OPEN ACCESS

Cellular pathology in the COVID-19 era: a European perspective on maintaining quality and safety

John R Gosney,[1] Paul Hofman ,[2] Giancarlo Troncone ,[3] Fernando Lopez-Rios [4]

[1]Cellular Pathology, Royal Liverpool and Broadgreen Hospitals NHS Trust, Liverpool, UK
[2]Pathology, INSERM, Nice, France
[3]Public Health, University of Naplese Federico II, Napoli, Italy
[4]Pathology-Targeted therapies laboratory, HM Hospitales, Madrid, Spain

Correspondence to
Professor John R Gosney, Cellular Pathology, Royal Liverpool and Broadgreen Hospitals NHS Trust, Liverpool L7 8XP, UK; J.Gosney@liverpoolft.nhs.uk

Received 22 May 2020
Accepted 27 May 2020
Published Online First 1 June 2020

Check for updates

© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Gosney JR, Hofman P, Troncone G, *et al*. *J Clin Pathol* 2021;**74**:64–66.

ABSTRACT

COVID-19 is a zoonotic viral infection that originated in Wuhan, China, in late 2019. WHO classified the resulting pandemic as a 'global health emergency' due to its virulence and propensity to cause acute respiratory distress syndrome. The COVID-19 pandemic has had a major impact on diagnostic laboratories, particularly those handling cell and tissue specimens. This development carries serious implications for laboratory practice in that safety of personnel has to be balanced against high-quality analysis and timely reporting of results. The aim of this article is to present some recommendations for the handling of such specimens in the preanalytical, analytical and postanalytical phases of laboratory testing and analysis in an era of high COVID-19 prevalence, such as that seen, for example, in the UK, Spain, Italy and France.

INTRODUCTION

In late 2019, patients in Wuhan, China, began presenting with an unusual form of pneumonia.[1] It was characterised by fever, dyspnoea, chest discomfort, coryza and cough, often progressing in severity to require respiratory support in an intensive care unit.[2] The pathogen responsible was subsequently identified as a betacoronavirus and named severe acute respiratory syndrome coronavirus 2.[3] The disease itself is known as COVID-19. In common usage, the term COVID-19 may refer either to the virus or to the disease.

Li *et al* described human-to-human transmission of COVID-19 to be via respiratory droplets and environmental contamination through fomites.[4] Public health measures like those recommended to mitigate the spread of diseases such as influenza[5] are equally applicable to an outbreak of COVID-19. Aggressive containment measures, including restrictions to freedom of movement and curtailment of everyday activities, were deemed necessary in our four countries, first in Italy and then in Spain, France and the UK.

Due to the high transmissibility of COVID-19, staff in pathology laboratories face obvious pressures, as histological and cytology specimens in particular can contain viable, and therefore transmissible, virus. Fear of contracting the disease within an often diminished workforce augments the challenges of modifying practice to maintain safety and quality, between which there is always a tension. Here, we aim to outline the important operational, preanalytical, analytical and postanalytical considerations necessary to ensure that the impact of the pandemic on laboratory personnel and practice is managed and minimised.

Laboratory and operational preparedness

While effective working must be maintained, team segregation and social distancing within hospitals and laboratories are important in reducing the potential for cross-infection between individuals and teams. Practical examples include distancing staff from each other within the laboratory, working in shifts, staggering breaks and mealtimes and deferring large group gatherings. Twice daily monitoring of temperature allows early screening for possible infection. Quarantining of all close contacts should be implemented in the event of a laboratory worker becoming infected. Sanitation provisions for staff and work areas should be readily available

Business continuity and contingency planning in cooperation with other departments and laboratories should be reinforced in the event that large numbers of staff fall ill or are quarantined. Staff should be monitored for 'burn-out' and psychological fatigue arising from fear of contracting infection, segregation from colleagues and handling of an increased workload. Education and training should continue in the spirit of learning but should be conducted remotely as far as possible.

Preanalytical considerations

According to international consensus, COVID-19 is classified as a 'risk group 3' human pathogen.[6] In consequence, it is mandatory to follow well-defined procedures and institute precautions to minimise risk in all pathology laboratories handling cell and tissue specimens.

