PATH TALK

April 2020 Issue—Special COVID Edition

COVID Message from the CPath EXCO

Dear Colleagues,

The COVID-19 pandemic presents to each of us a unique situation unlike any other experienced in our lifetime. Its repercussions continue to be felt across all segments of our societies.

We realise that the implementation of the much needed Movement Control Order (MCO) has taken a toll, both personally and professionally. Though we are pathologists in different specialties, we play similar roles in different settings during this crisis: we could be decision makers on constant vigilance of changing situations, helping to control the spread of the pandemic; we could be supervising the newly added load of Covid testing at the front lines; or we could still be providing the non-Covid laboratory services that may have decreased.

We all have families and loved ones to care for. The disruptions brought about by the MCO drastically affect our daily lives. There is dire need to maintain some level of productivity, normality, composure and sanity, especially for those who are heads of the family. While taking care of the wellbeing of those around us, please look after your own welfare and seek assistance when needed. The College and its Council are ready to give a hand when sought.

This is why we write to you personally today. We must acknowledge and sustain one another as this Covid storm progresses. It is a storm which will come to pass with our concerted effort. We must maintain the responsibilities that we each continue to hold dear and extend our assistance beyond our membership to others in need.

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Inside This Issue:

In this critical moment in history, we applaud you, as colleagues and friends within the College of Pathologists, Academy of Medicine of Malaysia. We applaud your resilience, your strength, and your continued commitment to the well-being of your communities. We applaud your connection and commitment to this College, and we are honoured that you are a part of it.

Though we may not have the joy of seeing one another in person this year at our ICPaLM 2020, we are determined to organise this event, but have postponed it to January 2021. We will let you know the date once we have finalised the arrangement.

Meanwhile, please stay safe and keep well.

With best wishes,

Members of the Executive Committee,
Council of the College of Pathologists, Academy of Medicine of Malaysia:

Emeritus Professor Dr Cheong Soon Keng
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THE COVID-19 PANDEMIC

An outbreak of a novel coronavirus, officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019. Today, Coronavirus disease 2019 (COVID-19) is a global pandemic.

In view of unparalleled stress on the local healthcare system as the number of individuals infected with SARS -CoV-2 continues to rise in Malaysia, the role of the diagnostic laboratory becomes increasingly essential in this crisis. Pathology services must be in a position to continue to cope with the viral outbreak in terms of patient screening, diagnosis, monitoring/treatment, and epidemiologic recovery/surveillance as well as safeguard core services whilst moving to minimal staffing levels to promote resilience and social distancing. As such, The College of Pathologists Academy of Medicine of Malaysia (CPath AMM) has extracted recommendations from various official resources such as World Health Organization (WHO), Centre for Disease Prevention and Control (CDC), International Federation of Clinical Chemistry and American Association for Clinical Chemistry (AACC) with respect to SARS-CoV-2 epidemic testing.

The estimated incubation period of SARS-CoV-2, which is the duration between exposure to the virus and symptom onset ranges from 1 to 14 days, with a median of approximately 5 days. The majority of transmission occurs from symptomatic cases although asymptomatic and pre-symptomatic transmission 1 to 3 days before manifestation has been documented. It is estimated that approximately 80% of cases will have a mild illness, 20% will require hospitalisation, and 3-5% will be admitted to the ICU. Cases classified as critical (respiratory failure, septic shock, and/or multi-organ failure) have a case fatality rate of approximately 50% and tend to be elderly with comorbidities.

There are two main factors to consider when screening patients for COVID-19 according to WHO, which are i) epidemiological history: within the last 14 days of symptom onset, the patient has a travel history or residence in a location with community transmission or contact with a probable or confirmed case; and ii) clinical manifestation: acute respiratory illness, which is characterised by fever and at least one respiratory sign/symptom, such as cough or shortness of breath. Suspect cases are defined as a patient with acute respiratory illness AND epidemiological history OR a patient with severe acute respiratory illness (characterised as described above AND requiring hospitalisation) AND no alternative diagnosis that fully explains the clinical signs/symptoms.

Upon confirmation of a suspected case, specimens should be rapidly collected and tested. The CDC recommends collecting an upper respiratory specimen for initial diagnostic testing. The following specimens can be collected for swab-based testing: nasopharyngeal specimen (preferred), oropharyngeal specimen, nasal mid-turbinate specimen and anterior nares specimen. Lower respiratory tract specimen testing is also recommended by the CDC, if the specimens are available.

