

# The biosafety and risk management in preparation and processing of cerebrospinal ...

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## Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has caused the coronavirus disease 2019 (COVID-19) pandemic, an illness with the high transmissibility and a broad spectrum of clinical manifestation. As of December 15, 2020, the World Health Organization (WHO) reported more than 70 million cases and over 1.6 million deaths globally in the COVID-19 pandemic ([1](#)). COVID-19 is the third epidemic of human coronavirus diseases after the severe acute respiratory syndrome (SARS) in November 2002, and the Middle East respiratory syndrome (MERS) in September 2012 ([2](#)). In comparison with other epidemic coronaviruses, SARS-CoV-2 is less lethal but far more transmissible than MERS coronavirus (MERS-CoV) and SARS coronavirus (SAR-CoV) ([3](#), [4](#)). It is believed that SARS-CoV-2 can spread by respiratory droplets, unprotected direct contact with patients, and touching contaminated objects ([5](#), [6](#)). Since symptoms of COVID-19 can be in a wide variety of severity, medical professionals are in particular at risk of exposure to SARS-CoV-2 through close contact via respiratory droplets and contaminated surface and direct handling of contagious materials from patients with COVID-19 ([7](#)). With regard to the safe collecting and handling clinical specimens in the pandemic, a few reports have emphasized the need for the worldwide standardization of biosafety protocols ([5](#), [8](#), [9](#)). Notably, the neurological manifestation and morbidities of COVID-19 have been widely reported ([10](#) - [16](#)). Mao et al. ([15](#)) reported that neurologic symptoms were present in 36.4% of all patients with COVID-19, especially more frequent in patients with severe illness. Moreover, in a patient with acute cerebellitis, the viral RNA of SARS-CoV-2 was detected in his <https://assignbuster.com/the-biosafety-and-risk-management-in-preparation-and-processing-of-cerebrospinal-fluid-and-other-neurological-specimens-with-potential-coronavirus-infection/>

oropharynx, nasopharynx, and cerebrospinal fluid (CSF) ( [17](#) ). However, the biosafety and risk assessment in preparation and processing of CSF and other neurological specimens were seldom discussed. This mini-review aims to provide an integrative, evidence-based review to guide the preparation and processing of neurological specimens with potential coronavirus infection and therefore to prevent nosocomial infection.

## **Coronaviruses and Neurologic Diseases**

Although COVID-19 primarily presents as a respiratory disease, SARS-CoV-2 affects multiple organs or systems, including the central nervous system (CNS), peripheral nervous system (PNS), and neuromuscular system ( [15](#), [18](#) - [20](#) ). In a large case cohort of COVID-19, 24. 8% had CNS symptoms (e. g., dizziness, headache, and impaired consciousness), 8. 9% had PNS symptoms, and 10. 7% had skeletal muscle injury ( [15](#) ). In a nationwide surveillance of 125 patients with COVID-19 and neurological or psychiatric disease, 62% of them had a cerebrovascular event, while 31% of them presented with altered mental status ( [19](#) ). Similarly, the epidemic of SARS was reported with various neurological complications including encephalopathy, seizures, stroke, cranial nerve palsies, peripheral neuropathy, and myopathy ( [20](#) - [24](#) ). Also, patients with MERS were occasionally presented to have neurological symptoms and neuromuscular complications ( [24](#) - [27](#) ). The prevalence of CNS complications reached 0. 04% for SARS and 0. 20% for MERS, and besides the prevalence of PNS complications was 0. 05% for SARS and 0. 16% for MERS ( [14](#) ).

Although the mechanism of CNS involvement of COVID-19 remains unclear, there is a three-step model which refers to viral neuroinvasion, CNS clearance, and immune response ( [28](#) ). In the first stage, SARS-CoV-2 may enter the brain via the bloodstream and/or transcribriform route along the olfactory nerve, and the viral load in CSF should increase ( [28](#) ). The respiratory symptoms are minimal in the early stage. With the interaction between the spike protein S1 of SARS-CoV-2 and the host angiotensin-converting enzyme 2 receptor (ACE2), SARS-CoV-2 may enter both glial and neuronal cells ( [29](#) ). In some cases, the neuroinvasion may cause a direct neuronal damage and subsequently result in neurological symptoms. Moreover, the consumption and downregulation of ACE2 by SARS-CoV-2 virus may lead to imbalance of the renin angiotensin system resulting in endothelial dysfunction, vasoconstriction, and subsequently ischemic events ( [30](#) ). In the second stage, SARS-CoV-2 may infect the brainstem affecting the respiratory drive. The viral load in respiratory secretions would increase predominantly, but the viral load in CSF significantly decreases. The CSF clearance of SARS-CoV-2 may greatly contribute to a low virus detection rate in CSF samples from patients with COVID-19 and CNS involvement. In the third stage, an immuno-mediated CNS damage may form, since SARS-CoV-2 can trigger the production of antibodies against glial cells, as a para-infective or post-infective phenomenon ( [28](#) ). In consequence, the respiratory system would be severely affected and cause neurotoxic hypoxia with subsequent brain damage ( [28](#) ).

