Could the Mystery of Severe COVID-19 be Solved by Mast Cell Activation Syndrome?

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Abstract

A key mystery about the COVID-19 pandemic is why the disease presents as mild or asymptomatic in the majority of the population, while presenting as severe or even life-threatening in approximately 15% of the population. An additional mystery is why COVID-19 generally presents more severely in adults than in children. A common underlying disease, Mast Cell Activation Syndrome (MCAS), may provide vital clues to solving these mysteries. MCAS is thought to be present in approximately 17% of the population, but most individuals who have MCAS remain undiagnosed. Our hypothesis is that many – perhaps even most – severe cases of COVID-19 can be attributed to pre-existing Mast Cell Activation Disease in those patients.

Severe cases of COVID-19 are characterized by multi-system inflammation, caused by the body's overreaction to the virus. Many times, it is this overreaction, not the virus itself, which becomes life-threatening. Mast cells which catastrophically over-activate in response to the virus could very well explain this phenomenon.

Mast cells are tissue-resident immune system cells which act as the "sentries" of the immune system. They maintain numerous receptors on their surface, including histamine receptors as well as receptors to detect invading pathogens (PAMPS). When an invading pathogen (such as a virus) is detected, the mast cells release a variety of chemical mediators in a process called degranulation. These mediators both facilitate and coordinate the immune response, as well as provide signals to potentially every system in the body. In a normal individual, this degranulation process is well regulated and proportional to the detected threat. In an individual with MCAS, defective mast cells activate out of proportion with the need to defend the body from the perceived danger. This hyperreactivity can result in inappropriate continued activation even after the infection has passed. In our model, this underlying hyperreactivity is the "gun", and the virus which causes COVID-19 merely "pulls the trigger". In MCAS patients, some of the mast cell's surface receptors (which typically function like an on/off switch) can become stuck in the "on" position. When this happens, MCAS patients can severely react to trace amounts of triggers which would be undetectable to normal individuals. When stuck in this "on" position, the mast cells will continue to release their proinflammatory mediators. This inappropriate activation in turn leads to the presentation of a multi-system inflammatory disease, affecting multiple, diverse systems in the body.

Mast cells are central to the body's immune response – as long as mast cells are activating in response to a perceived viral threat, they will both signal for more white blood cells to migrate to the infection site, and also cause the nearby tissue to expand in order to allow sufficient room for this migration to occur. Furthermore, the histamine released by mast cells activates the receptors on neighboring mast cells, causing them to degranulate, which then activates their neighboring mast cells in turn. In this manner, a cascading activation effect can sweep through all nearby mast cells, causing them to continually degranulate and release their mediators into the body. These inflammatory "cytokine storms", which are characteristic in severe COVID-19, can affect such disparate systems as the lungs, the skin, and the blood. As a result, some of the unusual symptoms of the disease, such as blood clotting, skin rashes, and lung failure can all be explained by an underlying case of MCAS which becomes triggered by COVID-19.

Further evidence for our hypothesis is seen in the correlation of the risk factors for severe COVID-19 with the most common symptoms of MCAS. High blood pressure is the primary comorbidity for COVID-19 patients who go on to develop Acute Respiratory Distress Syndrome. High blood pressure is also the second most common comorbidity seen in MCAS. Heartburn, the most common comorbidity seen in MCAS, has also been found to be highly prevalent in hospitalized COVID-19 patients. Severe COVID-19 is also correlated with a number of other

inflammatory diseases, which are also comorbid with MCAS. The symptoms of the recently described Multisystem Inflammatory Syndrome in Children also fit an underlying diagnosis of MCAS extremely well.

MCAS is frequently a lifelong, progressive disease, which tends to "step up" in severity over the patient's lifetime. In the event our hypothesis is correct, this feature also describes why it is far more common to see severe COVID-19 in adults than in children. In our model, adults are far more likely to have severe MCAS, so they are far more likely to have severe COVID-19.

Some of the treatments which are showing promise for severe COVID-19 – such as the drugs tocilizumab, famotidine, and vitamin D – are exactly the drugs one would expect to be effective if an underlying case of MCAS is present. The early evidence which shows famotidine (an H2 antihistamine sold under the brand name Pepcid) as a potentially effective treatment for severe COVID-19 is particularly striking. Two separate studies have found that famotidine use is associated with a 50% reduction in severe COVID-19 outcomes. Famotidine is a common over the counter medication which has no known anti-viral properties. However, it is commonly used to treat MCAS by suppressing overly active mast cells. If additional famotidine studies continue to substantiate the 50% reduction in severe COVID-19 outcomes, then it becomes imperative to determine the drug's mechanism of action. In our model, famotidine is doing in COVID-19 patients what it is known to do in MCAS patients – block the histamine cascades, stabilize the patients mast cells and prevent the patient's immune system from inappropriately overreacting.

If an underlying case of MCAS is indeed the "gun" and the virus that causes COVID-19 merely "pulls the trigger", then awareness of this connection is vital to proper treatment. This awareness can then lead to the necessary actions for better outcomes and a lower mortality rate during the COVID-19 pandemic.

Mast Cell Activation Syndrome affects a large minority of the population, but it is a disease that most people have never heard of. If MCAS is indeed the key to the COVID-19 mystery, there may be no better time than this moment to raise the profile of this important disease.

Hypothesis

Our hypothesis is that many – perhaps even most – severe cases of COVID-19 can be attributed to pre-existing Mast Cell Activation Disease in those patients. In our model, the patient's underlying Mast Cell Disease is the "gun", and the virus that causes COVID-19 merely "pulls the trigger". Our goal is to provide a summary of this hypothesis, and to stimulate a discussion among health care providers and the public about this potential connection.

