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Editorial

Severe acute respiratory syndrome coronavirus 2 (the cause of COVID 19) in different types of clinical specimens and implications for cytopathology specimen: An editorial review with recommendations

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EDITOR'S LETTER

Coronavirus disease 2019 (COVID-19) caused by "Severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) was first reported in China.[1] This is the third extremely pathogenic human coronavirus which has emerged recently after severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome (MERS) coronavirus. SARS-CoV-2 is mainly transmitted by person-to-person contact in community and health-care settings.[2] This pattern of spread demands large-scale and proactive measures to avoid further widespread dissemination. SARS-CoV-2 survives on contaminated dry surfaces and fomites, which facilitate hand to mucous membranes (of the mouth, nose, and eyes) spread.[3,4] This emphasizes the significance of in-depth knowledge about the perseverance of coronavirus on inanimate surfaces.[5] Various fixatives and biocidal agents are widely used in health-care settings including cytopathology laboratories which may impact (and help negate) the spread of this virus.[6,7]

The current review summarizes the available relevant data on this topic about cytopathology laboratory protocols and suggests precautions based on this data. These recommendations may change as new information comes to light. Each institution and laboratory has to adapt and adjust depending on local regulatory limitations. The recommendations suggested at the end of the review discussion should be considered with these things in mind.

At present, the diagnosis of COVID 19 is mostly being accomplished by performing real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) for SARS-CoV-2 on respiratory specimens such as nasopharyngeal swabs.[8] The primary mode of spread, which has led to the global pandemic, is the respiratory route. A report studying different types of clinical specimens from patients (most cases 1–3 days after hospital admission) detected a positive PCR test in about 1% (n = 307) of blood samples, suggesting the systemic nature of the disease in at least a portion of the cases.[9] This study also reported positive results in 29% (n = 153) of fecal samples.[9] Although tests based on PCR have been reported positive in non-respiratory specimens, it does equate with infectivity and so the non-respiratory route of viral transmission is possible but is not proven at this stage.

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As mentioned previously, the molecular test to detect SARS-CoV-2 is based on rRT-PCR. This test amplifies viral RNA in a patient's specimen for the detection of SARS-CoV-2 genetic material.[10] False negatives are possible due to multiple variables including simple technical errors, inadequate collection, improper handling, and shipping. Other possibilities for incorrect results include flawed key reagents in the kit.[11] One study comparing rRT-PCR with computerized tomography (CT), reports that the sensitivity of the test is only 70%.[12] Further compounding the issue, the sensitivity may be lower in some symptomatic cases due to a smaller viral load,[13] but usually the viral load is higher in the early stages of the disease. However, newer tests suggest higher sensitivity with the potential of false positives due to very high sensitivity and possible cross contaminations during the pandemic with the widespread presence of virus (at the level of collection of sample and later during the technical procedure).

As a result, even if the specimen in the cytopathology laboratory is not expected to be positive or even if the molecular test is negative for SARS-CoV-2, all of the specimens should be considered potentially positive. It is therefore mandatory to practice all the universal/standard precautions with basic protective measures while handling any biological specimen irrespective of SARS-CoV-2 status [Tables 1-3].[14-16] All cytology personnel should follow the basic protective measures against SARS-CoV-2 recommended by the World Health Organization (WHO) [Table 2].[16]

Although, appropriate disinfectants and precautions related to cytopathological/histological fixation and processing of samples during the current COVID 19 pandemic are not known, information can likely be extrapolated from other recent coronaviruses (e.g., SARS and MERS). Similar

Table 1: Standard precautions – Summary modified for cytopathology laboratory specimens based on the CDC guidelines.[14,15]

