Editorial

Giuseppe Lippi, Andrea Horvath and Khosrow Adeli* On behalf of the IFCC Taskforce on COVID-19

Editorial and executive summary: IFCC Interim Guidelines on clinical laboratory testing during the COVID-19 pandemic

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the novel coronavirus which causes coronavirus disease 19 (COVID-19). As of September 19, 2020, more than 30 million confirmed COVID-19 cases and over 900,000 deaths have been reported. Laboratory testing has played a crucial role in managing the COVID-19 pandemic across the globe [1]. Hundreds of medical tests have been rapidly produced in-house, or released to the market via emergency use authorization by various regulatory bodies, to assist governments in managing outbreaks during this pandemic. These medical assays include molecular tests for detecting SARS-CoV-2 RNA along with serological tests for detecting antibodies against SARS-CoV-2. The rapid development of these tests, combined with the urgency to support clinical care, has resulted in much debate regarding their appropriate clinical applications as well as their respective analytical and clinical performance in populations of interest [2–5]. The interpretation of laboratory test results for both molecular and serological assays is complicated by their dynamic profile, varying significantly in the detection window and in response to severity of symptoms (Figure 1) [6].

***Corresponding author: Khosrow Adeli,** Clinical Biochemistry, DPLM, Hospital for Sick Children, Pediatric Laboratory Medicine, University of Toronto, Toronto,ON M5P 2R6, Canada; and University of Toronto, Laboratory Medicine and Pathobiology, Toronto, ON, Canada, E-mail: khosrow.adeli@sickkids.ca; and IFCC Taskforce on COVID-19.
Giuseppe Lippi, University Hospital of Verona, Verona, Italy. https://orcid.org/0000-0001-9523-9054
Andrea Horvath, University of New South Wales, Sydney, ACT, Australia

Laboratory test results for molecular and serological assays are very important tools in population health, infection control and economic decisions. It is hence very important that these assays are used and interpreted appropriately, with full understanding of the clinical performance characteristics and analytical limitations. In addition to providing diagnostic information through molecular and serological testing, clinical laboratories have also supported the prognostication of patients with COVID-19 throughout this pandemic, by providing valuable objective data through routine biochemical and hematological testing. While these tests are already well established in most laboratories, the clinical value of various biochemical and hematological parameters in stratification and clinical management of COVID-19 patients continues to be underrated and debated.

In response to the current pandemic, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established a COVID-19 Taskforce, with the primary objective of providing recommendations for harmonizing use and evaluation of laboratory tests worldwide during the COVID-19 pandemic. This executive document summarizes these interim recommendations to support the ongoing fight against the COVID-19 pandemic, with particular focus on the needs of clinical laboratories in developing countries.

This document provides practical recommendations on the intended use, selection, evaluation and implementation of laboratory tests used in the diagnosis of SARS-CoV-2 infection and management of COVID-19. It also discusses the various analytical and clinical considerations required prior to test implementation, along with test result interpretation. These guidelines have been developed by critically reviewing published peer-reviewed evidence available to date, and establishing a consensus of experts from the IFCC COVID-19 Taskforce and other experts in the field. The international authorship of this guideline document represents medical/clinical biochemists, clinical microbiologists/virologists, together with scientists representing the *in vitro* diagnostics

