

IN THIS ISSUE: COVID-19 OUTBREAK IN WASHOE COUNTY (5)–CLINICAL PRESENTATIONS

COVID-19 OUTBREAK IN WASHOE COUNTY (5)

Clinical Presentations - From an Asymptomatic Infection to Attacking the Entire Body

Introduction

The Washoe County Health District (WCHD) reported the first case of COVID-19 on March 5, 2020. As of May 28, a total of 1,514 cases have been reported, which corresponds to an incidence rate of 321 cases per 100,000 population. See following table for an overview of morbidity, mortality, and testing of COVID-19 outbreak from the national, statewide, and local perspective.

Characterization	US	NV	Washoe
No. Cases	1,698,523	8,208	1,514
Cases per 100,000 population	517	266	321
Number of Deaths	100,446	406	55
Case Fatality Ratio (%)	5.914	4.946	3.633
Deaths per 100,000 population	30.61	13.18	11.66
Number of tests	15,646,041	151,938	23,932
Tests per 1000 population	47.67	49.33	50.76

Data as of 5/28/2020

The epidemiological investigations and contact tracing are resource intensive and ongoing. Daily updates can be found at <https://covid19washoe.com>. WCHD has published a series of Epi-News on COVID-19. Topics included in the previously published Epi-News are: epidemiological findings from the first 115 cases, therapeutic options, asymptomatic infection and its role in transmission, as well as laboratory testing. Those issues can be found at [www.TinyURL.com/WashoeEpiNews](http://www.TinyURL.com/WashoeEpiNews). This newsletter will focus on clinical presentations of COVID-19 on an in-depth level.

Incubation Period

The incubation period for COVID-19 is thought to extend to 14 days, with a median time of 4-5 days from exposure to symptom onset. One study reported that 97.5% of persons with COVID-19 who develop symptoms will do so within 11.5 days of infection.<sup>i</sup>

Major Clinical Presentation

Signs and Symptoms	CDC Publication	Washoe Cases
Fever	83-99%	~90%
Cough	59-82%	77%
Fatigue	44-70%	66%
Anorexia	40-84%	32%
Dyspnea	31-40%	40%
Sputum production	28-33%	Not Available
Myalgia	11-35%	68%
New loss of taste or smell	NA	69%

The signs and symptoms of COVID-19 present at illness onset vary, but over the course of the disease, most persons with COVID-19 will experience the major symptoms in the above table.<sup>ii</sup>

People with COVID-19 have had a wide range of symptoms – ranging from asymptomatic infection, mild symptoms to severe illness. The mechanisms behind the variety of presentations are not well understood.

On April 17, 2020, the *Science* magazine published an article entitled "How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes".<sup>iii</sup> The following section includes some important contents extracted from this article and local statistics are combined in order to understand what systems can be impacted and how they can be attacked. In fact, "this disease can attack almost anything in the body with devastating consequences", says cardiologist Harlan Krumholz of Yale University and Yale-New Haven Hospital, who is leading multiple efforts to gather clinical data on COVID-19.

Understanding the "rampage" could help the doctors on the front lines treat the fraction of infected people who become desperately and sometimes mysteriously ill.

- Does a dangerous, newly observed tendency to blood clotting transform some mild cases into life-threatening emergencies?
- Is an overzealous immune response behind the worst cases, suggesting treatment with immune-suppressing drugs could help?
- What explains the startlingly low blood oxygen that some physicians are reporting in patients who nonetheless are not gasping for breath?

"Taking a systems approach may be beneficial as we start thinking about therapies," says Nilam Mangalmurti, a pulmonary intensivist at the Hospital of the University of Pennsylvania.