1. Ensure that the technologist use personal protective equipment (PPE) such as medical mask, gloves, eye protection, and a long-sleeved gown.
2. If the specimen with potential of aerosol-generation, such as squirting of aspirates from fine-needle aspiration biopsy procedure is being processed, the personnel should wear at least the protective mask such as NIOSH certified N95, an EU standard FFP2, or the equivalent.
3. All personnel involved in handling and transporting the specimens should be trained for safely handling the process, including spill decontamination methods.
4. Transport the primary specimen container with the patient's label in a leak-proof secondary containers, such as sealable plastic biohazard specimen bag with properly filled laboratory requisition.
5. Adhere to all biosafety practices including transport precautions (6c) depending on the pathophysiology of the organism being considered.
6. Preferably transport fresh, unfixed specimens by hand, and DO NOT ship the specimen with pneumatic-tube systems.
7. Each specimen must be clearly labeled with at least two patient identifiers including full name and date of birth with other details with specific warnings as applicable (e.g., suspected or confirmed SARS-CoV-2 virus) on the form. Let the laboratory know immediately that such a specimen is on the way.

Table 2: Summary of the WHO-recommended basic protective measures.[16]

a. Wash your hands frequently with soap and water counting up to 20 (approx. 20 s).
b. Maintain social distancing and maintain at least 1 m (3 ft) distance between yourself and anyone to avoid droplet/microparticle infection due to coughing, sneezing, and even talking.[36,37]
c. Avoid touching face (eyes, nose, and mouth) is the most important component as final personal protection. Studies showed that rate of unknowingly touching the face is up to 15–23/h.[38,39] The most probable mode of getting infection is from many inanimate surfaces [Table 4].
d. If you are sick with fever, cough, or difficulty breathing, seek medical advice early and stay informed to follow updated advice by your health-care provider and official resources.

Table 3: Summary of the Interim Laboratory Biosafety Guidelines from the CDC for the specimens suspected for or positive for SARS-CoV-2.[32]

1. Follow standard precautions when handling clinical specimens, all of which may contain potentially infectious materials mentioned in Table 1.
2. Any technique which may generate aerosols or droplets (e.g., squirting [instead of gently delivering as tiny drops] of the specimen through a needle, vertexing) should be avoided, but is required to be practiced then it should be executed in a certified Class II Biological Safety Cabinet (BSC). Similarly, for centrifugation suitable physical containment should be practiced with securely capped specimen tubes. Ideally, such procedures should also be performed in a Class II Biological Safety Cabinet.
3. Clean and disinfect the equipment(s) and work surfaces after specimens are processed using appropriate disinfectants which are used for disinfecting other respiratory pathogens, such as other human coronaviruses and seasonal influenza viruses.
4. Practice standard procedures applied for other respiratory pathogens, such as other human coronaviruses and seasonal influenza viruses.
5. If the diagnostic testing specimens are processed outside of a BSL-2 laboratory,[33] such as preparation of cytology direct smears, rinsing of FNAB aspirates for cell block, the Standard Precautions (similar to those mentioned under Table 1) should be practiced as a barrier between the specimen and personnel.[34]
6. Preparation and fixing of cytology smears should be performed under certified a Class II[35] Biological Safety Cabinet.

protocols should be effective to disinfect and inactivate SARS-CoV-2.[17] Thus, once the processing is complete as cytopathologic preparation and after formalin fixation and paraffin embedding for cell-blocks, SARS-CoV-2 if present in the specimen should be inactive.[17]

A study reported that aerosol and fomite transmission of SARS-CoV-2 is possible because the pathogen continues to be infectious for hours in aerosols and for days on surfaces.[18] The findings are comparable to those observed with SARS-CoV-1[19] providing useful information for the current mitigation efforts during this pandemic. The study observed that SARS-CoV-2 survives for up to 24 h on cardboard and plastic/stainless-steel surfaces up to 2–3 days.[18-20]

Many ostensibly clean surfaces and devices within a pathology department (including but not limited to doorknobs, tables and chairs, countertops, desks, keyboards, phones, microscopes, glass slides, slide trays/boards, on-site adequacy carts, door handles, light switches, toilets, faucets, and sinks) may be contaminated with the virus and should be considered potential fomites.[21] The duration for which SARS-CoV-2-like viruses have been reported to persist on various surfaces is listed in Table 4.[22]