The recent laboratory biosafety recommendations associated with COVID-19 released by WHO in 2019 state that 'non-propagative diagnostic laboratory work (such as sequencing and nucleic acid extraction) should be conducted in a facility using procedures equivalent to biosafety level 2 (BSL2)'.[7] While this document does not refer specifically to laboratories handling cell and tissue specimens, the activities of pathologists and technical staff within such laboratories can be considered 'non-propagative'. The Centers for Disease Control and Prevention advises that surgical pathology activities and molecular analyses performed on formalin-fixed or inactivated samples pertaining to patients affected by COVID-19 should be carried out in a BSL2 laboratory.[8]

In order to provide safe infection control during the current outbreak, a robust transportation

J Clin Pathol: first published as 10.1136/jclinpath-2020-206789 on 1 June 2020. Downloaded from http://jcp.bmj.com/ on January 12, 2021 at Seoul National University Medical Library and Hospital. Protected by copyright.

protocol for samples should be designed. Based on the WHO guidelines,[7] all specimens must be considered potentially infectious and appropriate personal protective equipment (PPE) must be worn when obtaining or handling specimens. Typically, this includes a disposable gown, gloves, cap, shoe covers, protective eyewear and a mask (FFP2/FFP3 or an N95 respirator mask). Staff must be trained in how to don and dispose of PPE. The importance of thorough, repeated hand-washing cannot be overemphasised. The number of staff within any laboratory space, at any time, must be minimised. These measures apply also to pathologists and other laboratory staff who perform fine needle aspiration. Careful handling of the fresh material generated by these procedures to reduce aerosol formation is crucial.[9] Working in pairs, whenever possible, significantly reduces the time taken for the procedure to be performed and also minimises the time spent in the clinic by the patient.

Specimens should be placed in tightly capped containers and transported to the laboratory in biohazard zip-lock bags within a leak-proof container of a type appropriate to the specimen and with a clearly visible 'biohazard' label. Specimens should be hand-delivered and not sent via pneumatic tube. Adequate specimen processing and storage space should be pre-emptively dedicated to manage specimens considered at risk of carrying the COVID-19 virus. Ideally, the COVID-19 status of a patient as determined by an appropriate PCR-based test should be known, but false-negatives and infection post-testing are recognised hazards and all specimens should be considered potentially infective.

For specimens requiring transportation to a secondary laboratory, WHO and International Air Transport Association guidelines for transport of infectious samples should be followed.[10] To this end, it is recommended that a triple packaging system is used, comprising the primary receptacle, secondary watertight and leak-proof packaging to protect it, and a third outer layer of packaging to prevent physical damage in transit.

Timely communication between hospital healthcare workers and laboratory professionals is paramount in ensuring mutual understanding and collaboration. This might include memos to inform laboratory users about potential delays arising from increased workload and reduced staffing, and any changes in the nature or range of analyses performed. Effective communication also minimises enquiries about test results. Round-the-clock communication via telephone and email should be available. As the virus can persist on paper for several hours, electronic 'paperless' requesting is preferred.

Analytical considerations

The specimens handled by Cellular Pathology laboratories range from cells dispersed in fluid, as in fine needle aspirates, to resection specimens that often comprise a large part of, or even an entire, organ. Among these, the handling of fresh tissue specimens for rapid, intraoperative diagnosis by examination of frozen sections carries a particular risk. A significant challenge, for obvious reasons, is fresh specimens of lesions in the lung and from the head and neck, although similar specimens from other anatomical sites such as the gastrointestinal tract also carry a significant risk of being infected.

The practice of laboratories in the UK and many elsewhere is based on current advice of the Royal College of Pathologists of the UK, with local amendments.[11 12]

Essentially, there is considered to be no risk from fully fixed specimens. Unfixed or partly fixed specimens (such as those received in formalin but which require dissecting to permit further fixation) from patients known to have COVID-19, should be treated as 'category 3' and handled in an appropriate biological safety cabinet (BSC) by medical or laboratory staff wearing PPE as described above. Procedures that generate aerosols, such as forced distention of lungs with formalin, should not be performed. All other unfixed specimens, including those from patients suspected but not confirmed of having COVID-19, should be treated as 'category 2' and can be opened on a downdraft bench by staff wearing PPE and with subsequent cleaning of the area. It is more cost-effective to batch-up this procedure (ie, the minimum number of staff deals with this at the end of the working day).

