REVIEW ARTICLE

COVID-19 in adults: test menu for hospital blood science laboratories

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Abstract

Introduction Coronavirus disease 2019 (COVID-19), is a respiratory illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The Clinical Blood Sciences Laboratory (CBSL) plays a key role in supporting the monitoring and management of patients with COVID-19 disease.

Objective To provide a comprehensive CBSL testing protocol to support the medical management of SARS-CoV-2 infection.

Methods Description of the biochemical, haematological and immunological tests that have a role in the assessment and monitoring of patients with COVID-19 infection.

Results We provide a test menu for clinical laboratories to ensure the effective monitoring, management and prognostication of COVID-19 patients in hospital.

Conclusion Given the rapidity with which patients with COVID-19 disease can deteriorate, we recommend regular testing with vigilance paid to the rate and trajectory of change in each of these parameters.

Keywords Blood science testing · COVID-19 · Hospital laboratories · Monitoring and management

Background

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 disease was first described in Wuhan, China in December 2019 and is now a global pandemic. As of the 12th of April 2020, there were 1,696,588 confirmed COVID-19 cases worldwide, 10–15% of which have severe disease and over 105,952 deaths reported [1]. Most of those affected have milder illness (80%), 15% are severely ill (require oxygen) and 5% will require admission to the intensive care unit (ICU). The Clinical Blood Sciences Laboratory (CBSL) plays a key role in

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Table 1 Clinical blood science testing for COVID-19 patients in hospital

Parameter	Abnormality	Utility for prognostication
Biochemistry		
Inflammatory biomarkers		
Interleukin 6	↑+ Velocity	Hyperinflammatory syndrome
Procalcitonin	↑+ Velocity	Bacterial (Super) infection
Acute phase proteins		
C-reactive protein	↑	Inflammation/sepsis
Albumin	↓	Response to severe inflammation
Ferritin	↑	
Lung		
pH	↑	Assessment of pulmonary function
Partial pressure of oxygen (pO_2)	↓	Check blood gases regularly (every 30 minutes if patient deteriorating)
Partial pressure of carbon dioxide (pCO_2)	↓	
Bicarbonate (HCO_3)	N/ ↑	
Fraction of inspired oxygen (FIO_2)	↓	
Lactate	↑	
Renal		
Electrolytes ($Na^+/K^+/CL^-$)	↑Na^+	Insensible losses and diuretic therapy
		May portend acute kidney injury
Urea	↑	Acute kidney injury (AKI)
Creatinine (Cr)	↑	Cr increase 26 μmol/L/48 h; or 1.5× baseline/7 days
Liver		
Total bilirubin	↑	Liver injury
Alanine transaminase (ALT)	↑	
Aspartate aminotransferase (AST)	↑	
Lactate dehydrogenase (LDH)	↑	Tissue damage/multiple organ failure
Heart		
High-sensitivity cardiac troponin	↑	Cardiac myositis/increased oxygen demand/inflammation
B-type natriuretic peptide	↑	Severity of inflammation/ventricular dysfunction
Other		
Creatine phosphokinase (CPK)	↑	Muscle injury
Triglycerides	↑	Increased lipolysis
Glucose	N/↑	Increased stress response
Ionized calcium	↓	RI/impaired PTH action/chelation precipitation
Phosphate	↓	Required for multiple enzyme function
Magnesium	↓	
Vitamin D (25(OH)D)	↓	Inflammatory response/decreased synthesis
Haematology		
Full blood count		
White cell count (WCC)	↑	Response to bacterial infection
Neutrophils	↑	
Leucocytes	↑	
Lymphocytes	↓	Immunological response to COVID-19
Platelets	N/↓	Counts fall consequent to consumption/DIC
Coagulation profile		
D-dimers	↑	Activation of blood coagulation
Fibrinogen	↑	Fibrinogen concentration falls in DIC or consumptive coagulopathy
Prothrombin time (PT)	↑	
Immunology		
Cytokine panel		
IL-1ß, IL6, IL8, TNF-α	↑	Disease severity/cytokine storm syndrome

DIC disseminated intravascular coagulopathy, *N* normal, *RI* renal impairment, *PTH* parathyroid hormone

supporting the monitoring and management of COVID-19 disease. Routine CBSL tests recommended to support medical decision-making and prognostication based on the current literature are detailed in Table 1 [2]. Recent evidence suggests that patients with severe COVID-19 are at risk for cytokine storm syndrome [3] and that where possible, Interleukin 6 (IL-6) should be used to assess these patients for suspected hyperinflammation [3, 4]. Furthermore, elevated concentrations of procalcitonin (a peptide precursor of the

hormone calcitonin) in the circulation is associated with ~5-fold higher risk of developing the severe form of the disease [5].

Septic shock

Septic shock in adults is recognised when infection is suspected or confirmed, lactate is ≥ 2 mmol/L and vasopressors are needed to maintain a mean arterial pressure (MAP) of 60–65 mmHg in the absence of hypovolemia [6].