Virus infectivity is defined as the ability of the virus to enter and colonize the host to replicate and reproduce itself with the potential to establish itself as an infection resulting in disease.[22] A previously suggested benchmark, a $\log_{10}$ viral reduction factor of more than 3, is considered as virucidal effectivity against viruses including coronaviruses on surfaces.[23] Formalin and ethanol used in low concentration (usually used as a preservative) decrease the viral infectivity to more than 3 $\log_{10}$.[22]

The effect of time and concentrations of various fixatives and biocidal agents on SARS and a few other viruses are summarized in Table 5. The table shows that for ethanol, 95%

Table 4: Persistence of coronaviruses and other viruses on different types of inanimate surfaces (modified from Ref #22).

Type of surface	Virus	Strain/isolate	Inoculum (viral titer)	Temperature	Persistence
Glass	SARS-CoV	P9	10^5	RT	4 d
	HCoV	229E	10^3	21°C	5 d
Plastic	SARS-CoV	HKU39849	10^5	22–25°C	<5 d
	MERS-CoV	HCoV-EMC/2012	10^5	20°C	48 h
				30°C	8–24 h
	SARS-CoV	P9	10^5	RT	4 d
	SARS-CoV	FFM1	10^7	RT	6–9 d
	HCoV	229E	10^7	RT	2–6 d
PVC plastic	HCoV	229E	10^3	21°C	5 d
Paper	SARS-CoV	P9	10^5	RT	4–5 d
	SARS-CoV	GVU6109	10^6	RT	24 h
			10^5	RT	3 h
			10^4	RT	<3 min
Surgical glove (latex)	HCoV	229E and OC43	5×10^3	21°C	<8 h
Disposable gown	SARS-CoV	GVU6109	10^6	RT	2 d
			10^5	RT	24 h
			10^4	RT	1 h
Aluminum	HCoV	229E and OC43	5×10^3	21°C	2–8 h
Metal	SARS-CoV	P9	10^5	RT	5 d
Steel	MERS-CoV	HCoV-EMC/2012	10^5	20°C	48 h
	TGEV	Unknown	10^6	4°C	>28 d
				20°C	3–28 d
				40°C	4–96 h
	MHV	Unknown	10^6	4°C	>28 d
				20°C	3–28 d
				40°C	4–96 h
	HCoV	229E	10^3	21°C	5 d
Silicon rubber	HCoV	229E	10^3	21°C	5 d
Wood	SARS-CoV	P9	10^5	21°C	4 d
Ceramic	HCoV	229E	10^3	21°C	5 d
Teflon	HCoV	229E	10^3	21°C	5 d

CCV: Canine coronavirus, HCoV: Human coronavirus, MHV: Mouse hepatitis virus, MERS-Cov: Middle East respiratory syndrome coronavirus, RT: Room temperature, SARS-CoV: Severe Acute respiratory syndrome coronavirus, TGEV: Transmissible gastroenteritis virus, d: Day(s), h: Hours(s), min: Minute(s)

Table 5: Inactivation of coronaviruses by different types of fixative and biocidal agents in suspension tests (modified from Ref #22).

