Health Technology Update

CADTH

A newsletter on new and emerging health care technologies in Canada

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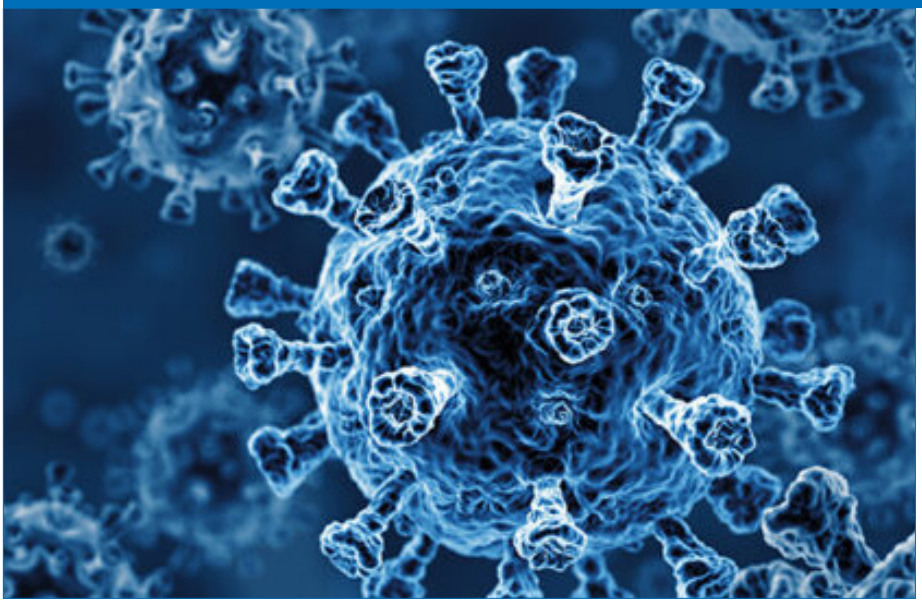

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Informing Decision-Makers About Emerging Medical Technologies

This issue of *Health Technology Update* features brief summaries of information on a broad range of medical technologies — from a saliva-based test for COVID-19 to salt-based surfaces to help stop the spread of viruses. These technologies were identified through the CADTH Horizon Scanning Service as topics potentially of interest to Canadian health care decision-makers.

TECHNOLOGIES IN THIS ISSUE

FEEDBACK

Have you heard of a new health technology you think will have an impact on health care in Canada?

Please let us know!

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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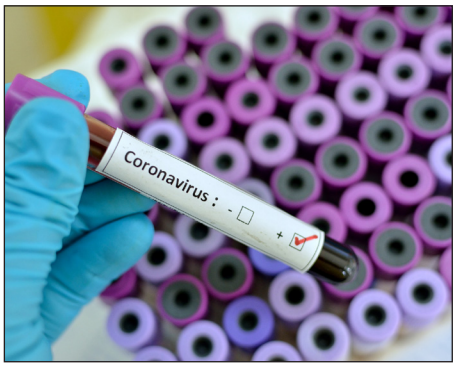

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Saliva-Based Tests to Detect Active Severe Acute Respiratory Syndrome Coronavirus 2 Infection

New saliva-based tests for severe acute respiratory syndrome coronavirus 2 are more comfortable for individuals being tested and may pose less risk to health care workers than alternative tests.

Nasopharyngeal, deep nasal, and throat swabs are commonly used to collect the sample needed for testing to detect diseases of the upper respiratory tract like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1-3] However, widespread testing using traditional nasopharyngeal swabs has proven to be challenging given shortages of critical testing supplies such as swabs and reagents, as well as shortages of personal protective equipment for the health care practitioners who perform the tests.[4,5] In addition to these shortages, nasopharyngeal, deep nasal, and throat swabs are difficult to perform and can be quite uncomfortable for the individual undergoing testing.[6]

Saliva-based tests for SARS-CoV-2 are an emerging alternative to traditional testing. These tests require different supplies than the standard swabs, which could help ease medical supply shortages. Additionally, some saliva tests can be self-collected, so they may result in less risk of exposure to the SARS-CoV-2 pathogen for health care workers. They are also easier to obtain and less invasive than standard nasopharyngeal, deep nasal, and throat swabs. If proven to be effective and accurate, these tests could be a component of the robust testing strategy necessary for controlling the COVID-19 pandemic.

How It Works

There are two saliva-based or oral fluid-based tests that have received Emergency Use Authorization (EUA) from the FDA to diagnose active SARS-CoV-2 infection: the Rutgers Clinical Genomics Laboratory TaqPath SARS-CoV-2 Assay (the Rutgers test) and the Curative-Korva SARS-CoV-2 Assay (the Curative-Korva test).[7,8] They are both molecular reverse transcriptase polymerase chain reaction tests that detect the virus's genetic material in a specimen provided by an individual deemed by their health care provider to be at risk for COVID-19.[7,8]

The first saliva test to receive EUA by the FDA was the Rutgers test.[7] This test can be used to detect SARS-CoV-2 in multiple sample types, including a saliva sample. The assay is designed as a diagnostic test to detect ribonucleic acid from SARS-CoV-2 in respiratory droplets from patients with suspected COVID-19.[7] For saliva sample testing, the sample must be collected using the Spectrum Solutions LLC SDNA-1000 Saliva Collection Device.[7] Under an update to the original EUA, the saliva specimen can be self-collected.[9] To collect the sample, the individual spits directly into the collection device. The sample is then stored and transported to the Rutgers clinical genomics laboratory for testing.[7] Testing of the specimen must take place within 48 hours of collection.[7]

The Curative-Korva test also received EUA by the FDA.[8] The test can be used to detect SARS-CoV-2 in respiratory specimens from a variety of sample types, including oral fluid specimens.[8] Unlike the Rutgers test, the Curative-Korva test requires the oral fluid specimens to be collected using a swab. In general, the collection of samples for swab-based oral fluid tests usually involves having an individual cough several times before swabbing the inside of both cheeks for several seconds.[10] Although the specimens can be self-collected according to the EUA, the specimens must be collected under the supervision of a trained health care worker.[8] The swab containing the specimen is then sealed in a tube for transportation to KorvaLabs, where it can be tested.