COVID-19 Background

COVID-19 is a disease caused by new coronavirus, SARS-CoV-2, which was first identified in 2019. COVID-19 presents a wide variety of symptoms, including fever; cough; shortness of breath or difficulty breathing; chills; repeating shaking; muscle pain; headache; sore throat; and loss of taste or smell. [1] While most individuals with COVID-19 experience mild or moderate symptoms, other individuals present with a life-threatening form of the disease. As of the time of this writing, no unified explanation for COVID-19's many mysteries has been determined.

Mast Cell Activation Syndrome (MCAS) Background

[1] CDC. *Symptoms of Coronavirus*. Retrieved April 2020, from https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

Mast Cell Activation Syndrome (MCAS), is a disorder of the mast cells. Mast cells are tissue-resident immune system cells, which serve as the "first line of defense" in detecting potential threats and mobilizing the body's immune system to counteract those threats. Mast Cell Activation Syndrome occurs when the body's mast cells inappropriately overreact to potential threats, which can lead to a cascade of symptoms across many different systems. MCAS is both common and is also uncommonly diagnosed.[2] A significant minority – perhaps 17% [3] – of the population may have MCAS, but most are likely unaware of its presence.

Mast Cells primarily act as the "sentries" of the immune system. As such, Mast Cells are found primarily in the interfaces between the body and the outside world – the nose, throat, eyes, skin, lungs, and gastrointestinal tract. Mast cells manufacture and store thousands of distinct chemical mediators (including specialized mediators called "cytokines") within pockets or "granules" inside the mast cells. These mediators serve as messages, instructing cells all over the body to change their behavior.

Mast Cells also maintain many different types of receptors embedded in their cell walls. These receptors are the sensors which detect a variety of chemical "triggers", including allergy antibodies, as well as bacterial and viral infections. [4] When these receptors are triggered by the presence of a potential threat, the mast cell releases a set of unique, stimulus-specific mediators in a process called degranulation. As such, when the mast cell "sentry" detects a potential threat, it has the ability through its mediators to affect the function of potentially every organ system in the body, often without causing abnormalities in routine laboratory or radiologic testing.[5] These organ system changes in turn can lead to the rapid onset of multiple, diverse symptoms that can span the body, including heart-related symptoms such as rapid pulse, low blood pressure, and passing out; skin-related symptoms such as rashes, hives, redness, and itching; blood related symptoms such as excessive bleeding or excessive clotting; GI-tract symptoms such as heartburn and diarrhea; and lung-related symptoms, such as wheezing and shortness of breath, as well as many others.[6]

In the case of normal mast cells, this process of mast cell activation and degranulation is highly regulated and proportional to the perceived threat. In the case of Mast Cell Activation Syndrome, some number of the body's mast cells have become defective and overreactive. These overly active mast cells tend to inappropriately and immediately degranulate in response to various stimuli, far out of proportion to the significance of the perceived threat. This inappropriate activation in turn leads to the presentation of a multi-system inflammatory disease, affecting multiple, diverse systems in the body. The fact that the disease simultaneously affects so many diverse systems in the body, while also not registering on routine lab tests, can lead to a variety of "unusual" or "strange" clinical presentations. [7]

COVID-19's Severity Mystery

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A mystery about the COVID-19 pandemic is why the disease presents as mild or asymptomatic in most of the population, while presenting as severe or life-threatening in others. An early study of the disease in the Chinese population reported that severe illness occurred in 15.7% of COVID-19 patients. [8] Preexisting conditions, such as hypertension, obesity, chronic lung disease, diabetes, and kidney disease are known risk factors for severe cases of the disease, as is age. [9] However, the severe form of the disease is also known to attack seemingly healthy, younger people. Furthermore, while age and preexisting conditions put patients at higher risk of contracting the severe version of the disease, many patients with advanced age and preexisting conditions do survive. The death rate for COVID-19 patients aged 80+ is the highest of any age group, at approximately 15% - 22%. The death rate for 70 – 79-year-old patients is approximately 8%. By comparison, the death rate for 40 - 49-year-old patients is 0.4% and 0.2% for those younger than 40. [10] Clearly, older individuals are at much higher risk of dying of COVID-19 than younger individuals. And yet the COVID-19 death rate for younger adults is far higher than the death rate for other viral infections, such as seasonal influenza. The death rate for younger adults (aged 18 – 49) from the 2018-2019 influenza season was approximately 2 deaths for every 100,000 infections.[11] The death rate for this same group of COVID-19 patients would be approximately 260 deaths per 100,000 individuals – two and a half orders of magnitude greater than seasonal influenza. Even a rough order of magnitude adjustment to account for uncertainty around sufficient testing would still put the death rate at one and a half orders of magnitude higher than seasonal influenza for young adults. The mystery is what makes COVID-19 particularly severe in certain individuals, while most individuals tend to have milder courses of the disease.

One striking feature in those patients with severe COVID-19 cases is the prevalence of "cytokine storms". Cytokines are proteins released by various cells which serve as messages and instructions to coordinate and regulate the immune system. Cytokines are released as part of the immune system's normal response to infection. Cytokine storms, however, are catastrophic overreactions to triggers such as viral infections, in which the immune system continually floods the body with cytokines. For some patients – as many as 15 percent of people battling any serious infection – the immune system continues to release these massive numbers of cytokines even after the virus is no longer a threat. [12] In these people, it is the immune system's severe overreaction, not the virus, which can lead to severe inflammation, multiple organ failure, and death. Initial studies have shown markedly elevated numbers of cytokines in hospitalized COVID-19 patients, with higher levels of certain cytokines (including IL-2 and IL-6) persisting throughout the severe cases. [13] [14] [15] Multiple clinical reports also describe many severe COVID-19 cases with the all the features of cytokine storms. According to Dr. Randy Cron, who specializes in cytokine storms at the University of Alabama at Birmingham, "We don't know the numbers, but among previously healthy people

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ages 20 to 60 who require hospitalization, a significant number are suffering from cytokine storms in addition to the virus." [16] One of the most frequent negative outcomes from COVID-19 associated cytokine storms is the rapid accumulation of abnormally large numbers of white blood cells (including neutrophils, NK cells, and T cells) in the patient's lungs. The fluid buildup, which results from this massive number of dead white blood cells in the lungs, leads to a severe condition called Acute Respiratory Distress Syndrome (ARDS), which can often require mechanical ventilation and lead to death.