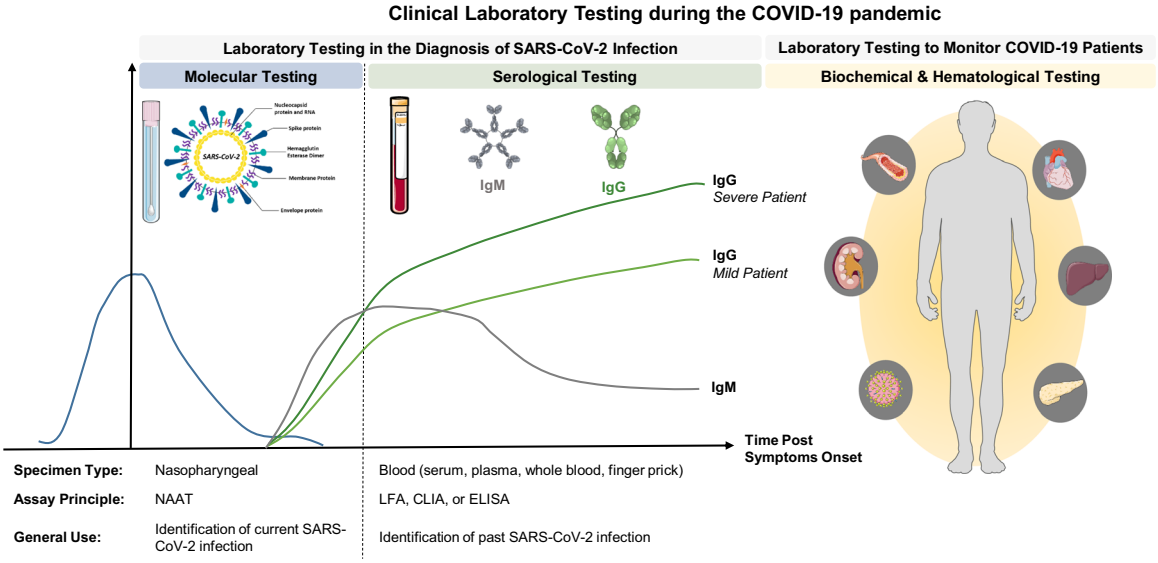

Figure 1: Overview of the role and types of clinical laboratory testing during the COVID-19 pandemic.
Antibody and viral RNA dynamics are projections based on current evidence. NAAT, nucleic acid amplification test; IgM, immunoglobulin M; IgG, immunoglobulin G; LFA, lateral flow assay; CLIA, chemiluminescent assay; ELISA, enzyme-linked immunosorbent assay.

Table 1: Executive summary of recommendations on molecular testing of SARS-CoV-2 infection (see accompanying publication [7], for details).

Clinical indications and target population for molecular testing

a. The following molecular test indications are supported by current evidence and of clinical value:
   - To diagnose viral infection in the acute phase of symptomatic illness (0–<14 days).
   - To assist in clinical assessment of asymptomatic, pre-symptomatic or mildly symptomatic patients with known exposure to positive COVID-19 cases.
   - To assist in screening of asymptomatic, pre-symptomatic or mildly symptomatic individuals in various contexts, including but not limited to: prior to scheduled surgery or delivery, travel, hospital discharge, return to work/school and to manage small outbreaks (retesting should be considered).

b. Populations that should be prioritized for molecular testing include:
   - Patients with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath) and all individuals having been in contact with a confirmed or probable COVID-19 case in the last 14 days (in resource limiting settings).
   - Higher risk groups, including the elderly and patients with pre-existing co-morbidities (e.g., cardiovascular disease, diabetes, cancer, hypertension, immune-compromised etc.).

Molecular test selection

a. Clinical laboratories should select an appropriate nucleic acid amplification assay that best serves the intended clinical application, keeping in mind that the performance of current point-of-care assays has not been well demonstrated.
b. There is currently insufficient evidence to suggest a definitive advantage of selecting an assay based on a specific SARS-CoV-2 gene target (i.e., N, E, R, RdRp or ORF1ab genes).
c. Assays for molecular diagnosis should employ a minimum of two gene targets to minimize the risk of false negatives.
d. The acceptable specimen type for molecular testing should follow manufacturers' recommendations.
e. At minimum, an upper respiratory tract specimen should be collected for molecular testing of SARS-CoV-2 infection.
f. More evidence is needed to support the use of saliva as a sample type for molecular testing of SARS-CoV-2 infection.
g. Self-collection kits are not recommended unless there is appropriate instruction or patient education. Results should always be interpreted with caution.
h. Pooling specimens should only be used in low prevalence (<1%) or low resource settings after appropriate validation.