Who Might Benefit?

The benefits of these types of tests vary depending on how they are deployed. As samples can be self-collected, the tests do not require the same degree of direct contact between a health care worker and an individual suspected of having COVID-19 that a traditional nasopharyngeal swab requires. This is a potential benefit to health care workers, as they would have less risk of exposure to the SARS-CoV-2 pathogen.[11]

Another group that might benefit from these new saliva-based tests would be individuals who are symptomatic for COVID-19 and require testing for a diagnosis. Increased availability of tests could result in increased testing capacity, which may lead to shorter waiting times for testing. Furthermore, providing a saliva sample is more comfortable and less invasive than a nasopharyngeal swab, which might decrease the stress experienced by an individual being tested for the pathogen that causes COVID-19.[12,13]

Saliva-based tests for SARS-CoV-2 are an emerging alternative to traditional testing.

Finally, if these new saliva-based tests are proven to be accurate, the additional tests could contribute to an increased capacity for widespread testing. The ability to test large groups of people with or without COVID-19 symptoms is a necessary part of a public health strategy to manage the pandemic.[14]

Availability in Canada

At the time of this report, neither the Rutgers test or the Curative-Korva test are authorized for use in Canada as a testing device for use against COVID-19,[15] nor does either test appear on the list of applications received by Health Canada for diagnostic devices for use against COVID-19.[16]

What Does It Cost?

The Rutgers test is available in New Jersey at a cost of between US$65 and US$100 per test.[17] No cost information about the Curative-Korva test was found.

The availability of multiple types of diagnostic tests for SARS-CoV-2 might help to reduce costs for the health care system, as multiple tests could reduce shortages of testing supplies, which may prevent surge pricing. Additionally, tests that allow for self-collection could contribute to reduced costs, as some do not require the presence of a trained health care worker for specimen collection.[2,3]

Current Practice

In Canada, diagnostic testing for SARS-CoV-2 has been done by the National Microbiology Laboratory in close collaboration with provincial and territorial public health laboratories.[19] Criteria for testing varies by jurisdiction and has changed over time. While nasopharyngeal swabs are often used for diagnosing active SARS-CoV-2 infection, testing may be performed in a variety of ways and could be based on several specimen types such as nasopharyngeal swab, deep nasal swab, throat swab, or sputum sample.[2,3]

What Is the Evidence?

Testing for an Individual Diagnosis

Saliva samples can be used to detect diseases of the upper respiratory tract and scientists have theorized that saliva-based tests might be useful for detecting SARS-CoV-2.[6,11,20-25] There are some published studies that report on the detection of the SARS-CoV-2 pathogen in saliva and oral fluids;[13,26-28] however, due to the novelty of the pathogen, the body of research is limited and study populations are very small. It should be noted that while SARS-CoV-2 can be detected in saliva, there is evidence that suggests that different specimen types from the same individual can yield conflicting results.[13,26,29] In addition to these studies, there are several ongoing clinical trials to evaluate tests that use saliva to detect SARS-CoV-2.[30-34]

Due to the nature of the COVID-19 pandemic, there is a push to make research about the topic accessible. In some cases, publishers have made information about COVID-19 accessible by not putting this research behind a paywall. Another way research results are more accessible during the pandemic is by posting online before peer review. While posting before peer review can speed up the time frame for access to emerging COVID-19 research, it may also have the effect of compromising the quality of the research. There are several preliminary reports on testing saliva for SARS-CoV-2 infection that have not yet been peer reviewed.[35-38] The early results of these non–peer reviewed studies support the use of saliva-based testing to detect SARS-CoV-2; however, it is important to note that many of these studies report that different types of tests had conflicting results. The same individual might test both positive and negative for SARS-CoV-2 based on different specimen types, and none of the sample types was able to detect all instances of SARS-CoV-2.[36,37]

Screening of the General Population

There is no universally agreed upon gold standard or reference test for diagnosing the SARS-CoV-2 pathogen because it is so new.[39,40] It is difficult to establish the diagnostic accuracy of any new test without a reference standard test. While information about diagnostic accuracy and disease prevalence are linked, when the prevalence of a disease is low, even small imperfections in test accuracy lead to substantial numbers of misdiagnoses.[14] In order to discover the prevalence of COVID-19 cases in a population, it is necessary to test a random sample of both symptomatic and asymptomatic people.[14] Critically, the saliva tests that are available are expressly meant to be used to test individuals who are symptomatic.[7,8] More data is needed to establish a reference test or gold standard for the diagnosis of COVID-19, saliva-based or otherwise, in order to establish prevalence of COVID-19 in the population. One protocol was identified that proposes to validate home specimen collection methods for SARS-CoV-2.[5] This research is intended to contribute to the evidence base to guide public health responses to the COVID-19 pandemic.[5]

Issues to Consider

Scalability

The saliva-based tests that have received FDA EUA are proprietary, and all specimens collected for each test must be processed by the lab that created the assay. This could make scaling up difficult, as the number of tests would be limited by how many tests an individual lab can process each day.[7,8]

Comparing Test Results

There is emerging evidence that different types of samples collected may yield different results in the same individual being tested.[13,29] This finding makes it difficult to directly compare test results of different tests.[14]

When to Test

There is evidence emerging that viral loads of SARS-CoV-2 in saliva are highest during the initial phase of infection (the first week) and decline over time.[28] This is consistent with other data that suggests pharyngeal virus shedding is highest in the first week of symptoms.[41] It is therefore likely important to use these types of tests in the initial stage of infection.

Related Developments

In addition to the previously mentioned saliva-based tests, there are at-home tests for COVID-19 emerging. The nasal swab test created by Laboratory Corporation of America (LabCorp) is an at-home nasal swab test that can be self-administered.[42] The Pixel test was the first at-home test granted EUA by the FDA.[42] The Pixel is a reverse transcriptase polymerase chain reaction test that detects genetic material from the SARS-CoV-2 virus in upper and lower respiratory specimens.[42] As the Pixel test can be used with a home specimen collection method, this test does not need to be performed in the presence of a health care worker. Like the Rutgers test and the Curative-Korva test, the Pixel test is designed to diagnose an individual whose health care provider suspects they have contracted COVID-19.[42] The test is performed by collecting a nasal swab from just inside both nostrils.[43] After the specimen has been collected, the swab is placed in a collection tube and stored in a biohazard specimen bag for transportation to LabCorp for testing.[43] The testing kits by LabCorp cost US$119.[18]

Looking Ahead

There is information emerging that shows that saliva tests may be useful for making an individual COVID-19 diagnosis. Saliva-based tests may result in safer and more comfortable testing for health care workers and those being tested. However, more research is needed about the diagnostic accuracy of these tests in order for them to be deployed for widespread testing of the population.