Identifying and calming a cytokine storm as early as possible, before the storm can cause its damage, is key to a positive outcome. In terms of identification, one common marker to detect a cytokine storm in process is an elevated level of serum ferritin. In terms of calming storms that have already begun, treatments which target key inflammatory cytokines (such as IL-1, IL-6, and interferon-gamma) may be effective. [17] However, cytokine storms can escalate and cause damage extremely rapidly, and hospital and ICU resources are already stretched thin during an ongoing pandemic. Even initially mild and moderate cases of COVID-19 have rapidly escalated into ICU admissions and death.[18] As such, it would be far better to be able to predict in advance which patients would be more likely to suffer from cytokine storms before such storms actually start. The severity mystery becomes: what causes the immune system to suddenly overreact so catastrophically in certain COVID-19 patients, while remaining properly regulated in the majority of such patients? What makes these two sets of patients different from each other?

Our hypothesis provides a model to explain the reports surrounding the severity mystery. Mast cells play a key role as modulators of immune system function in interface organs, including but not limited to the lungs. As tissue-resident sentries lining these interface organs, mast cells constitute the first line of defense against threats. Due to their prevalence in the interface organs, their diverse array of sensors, and their ability to rapidly degranulate, they are able to respond almost instantaneously to invading pathogens, and many times they are the cells which are responsible for initiating the immune response. [19] Among the many receptors studding the surface of mast cells, one type of receptor (called pathogen-associated molecular patterns or PAMPs) is specifically triggered by invading pathogens, such as viruses. When the mast cell detects an invading pathogen, it releases a number of cytokines, including the proinflammatory cytokines IL-1, IL-2, and IL-6, and can also be made to release the ferritin [20] which can be detected in COVID-19 patients experiencing cytokine storms.

After detecting an invading threat, the local mast cells at the site of the infection (such as the lungs for an airborne pathogen such as the virus that causes COVID-19) play a critical role in recruiting other immune system cells. By releasing their mediators, the mast cells begin to recruit other white blood cells to the infection site. It is these white blood cells which can ultimately build up in the lungs and cause ARDS. The mast cells recruit these effector cells by releasing chemical mediators called chemokines, which the white blood cells follow as a chemical gradient. The mast cells' mediators also trigger important changes in the surrounding tissue – causing the tissue to relax and swell in order to allow white blood cells the room they need to migrate to the infection site. Studies have shown

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[20] Ward B, et al. *Ferritin Particles Accumulate in Human Mast Cell Secretory Granules and Are Released upon FcεRI mediated Activation*. (J Allergy Clin Immunol Vol 141, Num 2): https://www.jacionline.org/article/S0091-6749(17)32622-2/pdf

that in the absence of the mediators that the mast cells produce, the ability of white blood cells to migrate to an infection site is substantially impaired. [21] Put simply, additional white blood cells can't effectively migrate to the infection site (for example, the lungs) without the nearby mast cells continuously releasing their mediators. As such, continuous activation of the mast cells is required for these white blood cells' continued migration and potential buildup.

Mast cells express additional important receptors on their surface, called damage-associated molecular pattern (DAMPs), which can detect danger signals, including cell death in nearby cells. As cells are killed either by the virus or by the body's own white blood cells, the remnants of the dead cells further trigger the nearby mast cells and causes them to continue activating. This activation sequence – where mast cells call for and enable the movement of white blood cells, and then re-activate as those cells are fighting the virus – can lead to a vicious outcome. As long as the patient's mast cells activate continuously at the infection site, more and more NK cells, T-cells and neutrophils will be recruited and move to the site. If the mast cell activation is not properly regulated, this white blood cell migration can ultimately lead to the fluid buildup in the lungs which causes ARDS.

In patients with Mast Cell Activation Syndrome, defective mast cells activate out of proportion with the need to defend the body from the perceived danger. This hyperreactivity can result in inappropriate continued activation even after the infection has passed. This is the "gun" which the COVID-19 virus uses to "pull the trigger". In MCAS patients, some of the mast cell's surface receptors (which typically function like an on/off switch) can become stuck in the "on" position.[22] When this happens, MCAS patients can severely react to trace amounts of triggers which would be undetectable to others. When stuck in this "on" position, the mast cells will continue to release the proinflammatory cytokines which continuously recruit additional white blood cells to the infection site. Furthermore, another vicious cycle can develop. When defective mast cells release their cytokines, those cytokines can also activate their neighboring mast cells, even if those mast cells are healthy. This cascade can lead to more mast cell activation, more cytokines being released, and more white blood cells migrating to the infection site. As such, a cytokine storm that results in the buildup of excess fluid in the lungs such as we are seeing in severe cases of COVID-19 is exactly the kind of effect that overactive mast cells could produce.

