

They note that the generation of false-positive or false-negative test results not only jeopardizes the health of the individual patient, but may also impact the efficacy of public health policies, emergency plans and restrictive measures established by national and international authorities for containing the pandemic. They note that a false positive result might keep vital workers from their jobs and that a false negative might result in an individual exposing others to COVID-19.

While they acknowledge that there will be multiple forms of testing related to COVID-19, they focus on the current gold standard for the etiological diagnosis of SARS-CoV-2 infection: reverse transcription polymerase chain reaction (rRT-PCR) on respiratory tract specimens. They then provide an overview of the potential preanalytical and analytical vulnerabilities of RT-PCR testing for diagnosing SARSCoV-2 infection. It's really a reiteration of all the things we've noted that can go wrong with almost any laboratory test (see, for instance, our March 6, 2012 Patient Safety Tip of the Week ""Lab" Error").

They cite preanalytical and analytical vulnerabilities in RT-PCR testing for diagnosing COVID-19 as below:

Preanalytical

General

- Lack of identification/misidentification

- Inadequate procedures for specimen (e.g. swab) collection, handling, transport and storage
- Collection of inappropriate or inadequate material for quality or volume
- Presence of interfering substances
- Manual (pipetting) errors

Specific

- Sample contamination
- Testing in patients receiving antiretroviral therapy

Analytical

- Testing carried out outside of the diagnostic window
- Active viral recombination
- Use of non-adequately validated assays
- Lack of harmonization of primers and probes
- Instrument malfunctioning
- Insufficient or inadequate material
- Non-specific PCR annealing
- Misinterpretation of expression profiles

Failure to comply with recommended procedures may be a significant cause of diagnostic errors. Examples might include use of wrong swabs, inappropriate absorption of diagnostic material, insertion into inadequate vials, contamination, and others.

In the US there has been a plethora of tests, both for the identification of the virus and for identification of antibodies to the virus. Unfortunately, there has been wide variation in the accuracy, sensitivity, and specificity of the tests and apparently not all have been properly validated. Lippi et al. note that the diagnostic accuracy of many of the currently available RT-PCR tests for detecting SARS-CoV-2 may be lower than optimal. They note that, according to clinical history and serial CT features, 11.6% and 16.6% of all patients with initially negative RT-PCR results were finally considered as probable or highly likely COVID-19 cases. Studies have shown as many as 93% of all patients whose RT-PCR became positive for SARSCoV-19 after an initially negative test result actually had CT features suggestive of COVID-19. In such cases there was a mean interval period of 5.1 days for turning positive.

They note that it's important to remember that **active virus shedding may occur in asymptomatic individuals, in pre-symptomatic individuals (infected individuals before any symptoms or signs have begun), and even for several days after resolution of symptoms in symptomatic individuals**. Those are points we reiterated in our May 5, 2020 Patient Safety Tip of the Week "COVID-19 and the Dental Office", implying that we should approach every patient as if they might be shedding coronavirus.

On the pre-analytical side, it's important to know how the specimens, especially nasopharyngeal and oropharyngeal swabs, should be collected, managed and stored before testing. Similarly, on the analytical side, assay procedures must be thoughtfully followed, including standard confirmatory testing and test report guidelines, and quality assurance carried out to validate each analytical session. The need for quality assurance is

highlighted by an "outbreak" in Thailand of 40 reported positive cases (The Star 2020). Subsequent testing showed that control samples of pure water used at that lab tested positive rather than negative, indicating a problem had occurred in the process.

Other technical and analytical issues include instrument malfunctioning (including inappropriate PCR cycling conditions), use of insufficient or inadequate material, non-specific annealing of PCR to homologous sequences, misinterpretation of expression profiles and others.

Note, however, that the current article by Lippi et al. leaves out an important source for error that we discussed in our March 6, 2012 Patient Safety Tip of the Week ""Lab" Error" – namely the **post-analytic** phase or what happens once the result is reported to the ordering clinician. There is plenty that can go wrong at and after that step. See that column for the sorts of errors that can occur in:

- Results Reporting
- Physician Acknowledgement of the Result
- Physician Action on the Result
- Patient Notification of the Result
- Analysis of Impact of the Test
- What Was Done if an Error Occurred

These steps are all important components of "**closing the loop**"

Also, Step 2 in our March 6, 2012 Patient Safety Tip of the Week ""Lab" Error" dealt with ordering the test in the first place. One question, in particular, is "**Was the correct test ordered?**". Pertaining to COVID-19 there is a myriad of diagnostic tests out there. The Lippi article focuses on the PCR testing and does not address antibody testing. So, you need to consider what you are looking for and where in the natural history of COVID-19 infection your patient might be. A great summary of COVID-19 diagnostic tests was just published (Sethuraman 2020) and includes a graph that nicely outlines the timeframes for specific tests in relation to onset of symptoms. So, knowledge of the natural history of COVID-19 is important. In addition to that graph, the Lippi article notes that the incubation period of SARS-CoV-2 is around 6 days (interquartile range 2–11 days), the median period between symptom onset and hospital admission is 7 days (IQR, 4–8 days), median period of symptom duration around 13 days (IQR, 5–24 days) and slightly longer in patients with severe disease (16 days; IQR, 10–20 days).