Cytokine storm syndrome

Inflammation is the body's first line of defence against infection, responding to challenges by activating innate and adaptive immune responses. Ironically, hyperinduction of proinflammatory cytokine production (cytokine storm syndrome) can put a patient at risk for complications associated with COVID-19. Early recognition of this possibility is required to inform management and treatment decisions. This is important as potential treatments with existing approved therapies with proven safety profiles such as tocilizumab (an IL-6 receptor blocker) and Janus kinase (JAK) inhibitors have been mooted to address the rising mortality in patients with COVID-19 pneumonia and elevated IL-6 [3]. Identifying patients to direct these specific treatments is aided by measuring C-reactive protein (CRP), interleukin 6 (IL-6), ferritin and procalcitonin. IL-6 drives CRP and is an earlier marker of the status of a patients' inflammatory status. Elevated IL-6 concentrations together with the velocity of an increasing result portend an impending deterioration in clinical status.

Procalcitonin (PCT) is released into the circulation during bacterial infections and sustained by interleukins IL1-β, IL-6 and tumour necrosis factor alpha (TNF-α). PCT is inhibited by interferon gamma (IFN-γ), the primary activator of macrophages and stimulator of natural killer cells and neutrophils. Hence, PCT levels should remain within the reference interval in uncomplicated COVID-19 disease. Markedly abnormal PCT results on the other hand are consistent with bacterial coinfection in those developing severe forms of the disease [5, 7–10].

Lung

Angiotensin-converting enzyme 2 (ACE2) is the functional receptor for SARS-CoV-2. Human tissue studies have determined that ACE2 is expressed in some 15 organs, including the heart, kidneys and lung [11]. ACE2 is a key counterregulatory enzyme of the renin-angiotensin-aldosterone system (RAAS) that degrades angiotensin II to angiotensin-(1–7) reducing its effects on vasoconstriction, sodium retention and blood pressure. SARS-CoV-2 has a predilection for type II epithelial cells of the alveoli, with the lower airways being the dominant site of injury in COVID-19 [12]. The spectrum of COVID-19 lung illness spans asymptomatic infection and mild upper respiratory tract illness to severe viral pneumonia with respiratory failure and even death [13]. Arterial/venous blood gas parameters (pH, pO_2, pCO_2, HCO_3, FIO_2 and lactate) are used to monitor the patients' respiratory function and inform clinical decision-making. Criteria used to evaluate the severity of COVID-19 disease are detailed in Table 2.

Kidney: acute kidney injury

Acute kidney injury (AKI) requiring dialysis is reported in a subset of patients admitted to ICU. The exact mechanism is unclear at this point, but AKI is present in ~7% of patients with pathology demonstrating acute tubular necrosis. AKI correlates with an overall poor prognosis and seems to be the strongest predictor of mortality [14].

Many factors can affect the metabolism of creatinine from creatine in muscles and the rate of secretion of creatinine in the renal tubules, influencing both creatinine measurements and estimates of glomerular filtration rate (eGFR), the best overall index of kidney function. The National Kidney Foundation recommends using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula for eGFR [15]. However, the population used to derive this formula contained a limited number of elderly people and racial and ethnic minorities with measured GFR. Moreover, renal function in these patients is not in a steady state. Routine urine tests recommended to support medical decision-making are detailed in Table 3.

Liver: hepatocyte injury and disseminated intravascular coagulopathy

Elevated liver chemistries (alanine transaminase (ALT) aspartate aminotransferase (AST)) in COVID-19 disease are indicative of hepatocyte injury. While increased concentrations of bilirubin, prothrombin (a vitamin K-dependent coagulation factor) and fibrinogen (a 340-kDa glycoprotein) synthesised in the liver are indicative of liver dysfunction. Prothrombin is proteolytically cleaved to form thrombin which converts fibrinogen to fibrin and then to a fibrin-based blood clot to occlude blood vessels and arrest bleeding. A D-dimer is a fibrin degradation product present in the blood after a blood clot is degraded by fibrinolysis. In acute sepsis, the coagulation system becomes diffusely activated with consumption of multiple clotting factors resulting in disseminated intravascular coagulopathy (DIC) [16]. Pathogenesis is driven by an upregulation of procoagulant mechanisms and simultaneous downregulation of natural anticoagulants. The prevention of DIC in COVID-19 patients is critical to prevent multiorgan failure and efforts should centre on stratifying patients at high

Table 2 Criteria used to evaluate the severity of COVID-19 patients in hospital

Criterion	
If any of the following 3 criteria are met or exceeded	
Respiratory rate	≥ 30 breaths/min
SpO_2	$< 93\%$ while breathing room air
PaO_2/FIO_2	≤ 300 mmHg/40 kPa
A critical case is defined if in addition any of the following 3 criteria are met	
Respiratory failure	Requiring mechanical ventilation
Shock	Vasopressors required to maintain MAP, lactate ≥ 2 mmol/L and absence of hypovolaemia
Multiorgan failure	Other organ failure (SOFA) and ICU admission

SpO_2 peripheral capillary oxygen saturation (estimate of the amount of oxygen in blood), PaO_2 partial pressure of oxygen in arterial blood, FIO_2: fraction of inspired oxygen, MAP mean arterial pressure (60–65 mmHg), SOFA sequential organ failure assessment

risk for DIC. The prothrombin test (PT) (which measures the time it takes blood to clot (Normally: 11–12.5 s)), fibrinogen, D-dimers and the platelet count are significant predictors of disease severity as test abnormalities herald the onset of DIC. Klok et al. report a 31% incidence of thrombotic complications in ICU patients with COVID-19 and reinforce the recommendation for strict adherence to thrombosis prophylaxis [17].