If cytokine storms in COVID-19 patients are indeed produced by overly active mast cells, then a treatment which inhibits either the activation or the products of those mast cells would be expected to provide substantial relief. Interestingly, there have been recent promising reports using a drug called tocilizumab (an IL-6 inhibitor) in patients with severe cases of COVID-19 who are undergoing cytokine storms. [23] Significantly, multiple studies have shown that IL-6 plays a crucial role increasing the heightened reactivity of mast cells. The more IL-6 that is present, the more overreactive the mast cells become. This heightened reactivity also includes a tendency to increase the production of PGD_2, one of the key mediators which helps to attract the white blood cells to an infection site. [24] [25]

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[21] Dudeck A, Koberle M, et al. (November 20, 2018). *Mast Cells as Protectors of Health.* (J Allergy Clin Immunol 2019;144:S4-18. https://www.jacionline.org/article/S0091-6749(18)31605-1/pdf

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As such, by inhibiting IL-6, we would expect that the body's mast cells would become less over-reactive and therefore calm the cytokine storm. We would also expect that IL-6 inhibition would reduce the number of white blood cells recruited to the infection site, which would therefore reduce the amount of fluid buildup in the lungs. The promising reports about tocilizumab appear to confirm that exactly these effects are occurring.

In summary, the role that cytokine storms play in severe cases of COVID-19 is what we would expect to see if our hypothesis is correct. Hyperactive mast cells can get into a continuous activation loop, leading to cytokine storms, which can then result in the fluid buildup and lung damage we so often see in severe COVID-19 patients. Blocking mast cell mediators in COVID-19 patients can help calm the mast cells and calm those cytokine storms, with a result of better outcomes and lower mortality rates.

The Age Mystery

Another COVID-19 mystery is why the severe form of the disease appears to disproportionately affect adults, with far fewer severe cases in children. According to a recent CDC study, only 1.7% of confirmed COVID-19 cases occurred in US children under the age of 18, even though this group makes up 22% of the US population. [26] It should be noted that the difference in confirmed cases between the two age groups is most likely explained by data bias due to inadequate testing of seemingly healthy individuals. Individuals presenting with symptoms, especially more severe symptoms, are far more likely to be tested than seemingly healthy individuals. As such, the most likely interpretation of the data is not that children have a much lower infection rate of COVID-19, but rather that children appear to be far less likely to present with severe symptoms than adults.

Even though children and adolescents are statistically less likely to develop a severe case of COVID-19, severe cases among this age group do occur. Notably, the UK's Paediatric Intensive Care Society recently released an alert, warning of an increased number of reported cases of novel presentation of multi-system inflammatory disease. The report described an unusual presentation of "overlapping features of toxic shock syndrome and atypical Kawasaki disease with blood parameters consistent with severe COVID-19 in children. [27] Abdominal pain and gastrointestinal symptoms have been a common feature, as has cardiac inflammation." Notably, toxic shock syndrome and "atypical" Kawasaki disease both present as multi-system inflammatory diseases that are characterized by pervasive rashes, redness of the eyes and mouth, fever, muscle aches, confusion, and gastrointestinal issues. These observations in children have become so widespread that the name "Multisystem Inflammatory Syndrome in Children (MIS-C)" has been assigned to the condition. The diagnostic criteria for MIS-C includes elevated markers of inflammation, plus rash or redness of the eyes, low blood pressure or shock, heart anomalies, blood coagulation anomalies, and acute gastrointestinal problems. [28]

Why at this moment is there a sudden increase in a multi-system inflammatory disease in children, many of whom have also tested positive for COVID-19? UK researchers have stated that "there is a growing concern that a

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cytokine signaling 3. The Journal of allergy and clinical immunology, 137(6), 1863–1871.e6. https://doi.org/10.1016/j.jaci.2015.09.059

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[COVID-19] related inflammatory syndrome is emerging in children in the UK, or that there may be another, as yet unidentified, infectious pathogen associated with these cases."[29]

Similarly, a physician at a US Children's hospital, has indicated that "we are just starting to see an increase in the number of older adolescents that are being hospitalized with fairly severe COVID disease that is requiring treatment…some of the kids have some of the underlying conditions that would predispose you to getting more severe COVID-19 disease, such as obesity and hypertension."[30]

Our hypothesis can provide a unifying model to explain the various COVID-19 reports we are seeing related to children. First, regarding the age mystery: MCAS is often a lifelong disease, with the earliest symptoms presenting in childhood. However, it is also a progressive disease whose severity tends to progressively step-up over the patient's lifetime. Due to the disease's progressive nature, it is uncommon (but not unheard of) to find children who have severe mast cell disease. As a result, many more adults will have severe Mast Cell Activation Disease than children will. This fact pattern aligns extremely well with the reports we are seeing regarding the ratio of severe COVID-19 in children compared to adults. In our model, the more severe the mast cell disease, the higher the likelihood there will be of a severe case of COVID-19. Because children are less likely to have severe mast cell disease, they are also less likely to have a severe case of COVID-19.

Secondarily, the reports which describe an emerging "[COVID-19] related inflammatory syndrome" also fit our hypothesis extremely well. The symptoms described in the reports – including redness of the eyes and mouth, gastrointestinal issues, confusion, and inflammation of the heart – are all inflammatory symptoms that can easily be described by MCAS. Furthermore, the report mentions the "atypical" nature of the symptoms – a description which aligns well with the observed behavior of MCAS, which often masquerades as a "strange" or "unique" presentation of symptoms. Furthermore, since mast cells are most prevalent in the interfaces to the body – such as the skin, the eyes, the lungs, and the digestive tract – the skin rashes, redness of the eyes, and acute gastrointestinal issues described in the diagnostic criteria are presenting exactly in the areas where mast cells are found in the greatest numbers. Finally, the diagnostic criteria of low blood pressure in the children with MIS-C is especially interesting when viewed through the lens of MCAS. Mast cells are known to regulate the coagulability of the blood. Heparin, a blood thinner, is one of the mediators that mast cells release when activated. In fact, mast cells are now thought to be the main, if not the only, source of naturally occurring heparin in the body.[31] And heparin is known to drop blood pressure. [32] If the low blood pressure in the MIS-C children is due to an excess of heparin, then activated mast cells are almost certainly involved in the disease.