Fixative/Biocidal agent	Concentration (%)	Virus	Strain/Isolate	Exposure time	Reduction of viral infectivity (log_{10})
Ethanol	95	SARS-CoV	FFM-1	30 s	>5.5
	85	SARS-CoV	FFM-1	30 s	>5.5
	80	SARS-CoV	FFM-1	30 s	>4.3
	80	SARS-CoV	EMC	30 s	>4.0
	78	SARS-CoV	FFM-1	30 s	>5.0
	70	MHV	MHV-2 and MHV-N	10 min	>3.9
	70	CCV	I-71	10 min	>3.3
Formaldehyde	1%	SARS-CoV	FFM-1	2 min	> 3.0
	0.7%	SARS-CoV	FFM-1	2 min	> 3.0
	0.7%	MHV		10 min	> 3.5
	0.7%	CCV	I-71	10 min	> 3.7
	0.009%	CCV		24 h	> 4.0
Glutardialdehyde	2.5%	SARS-CoV	Hanoi strain	5 min	> 4.0
	2.5%	SARS-CoV	FFM-1	2 min	> 4.0
2-Propanol	100%	SARS-CoV	FFM-1	30 s	>3.3
	75%	SARS-CoV	FFM-1	30 s	>4.0
	75%	MERS-CoV	EMC	30 s	>4.0
	70%	SARS-CoV	FFM-1	30 s	>3.3
	50%	MHV	MHV-2 & MHV-N	10 min	>3.7
	50%	CCV	I-71	10 min	>3.7
2-Propanol (a) and	a-45% & b-30%	SARS-CoV	FFM-1	30 s	>4.3
1-propanol (b)		SARS-CoV	FFM-1	30 s	>2.8
Sodium hypochlorite	0.21%	MHV	MHV-1	30 s	>4.0
	0.01%	MHV	MHV-2 & MHV-N	10 min	2.3-2.8
	0.01%	CCV	I-71	10 min	1.1
	0.001%	MHV	MHV-2 & MHV-N	10 min	0.3-0.6
	0.001%	CCV	I-71	10 min	0.9
Hydrogen peroxide	0.5%	HCoV	229E	1 min	> 4.0
Benzalkonium chloride	0.2%	HCoV	ATCC VR-759 (strain OC43)	10 min	0.0
	0.05%	MHV	MHV-2 & MHV-N	10 min	>3.7
	0.05%	CCV	I-71	10 min	>3.7
	0.00175%	CCV	S378	3 d	3.0
Povidone-iodine	7.5%	MERS-CoV	HCoV-EMC/2012	15 s	4.6
	4%	MERS-CoV	HCoV-EMC/2012	15 s	5.0
	1%	SARS-CoV	Hanoi strain	5 min	>4.0
	1%	SMES-CoV	HCoV-EMC/2012	15 s	4.3
	0.47%	SARS-CoV	Hanoi strain	1 min	3.8
	0.25%	SARS-CoV	Hanoi strain	1 min	>4.0
	0.23%	SARS-CoV	Hanoi strain	1 min	>4.0
	0.23%	SARS-CoV	FFM-1	15 s	>4.4
	0.23%	MERS-CoV	HCoV-EMC/2012	15 s	>4.4
Didecyldimethyl ammonium chloride	0.0025%	CCV	S378	3 d	> 4.0
Chlorhexidine	0.02%	MHV	MHV-2 & MHV-N	10 min	0.7-0.8
digluconate	0.02%	CCV	I-71	10 min	0.3

CCV: Canine coronavirus; HCoV: Human coronavirus; MHV: Mouse hepatitis virus; MERS-Cov: Middle East respiratory syndrome coronavirus; SARS-CoV: Severe acute respiratory syndrome coronavirus; min: Minute(s); s: Second(s)

ethanol with SARS-CoV (Isolate FFM-1) for 30 s reduces the viral infectivity to more than 5.5 log_{10}; 85% ethanol with SARS-CoV (Isolate FFM-1) for 30 s reduces the viral infectivity to more than 5.5 log_{10};[24] 80% ethanol with SARS-CoV (Isolate FFM-1) for 30 s reduces the viral infectivity to more than 4.3 log_{10};[24] 80% ethanol with MERS-CoV (Strain EMC) for 30 s reduces the viral infectivity to more than >4.0 log_{10};[25] 78% ethanol with SARS-CoV (Isolate FFM-1) for 30 s reduces

Table 6: Summary of measures recommended for routine cytopathology division (in addition to the *basic protective measures* summarized in Table 2) during SARS-CoV-2 pandemic.