Ideally, fresh specimens received for intraoperative frozen section diagnosis should be handled in a class 3 BSC, although this may be a difficult recommendation to follow in all pathology laboratories, many of which across Europe are equipped with chemical rather than higher-specification microbiological (Process Safety Management (PSM2)) hoods for dissection and sampling of tissue specimens, the use of the latter being generally confined to handling 'cytology' samples. In all cases, it is crucial that the pathologist is satisfied after conferring with the appropriate clinician that intraoperative diagnosis is essential for immediate management of the patient. The number of staff present should be at a minimum, all should wear PPE and the area of preparation and cryostat used to cut the sections should be disinfected after the procedure. It is crucially important that surgeons send for frozen section diagnosis only as much tissue as is absolutely necessary for an appropriate diagnosis to be made. Ideally, frozen sections should be cut on cryomicrotomes which allow aerosol containment. Decontamination of the cryostat is critical; it should be cleaned after every procedure with 100% ethanol with or without ultraviolet light to avoid ice formation.

For cytology specimens, ethanol-fixed smears, cell-blocks and liquid cytology vials are preferred over air-dried slides.[9] Fresh cytology samples should be immediately fixed inside a BSC following the same precautions described above. For laboratories performing liquid-based cytology, it is important to be aware that fixatives such as PreservCyt and CytoLyt (Hologic) and SurePath (Becton Dickinson and Company) have low alcohol concentrations and might not adequately inactivate the virus.[13]

On a more general note, prolonging fixation certainly reduces the risk of infection, but is likely to significantly impair the quality of DNA, and especially RNA, required for genomic analysis, particularly next-generation sequencing.[9] Decontamination before archiving of cassettes containing paraffin wax-embedded material might be considered prudent, particularly if they contain material from the thorax or head and neck.[14] Comprehensive risk assessment should be performed to review and consider all instances in all areas in the laboratory which might be susceptible to transmission of infectious pathogens. Following specimen handling, processing and analysis, we recommend, as suggested by Tan *et al*,[15] that specimen transport boxes and all surfaces and equipment be cleaned with an appropriate disinfectant. WHO recommends disinfectants with activity against enveloped viruses, such as sodium hypochlorite 0.1%, a minimum of 62%–71% ethanol, 0.5% hydrogen peroxide, ammonium or phenolic compounds.[16] In the event of spillage, Tan *et al* recommend a decontamination protocol involving hypochlorite 10 000 ppm (1%) solution.[15] Strict adherence to these protocols is of utmost importance as it has been shown[17] that the air, surfaces and PPE are all commonly contaminated by COVID-19. It is sensible to have all work areas, including computers and doorknobs included in a decontamination checklist two times a day.

J Clin Pathol: first published as 10.1136/jclinpath-2020-206789 on 1 June 2020. Downloaded from http://jcp.bmj.com/ on January 12, 2021 at Seoul National University Medical Library and Hospital. Protected by copyright.

Postanalytical considerations

Mention has been made above in the context of 'requesting' of the desirability of using an electronic rather than paper-based format and the same applies equally to 'reporting'.

The pressures on cellular pathology laboratories enforced by the COVID-19 pandemic are already encouraging the implementation and development of digital pathology, not only for use in day-to-day practice, but also as a means of maintaining teaching and education. It has an important role also in consultancy between pathologists and in providing ready access to second, 'expert' opinion for difficult cases. Increasing use is being made also of web-based networking and conferencing software. As with the use of digital images, this technology is not only allowing teaching and education to continue,[18] but is also being widely implemented to maintain the communication between pathologists, clinicians and other healthcare professionals that is essential to the efficient functioning of the multidisciplinary teams or tumour boards that are now so central to the fully informed and timely management of patients. On this point, the reader is encouraged to refer to a recent publication developed as a resource for pathologists and pathologists-in-training who wish to leverage technology to continue collaboration, teaching and education in this era.[18]

SUMMARY

The timely reporting of results from high-quality diagnostic analyses is fundamental to effective clinical management and is the overriding imperative for the laboratories that provide this crucial service. The current crisis presents such laboratories with an even greater challenge than usual with the particular requirement of ensuring that those working in them are able to provide these essential services at minimal risk to their own health and that of their colleagues. This involves adopting and adhering to additional measures and new practices that affect all aspects of the laboratory workflow and will undoubtedly evolve and be refined as experience is gained. The recommendations we present are an attempt to assist colleagues in maintaining as safe an environment as possible while providing a service of the highest quality. It is inevitable that, even on return to a more 'normal' situation, some of the adaptations and innovations enforced by the current pandemic will be seen to carry clear, maybe unexpected, advantages and will become embedded as part of future best practice.