With the fact pattern we are seeing, we hypothesize that there is no new "inflammatory syndrome", and no additional "as yet unidentified pathogen". We hypothesize that what appears to be a separate combination of toxic shock syndrome and atypical Kawasaki syndrome (also known as MIS-C) is really an underlying case of Mast Cell Activation Disease which is being triggered by COVID-19.

Finally, our hypothesis can also speak to the observation from the US Children's hospital regarding the correlation between severe COVID-19 and underlying conditions, such as obesity and hypertension. It is only relatively recently that obesity has been recognized as a chronic inflammatory disease. Fat tissue contains large numbers of

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[29] Woodyat A, Howard J (April 27, 2020). Coronavirus could be tied to a rare but serious illness in children, UK doctors say. CNN.com. Retrieved May, 2020 from: https://www.cnn.com/2020/04/27/health/children-covid-19-illness-intl-scli-gbr/index.html

[30] Woodyat A, Howard J (April 27, 2020). Coronavirus could be tied to a rare but serious illness in children, UK doctors say. CNN.com. Retrieved May, 2020 from: https://www.cnn.com/2020/04/27/health/children-covid-19-illness-intl-scli-gbr/index.html

[31] Zehnder, J., Galli, S. *Mast-cell heparin demystified.* Nature 400, 714–715 (1999). https://doi.org/10.1038/23360

[32] Mandal et al. (1995). *Heparin lowers blood pressure: Biological and clinical perspectives.* Perspectives in Clinical Nephrology. https://www.kidney-international.org/article/S0085-2538(15)58911-4/pdf

mast cells which increase and promote inflammation.[33] Individuals with high blood pressure (hypertension) are at far greater risk of presenting a severe form of COVID-19. One report showed that hypertension was the most frequent comorbidity in those COVID-19 patients who went on to develop Acute Respiratory Distress Syndrome, with a comorbidity rate of 30%.[34] Interestingly, high blood pressure is extremely common in MCAS patients – indeed it is the second most common comorbidity associated with the disease, with a comorbidity rate of 29%. [35] As we have seen, mast cells can regulate blood coagulability and blood pressure. As a result, whether we are seeing a correlation between low blood pressure or high blood pressure with severe cases of COVID-19, both can suggest an underlying case of mast cell disease. Indeed, when we look at inflammatory conditions through the MCAS lens, symptoms or conditions such as high blood pressure, rash, red eyes, and gastrointestinal issues are seen as clues to identify the underlying mast cell disease, rather than a laundry list of standalone inflammatory diseases. As such, it isn't at all surprising (in fact it would largely refute our hypothesis if it wasn't the case) that known underlying inflammatory conditions such as obesity and hypertension are present in patients with severe cases of COVID-19. Put another way, if a patient has high blood pressure, then that is a clue that they may have a preexisting mast cell disease. If they have a pre-existing mast cell disease, then that is a clue that they may have a more severe form of COVID-19.

An underlying case of MCAS can explain the age mystery, and it can also explain many of the "strange", "bizarre", and "atypical" symptoms seen in the disease. What may at first look like separate risk factors and separate diseases (such as the symptoms of Kawasaki Disease and toxic shock syndrome) may just be different presentations of the patient's underlying mast cell disease. Those preexisting conditions which signal worse outcomes for COVID-19 could very well be the result of underlying mast cell disease.

Famotidine

A recent report has described famotidine (sold as the over the counter brand Pepcid) as a potential treatment for COVID-19. [36] A recent preprint study tracking severe COVID-19 outcomes in hospitalized patients compared the outcomes of patients taking famotidine to a control group. The study showed more than a 2-fold reduction in the risk of dying or intubation for the patients who took famotidine, compared to the control group. [37] Anecdotal evidence for famotidine also suggests promise. An American doctor at the Cold Spring Harbor Laboratory Cancer Center recommended famotidine to his 44-year old sister who had tested positive for COVID-19. She had developed a fever and her lips became dark blue from hypoxia. She took an oral megadose of famotidine on March 28, 2020. Her fever broke and her oxygen saturation returned to normal range the next morning, a result which the physician referred to as "a penicillin effect". Five sick coworkers in the New York City hospital system,

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[33] Wang, J., & Shi, G. P. (2011). *Mast cell stabilization: novel medication for obesity and diabetes. Diabetes/metabolism research and reviews*, 27(8), 919–924. https://doi.org/10.1002/dmrr.1272

[34] Ernesto L Schiffrin, John M Flack, Sadayoshi Ito, Paul Muntner, R Clinton Webb, *Hypertension and COVID-19*, American Journal of Hypertension, Volume 33, Issue 5, May 2020, Pages 373–374, https://doi.org/10.1093/ajh/hpaa057

[35] Afrin, L. B., Self, S., Menk, J., & Lazarchick, J. (2017). *Characterization of Mast Cell Activation Syndrome*. The American journal of the medical sciences, 353(3), 207–215. https://doi.org/10.1016/j.amjms.2016.12.013

[36] Borrell B (April 26, 2020). *New York clinical trial quietly tests heartburn remedy against coronavirus*. Science. Retrieved April, 2020 from: https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus

[37] Freedberg D, Conigliaro J, et al. (2020) *Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study*. medRxiv 2020.05.01.20086694; doi: https://doi.org/10.1101/2020.05.01.20086694

including three with confirmed COVID-19, also showed dramatic improvements after taking the over-the-counter drug. [38]

Even more intriguing is how researchers became interested in the drug in the first place. An American doctor named Callahan, working with Chinese doctors in Wuhan, noticed an interesting trend when reviewing over six thousand COVID-19 patient records. The doctors noted that many hospitalized COVID-19 patients had been suffering from chronic heartburn. Furthermore, they noted a surprising discrepancy in the survival rate between rich and poor COVID-19 patients. The breakthrough came in the form of the medication each was taking to manage their chronic heartburn. Poorer Chinese tended to take the cheaper famotidine, while more affluent Chinese tended to choose the more expensive omeprazole. The difference in survival rate between the two groups was nearly 50% - with a fatality rate of approximately 14% for the patients on famotidine, compared to a fatality rate of 27% for the patients taking omeprazole.[39] Put simply, in the Wuhan data, patients using famotidine died half as often as those using omeprazole.