Category/procedure	Measure(s) recommended***
General cytopathology division	Routine standard precautions [Table 1].[14,15] In the case of SARS-CoV-2 suspected or known case-avoid exposure to older personnel over 60 years and personnel with compromised immunity.
Cytoprep laboratory	Routine standard precautions [Table 1].[14,15] In cases suspected or positive for SARS-CoV-2 virus-perform the processing in certified Class II[35] Biological Safety Cabinet
FNAB procedure	To minimize the risk of exposure with rapid dissemination of the virus, the "on-site adequacy evaluation services" may be suspended during COVID 19 pandemic related suspension of elective procedures.** However, if FNAB has to be performed without on-site adequacy evaluation: • DO NOT squirt the specimen on the slide but drop gently on the slide without letting the specimen aerosolized. • Spread the specimen between two slides with two patient identifiers as routine to make direct smears* to be processed according to individual laboratory protocol(s). • If cell-block is indicated (discuss with associated pathologist), collect the needle rinses directly in 10% formalin (avoid any alcohol-based fixative to prevent potential compromisation of immunohistochemistry results[29] without contaminating the needle with formalin if that needle is to be re-used. • (Recommended to be performed under Class II[35] Biological Safety Cabinet for cases suspected or positive for SARS-CoV-2 virus). • Send all the material (direct smears in slide container(s) and appropriately labeled 10% formalin container with needle rinses for cell-block) in a leak-proof sealed (Ziploc) specimen bag with properly filled requisition form.
EUS-FNA procedure	Same guidelines as for "#3 FNAB procedure" with extra precaution, because the endoscopes travel through anatomical sites with the highest proportion of viruses in potentially positive cases, especially asymptomatic ones.
Respiratory specimens such as bronchoalveolar lavage, bronchial lavage, bronchial brush, tracheal brush, sputum, and others such as rare percutaneous sampling of lung lesions	Routine Standard precautions [Table 1].[14,15] In cases suspected or positive for SARS-CoV-2 virus-perform the processing in certified Class II[35] Biological Safety Cabinet.
Other body fluids such as peritoneal, pleural, pericardial, and other fluids (with potential positivity considered to be similar to blood positivity for SARS-CoV-2 virus) except urine	Routine Standard precautions [Table 1].[14,15] In cases suspected or positive for SARS-CoV-2 virus-perform the processing in certified Class II[35] Biological Safety Cabinet.
Cell-block	Routine Standard precautions [Table 1].[14,15] In cases suspected or positive for SARS-CoV-2 virus-perform the processing in certified Class II[35] Biological Safety Cabinet Fix the cell-block for at least 2 h (for 2–3 mm thick cell-block material, formalin diffuses at the rate of 1 mm/h and 10% formalin (3.7% formaldehyde) would inactivate the virus in the interior of the cell- block). Most of the lab protocols require more than 6 h (up to 72 h) fixation.[29]
All specimens received in 10% formalin and alcoholic fixatives	Routine Standard precautions [Table 1].[14,15] Concerning the surfaces of transport containers and paperwork, etc. In cases suspected or positive for SARS-CoV-2 virus-perform the processing in certified Class II[35] Biological Safety Cabinet.
Splitting of specimens	Depending on individual institutional/laboratory protocols, some labs may split the specimen between various subspecialty labs. In such cases, the microbiology lab should split the specimen under microbiology precautions and send most of the specimen to the cytopathology lab for further processing.

*Air-drying both the direct smears spread between slides allows staining the smears with Diff-Quik and Pap stain (as saline-rehydrated alcohol-fixed air-dried smears).[40] The saline used for rehydration should be discarded as biological waste similar to other biological specimens. The air-dried smears are easy to be transported to Cytoprep lab in slide containers, which should be sanitized/disinfected by rinsing in 95% for 2–5 min, if the slide containers are reused. **If on-site adequacy evaluation services are resumed, all personnel associated with performing the procedure and performing the onsite adequacy service should follow Routine Standard precautions [Table 1].[14,15] ***Modify as per local regulatory issues and geopolitical limitations based on general information reviewed in this editorial.