Author: Sarah Jones

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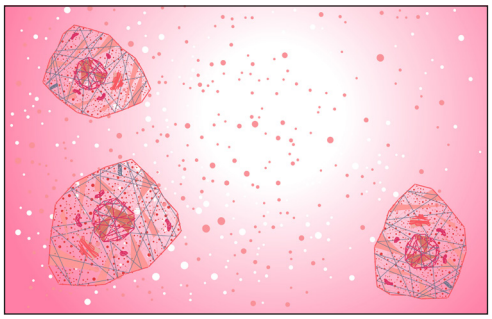

iStock Photo: Cytokine storm

Blood Purification Using Cytokine Adsorbers to Reduce Cytokine Storm in Severe COVID-19 Illness

Severe coronavirus disease 2019 (COVID-19) illness has been associated with high levels of cytokines — small proteins in the blood that both promote and control inflammation.[1-3] Instead of enhancing the immune response to the infection, excessive levels of cytokines may result in a "cytokine storm" that can lead to systemic inflammatory response syndrome, acute respiratory distress syndrome, acute kidney injury, multiple organ dysfunction, and death.[1,4-6]

Cytokine storms have also been associated with severe illness in past outbreaks of infectious respiratory viruses, including the 1918 influenza pandemic, H5N1 influenza (avian influenza), Middle Eastern Respiratory Syndrome (MERS), and severe acute respiratory distress (SARS).[1,3,7,8]

Technologies that filter the blood to reduce levels of cytokines — sometimes also referred to as therapeutic apheresis — may help control the inflammatory response and improve the treatment of critically ill patients with COVID-19.

How It Works

Various types of extracorporeal blood purification systems are available. All of these use a blood pump to remove a patient's blood, separate blood components or remove particular substances (such as toxins or antibodies), and return the blood to the patient.[9,10] Blood purification is used in addition to standard care.[11] The focus of this article is on hemoperfusion and hemofiltration devices, but other techniques, such as plasmapheresis (replacing plasma with fresh frozen plasma or albumin), may also be used.[7,12]

- **Hemoperfusion** — use of a sorbent cartridge or column to remove certain agents from the blood.[6,7] Examples of hemoperfusion devices include: PMX (also known as Toraymyxin), CytoSorb, Jafron HA380, and the D2000 Adsorption Cartridge.
- **Hemofiltration** — use of an adsorptive filtering membrane to remove inflammatory mediators.[7] An example of a hemofiltration membrane device is oXiris (an AN69 membrane).

The **PMX (Toraymyxin)** cartridge consists of composite woven polystyrene fibres coated with polymyxin B.[12] The polymyxin B has electrochemical properties that remove endotoxins from the blood. Removal of endotoxins also reduces the release of cytokines and other inflammatory agents.[13,14] The manufacturer's recommended protocol for hemoperfusion is two two-hour procedures over a 24-hour period.[14]

The **CytoSorb** cartridge is filled with biocompatible polymer beads about the size of grains of salt. The pores in each bead are sized to allow larger components, such as blood cells, to pass around the beads and smaller components, such as electrolytes, to pass through. However, hydrophobic substances, such as cytokines, are trapped inside the beads and removed from the bloodstream.[15] Blood may be continuously recirculated through the filtering system until a replacement cartridge is needed (for up to 24 hours). The manufacturer recommends an initial three-day-course of therapy for patients with severe COVID-19, with a cartridge change every 12 hours on day one and every 24 hours on days two and three.[16] The higher the concentration of cytokines in the blood, the faster cytokine levels are reduced.[11,12] After the third day of treatment, patients should be assessed to determine whether there are signs of benefit, in which case CytoSorb treatment can continue until their conditions are stable. If no benefit is apparent at 72 hours, the manufacturer suggests that the treatment should be discontinued.[16]

The **Jafron** adsorption cartridge consists of a "neutral, macroporous resin," with a large surface area that adsorbs inflammatory agents, including cytokines.[17] Instructions for the Jafron hemoperfusion cartridges recommend a three-day-course of therapy, with two treatments (cartridges) in the first 24 hours and one treatment on days two and three.[17,18]

The **D2000** plasma **Adsorption Cartridge** consists of a proprietary blend of resins intended to remove cytokines, toxins, and metabolic wastes from plasma

in patients with acute respiratory distress syndrome, sepsis, liver failure, drug overdoses, and other conditions that involve an inflammatory response.[19] According to the FDA Emergency Use Authorization notification, the D2000 adsorbents can remove statistically significant levels of proinflammatory cytokines.[20]

The **oXiris** filter consists of a multi-layer, high adsorption, polymer membrane (AN69) that can adsorb substances such as certain toxins, as well as cytokines, and excess fluid.[1,21,22] OXiris also has a heparin coating that allows it to be used without anticoagulation in patients at increased risk of bleeding.[1]

With some devices, such as the CytoSorb and the Jafron devices, the filter cartridge can be used with standard hospital equipment, such as dialysis equipment, hemoperfusion pumps, continuous renal replacement therapy, or extracorporeal membrane oxygenation.[15-17] Other devices are designed for use with certain systems; for example, oXiris is intended to be used only with Baxter blood purification units (PrisMax and Prismaflex).[21] The D2000 cartridge can be used with validated existing plasma separation platforms, including plasma exchange and continuous renal replacement therapy systems; however, under the FDA Emergency Use Authorization in the treatment of patients with COVID-19, it is being used exclusively with the Spectra Optia Apheresis System.[19,23]

Who Might Benefit?