The early famotidine reports provide multiple intriguing clues about a potential connection between MCAS and severe cases of COVID-19. The first clue is the fact that many of the hospitalized COVID-19 patients in the Chinese data had been suffering from chronic heartburn prior to their infection. Gastrointestinal issues, such as heartburn, are extremely common in MCAS patients. In fact, gastroesophageal reflux disease is the single most common comorbidity reported for MCAS.[40] This should be no surprise. Since mast cells are found in the greatest numbers in the body's interfaces to the world, the GI tract is one of the largest repositories of mast cells in the body. If pre-existing MCAS is indeed a predictor of those individuals who are more likely to develop severe COVID-19, then a prevalence of pre-existing heartburn is exactly what we would expect to see.

The second clue about the potential connection between MCAS and severe COVID-19 is the efficacy of famotidine in COVID-19 patients. Famotidine is a type of H2 antihistamine, which prevents histamine from binding with H2 receptors on the surfaces of cells. When viewed through an MCAS lens, it is not at all surprising that an H2 antihistamine would be effective in treating severe cases of COVID-19. Of all the different receptors expressed on mast cell surfaces, perhaps the most well-known are the histamine receptors. Mast cells not only maintain sensors on their surface to detect histamine, they are also the primary producers of histamine in the human body. [41] Mast cells manufacture and store histamine within their granules, and they release the preformed histamine immediately upon being triggered. This newly released histamine binds to receptors not only on the releasing mast cell, but on its neighbor mast cells as well. When it does so, the histamine serves as an additional trigger, both for the releasing mast cell, as well as its neighbors. Upon being triggered, these neighbor mast cells release their own histamine in turn – further triggering both themselves as well as their neighbors in turn. In this fashion, an initial trigger on a single subset of mast cells snowballs into an intensifying feedback loop and cascading trigger for the entire population of nearby mast cells. These cascades can lead to the dangerous cytokine storms that are so prominent in COVID-19. Furthermore, histamine is the primary mast cell mediator which allows the nearby tissue to expand, allowing white blood cells to migrate to the infection site. [42] As such, it is not surprising that

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[38] Borrell B (April 26, 2020). *New York clinical trial quietly tests heartburn remedy against coronavirus*. Science. Retrieved April, 2020 from: https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus

[39] Borrell B (April 26, 2020). *New York clinical trial quietly tests heartburn remedy against coronavirus*. Science. Retrieved April, 2020 from: https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus

[40] Afrin, L. B., Self, S., Menk, J., & Lazarchick, J. (2017). *Characterization of Mast Cell Activation Syndrome*. The American journal of the medical sciences, 353(3), 207–215. https://doi.org/10.1016/j.amjms.2016.12.013

[41] Thangam, E. B., Jemima, E. A., Singh, H., Baig, M. S., Khan, M., Mathias, C. B., Church, M. K., & Saluja, R. (2018). *The Role of Histamine and Histamine Receptors in Mast Cell-Mediated Allergy and Inflammation: The Hunt for New Therapeutic Targets*. Frontiers in immunology, 9, 1873. https://doi.org/10.3389/fimmu.2018.01873

[42] Dudeck A, Koberle M, et al. (November 20, 2018). *Mast Cells as Protectors of Health.* (J Allergy Clin

medications which block the histamine receptors on mast cells serve as an effective treatment in dampening the mast cell activation loop, slowing the cascade of degranulation, inhibiting the immune response, and dampening the resulting cytokine storms. Indeed, H1 and H2 histamine blocking medications are the cornerstone of any MCAS treatment regimen. In the event our hypothesis about the connection between severe COVID-19 and MCAS is true, then H1 and H2 antihistamines would be expected to be an effective component of the treatment regimen for severe cases of COVID-19.

The third clue is the lack of efficacy of omeprazole compared to famotidine in the fatality rate seen in the Wuhan data. Omeprazole and famotidine have different mechanisms of action to prevent heartburn. Famotidine blocks the H2 receptor on parietal cells, which then indirectly blocks the acid secretion messages to the proton pump. Omeprazole blocks the proton pump of the gastric parietal cells directly, rather than the more indirect route of blocking the H2 receptor. So, famotidine blocks histamine (including on mast cells), while omeprazole does not. As such, if our hypothesis is correct, then we would predict that treatment with an H2 antihistamine would have a positive impact on outcomes for severe COVID-19 infections, and we would predict no material improvement in outcomes for those treated with omeprazole. This is exactly what we see in the Wuhan report.

Taking a step back – by what mechanism could famotidine, an over-the-counter antihistamine used by millions of people to control heartburn, potentially reduce the fatality rate of severe COVID-19 by as much as 50%? Expecting famotidine to provide significant anti-viral effects seems extremely unlikely. Instead, we hypothesize that the most likely answer is that famotidine is doing in COVID-19 patients exactly what it is already known to do in MCAS patients – reduce the cascading reactivity of their mast cells, which calms the cytokine storms and therefore leads to a lower mortality rate.

