Clinical pathology resident education during the COVID-19 pandemic

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Received 9 September 2020
Revised 3 November 2020
Accepted 29 November 2020
Published Online First 14 December 2020

To cite: Senzel L, Ahmed T, Batiste R. *J Clin Pathol* 2021;**74**:144–148.

ABSTRACT

COVID-19 arrived at our medical centre in March 2020 with substantial force. Clinical pathology concepts began to have a new, direct relevance to our residents' lives. As we wondered 'Have I been exposed? Do I need to self-isolate? Are the tests reliable? Am I protecting myself adequately while handling specimens?', these questions drew new interest in laboratory methods, test interpretation and limitations, supply chain issues, safety and quality. By incorporating SARS-CoV-2 teaching points into laboratory medicine lectures, we enlivened concepts of sensitivity, specificity, predictive value and methodologic issues in serologic, molecular and antigen testing for pathology residents. We drew from the emerging literature on SARS-CoV-2 to create lectures and added details from our own institutional experience with COVID-19. When the pandemic fades from memory, clinical pathology education can still benefit from mnemonics, analogies, anecdotes and creative efforts that capture the attention of the audience.

INTRODUCTION

COVID-19, the disease caused by SARS-CoV-2, arrived at our academic medical centre in March 2020 with substantial force. Amid the devastating loss of life and disruption to the economy caused by the pandemic, some positive aspects included the selfless dedication of healthcare and other essential workers and community volunteers. In clinical pathology, many concepts that faculty teach pathology residents began to have a new, direct relevance to their lives. As instructor and audience alike wondered 'Have I been exposed? Do I need to self-isolate? Are the tests reliable? Am I protecting myself adequately while handling specimens?', these questions drew new interest in laboratory methods, test interpretation and limitations, supply chain issues, safety and quality. This article discusses how our faculty delved into laboratory medicine topics that were 'ripped from the headlines' to teach pathology residents during the early stages of the pandemic. The topics are listed in the order they were covered in our weekly hour-long Clinical Pathology lecture series, which we converted to an online format using Microsoft Teams. All of our pathology residents attend this series throughout their residency years, regardless of what rotation they are doing. Finally, we propose strategies to invigorate clinical pathology education that can be incorporated into the teaching programme after the pandemic has passed.

ROLE OF THE LABORATORY DIRECTOR

Soon after cases appeared at our centre, faculty physicians began receiving email messages about ventilator operation refresher courses. Hence, lecture number one in our Clinical Pathology COVID-19 series began with the role of the laboratory medical director. Logically, if there were enough responsibilities on the list, running ventilators would simply not be practical to add. General laboratory director roles during 'peacetime' are listed in box 1 and are discussed both on College of American Pathologists (CAP) checklists and in the literature.[1 2]

Specifically among these responsibilities, priorities to prepare for COVID-19 included procuring personal protective equipment; sourcing and interfacing new send-out tests; bringing in new test reagents and instruments; becoming familiar with FDA Emergency Use Authorisation (EUA), state and CAP regulations for SARS-CoV-2 tests, including Clinical Laboratory Improvement Act (CLIA) waiver status, laboratory-developed test status and individualised quality control plan; extending point-of-care (POC) testing to pop-up units; cross-training staff and developing a contingency plan for possible staff shortages in the Core Laboratory including several tiers of service reduction that would increase turnaround time (TAT) for non-urgent tests due to batching and, in more severe tiers, eventually restrict the test menu; setting up procurement, collection and manufacture of convalescent plasma and reviewing new FDA regulations about qualification of blood donors. Babiker *et al*[3] discuss similar issues in an article outlining their laboratory's COVID-19 response, titled 'SARS-CoV-2 Testing: Trials and Tribulations'.