Verification of regulatory-approved molecular tests

a. Laboratories should verify the analytical performance claims of regulatory-approved molecular tests, including the parameters described in the accompanying publication [7], before routine use.
b. Laboratories should participate in a relevant Quality Assurance Program, where possible.

Table 1: (continued)

c. Laboratories should verify the clinical performance claims of the manufacturers of molecular tests in a representative local population in which the test is intended to be used.
d. When clinical samples (e.g., repeat positives, positives on 'gold standard' assays, or clinical criteria) are not available, contrived specimens can be used as outlined in the accompanying publication [7].
e. Laboratories should follow the STARD guidelines when designing and reporting clinical performance studies.

Molecular test interpretation

a. Positive test result:
   – SARS-CoV-2 RNA has been detected in the sample and the patient should be considered presumptively infected.
   – Active viral replication and potential for viral transmission cannot be concluded. Clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status.
b. Negative test result:
   – SARS-CoV-2 RNA was not present in the specimen above the limit of detection of the assay.
   – SARS-CoV-2 infection cannot be ruled out and this one test result should not be used as the sole basis for patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information.
   – Re-testing should be considered if: i) infection is still suspected after considering other differential diagnoses, ii) molecular testing is being used for hospital release and iii) if analytical inhibition is suspected.
c. Indeterminate test result:
   – Test result cannot be interpreted, and follow-up re-testing to yield a determinate result is recommended.

Table 2: Recommendations on serological testing of antibodies against SARS-CoV-2 infection (see accompanying publication [8] for details).

Clinical indications and target population for serological testing

a. The following indications are supported by current evidence of clinical value:
   – To serve as adjunct to molecular testing in patients presenting with suggestive clinical features (>14 days post symptom onset), but molecular testing for SARS-CoV-2 is negative, undetermined or unavailable.
   – To serve as adjunct to molecular testing where persistently positive molecular tests occur in the absence of infectious virus, such as late after resolved infection.
   – To assist in the diagnostic work-up of Multi-System Inflammatory Syndrome in Children (MIS-C).
b. The following indications are potentially valuable in the future, but not possible using currently approved assays or have minimal associated evidence:
   – To identify prior infection in non-hospitalized individuals (asymptomatic and symptomatic) and ascertain community exposure via seroprevalence surveys.
   – To quantitatively evaluate the degree of antibody response in COVID-19 patients.
   – To assist in identification of potential convalescent plasma donors.
   – To assist in identification of immunity and evaluation of antibody response to future vaccines.
   – To assist in monitoring the progression of herd immunity.
c. The following indication is not supported due to strong evidence against application:
   – To diagnose SARS-CoV-2 infection in the acute phase of illness (0–<14 days)
d. Populations that should be prioritized for serological testing include:
   – Patients presenting with possible COVID-19 symptoms but who were negative by molecular testing (e.g. delayed clinical onset).

Serological test selection

a. There is insufficient evidence to support any one specific immunoglobulin isotype as better than others in assay selection.
b. No commercially available serological test has proven capability to detect neutralization antibodies, regardless of antigenic target, and positive results should not be used to indicate immunity.
c. Neutralization assays should be used to determine the neutralization capacity of patient sera.
d. Currently available point-of-care assays for serological detection of antibodies against SARS-CoV-2 compare poorly in sensitivity to lab-based assays and should not be used without extensive clinical and analytical validation. When used, negative results with a high suspicion of infection should be followed up with a lab-based assay.