Heart: myocardial injury, high-sensitivity cardiac troponin and B-type natriuretic peptide

Clinical studies have demonstrated that patients with long-term coronary artery disease and those with risk factors for atherosclerotic cardiovascular disease (CVD) are at increased risk of developing an acute coronary syndrome during influenza [18, 19] and acute inflammatory infections [20]. The speculated mechanism is that severe systemic inflammation leads to atherosclerotic plaque instability and rupture. Elevated high-sensitivity cardiac troponin concentrations are indicative of myocardial injury. Shi et al. reported that greater proportions of COVID-19 patients with cardiac injury required non-invasive mechanical ventilation (38 of 82 [46.3%] vs 13 of 334 [3.9%]; $P < 0.001$) or invasive mechanical ventilation (18 of 82 [22.0%] vs 14 of 334 [4.2%]; $P < 0.001$) when compared to those without cardiac injury [21]. Further, that in this cohort, higher concentrations of high-sensitivity cardiac troponin were associated with higher

Table 3 Clinical laboratory urine testing of COVID-19 patients in hospital

Urine parameter	Criterion value	Utility for prognostication
Urine output	Volume < 0.5 mL/kg/h for 6 h	AKI
Osmolality		
True hyponatraemia:	> 100 mOsm/kg	Evidence of AVP action, from SIAD or baroregulated AVP release (hypotension/hypovolaemia)
Serum Na^+: < 133 mmol/L		
	< 100 mOsm/kg	Normal water excretion
Spot urine Na^+	< 30 mmol/L	> 30 mmol/L
Hypovolaemic	Depletion: GI/skin/mucosa/diuretics	Addison's disease CSWS/SWN/diuretics
Euvolaemic	Hypothyroidism	SIADH
	SIADH with fluid restriction	Hypopituitarism
Hypervolaemic	Cirrhosis CCF	Renal impairment CCF Diuretics
Proteinuria		
Albumin: creatinine ratio (ACR)	> 30 mg/mmol	Classification: degree of renal impairment/target organ damage
Protein: creatinine ratio (PCR)	> 15 mg/mmol	

AKI acute kidney injury, SIAD syndrome of inappropriate antidiuresis, GI gastrointestinal, AVP arginine vasopressin, CSWS cerebral salt wasting syndrome, SWN salt wasting nephropathy, CCF congestive cardiac failure

mortality [21]. Ruan et al. also reported that patients with CVD infected with SARS-CoV-2 had a significantly increased risk of death [4]. These authors determined that some of their patients with SARS-CoV-2 died of fulminant myocarditis. Direct viral infection of the vascular epithelium and myocardium has been promulgated based on the unique affinity of SARS-CoV-2 for the host ACE2 receptor [22]. Hence, raising the possibility of myocarditis occurring in some COVID-19 patients irrespective of existing or pre-existing CVD [20, 21, 23].

Patients with heart failure are prone to haemodynamic decompensation and an unfavourable course when infected with SARS-CoV-2 [24]. Recent insights have been provided by Guo et al. demonstrating that cardiac troponin levels are significantly associated with C-reactive protein (CRP) and B-type natriuretic peptide, linking myocardial injury to severity of inflammation during hospitalisation in patients who follow a deteriorating clinical course toward death [25]. Patients with myocardial injury also have evidence of elevated leukocyte counts, CRP, procalcitonin (PCT) and creatinine phosphokinase (CPK).

Muscle

Muscle breakdown as evidenced by raised levels of creatine phosphokinase (CPK) and myoglobin has been reported to occur in patients with COVID-19 disease [4, 9, 13].

Vitamin D: 25(OH)D

Vitamin D insufficiency/deficiency is a global health pandemic, more common in patients in nursing homes and inpatients than patients in the community or outpatients [26]. The older person is most vulnerable to COVID-19 and death [9, 13]. Human dipeptidyl peptidase-4 receptor (DPP-4/CD26) binding has recently been shown to interact with the S1 domain of the COVID-19 spike glycoprotein, suggesting that it may be an important virulence factor in SARS-CoV-2 infection [27]. Of note, DPP-4/CD26 receptor expression has been shown to be significantly reduced in vivo on correction of vitamin D deficiency [28]. Vitamin D has also been shown to reduce IL-6 production in monocytes [29]. This evidence provides a rationale for supplementing COVID-19-positive patients with vitamin D [30].

To conclude, this test menu covers the requirements to manage and assist prognostication of COVID-19 patients in hospital. Given the rapidity with which these patients can deteriorate, we recommend regular testing with vigilance paid to the rate and trajectory of change in each of these parameters.

Compliance with ethical standards

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