With regard to neuromuscular involvement of SARS-CoV-2, myositis, acute myelitis, Guillain Barre syndrome, Miller Fisher syndrome, polyneuritis cranialis, oculomotor paralysis and Bell's Palsy have been discussed to be associated with COVID-19 ( [18](#), [30](#) – [34](#) ). On electrodiagnostic testing, most of the abovementioned patients had demyelinating pattern, some had acute sensory motor axonal neuropathy, and few had acute motor axonal neuropathy ( [18](#) ). In a patient with COVID-19 and myositis, the muscle biopsy revealed inflammatory infiltration around vessels and endomysial extension, regeneration of muscular fibers, and elevated HLA Class ABC expression ( [33](#) ). The exact mechanism remains unknown, although a few hypothetic theories were proposed, including ACE2 mediated pathway, olfactory pathway, trans-synaptic pathway, and immune mediated pathway ( [18](#) ). Since the muscle cells express ACE2, the direct invasion by the SARS-CoV-2 entering the muscle cells via the ACE2 may be possible ( [30](#) ). In addition, cytokine storms in the advanced phase of COVID-19 could lead to immune-mediated muscle damages ( [30](#) ).

## **The Clinical Sampling and Preparation: Lumbar Puncture and Muscle Biopsy**

Lumbar puncture (LP) is a medical procedure at the level of L2 to L5 vertebrae to collect CSF for examining infectious, inflammatory, and neoplastic diseases involving the CNS. In viral encephalitis, there is usually a mild to moderate CSF pleocytosis with predominant lymphocytes, normal glucose ratio, and slightly elevated protein ( [14](#), [35](#) ). The standard of diagnosing a CNS viral infection is to demonstrate the virus in the CNS, either from culture or polymerase chain reaction (PCR) of brain tissue or CSF. <https://assignbuster.com/the-biosafety-and-risk-management-in-preparation-and-processing-of-cerebrospinal-fluid-and-other-neurological-specimens-with-potential-coronavirus-infection/>

Muscle biopsy (MB) is important for the evaluation and diagnosis of patients who are suspected of having an underlying neuromuscular disorder ( [36](#) ). With an open biopsy or needle biopsy technique under local anesthesia, bundles of skeletal muscles are taken for the required tests, including frozen sections for enzyme histochemistry, paraffin embedding for muscle fiber morphology and inflammatory patterns, electron microscopy for ultrastructural analysis, and biochemical testing for assessing storage and mitochondrial diseases ( [36](#) ).

In the pandemic, to perform a LP or a MB might be at risk to expose coronaviruses, since direct contact or respiratory droplets might be infectious. Since both LP and MB are time-consuming, the performer and all teammates would expose to patients' droplet aerosols in a poorly ventilated room. In closed rooms, the SARS-CoV-2 can be detectable in aerosols for 3 h and persists on surfaces (such as cardboard, stainless steel, and plastic surfaces) from 24 to 72 h ( [6](#) ). Thus, the sampling or collecting biological materials from patients should be careful and need to follow the recommendations or guidelines in the pandemic ( [5](#) , [37](#) – [39](#) ). First, a site-specific and activity-specific risk assessment should be regularly performed to ensure the competency level of the healthcare workers, the equipment and facility, and the resources that are available. Meanwhile, clinical triage should be ensured by assessing all patients for early detection of COVID-19, and immediate isolation of patients with suspected COVID-19 in an area separate from others ( [37](#) ). Regarding the environment, LP and MB should be performed in an adequately ventilated room with at least of 60

liters/s/patient air flow ( [37](#) ). The environmental cleaning and disinfection procedures should be consistently and correctly performed. Notably, coronaviruses can be inactivated by surface disinfectants with 62–71% ethanol (C<sub>2</sub>H<sub>6</sub>O), 0.5% hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) or 0.1% sodium hypochlorite (NaClO) within 1 min ( [40](#) ).