Blood Clots

Blood clots are also one of the symptoms that frequently occur in COVID-19 patients. A recent study showed that 38% of patients with severe COVID-19 had blood that clotted abnormally, and approximately one-third of patients already had clots.[43] This remarkably high incidence of clotting has led hematologists to recommend prophylactic treatment in all COVID-19 patients admitted into the ICU. [44] Even more striking is the fact that blood clots seem to form in younger patients with milder courses of the disease, people who normally would not be considered at risk for clotting issues. One New York doctor reported that he saw 32 patients with large blood blockages in the brain over a three-week period – double the usual number for that period. Five of those were unusually young – under age 49 – with no obvious risk factors for strokes, "which is crazy", the doctor said. "Very, very atypical. The youngest was only 31." [45] Nephrologists have also noticed that kidney dialysis machines are were often getting blocked up by clots. [46] "I'm a hematologist, and this is unprecedented," says Jeffrey Laurence of Weill Cornell Medical College, who has been practicing for three decades. "This is not like a disease we've seen before. These

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Immunol 2019;144:S4-18. https://www.jacionline.org/article/S0091-6749(18)31605-1/pdf

[43] Wadman M, Couzin-Frankel J, Kaiser J, Matacic C (April 17, 2020). *How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes*. Science. Retrieved May, 2020 from: https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes#

[44] F.A. Klok, et al., (2020) *Incidence of thrombotic complications in critically ill ICU patients with COVID-19*. Thrombosis Research, https://doi.org/10.1016/j.thromres.2020.04.013

[45] Allen J (April 22, 2020). *Alarmed as COVID patients' blood thickened, New York doctors try new treatments.* Reuters. Retrieved May, 2020 from: https://www.reuters.com/article/us-health-coronavirus-usa-blood/alarmed-as-covid-patients-blood-thickened-new-york-doctors-try-new-treatments-idUSKCN22421Z

[46] Allen J (April 22, 2020). *Alarmed as COVID patients' blood thickened, New York doctors try new treatments.* Reuters. Retrieved May, 2020 from: https://www.reuters.com/article/us-health-coronavirus-usa-blood/alarmed-as-covid-patients-blood-thickened-new-york-doctors-try-new-treatments-idUSKCN22421Z

people are clotting, and we can't shut it off." [47] The blood clots are also leading to strokes, heart disease, and a number of other complications.

Our hypothesis can help provide some clues about how the virus that causes COVID-19 causes blood clots. As we have seen, mast cells are known to regulate blood coagulation. Heparin, the naturally occurring anticoagulant, is a well-known mast cell mediator. Furthermore, research has shown that mast cell granules are also crucial in inducing clotting. In a striking mouse model, researchers have shown that two strains of mice which were genetically deficient in mast cells were completely protected from deep vein blood clots. In addition, when the researchers transplanted live mast cells into those deficient mice, the mice started clotting again. When the researchers used medication to prevent the mast cells from degranulating, blood clotting was also reduced. Finally, the same researchers also found that histamine, such as that released by mast cells, was responsible for increasing the amount of blood clotting in mice. [48] The multiple findings from this study demonstrate the crucial role that mast cells play in blood clotting. If our hypothesis is correct that many of the severe effects of COVID-19 are the result of hyperactive mast cells, then a high rate of abnormal blood clotting is exactly what we would expect to see.

Overactive mast cells can create blood clots, which can cause heart attacks, strokes, and kidney failure. All of which we are seeing in severe cases of COVID-19.

Skin Symptoms

An early report from dermatologists working with Italian COVID-19 patients stated that approximately 20% of confirmed positive patients developed a skin rash of various types. These rashes varied from patient to patient, and included patchy red rashes, hives, and blisters. Additional dermatological reports have detailed mottling and rashes due to broken blood vessels.[49] An additional early report from Spain notes additional skin symptoms associated with COVID-19, called pernio, or chilblains (also described as "pseudo-frostbite"), which is an inflammatory condition of the small blood vessels in the skin. The authors described these skin lesions as a sign of asymptomatic infection with coronavirus. [50] In one Italian case, a 13-year old boy presented with skin lesions on his toes (a symptom which has become known as "COVID toes") a week after his mother and sister had presented with the "classic" symptoms of Covid-19: fever, cough, and difficulty breathing. [51]

Skin disorders are extremely common in patients with MCAS. As we have seen, mast Cells are tissue-resident cells which are commonly found in the interfaces of the body to the outside world, and the skin is the largest of these interfaces. It is therefore not surprising (and would absolutely be expected) that patients with COVID-19 would present with certain skin-related symptoms in the event COVID-19 is activating the patient's mast cells.

The presence of skin conditions associated with COVID-19 may be surprising when seen through the lens of the virus alone, but is unsurprising when seen through the lens of an underlying MCAS disorder which is being

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[47] Courage K. (May 1, 2020). *Coronavirus's new mystery: It's causing strokes in healthy people*. VOX. Retrieved May, 2020 from: https://www.vox.com/2020/5/1/21244171/stroke-coronavirus-symptoms-blood-clots

[48] Ponomaryov, T., Payne, H., Fabritz, L., Wagner, D. D., & Brill, A. (2017). *Mast Cells Granular Contents Are Crucial for Deep Vein Thrombosis in Mice*. Circulation research, 121(8), 941–950. https://doi.org/10.1161/CIRCRESAHA.117.311185

[49] Cleveland Clinic (2020). *Skin Rashes: An Emerging Symptom of COVID-19*. Retrieved May, 2020 from: https://consultqd.clevelandclinic.org/skin-rashes-an-emerging-symptom-of-covid-19/

[50] Cleveland Clinic (2020). *Skin Rashes: An Emerging Symptom of COVID-19*. Retrieved May, 2020 from: https://consultqd.clevelandclinic.org/skin-rashes-an-emerging-symptom-of-covid-19/

[51] Mazzotta F., Troccoli T. (2020). *Acute Acro-Ischemia in the Child at the Time of COVID-19*. Retrieved May, 2020 from: http://sectcv.es/wp-content/uploads/2020/04/acroischemia-ENG.pdf

activated by the virus. In these cases, the skin symptoms should be interpreted as possible warning signs for additional severe symptoms, such as cytokine storms.