The Infection Begins Respiratory System

When SARS-CoV-2, the causative virus of COVID-19, is expelled from an infected person to others, the

virus enters the nose and throat of exposed persons. The cells in the lining of nose and throat are rich in a cell-surface receptor called angiotensin-converting enzyme 2 (ACE2). ACE2 normally helps regulate blood pressure, however these ACE2 enzymes are a primary binding site for SARS-CoV-2. Throughout the body, the presence of ACE2 marks tissues which are vulnerable to infection. Once inside, the virus hijacks the cell's machinery, making myriad copies of itself and invading new cells. An estimated 35% (20-50%) of people may not experience any symptoms.<sup>iv</sup> Some may develop fever, dry cough, sore throat, loss of smell and taste, or head and body aches. If the immune system does not beat back the virus, the virus will travel deeper to alveoli in the lungs that are also rich in ACE2 receptors which impacts oxygen supply. Others develop acute respiratory distress syndrome (ARDS). Often these patients end up on ventilators and some die. Autopsies show their alveoli became stuffed with fluid, white blood cells, mucus, and the detritus of destroyed lung cells.

**Local statistics:** fever or feverish ~90%, cough 77%, myalgia 68%, fatigue/malaise 66%, chills rigors 64%, sore throat 55%, dyspnea 40%, coryza 34%, congestion 11%, diagnosed pneumonia 9%, severe ARDS 7%, joint pain 2%.

### **An Invader's Impact – Cytokine Storm**

Some clinicians suspect the driving force in many gravely ill patients' downhill trajectories is a disastrous overreaction of the immune system known as a "cytokine storm," which other viral infections are known to trigger. Cytokines are chemical signaling molecules that guide a healthy immune response; but in a cytokine storm, levels of certain cytokines soar far beyond what's needed, and immune cells start to attack healthy tissues. Blood vessels leak, blood pressure drops, clots form, and catastrophic organ failure can ensue.

### **Striking the heart – Cardiovascular System**

An Italian woman aged 53 years went to the ER with classic heart attack symptoms and ended up diagnosed with COVID-19. Published articles show that 20% of COVID-19 patients of hospitalized patients have heart damage. A Dutch study reported that 38% had blood that clotted abnormally and almost one-third already had clots. Blood clots can break apart and lodge in the lungs and cause pulmonary embolism, one of direct causes of death. Clots from arteries can also lodge in the brain, causing stroke. Many patients have "dramatically" high levels of D-dimer, a byproduct of blood clots. *"The more we look, the more likely it becomes that*

*blood clots are a major player in the disease severity and mortality from COVID-19,"* (Behnood Bikdeli, Columbia University Irving Medical Center)

If COVID-19 targets blood vessels, that could also help explain why patients with pre-existing damage to those vessels, for example from diabetes and high blood pressure, face higher risk of serious disease. Scientists are struggling to understand exactly what causes the cardiovascular damage. The virus may directly attack the lining of the heart and blood vessels, which, like the nose and alveoli, are rich in ACE2 receptors. Or perhaps lack of oxygen, due to the chaos in the lungs, damages blood vessels. Or a cytokine storm could ravage the heart as it does other organs.

**Local statistics** shows that 14% of cases presented cardiovascular diseases.

### **Buffeting the brain – Central Nervous System**

Another striking set of symptoms in COVID-19 patients centers on the brain and central nervous system. Neurologists were needed to assess 5% to 10% of coronavirus patients at one hospital. Seizures, loss of consciousness, strokes, loss of sense of smell, infection depresses the brain stem reflex that senses oxygen starvation. This might explain why some patients are not gasping for air, despite dangerously low blood oxygen levels. The virus can penetrate the central nervous system based on a case study in Japan. ACE2 receptors are present in the neural cortex and brain stem. A cytokine storm could cause brain swelling, and the blood's exaggerated tendency to clot could trigger strokes. Sherry Chou, a neurologist with the University of Pittsburgh Medical Center, speculates about a possible invasion route: through the nose, then upward and through the olfactory bulb—explaining reports of a loss of smell—which connects to the brain.

**Local statistics:** headache 74%, new loss of taste and/or smell 69%, neuro-disability 7%, other neurological symptoms such as depression, dizziness, lighted head 6%, numbness or burning skin 1%.

### **Reaching the Gut – Gastrointestinal System**

The new coronavirus, like its cousin SARS, can infect the lining of the lower digestive tract, where the crucial ACE2 receptors are abundant. Viral RNA has been found in as many as 53% of sampled patients' stool samples. CDC says that based on experiences

with SARS and with the virus that causes Middle East respiratory syndrome (MERS), another dangerous cousin of the new coronavirus, the risk from fecal transmission is probably low.