In addition, our outpatient cancer centre was temporarily converted into a COVID-19 unit, so we accommodated outpatient transfusions in our apheresis suite and secured regulatory approval for phlebotomy in a new satellite location while those patients were accommodated in other areas. With the onslaught of convalescent plasma donors, our blood bank and apheresis suite took many additional procedures over the usual volume. Lippi and Plebani describe the role of laboratory medicine in viral outbreaks such as COVID-19.[4]

COAGULATION AND INFLAMMATION

Our lecture on the pathophysiology of COVID-related thrombosis and hypercoagulability began with the aetiology and diagnosis of disseminated intravascular coagulation and incorporated literature on COVID-related inflammation[5] and direct endothelial damage.[6] Immunothrombosis is a mechanism to protect against both bleeding and infection that can result from a breach in the endothelium.[7]

Box 1 A. Laboratory director responsibilities

- Definition of quality goals and process objectives for each of the quality system essentials (QSE, COM.04000).
- Approval of specifications and requirements established to achieve stated goals and objectives (COM.04000).
- Review of quality assessment reports (COM.04000).
- Approval of process improvement initiatives (COM.04000).
- Provision of effective and efficient administrative direction of the laboratory, including budget planning and controls (DRA.11475).
- Direct involvement in the selection of all laboratory equipment, supplies and services with respect to quality (DRA.11475).
- Selection of all reference laboratories.
- Ensure a sufficient number of qualified personnel are employed, and are working in the scope of their licensure (DRA.11300).
- Ensure appropriately trained supervisory and testing personnel including assistant directors designated in the permit application material with their technical and administrative responsibilities in writing (DRA.11300).
- Provision of relevant continuing education to laboratory technical staff, strategic planning and research and development (DRA.11200).
- Promoting a safe laboratory environment (DRA.11400).
- Ensure an approved procedure manual is available to all personnel (DIR S3).
- Ensure the laboratory participates in monitoring and evaluating the quality and appropriateness of services rendered (DRA.10440).
- Ensure enrolment in Centers for Medicare & Medicaid Services (CMS)-approved proficiency testing programmes or alternative assessment sufficient for the extent of testing performed by the laboratory and adherence to testing requirements (DRA.10460).
- Maintain an effective working relationship with applicable accrediting and regulatory agencies, administrative officials and the medical community (DRA.11450).
- Ensuring that an effective interim self-inspection is performed and all deficiencies are corrected in a timely manner (DRA.10445).
- Provides advice to referring physicians regarding the significance of laboratory findings and interpretation of laboratory data (DRA.10700).
- Monitors all work performed in the laboratory to ensure that medically reliable data are generated (DRA.10500).
- Ensures performance specifications for new tests, instruments, methods are properly validated/verified prior to patient testing (DRA.10475).
- Implement plans of corrections to deficiencies identified.
- Review and approve the content and format of laboratory patient reports (GEN.41067).

B. Director duties that cannot be delegated: specific duties not delegated and are the sole responsibility of the laboratory director:

- Definition of quality goals and process objectives for each QSE (DRA.10440).
- Approval of specification and requirements established to achieve stated goals and objectives (DRA.11200).
- Review of quality assessment reports.
- Approval of process improvement initiatives.

Continued

Box 1 Continued

- Provision of appropriately trained supervisory and technical staff and the identification of their responsibilities (DRA.11425).
- Specifying in writing the technical and administrative responsibilities of assistant directors and direct report supervisors.
- On-site assessment of staffing adequacy (DRA.11425).
- On-site assessment of physical and environmental conditions of the laboratory (DRA.11425, 11400, GEN.73200).
- Initial approval of technical policies and procedure and substantial changes to existing documents (DRA.11425, COM.10200).
- Direct involvement in the selection of all laboratory equipment (DRA.11475).
- Initial approval of Individualised Quality Control Plans (DRA.11425, COM.50400).
- Reference laboratory selection.
- Competency assessment (annual) of assistant directors and direct report supervisors.
- Provision for intralaboratory consultation and clinical consultation (DRA.10700).
- Annual review of biosafety programme (risk assessment).