Based on early reports from China, approximately 80% of people who contract COVID-19 will have only mild to moderate symptoms of the disease, while about 14% will experience more severe illness, and an estimated 6% will be critically ill, requiring intensive care.[24] Reports on clinical experience with COVID-19 in China indicate from 5% to 10% of intensive care patients received extracorporeal therapies, such as continuous renal replacement, hemoadsorption, and hemoperfusion.[25]

Critically ill patients with COVID-19 have a cascade of immune system reactions, which include the release of cytokines into the blood.[26] Sometimes referred to as systemic inflammatory response or cytokine release syndrome, or a "cytokine storm," this response is associated with elevated levels of inflammatory agents, such as tumour necrosis factor alpha and interleukins.[26-32]

In some patients, the immune response becomes overwhelming, attacking healthy tissue, organs (such as the lungs, liver, and kidneys), and blood cells.[28,29] This may cause respiratory failure, organ failure, and shock.[11] One US estimate is that 20% to 30% of patients with severe COVID-19 and respiratory symptoms may experience a cytokine storm.[29,33] Reducing levels of cytokines may lower the inflammatory response and, potentially, reduce the risk of morbidity and death.[11,33]

Availability in Canada

- The PMX (Toraymyxin) hemoperfusion cartridge (Spectral Medical Inc./Baxter) received an Interim Order from Health Canada, allowing its use for patients with COVID-19 who have acute respiratory failure and hypotensive shock.[13] PMX (Toraymyxin) initially received a Health Canada medical device licence in 2003.[34]
- The oXiris Blood Purification Filter (Baxter) received a Health Canada medical device licence in 2009.[34] In April 2020, oXiris received US FDA Emergency Use Authorization for use in reducing proinflammatory cytokine levels in patients with severe COVID-19 who are receiving intensive care, including those receiving continuous renal replacement therapy.[21]

Other systems commercially available elsewhere but not currently in Canada include:

- CytoSorb (CytoSorbents Inc.) — has a CE mark for use in [11,33] and received US FDA Emergency Use Authorization for the emergency treatment of COVID-19.[16] According to the manufacturer, more than 750 COVID-19 patients have been treated with CytoSorb in China, Germany, and Italy.[35] CytoSorbents has prepared a rationale for using CytoSorb therapy in critically ill COVID-19 patients where elevated cytokines are present.[36]
- Jafron HA380 hemoperfusion cartridge (Jafron Biomedical Co.) — is available in China and has a CE mark for use in Europe, including the use for COVID-19 rescue therapy.[4,11,17]
- The Spectra Optia Apheresis System (Terumbo BCT. Inc.) — received a Health Canada medical device licence in 2008.[34] The US FDA issued an Emergency Use Authorization (for use during the COVID-19 pandemic) for the Spectra Optia Apheresis System with the D2000 Adsorption Cartridge(Marker Therapeutics AG).[23] The D2000 Adsorption Cartridge has a CE mark for use in Europe.[11] The D2000 cartridge does not currently have a Health Canada medical device licence, but the manufacturer plans to apply for one in the near future (Sam Haddaway, Marker Therapeutics AG, Zug, Switzerland: personal communication, Jun 2, 2020).

What Does It Cost?

Spectral Medical recently announced the PMX (Toraymyxin) cartridges will be provided free of charge for COVID-19 patients.[13]

The 2020 UK NICE–National Institute for Health and Care Excellence briefing on cytokine adsorption devices estimated the cost of the CytoSorb cartridge as £920 per single-use cartridge.[11,33] A three-day treatment with CytoSorb, as recommended by the manufacturer, would require four cartridges.[16]

The Health Technology Wales scoping and the NICE briefing both cited the cost of the Jafron HA380 hemoperfusion cartridge as £450 for each single-use cartridge.[4,11] The manufacturer also recommends a three-day course of therapy, with two treatments (cartridges) used in the first 24 hours and one cartridge treatment each on days two and three.[17]

The D2000 column costs US$2,000 per column, and patients typically receive two to five columns administered once per day for two to three hours per treatment (Sam Haddaway: personal communication, Jun 2, 2020).

Current Practice

Recent Canadian and international guidelines on therapies for COVID-19 have not included blood purification technologies.[11,37-39] However, some treatment protocols from clinicians in China and Europe have included the use of cytokine adsorption technologies to manage a cytokine storm.[4,6,40]

Cytokine storms can happen rapidly and clinicians are beginning to test for indicators of this condition using tests for blood ferritin, elevated C-reactive protein, and biomarkers of acute kidney injury.[6,29] A recent letter to *The Lancet* highlighted the importance of looking for signs of cytokine storm, including laboratory test results to assess the "Hscore" (indicators of inflammation), and considering appropriate immunomodulatory treatments.[41]

A recent consensus statement from critical care specialists in China proposes a four-step process for the use of blood purification treatments in patients with severe COVID-19.[42] The steps are:

- **Assess whether the patient requires blood purification.** Patients who may benefit from blood purification include those with kidney disorders, SARS, sepsis, liver failure, or multiple organ dysfunction syndrome.
- **Prescribe the type of blood purification treatment.** This depends on the treatment goal. For example, to remove inflammatory mediators, recommended treatment modalities are various modes of hemofiltration, blood or plasma perfusion, adsorption, or continuous plasma filtration. For acute liver failure, however, plasma exchange is recommended.
- **Patient monitoring and treatment adjustment.** For example, monitoring vital signs, fluids, electrolytes, anticoagulation, and lung imaging.
- **Determining when to discontinue blood purification therapy.** The authors note that there is no consensus for this step, but, in general, to discontinue blood purification therapy when vital signs, fluids, urine output, and inflammatory response have improved.[42]

What Is the Evidence?