Handling editor Runjan Chetty.

Acknowledgements FL-R wishes to thank Marta Alonso, TEAP, Rebeca Martinez, TEAP, and Raquel Lopez for quickly implementing the necessary changes in the COVID-19 crisis. PH wishes to thank the LPCE members (Nice, France) for implementing the necessary changes during the COVID-19 pandemic. The authors would like to acknowledge Amy Turner-Duff PhD of Indigo Medical, for editorial support that was provided in accordance with GPP3 guidelines (http://www.ismpp.org/gpp3) and support from AstraZeneca.

Contributors All authors have contributed equally to the intellectual design, critical appraisal and approval of the final manuscript.

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; internally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Paul Hofman http://orcid.org/0000-0003-0431-9353
Giancarlo Troncone http://orcid.org/0000-0003-1630-5805
Fernando Lopez-Rios http://orcid.org/0000-0001-6813-0395

REFERENCES

1 The coronavirus APP, 2020. Available: https://coronavirus.app/map?selected=mab [Accessed 7 May 2020].
2 Zhu N, Zhang D, Wang W, *et al*. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33.
3 Lai C-C, Shih T-P, Ko W-C, *et al*. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents* 2020;55:105924.
4 Li Q, Guan X, Wu P, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;382:1199–207.
5 Lee VJ, Yap J, Cook AR, *et al*. Effectiveness of public health measures in mitigating pandemic influenza spread: a prospective sero-epidemiological cohort study. *J Infect Dis* 2010;202:1319–26.
6 Public Health Agency of Canada. ePATHogen - Risk Group Database, 2020. Available: https://health.canada.ca/en/epathogen [Accessed 5 May 2020].
7 World Health Organization. *Laboratory biosafety guidance related to the novel coronavirus (2019-nCoV)*, 2020.
8 Centers for Disease Control and Prevention. Laboratory biosafety and COVID-19: questions and answers, 2020. Available: https://www.cdc.gov/coronavirus/2019-ncov/lab/biosafety-faqs.html [Accessed 7 May 2020].
9 Vigliar E, Iaccarino A, Bruzzese D, *et al*. Cytology in the time of coronavirus disease (covid-19): an Italian perspective. *J Clin Pathol* (Published Online First: 20 April 2020).
10 World Health Organization. Guidance on regulations for the transport of infectious substances 2019 – 2020, 2020. Available: https://www.who.int/ihr/publications/WHO-WHE-CPI-2019.20/en/ [Accessed 5 May 2020].
11 The Royal College of Pathologists. RCPath advice on the opening of fresh or unfixed histopathological specimens during infectious disease outbreaks, 2020. Available: www.rcpath.org [Accessed 5 May 2020].
12 Royal College of Pathologists. *RCPath advice on histopathology frozen sections and cytology fine needle aspiration during infectious disease outbreaks*, 2020.
13 Rossi ED, Fadda G, Mule A, *et al*. Cytologic and histologic samples from patients infected by the novel coronavirus 2019 SARS-CoV-2: an Italian institutional experience focusing on biosafety procedures. *Cancer Cytopathol* 2020;128:317–20.
14 Hofman P, Puchois P, Brest P, *et al*. Possible consequences of the COVID-19 pandemic on the use of biospecimens from cancer biobanks for research in academia and bioindustry. *Nat Med* 2020:1.
15 Tan SS, Yan B, Saw S, *et al*. Practical laboratory considerations amidst the COVID-19 outbreak: early experience from Singapore. *J Clin Pathol* 2020;0:1–4.
16 World Health Organization. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases, 2020. Available: https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117 [Accessed 5 May 2020].
17 SWX O, Tan YK, Chia PY, *et al*. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. *JAMA J Am Med Assoc* 2020;323:1610–2.
18 Mukhopadhyay S, Booth AL, Calkins SM, *et al*. Leveraging technology for remote learning in the era of COVID-19 and social distancing: tips and resources for pathology educators and trainees. *Arch Pathol Lab Med* 2020. doi:10.5858/arpa.2020-0201-ED

J Clin Pathol: first published as 10.1136/jclinpath-2020-206789 on 1 June 2020. Downloaded from http://jcp.bmj.com/ on January 12, 2021 at Seoul National University Medical Library and Hospital. Protected by copyright.