Specifically in COVID-19, immune mechanisms that can trigger thrombosis may include neutrophil extracellular traps.[8] Further, hyperactive platelets activate monocytes, leading to release of tissue factor.[9] We discussed institutional protocols for anticoagulation of COVID-19 patients,[10] guidelines from the International Society of Thrombosis and Hemostasis[11] and other haematology and pharmacy organisations.

NEW INSTRUMENT VALIDATION AND CRITICAL VALUE CRITERIA ADJUSTMENT

The laboratory director must review every new method validation to determine whether the new instrument shows acceptable performance. During our COVID-19 surge, erythrocyte sedimentation rate (ESR) suddenly took up too much technologist time. To improve efficiency and eliminate transcription errors, we upgraded to a fully interfaced analyser, the iSED ESR (Alcor Scientific). The validation included a set of correlations between the old and new methods which passed manufacturer's recommendations but struck the laboratory director as poorly correlated. A review of test performance on past CAP proficiency exercises provided reassurance as to the acceptability of these correlations.

Another laboratory director responsibility is to ensure that the laboratory's critical value criteria are meeting clinical needs. We consulted with our medical staff who agreed that we could suspend critical value calling for ESR >100 mm/hour. This critical value criterion was intended for the detection of temporal arteritis, whereas many COVID-19 patients had high ESR values causing the burden of making and receiving unnecessary critical value calls to already stressed units.

BLOOD GAS ANALYSIS

In April, pathology residents had donned their 'COVID-19 Warrior' face masks (figure 1) and were covering the 3 am to 6 am shift running blood gases. This allowed respiratory therapists more time to adjust ventilator settings, prone patients and carry out other clinical procedures. We devoted our CP lecture

Figure 1 Autopsy team (Emaan Alvi, PGY1 and Tiffany Huettemann) suit up for a case. From left to right, Karen Bai, MD (PGY1), other residents and volunteer PhD and MSTP students ran SARS-CoV-2 RNA testing around the clock. Felix Tavernier, MD (PGY3) implemented and trained staff in the use of a hydrogen peroxide vapour generator to sanitise laboratories, offices and the morgue following COVID-positive cases. Permission was granted by the persons in the images (Emaan Alvi, Tiffany Huettemann, Karen Bai, Felix Tavernier). MSTP, Medical Scientist Training Program.

to principles of blood gas measurement, pathophysiology of acute respiratory distress syndrome and of acid–base disorders and case management examples.

MOLECULAR TESTS

Pathology residents were also covering the midnight shift running RT-PCR for SARS-CoV-2, since the manual labour required to perform the testing had overwhelmed our staffing capabilities. POC molecular testing was limited by a relative shortage of cartridges, and so manual RNA extraction was also required 7 days per week. We reviewed principles of RT-PCR, various technologies for result readout, and test performance characteristics.[12 13] Residents noted there was no automated way to help clinicians check sample status and anticipate result times, so we discussed middleware.

SEROLOGIC TESTS

We addressed the principle of 'caveat emptor'[14] in light of reports that countries had spent millions of euros for bad antibody tests for SARS-CoV-2. We covered test performance characteristics,[15 16] the meaning, or lack thereof, of non-neutralising antibodies;[17 18] and the difference between 'positive agreement' and sensitivity, namely that sensitivity can only be claimed when the method is compared with a gold standard method. While 'neutralising antibodies' show antiviral effect against cultured live virus, antibody-dependent enhancement has been shown to work through non-neutralising or subneutralising levels of neutralising antibodies.[17] We pored over package inserts with a close eye to the prevalence of COVID-19 in the selected population, and also to the characteristics of the reference population used for the clinical study (prepandemic or synchronous, tested for other respiratory viruses or not). We reviewed lateral flow assays, immunometric assays and principles underlying the serologic methods offered in our laboratory, which were being used to qualify convalescent plasma donors. We discussed the utility of antibody testing for epidemiologic prevalence surveys. Our institution had its own clinical trial for convalescent plasma during the summer of 2020, until the FDA decision to grant EUA halted the trial. Next, we covered performance characteristics of certain antigen tests.