A 2020 Medtech innovation briefing by NICE in the UK appraised the evidence on cytokine adsorption for the treatment of respiratory failure in patients with COVID-19.[11] The evidence reviewed consisted of one observational study and numerous case reports (a total of 56 patients with COVID-19). Most of the evidence included was published on the manufacturers' websites and consisted of non-peer-reviewed case reports and one observational study.[11] The briefing concluded that, based on limited, low-quality evidence, cytokine adsorption devices can be used safely as an adjunctive therapy to reduce levels of cytokines, which may improve lung function.[11] However, the varying treatment protocols used and the quality of the available studies limit the generalizability of these conclusions.[11]

A 2020 scoping report from Health Technology Wales found no systematic reviews on the use of cytokine adsorbers in people with COVID-19.[4] However, it found two systematic reviews on blood purification treatments for patients with sepsis.[7,43] Based on low-quality evidence, blood purification to remove endotoxins appeared to improve mortality, but whether this might also benefit patients with COVID-19 is not yet known.[4]

The Health Technology Wales scoping report included information from an unpublished manuscript provided by the manufacturer of the Jafron device.[4] This reported on 47 patients with severe COVID-19 in a non-randomized study in China.[4] In the study, 26 of the patients received the hemoadsorption treatment in addition to standard treatment. In the hemoadsorption group, at 72 hours, blood cytokine levels were lower and oxygen levels were improved. The mortality rate at 28 days was lower in the hemoadsorption group (15.38%) compared to the patients who received only standard treatment (47.62%).[4] Additional evidence on the Jafron adsorption cartridges was included in the more recent NICE briefing.[11] The additional evidence was from mainly unpublished case reports of 21 patients treated in five different centres.[11]

A brief letter to the editor reported on three critically ill patients with COVID-19 in China who received blood purification to reduce cytokine storm.[5] Two of the patients received treatment with the oXiris filter system. Although one of the patients died, the authors speculate that an earlier reduction of cytokine storm through blood purification may be beneficial for selected patients.[5]

Safety

Blood purification technologies are somewhat unselective and they may inadvertently remove beneficial agents — such as antibiotics, anticoagulants, or other drugs — and nutrients from the blood.[6,12,15,18,40] As patients with COVID-19 are at increased risk for blood clots, ensuring anticoagulation therapy is adequate will be important.[11] Changing the timing of medication administration (to after blood purification treatment) or increasing the drug dosage accordingly may resolve this issue.[15]

A 2019 systematic review of blood purification techniques in patients with sepsis cautioned that the "unspecific removal of cytokines" may also negatively affect the healthy immune response and could potentially result in worse patient outcomes.[7]

The CytoSorb FDA documents note that little information is available on the potential removal of antiviral drugs during the treatment process.[16] However, because of their larger size, the removal of drugs such as tocilizumab, other biologics, and convalescent plasma antibodies is not expected to occur.[16]

Rarely, patients may experience an allergic reaction or anaphylaxis that requires

treatment.[16] Other potential complications could be related to the catheter and insertion of the blood line, or from the use of anticoagulants.[6,12] In addition, the overuse of blood filtration could exacerbate hypotension and decrease cardiac output.[6]

Issues to Consider

Individuals have different "inflammatory phenotypes" and levels of cytokines in their blood.[6] Currently, it is not possible to identify which severely ill patients could benefit from blood purification treatments.[6,44]

The optimal timing for initiating blood purification is not yet known, although some authors suggest that early application in severely ill patients may be most effective.[1,2,6,12]

UK specialists' comments on the use of cytokine adsorption (for patients with sepsis and with COVID-19) noted that, potentially, the use of cytokine adsorption could increase intensive care unit capacity and reduce costs (for example, if this treatment reduced the length of hospital stay, and reduced the use of vasopressor drugs or biological therapies). However, evidence to support this is not yet available.[11,33] A 2018 review of extracorporeal blood purification in sepsis also noted that evidence on the impact on mortality and length of intensive care unit or hospital stay is both "limited and somewhat conflicting."[12]

Related Developments

The Health Technology Wales scoping report noted an ongoing German study of cytokine hemoadsorption for patients with severe COVID-19 pneumonia.[4,45] This study is estimated to be completed in November 2020.[45] Several other clinical trials have been initiated.[11] For example, in Spain, a pilot study began in March 2020 to assess cytokine filtration in COVID-19 patients with acute respiratory distress syndrome.[46] The D2000 Adsorption Cartridge FDA Emergency Use Authorization allows Marker Therapeutics AG and Terumo BCT to treat up to 2,000 patients with COVID-19 at up to 15 US sites. The first patients have been treated. In parallel, the companies are collecting patient data under an approved institutional review board protocol to support an approval submission to the FDA (Sam Haddaway: personal communication, Jun 9, 2020).[47,48]

A Canadian study at the Lawson Health Research Institute in London, Ontario, is assessing the use of slow (or sustained), low-efficiency daily dialysis and a leucocyte modulation device (L-MOD) to reduce inflammation in patients with severe respiratory distress syndrome due to COVID-19.[49] This study is expected to be completed in January 2021.[49]

CytoSorbents' website notes that a new version of CytoSorb — CytoSorb-XL — is in development.[50] In addition to cytokine removal, CytoSorb-XL will remove endotoxins, for example, for use in the treatment of gram-negative bacterial infections.[50]

Drug therapies currently used for other conditions, such as monoclonal antibodies for immune suppression (for example, tocilizumab [Actemra]), are also being investigated as drugs that may block IL-6 and other proinflammatory cytokines in COVID-19 patients.[27,29,31,32,40] Currently, in a phase III clinical trial, the Janus kinase inhibitor (brand name Jakafi) is also intended to reduce cytokine storm in COVID-19 patients with severe pneumonia.[41,51]

An extracorporeal blood filtration device with US Emergency Use Authorization for patients with severe COVID-19, the Seraph 100 Microbind Affinity Blood Filter (ExThera Medical Corporation) removes viruses and bacteria from the blood, thereby also reducing inflammatory mediators.[52]

Researchers in China have developed an artificial liver blood purification system that is also intended to remove cytokines in critically ill patients with COVID-19.[3]

Therapeutic plasma exchange is also being explored for the treatment of patients with severe COVID-19 illness. This is another mechanism for removing cytokines and one that is sometimes used in combination with convalescent plasma therapy.[53-55]

Looking Ahead

Currently, there is limited evidence on the use of blood purification using cytokine adsorption in patients with severe COVID-19 illness.[4,6,11] As with many treatments for COVID-19, most of the available evidence is based on earlier studies in patients with other infectious respiratory diseases and sepsis.[4,12] Whether this evidence is generalizable to COVID-19 patients is not yet clear.[4] Hopefully, trials that are now underway will help to address these evidence gaps.