the viral infectivity to more than 5.0 $\log_{10}$;[26] 70% ethanol with MHV (Strains MHV-2 and MHV-N) for 10 min reduces the viral infectivity to more than >3.9 $\log_{10}$;[27] and 70% ethanol with CCV (Strain I-71) for 10 min reduces the viral infectivity to more than >3.3 $\log_{10}$.[27]

Similarly for formalin, 1% formaldehyde with SARS-CoV (Isolate FFM-1) for 2 min reduces the viral infectivity to more than >3.0 $\log_{10}$;[26] 0.7% formaldehyde with SARS-CoV (Isolate FFM-1) for 2 min reduces the viral infectivity to more than >3.0 $\log_{10}$;[26] 0.7% formaldehyde with MHV for 10 min reduces the viral infectivity to more than >3.5 $\log_{10}$;[27] 0.7% formaldehyde with CCV (Strain I-71) for 10 min reduces the viral infectivity to more than >3.7 $\log_{10}$;[27] and 0.009% formaldehyde with CCV for 24 h reduces the viral infectivity to more than >4.0 $\log_{10}$[28] [Table 5].

About 95% ethanol reduces the viral infectivity to more than 5.5 in 30 s and formaldehyde even in the concentration of 1% decreased the viral infectivity to more than 3 in 2 min [Table 5].[22] Various reagents such as ethanol and 10% formalin (3.7% formaldehyde) usually used in cytopathology processing at initial stages as fixative have virucidal activity.[22] Based on the aforementioned, SARS-CoV-2 in any specimen processed with routine fixatives in cytopathology should be inactivated [Table 5].[22,29]

The data presented thus far suggest that the susceptibility to infection follows the bell curve, with an increase in the severity of the disease with the higher mortality in members of the population over 50 years.[30,31] This observation should be considered while organizing cytology laboratory services, namely, the potential effect on the personnel associated with various cytology services in regard to their potential for SARS-CoV-2 exposure.

A summary of recommendations for procedure specific protocols in routine cytopathology is enumerated in Table 6. These guidelines are recommended in addition to the WHO basic protective measures at a personal level [Table 2].[16] The virus survives on various plastic/metal surfaces, cardboards, disposable gowns, and paper surfaces for a significant amount of time [Table 5].[18,19,21,22,38] To avoid dissemination of the virus, it is recommended that on-site adequacy services should be canceled or postponed during the pandemic. In case a particular procedure is deemed necessary to be performed, the on-site personnel should follow the guidelines generated based on the information discussed in this review and summarized in Table 6.

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COMPETING INTERESTS STATEMENT BY ALL AUTHORS

The authors declare that they have no competing interests.

AUTHORSHIP STATEMENT BY ALL AUTHORS

All authors of this article declare that we qualify for authorship as defined by ICMJE http://www.icmje.org/#author. Each author has participated sufficiently in the work and takes public responsibility for appropriate portions of the content of this article. VS conceived the idea, conducted literature review, and wrote the manuscript. All (VS, NF, and LL) critically reviewed the article. All authors read and approved the final manuscript.

LIST OF ABBREVIATIONS (IN ALPHABETIC ORDER)

BSC: Biological safety cabinet
BSL-2: Biosafety level 2
CCV: Canine coronavirus
CDC: Centers for Disease Control and Prevention
COVID-19: Coronavirus Disease 2019
CT: Computerized tomography
D: day(s)
FNAB: Fine needle aspiration biopsy
H: hours(s)
HcoV: Human coronavirus

MERS-CoV: Middle East Respiratory Syndrome Coronavirus
MHV: Mouse hepatitis virus
min: minute(s)
PCR: polymerase chain reaction
PPE: Personal protective equipment
rRT-PCR: Real-time reverse transcriptase–PCR
s: second(s)
SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
TGEV: transmissible gastroenteritis virus
WHO: World Health Organization

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