TESTING STATISTICS

When antigen testing became available, a limitation was low sensitivity especially at low viral copy numbers.[19] We discussed the importance of optimising sensitivity versus specificity in higher versus lower prevalence settings, and the benefit of a two-test strategy for screening and confirmation.[20] For example, for blood donor screening, we sacrifice inconvenience and possible anxiety to our donors from false positives in order to protect the blood supply. While imperfect sensitivity can pose a safety issue during COVID-19 outbreaks, false negatives are much rarer when screening preoperative patients prior to elective surgery, compared with testing exposed or symptomatic individuals. False positive results are common in low prevalence settings, and positive predictive value can be quite poor; this is true for both antigen and antibody tests.[21]

HISTOPATHOLOGIC FINDINGS

We reviewed biopsy and autopsy findings from COVID-19 toes (chilblains), lung and kidney specimens, and discussed both microvascular thrombosis and large vessel thrombosis resulting in strokes and amputations including inpatients under the age of 50.

EMERGING RESOURCES FOR PATHOLOGY RESIDENT EDUCATION

We used lively discussions from blogs to inform several of our lectures. For example, Dr James Westgard presents the predictive value of COVID-19 tests using examples such as 'prevalence of 20%, perhaps in New York City during the height of the pandemic' and 'prevalence of 2%, such as in Calfornia'.[22] Dr Westgard provides an interactive Predictive Value Calculator and a Clinical Agreement Calculator, among other tools in his COVID-19-specific coverage. Also, Lablogatory presents topics such as extraction-free and saliva COVID-19 testing in a clear and accessible style.[23] In addition, many remote learning tools are available for pathology resident education, and resources for distanced learning during the pandemic have been described in the literature.[24–27]

CLINICAL PATHOLOGY TEACHING STRATEGIES

While COVID-19 brings many concepts of clinical pathology directly into our laps, there are numerous examples of how laboratory medicine can be taught in an enjoyable manner after COVID-19 fades from memory. Below are selected examples.

Historic figures

Armand Trousseau described Trousseau's syndrome, migratory thrombophlebitis as a presenting feature of visceral cancer. On 1 January 1867, he noticed a phlebitis in his own upper left extremity, reportedly telling his student, Peter, 'I am lost: the phlebitis that has just appeared tonight leaves me no doubt about the nature of my illness'. Prescient as ever, Trousseau was to die of gastric cancer only a few months later.[28] One can also consider a lively debate on whether Jesus Christ died of a pulmonary embolism or not.[29 30]

Holiday discoveries

Rosemary Biggs *et al* described Haemophilia B in an article that appeared just before Christmas in 1952, naming Christmas disease after their first patient, Stephen Christmas. Since the Christmas edition of the *British Medical Journal* typically published light-hearted and even frivolous papers, some readers were concerned that this was a prank, and even requested an apology.[31] The authors promised that if they found the precursor protein, they would resist the urge to call it 'Christmas Eve factor'.[31] To honour a minor holiday, April Fool's Day, a protocol

Figure 2 Our entry for the pathology department's annual Halloween costume contest covered the theme of Death Granules. A green granule in the neutrophil cytoplasm portends imminent death when seen on the peripheral blood smear (see text for details). Cookies were decorated as neutrophils containing a death granule. Permission was granted by the persons in the images (co-authors Lisa Senzel and Tahmeena Ahmed).

for a potable facsimile of a blood sample separated over a Ficoll gradient was published in an April 1 edition of *Blood*, entitled 'Fauxcoll gradient'.[32]

Statistical fallacy: drawing conclusions from a very small sample size

On his recruitment visit to the University of Kansas while in high school, future NBA star Wilt Chamberlain played one-on-one basketball against Kansas standout and national champion, B.H. Born. After their session, Born was so dejected that he gave up a promising National Basketball Association (NBA) career and became a tractor engineer: 'If there were high school kids that good, I figured I wasn't going to make it to the pros'.[33]

Costume contest

Our entry for the pathology department's annual Halloween costume contest, on the theme of Death Granules, is shown in figure 2. The article pictured in the photo describes green granules in the neutrophil cytoplasm which portend imminent death when seen on the peripheral blood smear.[34] Various hypotheses for the contents of these granules are discussed in the haematology literature.[35–39] Figure 2 shows one of the cookies we distributed, decorated as neutrophil containing a death granule.