Author: Leigh-Ann Topfer

See references on page 16.

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iStock Photo: Different types of salt

Salt-Based Technologies to Help Stop the Spread of the Coronavirus

Canadian and international researchers are examining whether coating masks, air filters, and high-touch surfaces with sodium chloride (salt) might be an effective option to help prevent the spread of severe acute respiratory syndrome coronavirus 2 and other viruses and bacteria. This article is an update to the CADTH Health Technology Update article "Antimicrobial Compressed Salt for High-Touch Surfaces" published in 2017.[1] The update explores new developments in the use of salt coatings that may help in response to the COVID-19 pandemic.

How It Works

Antimicrobial surfaces work in one of three ways:[2]

- by changing the surface texture, thereby reducing the ability of bacteria to adhere
- by including an antimicrobial additive in the surface that kills or slows the growth of bacteria
- by using a material with natural antimicrobial properties, such as copper, silver, zinc, or, in this case, salt.

Salt is a natural substance that inhibits the growth of bacteria — partly through dehydration, and also by upsetting the enzyme activity of microorganisms, damaging their DNA.[3] Salt is essential to human and animal life, and has a long history of use in food preservation and flavouring, in pharmaceuticals, in home remedies (for example, as a mouthwash and wound cleanser), and in agriculture and industrial products.[4]

The theory behind salt's potential ability to inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is that when droplets containing virus particles come into contact with a salt-coated surface, the water in the droplets dissolves some of the salt. When the water evaporates, the salt recrystalizes and the jagged salt crystals pierce the virus membrane and kill it.[5] This method has been tested against influenza viruses[6] and bacteria.[7-9] Salt is therefore being investigated as an antimicrobial for use on high-touch surfaces (Outbreaker Solutions technologies),[10] facial masks[6] and air filter[7] materials, as well as a soaking solution for household materials and cloth masks.[9]

Who Might Benefit?

Potentially, these items could be useful to health care providers and anyone working in or visiting environments where they are at an increased risk of exposure to SARS-CoV-2 or other microbial pathogens. Antimicrobial surfaces able to mitigate the spread of the virus could be beneficial in health care and other public spaces. As the population is encouraged to wear masks in public spaces to decrease transmission, increasing the effectiveness of masks to prevent virus transmission could be a positive development in preventive public health interventions.

Availability in Canada

Currently, none of these salt-based and salt-coated technologies for the prevention of infection are commercially available in Canada or elsewhere.

Outbreaker Solutions has created surfaces made out of compressed sodium chloride that can be used in high-touch areas, like door-push plates, bed rails, toilet handles, and taps.[10] Pilot evaluations of Outbreaker products have been carried out at several Alberta facilities.[11] Currently, Outbreaker is using a grant received through the Roche Canada COVID-19 Open Innovation Challenge to continue with its research and test the effectiveness of compressed sodium chloride surfaces specifically against SARS-CoV-2.[12]

A University of Alberta research team is aiming to create face masks using salt-coated filter material and hope the masks will be ready for market in 12 to 18 months.[5] However, their effectiveness against SARS-CoV-2 has yet to be tested.[5,13]

A research team from Boston University examined whether soaking paper towel in saltwater could help increase its ability to filter virus particles.[9] The use of salt-soaked household materials is theoretically possible at any time; however, this method has not been vetted or recommended by any federal or public health authorities.[9]

What Does It Cost?

The potential price of these products in Canada is not yet known, but as the raw material to build or coat the surface (salt) is inexpensive, the price is likely to be accessible.[1]

Current Practice

There are currently no existing surfaces or masks that are known to kill SARS-CoV-2. While there is no evidence of surfaces that

can halt or inhibit the growth of SARS-CoV-2, Health Canada has compiled a list of hard-surface disinfectants with evidence against the virus.[14]

What Is the Evidence?

Compressed Salt Surfaces

As reported in the earlier CADTH article,[1] Outbreaker products are made up of over 99% compressed sodium chloride — similar to salt licks manufactured for livestock.[8,11] Laboratory results posted by the manufacturer report that Outbreaker technology reduced levels of surface bacteria by 90% to 100% one minute after contact compared to a stainless steel surface.[15] However, the test method used (contact agar) does not allow for the detection of a 100% decrease in the viable count and the test method's limit of detection was not stated.[1]

A 2016 pilot study assessed the time it took for compressed sodium chloride to inactivate methicillin-resistant *Staphylococcus aureus* (MRSA), relative to a stainless steel control surface and compared to a copper surface inactivation of MRSA, in a laboratory setting.[8] The compressed sodium chloride surface reduced MRSA contamination by 85% in the first 20 seconds and by 94% within the first 60 seconds compared to 30% to 35% (at 20 seconds) and 71% to 73% (at 60 seconds) for copper surfaces.[8] Outbreaker is currently examining whether the salt surfaces might have a similar impact on SARS-CoV-2.[12]

Salt-Coated Filter Materials

Quan et al.[6] studied the use of salt-coated filter material for surgical masks and tested them against influenza viruses. The results of the study suggested that the salt-coated filters were able to deactivate aerosolized influenza virus.[6] A team from the University of Alberta is hoping to use this type of salt-coated material to develop face masks that can effectively protect against SARS-CoV-2, which has a similar morphology to other tested viruses,[5] and is waiting on a grant to fund its continuing research (Dr. Hyo-Jick Choi, Department of Chemical and Materials Engineering, University of Alberta: personal communication, May 2020).

Jeong et al.[7] evaluated the antimicrobial performance of air filters coated by natural sea salt particles against two types of bacterial bioaerosols. The study results indicated that bacterial growth was inhibited by the salt-coated air filters (maximum reduction rate: 98%).[7] The authors found that the filters' ability to kill the bacteria increased with the amount of natural sea salt particles deposited on the filter.[7]

Salt-Soaked Household Materials

Based on the work by Quan et al.,[6] a research team in Boston soaked filter materials in a saltwater solution to determine whether this method of applying salt to materials would also be able to prevent the penetration of virus-sized particles.[9] Household paper towel, laboratory paper towel, and the middle filter layer of a surgical mask were soaked in a saltwater solution for five minutes and mixed to ensure that all surfaces were saturated.[9] The materials were lightly squeezed to remove excess solution and then placed on a flat surface to air dry overnight.[9] Using immunofluorescence images, the researchers determined that the materials were able to filter out particles the size of viruses in droplet testing and found similar results in both the surgical mask and paper towel. They also found that there was a decrease in bacterial growth beneath pieces of salt-soaked materials that were treated with *E. coli*.[9] The authors suggested that saltwater-treated kitchen paper towel could potentially be used as an inexpensive and easily accessible additional layer of protection for people wearing homemade cloth masks or for health care workers who need to extend the life of their personal protective equipment, or PPE.[9]

No mention was made about whether the addition of salt to these surfaces and filters might result in the degradation of the materials over time.