Other reports suggest liver damage: More than half of COVID-19 patients hospitalized in two Chinese centers had elevated levels of enzymes indicating injury to the liver or bile ducts. But several experts told *Science* that direct viral invasion isn't likely the culprit. They say other events in a failing body, like drugs or an immune system in overdrive, are more likely driving the liver damage.

**Local statistics** shows higher percentage of gastrointestinal symptoms than national average: diarrhea 45%, anorexia 32%, nausea 30%, abdominal pain 28%, constipation 7%, bloating 4%.

### Multiple battlefields – Renal System and Other Systems

The need for dialysis may be because the kidneys, abundantly endowed with ACE2 receptors, present another viral target. Viral particles were identified in electron micrographs of kidneys from autopsies in one study, suggesting a direct viral attack. But kidney injury may also be collateral damage. Ventilators boost the risk of kidney damage, as do antiviral compounds including Remdesivir, which is being deployed experimentally in COVID-19 patients. Cytokine storms also can dramatically reduce blood flow to the kidney, causing often-fatal damage. And pre-existing diseases like diabetes can increase the chances of kidney injury.

In addition, up to one-third of hospitalized patients develop conjunctivitis—pink, watery eyes—although it's not clear that the virus directly invades the eye. As previously stated, infection may also lead to blood vessel constriction. Reports are emerging of ischemia in the fingers and toes—a reduction in blood flow that can lead to swollen, painful digits and tissue death. The fortunate thing is that the reported cases of pseudo-chilblains coming out of Europe, the Middle East, and the United States fit more into the benign pattern described by researchers in Spain.<sup>v</sup> Anecdotally, most young patients with pseudo-chilblains seem to follow a benign course, often remaining otherwise asymptomatic.

<sup>i</sup> <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>

<sup>ii</sup> <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>

**Local statistics:** pink eye or conjunctivitis or eye pain 4%, rash 4%, ear pain 3%, COVID toes 1%.

Signs/Symptoms of COVID-19 cases, Washoe County, NV				
Signs and Symptoms	Yes	No	Total	Percent
Cough	573	169	742	77%
Headache	531	186	717	74%
New loss of taste and/or smell	267	NA	386	69%
Myalgia	487	229	716	68%
Fatigue/Malaise	395	199	594	66%
Chills Rigors	459	261	720	64%
Sore Throat	391	322	713	55%
Feverish (subjective)	360	301	661	54%
Diarrhea	321	397	718	45%
Dyspnea	285	432	717	40%
Fever (>=100.4 F)	251	405	656	38%
Coryza	223	435	658	34%
Anorexia	151	318	469	32%
Nausea	213	497	710	30%
Abdominal pain	197	505	702	28%
Cardiovascular disease	40	241	281	14%
Congestion	44	NA	386	11%
Pneumonia	73	706	779	9%
Abnormal Chest X Ray	64	694	758	8%
Constipation	28	NA	386	7%
Neuro-Disability	20	259	279	7%
Severe ARDS	19	250	269	7%
Dizzy, lighted head, depression	25	NA	386	6%
Rash	16	NA	386	4%
Eye pain, pink eye, conjunctivitis	15	NA	386	4%
Bloating, Gas	15	NA	386	4%
Ear pain	12	NA	386	3%
Chest Pain/Tightness	10	NA	386	3%
Joint pain	7	NA	386	2%
Sweating	6	NA	386	2%
COVID Toes	3	NA	386	1%
Numbness, burning	3	NA	386	1%
Data source: NBS as of 5/26/2020				

**The map of the devastation that COVID-19 can inflict on the body is still just a sketch. It will take years of painstaking research to sharpen the picture of its reach, and the cascade of cardiovascular and immune effects it might set in motion. (*Science*, 4/17/2020)**

<sup>iii</sup> <https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes>

<sup>iv</sup> <https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html>

<sup>v</sup> <https://www.medscape.com/viewarticle/930180>