Throwing projectile items

Dr Martin Swerdlow was known for his ability to make 'the vast expanse of his discipline seem not only digestible and essential, but enticingly interesting'. Numerous physicians throughout Chicago knew him from the second-year pathology course. He was most famous for throwing nutmegs sawed in half at the students when he lectured on 'nutmeg liver' described by W. Chamberlain, a former student, as an 'instant classic moment', or millet seeds when lecturing on miliary tuberculosis. One year, the class threw marshmallows back at him, and one class distributed 'Clone Swerdlow' buttons.[40]

Flash the cash

Dr Alice Ma provides mnemonics for the clotting cascade, and helps with Roman numerals, as part of her work for the American Society for Haematology.[41] She teaches that 'X' marks the spot where two pathways converge, and that the point at the bottom of a 'V' conveniently fits into the cleft at the top of an 'X'. Also, the numbers of the Common Pathway happen to correspond to all of the US bills under $20 if we continue to use the $2 bill.

Coagulation poetry

Haemophilia in the neonate
Known before the birth date,
Allows for factor injection
For circumcision or C-section.
Whether intron 22 mutation,
Missense, or other alteration,
Carrier blood collection
Is the key to prenatal detection.[42]

I use my own set of riddles when I teach coagulation, transfusion medicine and clinical chemistry. A subset are published[43 44] and I would be happy to provide the full collection on request. 'Clinical Chemistry is not very alluring!' proclaims an editorial entitled 'Pathology's Stepchild'[45] accompanying a survey on 'Attitudes and Beliefs of Pathology Residents Regarding the Subspecialty of Clinical Chemistry'.[46] With creative approaches, perhaps this can be changed.

Conclusions

In the time of COVID-19, many clinical pathology concepts have direct relevance to the lives of residents, faculty, staff and the general public. SARS-CoV-2 has generated interest in sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and methodologic issues in serologic, molecular and antigen testing. During the COVID-19 surge,

Take home messages

- The COVID-19 pandemic has brought a new, direct relevance to pathology residents' lives.
- SARS-CoV-2 teaching points can enliven laboratory medicine lectures, including concepts of sensitivity, specificity, predictive value, test interpretation and limitations, supply chain issues, safety and quality.
- During the COVID surge, the service and teaching schedule of residents changed, with some learning converted to online format. Many remote learning tools are available for pathology resident education, and resources for distanced learning during the pandemic have been described in the literature.
- When the pandemic fades from memory, clinical pathology education can still benefit from mnemonics, analogies, anecdotes and creative efforts that capture the attention of the audience.

the service and teaching schedule of residents changed. Our hospital cancelled all elective surgeries for several weeks during the height of the pandemic, which caused surgical pathology specimen volumes to drop significantly. Resident lectures were converted to online format using Microsoft Teams. Teaching at the microscope was limited to groups of 1 or 2 residents with one attending, in attendings' private offices rather than in the common area of the surgical pathology office. Residents helped with blood gases, molecular testing and preparing specimens for biobanking. Of these changes, the online format for resident lectures has persisted after the initial surge. When the pandemic fades from memory, clinical pathology education can still benefit from mnemonics, analogies, anecdotes and creative efforts that capture the attention of the audience.

Handling editor Tahir S Pillay.

Acknowledgements We are grateful to our Pathology Residents, staff and volunteers for their valued contributions to our hospital and departmental COVID response.

Contributors LS conceived the topic and wrote the manuscript. TA and RB assisted with writing the manuscript and figures.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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