Timely communication between clinical and laboratory staff is essential to minimise the risk incurred in handling specimens from patients with possible SARS-CoV-2 infection. Such specimens should be labeled accordingly and the laboratory should be alerted to ensure proper specimen handling. Standard precautions should be followed when collecting and handling clinical specimens that are suspected or confirmed for SARS-CoV-2. This includes hand hygiene and the use of personal protective equipment (PPE) such as laboratory coats or gowns, gloves, and eye protection.

The following laboratory procedures have been associated with the generation of infectious aerosols and droplets: centrifugation, pipetting, vortexing, mixing, shaking, sonicating, removing caps, decanting liquids, preparing smears, flaming slides, aliquoting and loading specimens, loading syringes, manipulating needles, syringes or sharps, aspirating and transferring blood and body fluids, subculturing blood culture bottles, spilling specimens, and cleaning up spills. A certified Class II Biological Safety Cabinet (BSC) can be used or additional precautions can be taken such as PPE (surgical mask or face shield), or a splash shield; centrifuge safety cups; and sealed centrifuge rotors to reduce the risk of exposure to the laboratory personnel. Work surfaces and equipment should be decontaminated with EPA-registered hospital disinfectants with label claims to be effective against SARS-CoV-2. Manufacturer's recommendations should be followed for use, such as dilution, contact time, and safe handling. Laboratory waste from testing suspected or confirmed COVID-19 patient specimens should be handled as all other biohazardous waste in the laboratory. Currently, there is no evidence to suggest that this laboratory waste needs any additional packaging or disinfection procedures.

Personnel should adhere to standard procedures associated with other respiratory pathogens, such as seasonal influenza and other human coronaviruses, when they transport specimens within a facility. All laboratories should perform a site-specific and activity-specific risk assessment to determine if additional biosafety precautions are warranted based on situational needs, such as high testing volumes, and the likelihood to generate infectious droplets and aerosols. Risk assessments and mitigation measures are dependent on:

- the procedures performed
- identification of the hazards involved in the process and/or procedures
- the competency level of the personnel who perform the procedures
- the laboratory equipment and facility
- the resources available

Real-time reverse transcription polymerase chain reaction (rRT-PCR) is the current gold standard for diagnosing suspected cases of COVID-19. rRT-PCR is a nucleic acid amplification test (NAAT) that detects unique sequences of the virus that causes COVID-19 (SARS-CoV-2) in respiratory tract specimens. The N, E, S, and RdRP are the viral genes currently targeted. Specimens should be stored at 2-8°C for up to 72 hours after collection. If a delay occurs in extraction, specimens should be stored at -70°C or lower. Extracted nucleic acid samples also should be stored at -70°C or lower.

There are a variety of pre-analytical and analytical issues that can affect diagnostic testing for COVID-19 infection. Some pre-analytical issues include improper collection, handling, transport and usage of swabs, as well as collection of inappropriate or inadequate material, interfering substances, and sample contamination. A common analytical issue is testing outside of the diagnostic window, in addition to active viral recombination and inadequately validated assays.

A positive test result for COVID-19 indicates that RNA from SARS-CoV-2 was detected, and the patient is presumptively infected with the virus and presumed to be contagious. Laboratory test results should always be considered in the context of clinical observations and epidemiological data in making a final diagnosis and patient management decisions. All laboratories using this test must follow the standard confirmatory testing and reporting guidelines according to their appropriate public health authorities.

A negative test result for this test means that SARS- CoV-2 RNA was not present in the specimen above the limit of detection. However, a negative result does not rule out COVID-19. When diagnostic testing is negative, the possibility of a false negative result should be considered in the context of a patient's recent exposures and the presence of clinical signs and symptoms consistent with COVID-19. The possibility of a false negative result should especially be considered if the patient's recent exposures or clinical presentation indicate that COVID- 19 is likely, and diagnostic tests for other causes of illness (e.g., other respiratory illness) are negative. If COVID-19 is still suspected based on exposure history together with other clinical findings, re-testing should be considered by healthcare providers in consultation with public health authorities. In some cases, a negative result may be returned for a suspected case with high likelihood of COVID-19 infection. If the negative result was concluded based on only an upper respiratory tract specimen, a lower respiratory tract specimen should be subsequently tested.