Safety

Sodium chloride is considered to be a chemical of low concern for human risk.[16] However, if exposed to high temperatures, it can produce a vapour that is an eye irritant and high doses of ingested salt can be toxic to humans and animals.[16]

Issues to Consider

As indicated in the previous article,[1] there are a number of particular issues to consider with antimicrobial coatings including:[2]

- which surfaces should be antimicrobial
- whether the coating will be active continuously or only for a period of time and, if the latter, how often the surface or coating will need to be replaced
- what cleaning and disinfecting solutions can be used (some antimicrobial surfaces will not work while covered in cleanser or will be deactivated by the solutions)
- how durable the surface is
- what benefits and disadvantages the surface has (e.g., environmental or safety concerns, or risk for the development of antimicrobial resistance).[2,17]

None of these studies have been done using SARS-CoV-2, as samples are not available to researchers outside of biohazard laboratories.[9] Researchers have made assumptions about the effectiveness of these technologies and techniques based on research done with influenza and other viruses that are of a similar viral size as SARS-CoV-2.[5]

Related Developments

Copper surfaces are another antimicrobial surface option that can reduce bacterial contamination.[18,19] A systematic review found the few studies that measured the impact of copper surfaces on health care-associated infections were flawed (at high risk for bias) and that the reduction in bacterial levels was likely "modest."[20] Moreover, copper surfaces appear to need a longer period of time to take effect against microorganisms and they are expensive relative to standard

fixtures.[8,18,21] The authors of a letter to the editor of *The New England Journal of Medicine* reported they had found no viable SARS-CoV-2 on copper surfaces after four hours of contact.[22]

Various other general antimicrobial surfaces are available or in development, including anti-adhesive surfaces — coatings impregnated with antimicrobial or photosensitive agents, such as titanium dioxide.[23] Researchers are testing a continuously active antimicrobial surface disinfectant technology on a variety of pathogens, including SARS-CoV-2.[24]

Looking Ahead

Research is underway examining the role salt might play in helping to manage the spread of SARS-CoV-2. The virus is still not fully understood, and the evidence is constantly changing and evolving. Information about new technologies and innovations to help manage the current global pandemic are likely to continue to be produced at a rapid pace.

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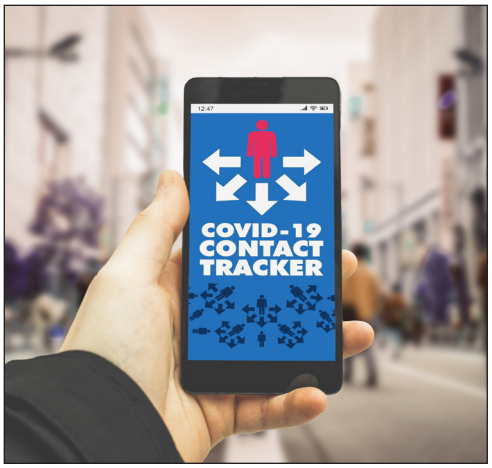

iStock Photo: Tracking COVID-19 app on smartphone software in crowd of people with Bluetooth notification.

Contact Tracing Apps to Identify Potential Exposure to SARS-CoV-2

Contact tracing is a public health intervention that prevents the spread of infectious diseases like COVID-19 by identifying, educating, and monitoring individuals who have been in close contact with infected persons.[1] Traditionally, contact tracing is performed manually, which is time-consuming and resource-intensive. New digital contact tracing tools that use smartphone apps to complement existing methods are emerging and may be a technological aide in the prevention of new SARS-CoV-2 (the virus that causes COVID-19) infections.[2] Use of contact tracing apps is being explored by governments across Canada.[3-5]

How It Works

Contact tracing apps use technologies in a smartphone to determine where the users have been or with whom they have been in contact.[6] While contract tracing apps that use a smartphone's GPS to track movement or require the user to produce a Quick Response, or QR, barcode to show they are healthy have been developed or are in use globally, apps that use Bluetooth are emerging as a preferred and less intrusive option for public health authorities.[6]

Alberta's ABTraceTogether is one app that uses Bluetooth.[7] Users turn on the app whenever they leave their home.[8] The app uses Bluetooth to detect other phones using the app and exchanges unique encrypted codes between the devices.[8] The app measures how close and how long the user is in "contact" with other devices to help public health officials determine with whom the user has been in close contact (within two metres).[8] If the user later tests positive for COVID-19, they are contacted by public health officials and asked to voluntarily upload the app's encrypted data from the last 21 days to Alberta Health Services.[8] Public health officials then use the encrypted data to identify probable close contacts and reach out to the contacts using the phone number provided when setting up the app.[8]

To help standardize the development and approval of apps, Google and Apple created a set of requirements governments must meet when developing contact tracing apps for Android smartphones and iPhones.[9] Groups in the European Union and at the Massachusetts Institute of Technology have also released design recommendations and standards.[10,11]

Who Might Benefit?

Contact tracing apps are intended to complement existing contact tracing systems.[2,11] They are not intended to replace existing methods of contact tracing, nor are they to be used in the absence of these methods.[2,11] Rather, the apps are designed to augment the ability of public health officials to identify potential cases of COVID-19 and take appropriate follow-up actions to prevent further spread of the disease.[2,11]

The apps are designed to augment the ability of public health officials to identify potential cases of COVID-19.