Although LP and MB are not aerosol-generating procedures, the neurological professionals should wear a medical mask, eye protection (goggles) or facial protection (face shield), a clean long-sleeved gown, and gloves ( [37](#) ). After procedures, personal protective equipment and wastes should be properly disposed, and hand hygiene should be performed before and after contact with each patient. Lastly, it is important to clean and disinfect the surfaces that the patient was in contact with. With regard to the transportation, CSF or muscle for virus detection can be shipped at 2–8°C and delivered promptly to the laboratory ( [41](#) ). Notably, patient specimens from suspected or confirmed SARS-CoV-2 infection should be transported as UN3373, “Biological Substance Category B” ( [42](#), [43](#) ). All the biosafety recommendations are summarized in [Table 1](#).

#### TABLE 1

A summary of biosafety recommendations to prevent coronavirus (COVID-19) for lumbar puncture and muscle biopsy.

## To Process CSF and Other Neurological Specimens

Since all specimens collected for laboratory investigations should be considered potentially infectious, all procedures must be performed according to risk assessment and strategies for biosafety ( [42](#), [43](#) ). Before inactivation of all specimens, the initial processing should be performed in a validated biological safety cabinet or primary containment device ( [42](#) ). In addition to detecting viruses by sequencing or PCR, all diagnostic laboratory works for neurological specimens, including biochemistry, cytology, and special stains should be performed at a facility using procedures equivalent to Biosafety Level 2 (BSL-2) ( [42](#), [43](#) ). In the light of inactivation of coronaviruses, fixatives with ethanol concentrations of 78%-95% for at least 30 s could inactivate SARS-CoV, and either 10% formalin or 4% paraformaldehyde for at least 30 min would efficiently inactivate MERS-CoV-infected cells ( [9](#) ). Alcohol fixed preparation also lyses red blood cells, reducing the risk of viremia. The abovementioned fixations are the reasons why specimens with Papanicolaou staining or formalin fixation can be taken as inactivated ( [9](#) ). Moreover, the external lysis buffer of common RNA extraction kits for viral detection is effective to inactivate SARS-CoV-2 without heat or other additional methods ( [42](#) ).

Currently, the identification of viral RNA through nucleic acid amplification technologies, such as reverse-transcription polymerase chain reaction (RT-PCR) in a patient's biological samples, remains the gold standard for identifying infections with coronaviruses. Notably, SARS-CoV was detected in CSF by RT-PCR in two cases of encephalopathy ( [44](#), [45](#) ) and was cultured



from brain tissues of an autopsy case ( [46](#) ). In the COVID-19 pandemic, although the neurological manifestations were not uncommon, SARS-CoV-2 RNA was rarely detected in CSF by RT-PCR ( [Table 2](#) ) ( [17](#), [47](#) - [65](#) ). And, to the best of our knowledge, there is no MB specimen demonstrating the evidence of SARS-CoV-2 infection via culture or RT-PCR. Based on the relative frequencies of detectable SARS-CoV-2 RNA in different samples from published reports, Chen and Chi ( [5](#) ) suggested to categorize the cytological and pathological samples into the high risk, intermediate risk, and low risk groups. Accordingly, CSF and MB specimens can be categorized into the low risk group with limited evidence of SARS-CoV-2 RNA detection and should subsequently follow the principles of good microbiological practices and procedures to be handled ( [5](#) ). Although the presence of viral RNA is not equivalent to live infectious viruses, RT-PCR is an important method to identify infectious agents ( [66](#) ).

## TABLE 2

The detection of SARS-CoV-2 in CSF from patients with COVID-19 and neurological symptoms.

## Conclusion

With the growing number of confirmed COVID-19 cases, it is essential that the neurological experts and clinical laboratories implement clinical triage, drastic measures, and appropriate procedures and facilities for ensuring the safety and interests of valuable healthcare workers in times of the pandemic.

The lessons learned from SARS and MERS could give us more insights to

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conduct efficient preventive measures in healthcare settings. Although LP and MB are important diagnostic procedures for CNS and neuromuscular diseases, neurological practitioners must be well-prepared and avoid of non-emergent procedures to prevent potential exposures to COVID-19. The collection, transportation, and processing of neurological specimens should warrant the use of WHO guidelines, academic recommendations, and BSL-2 procedures. Herein, although the biological safety and security issues were rarely discussed in neurology, we hope that both neurologists and laboratory professionals can benefit from this integrative mini-review in dealing with the COVID-19 crisis.

### **Author Contributions**

C-CC: study concept and design, acquisition of data, manuscript writing, critical revision of the manuscript for important intellectual content, and study supervision. P-CC: acquisition of data, analysis and interpretation, manuscript writing, and critical revision of the manuscript for important intellectual content. T-HC: critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

### **Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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