There has been much debate regarding the current value of serological testing in COVID-19 diagnosis and monitoring. Serologic based tests are not currently recommended by the CDC or other health organisations. There is general concern regarding their use in the acute phase of infection as they detect infection too late in the course of illness (usually more than 7-10 days) and they also may cross-react with serologic responses to seasonal coronaviruses. However, there is anticipated value in using improved serological testing in the future for public and occupational health monitoring and assessment. For serum antibody monitoring, serum IgM is detectable 10 days after symptom onset and IgG is detectable 12 days after symptom onset. A positive interpretation has been defined as a positive IgM, or an increased IgG titer more than 4 times than that in the acute phase.

The essential role of clinical laboratories in this pandemic extends beyond aetiological diagnosis of COVID-19. Biochemical monitoring of COVID-19 patients through *in vitro diagnostic* testing is critical for assessing disease severity and progression as well as monitoring therapeutic intervention. Several common *in vitro diagnostic* tests have been implicated in unfavourable COVID-19 progression, potentially providing important prognostic information. The table below summarises the recommendations by IFCC based on current literature along with the major laboratory abnormalities associated with adult COVID-19 patients and their potential clinical indications. In addition to more common laboratory tests, new evidence suggests that patients with severe COVID-19 could be at risk for **cytokine storm syndrome.** Cytokine tests, particularly IL-6, should be used where possible to assess severe patients suspected of hyperinflammation. Importantly, unlike adults, the laboratory profile in severe COVID-19 paediatric patients is not clear and does not appear to be consistent with SARS. A recent publication recommends clinicians monitor lymphocyte count, c-reactive protein, and procalcitonin to assess severe infection. IL-6 should also be investigated as a potential paediatric prognostic indicator.

IFCC Recommended Test List:

Laboratory Test	**Main laboratory abnormalities observed in adult patients with unfavorable COVID-19 progression**	**Potential clinical and biological significance**
Complete blood count	Increased white blood cell Increase neutrophil count Decreased lymphocyte count Decreased platelet count	Bacterial (super)infection Bacterial (super)infection Decreased immunological response to the virus Consumption (disseminated) coagulopathy
Albumin	Decreased	Impairment of liver function
Lactate Dehydrogenase	Increased	Pulmonary injury and/or widespread organ damage
Alanine Aminotransferase	Increased	Liver injury and/or widespread organ damage
Aspartate aminotransferase	Increased	Liver injury and/or widespread organ damage
Total bilirubin	Increased	Liver injury
Creatinine	Increased	Kidney injury
Cardiac troponin	Increased	Cardiac injury
D-Dimer	Increased	Activation of blood coagulation and/or disseminated coagulopathy
Prothrombin Time	Increased	Activation of blood coagulation and/or disseminated coagulopathy
Procalcitonin	Increased	Bacterial (super)infection
C-reactive protein	Increased	Severe viral infection/viremia/viral sepsis
Ferritin	Increased	Severe inflammation
Cytokines (IL-6)	Increased	Cytokine storm syndrome

There have been reports of apparent re-infection in a small number of cases. However, most of these describe patients having tested positive within 7-14 days after apparent recovery. Immunological studies indicate that patients recovering from COVID-19 mount a strong antibody response. It is likely that positive tests soon after recovery represent persisting excretion of viral RNA, and it should be noted that PCR tests cannot distinguish between "live" virus and non-infective RNA. Australian guidelines currently require patients who have had COVID-19 to test negative on two tests 24 hours apart before being released from isolation.

In conclusion, CPath AMM emphasises that the strategy to combat COVID-19 outbreak is two-fold: i) to reduce the total number of cases, and ii) to spread them out over a longer period of time ("flattening the peak") so that the healthcare capacity is not overwhelmed. This will allow us to conserve and allocate limited resources in more sustainable ways. The Ministry of Health is reallocating existing resources to cater for a possible surge in cases and also mobilising additional resources from the private sector, civil society organisations and other stakeholders. Last but not least, adhere to social distancing so that we can reduce the total number of cases and distribute them over a longer period of time. This will protect against suffering and allow us to save more Malaysians by allocating our resources more effectively and fairly.

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ANNOUNCEMENT

Attention: ICPaLM 2020 has been postponed to 25-27 Jan, 2021 due to global pandemic.