Context is everything. That means you should not interpret the result without considering the entire clinical picture. Lippi et al. advise that the most efficient strategy for diagnosing COVID-19 in suspected patients should encompass a combination of SARS-CoV-2 RT-PCR with clinical and epidemiologic evidence (probability of exposure, signs, symptoms, negative diagnostic tests especially for other respiratory illnesses) and chest CT findings. Repeated respiratory specimens should be collected (daily or, at least, every other day) and tested by RT-PCR in patients with initially negative results but high suspicion (or probability) of having COVID-19.

The FDA cautions that the risks to a patient of a **false negative** include: delayed or lack of supportive treatment, lack of monitoring of infected individuals and their household or other close contacts for symptoms resulting in increased risk of spread of COVID-19 within the community, or other unintended adverse events (FDA 2020).

False positives, of course, can also have adverse consequences, such as inappropriate treatment, unnecessary quarantine, or unnecessary hospitalization. An unexpected spike in positive tests should lead to checking for confirmation, as evidenced by the case in Thailand alluded to above where 40 reported positive cases were determined to be false positives (The Star 2020).

And. on the antibody testing side, there also remain significant issues. Some of the tests currently available simply identify that antibodies are present and don't quantify them. In addition, it is not known what titre of antibodies, if any, conveys immunity against COVID-19 and for how long if it does. There has also been some concern raised that antibodies in some cases may actually represent cross-reactivity against other coronaviruses rather than the COVID-19 virus (Whyte 2020). So, for the time being, it remains unclear what a positive antibody test means in practical terms.

The current article by Lippi et al. uses issues related to COVID-19 but is really an excellent reminder of the vulnerabilities we encounter in almost any laboratory test. It reiterates the many problems related to lab studies that we've highlighted in our previous columns listed below. Remember: most lab errors occur outside the lab, but errors may be seen in the pre-analytical, analytical, and post-analytical phases of laboratory diagnosis.

Some of our other columns on errors related to laboratory studies:

- October 9, 2007 "Errors in the Laboratory"
- November 16, 2010 "Lost Lab Specimens"
- October 11, 2011 "LEAN in the Lab"
- March 6, 2012 ""Lab" Error"
- April 2012 "Specimen Labeling Errors"
- January 22, 2013 "You Don't Know What You Don't Know"
- April 15, 2014 "Specimen Identification Mixups"
- November 25, 2014 "Misdiagnosis Due to Lab Error"
- March 24, 2015 "Specimen Issues in Prostate Cancer"
- May 26, 2015 "How Safe is the Lab You Use?"
- March 29, 2016 "Inappropriate Lab Testing"
- September 27, 2016 "Lab Errors Costly"
- November 15, 2016 "Surgical Specimen Mishaps"
- March 20, 2018 "Minnesota Highlights Lost Tissue Samples"
- October 9, 2018 "More on Lab Specimen Mixups"
- March 26, 2019 "Patient Misidentification"

See also our other columns on communicating significant results:

- May 1, 2007 "The Missed Cancer"
- February 12, 2008 "More on Tracking Test Results"
- October 13, 2009 "Slipping Through the Cracks"
- July 2009 "Failure to Inform Patients of Clinically Significant Outpatient Test Results"
- March 9, 2010 "Communication of Urgent or Unexpected Radiology Findings"
- March 1, 2011 "Tests Pending at Discharge"
- August 21, 2012 "More on Missed Followup of Tests in Hospital"
- October 2, 2012 "Test Results: Everyone's Worst Nightmare"
- March 12, 2013 "More on Communicating Test Results"
- October 2013 "New AHRQ Toolkit: Improving Your Office Testing Process"
- January 2014 "Email Alerts for Pending Test Results"
- July 2015 "Technology to Avoid Delays in Follow-up of Significant Results"
- November 17, 2015 "Patient Perspectives on Communication of Test Results"
- December 20, 2016 "End-of-Rotation Transitions and Mortality"
- September 2018 "ECRI Institute Partnership: Closing the Loop"
- September 24, 2019 "EHR-related Malpractice Claims"
- November 26, 2019 "Pennsylvania Law on Notifying Patients of Test Results"
- January 2020 "The Joint Commission on Closing the Loop"

See also our other columns related to COVID-19:

- April 7, 2020 "Patient Safety Tidbits for the COVID-19 Pandemic"
- May 5, 2020 "COVID-19 and the Dental Office"

References:

Lippi G, Simundic A, Plebani M. Potential preanalytical and analytical vulnerabilities in the laboratory diagnosis of coronavirus disease 2019 (COVID-19), Clinical Chemistry and Laboratory Medicine (CCLM) 2020; published online ahead of print, 20200285 https://www.degruyter.com/view/journals/cclm/ahead-of-print/article-10.1515-cclm-2020-0285/article-10.1515-cclm-2020-0285.xml

The Star. Lab cleared after result error. The Star (Thailand) 2020; May 7, 2020 https://www.thestar.com.my/news/regional/2020/05/07/lab-cleared-after-result-error

Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. JAMA 2020; Published online May 06, 2020 https://jamanetwork.com/journals/jama/fullarticle/2765837

FDA (US Food and Drug Administration). Fact Sheet for Healthcare Providers. New York SARS-CoV-2 Real-time RT-PCR Diagnostic Panel. FDA 2020; Updated: March 15, 2020
https://www.fda.gov/media/135662/download

Whyte J, Saag M. Hold on Antibody Testing: 'The FDA Has Done Us a Disservice'. Medscape Medical News 2020; May 06, 2020
https://www.medscape.com/viewarticle/930052?src=WNL_trdalrt_200509_MSCPEDIT&uac=14695HV&impID=2374316&faf=1

http://www.patientsafetysolutions.com/

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