Table 2: (continued)

Verification of regulatory-approved serological tests
a. Laboratories should verify the analytical performance of regulatory approved serological tests, including the parameters described in the accompanying publication [8], before routine use.
b. Laboratories should participate in a Quality Assurance Program for SARS-CoV-2 serology, when possible.
c. Laboratories should set clinical performance specifications together with clinicians and policy makers that reflect the intended use of the test in the intended population and clinical setting.
d. Clinical performance studies should verify if the test is fit for purpose in the local setting.
e. Laboratories should follow the STARD guidelines when designing and reporting clinical performance studies.
Serological test interpretation
a. Positive test result: – Antibodies against SARS-CoV-2 were detected in the sample indicating recent or prior COVID-2 infection. The results should be interpreted in the clinical context and considering assay specificity, sensitivity, and population prevalence.
b. Negative test result: – Antibodies against SARS-CoV-2 were not detected in the sample, but lack of SARS-CoV-2 exposure cannot be ruled out. Follow-up testing might be indicated. The results should be interpreted in the clinical context and considering assay specificity, sensitivity, and population prevalence.
c. Indeterminate test result: – Test result cannot be interpreted; follow-up re-testing to yield a determinate result is recommended.

Table 3: Recommendations on biochemical & hematological monitoring of COVID-19 patients (see accompanying publication [9] for details).

Clinical indications & test selection for biochemical & hematological monitoring
a. Abnormal hematology and biochemistry test results in infected patients may help: – diagnose infection-related tissue and organ injury; – identify infected patients at lower risk of severe disease; – recognize patients who are likely to have poor prognosis (e.g., need for mechanical ventilation or intensive care, progression to multisystem organ failure, death); – monitor disease course.
Test selection & interpretation for biochemical & hematological monitoring
a. Key hematology tests recommended to monitor COVID-19 patients are presented in the accompanying publication [9].
b. Key biochemical tests recommended to monitor COVID-19 patients are presented in the accompanying publication [9].
c. Considerations for laboratory testing in children: – Measurement of hematological and biochemical markers is unlikely to be indicated in asymptomatic children. – For those with clinical features of infection, measurement of a complete blood count and inflammatory markers (e.g., CRP and/or ferritin) and D-dimer may be indicated. – Given the common occurrence of co-infection with other bacterial pathogens in children, procalcitonin assessment may also be warranted.
d. Until clinical risk scores are validated in large, independent populations in whom these tests are to be used, we would advise against the use of clinical risk algorithms to diagnose or risk-stratify patients with COVID-19.
e. No one test should be considered in isolation. Groups of relevant tests should be reviewed in the context of the patient's clinical presentation.
f. The biological and analytical variation in test performance should be considered when interpreting available studies and intra-individual changes.
g. We would urge caution when translating study findings to local laboratory practice, especially when diagnostic cut-offs are recommended.

industry. The guideline group took into consideration the global applicability of recommendations in various resource settings, providing practical recommendations that can be of immediate impact worldwide.

The guidelines are divided into three essential publications:

I. IFCC Interim Guidelines on Molecular Testing of SARS-CoV-2 Infection [7]
II. IFCC Interim Guidelines on Serological Testing of Antibodies against SARS-CoV-2 [8]
III. IFCC Interim Guidelines on Biochemical & Hematological Monitoring of COVID-19 Patients [9]

Key recommendations regarding the clinical indications, target population, assay selection, test interpretation and limitations of molecular and serological tests are provided in Tables 1 and 2, respectively. Key recommendations regarding the selection of hematological and biochemical tests to monitor and assess pediatric and adult COVID-19 patients are provided in Table 3. Additional rationale and evidence summaries supporting these recommendations are provided in the appended publications that accompany this editorial [7–9].

Conclusions

These evidence-based recommendations will provide practical guidance to clinical laboratories worldwide and underscore the importance of laboratory medicine in our collective response to this unprecedented health crisis. Additional items for considerations, as more evidence becomes available, include antigen testing, test harmonization, point-of-care assays, and quantitative PCR and serological testing. The IFCC Taskforce will continue to evaluate the emerging evidence on these other testing paradigms and will develop further recommendations in the near future.

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