Availability in Canada

As of May 7, 2020, only Alberta has begun implementing a contact tracing app for COVID-19 — ABTraceTogether.[7] Officials in New Brunswick and Newfoundland and Labrador have also publicly begun exploring the use of contact tracing apps.[4,5]

Globally, contact tracing apps have been developed for use in Australia, China, Egypt, India, Israel, Singapore, and South Korea.[2,6,11,12]

What Does It Cost?

Our literature search did not identify any information about the costs of developing contact tracing apps or costs associated with their implementation, nor information about the impact contact tracing apps may have on the health care costs associated with COVID-19.

Digital contact tracing using smartphone apps is thought to be less costly compared with traditional contact tracing methods, in part due to their ability to automate manual processes and to scale up in large populations.[11] However, it is uncertain whether contact tracing apps are effective without being used with traditional contact tracing methods.[2]

In Alberta, ABTraceTogether is free to download and use for iPhone and Android smartphones.[7] The app requires a smartphone with an active data plan.[8]

Current Practice

The current standard for identifying individuals who have potentially been exposed to SARS-CoV-2 is traditional or manual contact tracing.[11,13] Traditional contact tracing uses public health service employees or volunteers to conduct phone or community outreach.[11] Traditional contact tracing processes for potential SARS-CoV-2 exposure may vary by jurisdiction[11] but follow the three general steps described by the WHO:[14]

- identify an infected individual
- list all the people the infected individual has encountered
- monitor and follow up with these contacts for symptoms, and testing for infection.

In the case of SARS-CoV-2, traditional contact tracing processes appear most concerned with people who have been in "close contact" with an infected person and encourage these contacts to self-isolate regardless of symptoms.[11]

Limitations to traditional contact tracing methods include the time and human resources required to effectively identify contacts and the ability of individuals to remember where they have been and with whom they have been in contact — up to 14 days for SARS-CoV-2 exposure.[1,11] The quick rate at which SARS-CoV-2 spreads before signs or symptoms appear also poses challenges to traditional contact tracing approaches.[13]

A CADTH Rapid Response (published on May 1, 2020) found no evidence-based guidelines, systematic reviews, or health technology assessments for contact tracing for potential exposure to SARS-CoV-2.[15]

What Is the Evidence?

Our literature search identified two rapid reviews[2,11] and one scoping review (pre-publication, not yet peer-reviewed)[16] about contact tracing apps or digital contact tracing to identify potential exposure to SARS-CoV-2.

The first rapid review (published on April 20, 2020) found insufficient evidence to support the use of digital contact tracing.[2] The authors recommended that readiness for implementing a contact tracing app take into consideration evidence of a need for the technology, availability of widespread testing for the public, the ability of the app to be used consistently by 60% of the population, and an understanding of how the app uses the data it acquires.[2] The authors also found that a contract tracing app would only be effective if it is used in addition to manual contact tracing and if it is based on a confirmed diagnostic test for SARS-CoV-2, as opposed to the self-reporting of symptoms.[2]

The second rapid review (published on April 24, 2020), while largely descriptive, found little published literature on contact tracing apps at that time.[11] The authors also noted that a lack of available testing may be slowing the potential impact of contact tracing apps.[11]

Authors of the scoping review found there was no evidence on uptake and engagement with apps, and a "dearth of evidence" on barriers and facilitators to uptake and engagement.[16]

Safety

No evidence on the safety of contact tracing apps was identified in our literature search.

Issues to Consider

Several important issues about the use of contact tracing apps have been raised.[11,12] Contact tracing is predicated on widespread availability of accurate testing.[11] Additional issues to consider when implementing this technology include accuracy, uptake, data privacy and security, and health equity.[2,11,12]

Accuracy

The accuracy of contact tracing apps that use Bluetooth has been raised as a potential impediment to their effectiveness.[11] Bluetooth has a range of 10 metres to 30 metres and it is possible that contact tracing apps may connect with devices outside the "close contact" range of two metres. Bluetooth signals can also penetrate walls, and older smartphones may have difficulty determining the user's orientation to other people.[11] Each of these issues creates the potential for false-positive contacts.[11] Accuracy may also be impacted should a fractured market of different contact tracing apps emerge.[2]

Uptake

The successful application of contact tracing apps also depends on widespread, consistent use in the population.[2,5] As of May 5, 2020, only approximately 3% of Alberta's population had downloaded ABTraceTogether below the estimated 56% to 60% necessary for contact tracing apps to be effective.[2,5] Greater adoption may be driven by public trust and confidence, which may in turn be driven by transparent rules and limits for the collection, use, and destruction of data, independent oversight, and legislation.[2] The mandatory use of contact tracing apps may be necessary to achieve a sufficient level of uptake but may in turn discourage their use.[2,13]

Data Privacy and Security

Concern has been expressed that, given the extraordinary nature of the COVID-19 pandemic, government actions such as implementing contact tracing apps may have significant impact on the privacy and fundamental rights of individuals.[12,13,17] To balance the right to privacy with the need to prevent the spread of COVID-19, the case for implementing contact tracing apps could be strengthened by minimizing any privacy intrusions, ensuring high standards for data security oversight and protection, and being transparent about how the data collected is used.[13] To this end, recommendations for data privacy and security for contact tracing apps have been produced by groups around the world.[17,18]

Steps taken to protect user privacy include an announcement from Apple and Google that the companies intend to allow only public health authorities to develop contact tracing apps and will bar the use of GPS in any apps developed for their platforms.[19]

Health Equity

Implementing contact tracing apps that require the user to have a smartphone and know how to use a smartphone may exacerbate existing issues of health equity, particularly in groups at higher risk, such as older adults and people with chronic conditions who may be less likely to use the app.[2,11,16]

Related Developments

Other strategies being explored to improve the ability to trace potential cases of SARS-CoV-2 include:[1,11]

- training non-public health staff and volunteers to perform contact tracing
- repurposing existing resources such as call centres or hotlines
- enhancing traditional contact tracing methods using digital tools for data collection.

Looking Ahead

Digital contact tracing is only one part of an holistic public health system.[2]

Success of digital technologies in the COVID-19 context, including contact tracing apps, may depend on the ability of governments to demonstrate transparency and foster public trust through regulation and oversight in the development, deployment, and phasing out of these solutions.[2]

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Saliva-Based Tests (page 3)

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