Vitamin D

Recent preprint reports have indicated that vitamin D deficiency may lead to higher risk of a severe case of COVID-19. The reports also suggest that vitamin D supplementation may reduce the severity of COVID-19 by helping to suppress its dangerous cytokine storms. [52] Recent genetic analysis provides additional support that Vitamin D may be a valuable treatment option for COVID-19 (The same genetic analysis also suggests the use of quercetin, another commonly used supplement for Mast Cell Activation Syndrome.) [53]

Vitamin D is known to be crucial for mast cell stability. Studies have shown that mast cells activate automatically in a vitamin D deficient environment, and that such a deficiency in Vitamin D leads to mast cell activation. [54] And vitamin D supplementation is a key component of the standard MCAS treatment cocktail.

The idea that vitamin D deficiency may lead to more severe presentations of COVID-19 fits our hypothesis well. Individuals with vitamin D deficiency have mast cells which activate inappropriately, and this inappropriate mast cell activation can lead to the cytokine storms that we witness in severe cases of COVID-19. Treatment with vitamin D supplementation would be expected to help stabilize the patient's mast cells and help reduce the risk of COVID-19 cytokine storms.

Conclusion

The reports we are seeing about COVID-19 present a picture of a complex disease whose symptoms and comorbidities can affect almost any system in the body – an inflammatory disease which can cause cytokine storms, lung failure, blood clotting, high blood pressure, low blood pressure, strokes, kidney failure, and skin rashes. These conditions are being caused by the body's response to the virus which causes COVID-19, not the virus itself. Even though older individuals with preexisting conditions are at higher risk, even younger patients with no previously known risk factors can present with sudden, severe conditions, such as lung failure and strokes. Furthermore, the primary risk factors for severe complications are those of an inflammatory nature – such as hypertension and obesity, and there is evidence that the severe form of the disease favors patients with a history of heartburn. Most individuals with the disease have mild symptoms, or no symptoms at all, while approximately 15% of patients develop severe symptoms and can present with catastrophic, system-wide conditions. Finally, multiple reports show the efficacy of treatment with antihistamines, vitamin D, and medications that block certain cytokines.

At this point, we should ask ourselves: what sort of disease 1) can affect so many disparate systems simultaneously; 2) is an autoimmune, inflammatory disease; 3) presents with mild symptoms in most patients but

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[52] Daneshkhah A, Agrawal V, et al. (2020). *The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID-19 Patients*. Medrxiv.org. Retrieved May, 2020 from: https://www.medrxiv.org/content/10.1101/2020.04.08.20058578v3

[53] Glinsky G. (May 2020). *Tripartite combination of potential pandemic mitigation agents: Vitamin D, Quercetin, and Estradiol manifest properties of candidate medicinal agents for mitigation of the severity of pandemic COVID-19 defined by genomics-guided tracing of SARS-CoV-2 targets in human cells*. Chemrxiv.org. Retrieved May, 2020 from: https://chemrxiv.org/articles/Harnessing_Powers_of_Genomics_to_Build_Molecular_Maps_of_Coronavirus_Targets_in_Human_Cells_A_Guide_for_Existing_Drug_Repurposing_and_Experimental_Studies_Identifying_Candidate_Therapeutics_to_Mitigate_the_Pandemic/12052512/10

[54] Liu, Z. Q., Li, X. X., Qiu, S. Q., Yu, Y., Li, M. G., Yang, L. T., Li, L. J., Wang, S., Zheng, P. Y., Liu, Z. G., & Yang, P. C. (2017). *Vitamin D contributes to mast cell stabilization*. Allergy, 72(8), 1184–1192. https://doi.org/10.1111/all.13110

presents with severe symptoms in approximately 15% of the population; 4) is more severe in patients with a history of heartburn and high-blood pressure and other inflammatory diseases; 5) could be treatable with anti-cytokine medication and over-the-counter antihistamines; and 6) can increase in severity in patients with vitamin D deficiency? Mast Cell Activation Syndrome fits this description extremely well. Mast Cell Activation Syndrome is an autoimmune, inflammatory disease which is present to various degrees of severity in approximately 17% of the population. It can affect almost every system in the body, from the skin to the blood to the lungs, and its primary comorbidities are heartburn and high blood pressure. Vitamin D deficiency is known to cause inappropriate mast cell activation. And MCAS is commonly treated with antihistamines, vitamin D, and other medications which block mast cell cytokines.

If our hypothesis (that many severe cases of COVID-19 are due to underlying, pre-existing Mast Cell Activation Disease in the patient) is correct, it suggests several next steps for individuals and health care professionals. Individuals already diagnosed with MCAS may want to take extra precautions, such as careful handwashing, additional social distancing, and wearing protective masks. Individuals who do not know if they have MCAS would be well served to educate themselves on the condition, and to help educate others. Health care professionals and hospitals may want to provide additional resources and briefings around MCAS. They may also consider expanding their intake process to take special note and observation of those individuals with multiple inflammatory diseases, including heartburn, high blood pressure, obesity, and skin rashes. Specialists should also start a conversation about whether or not to recommend prophylactic over-the-counter antihistamines, vitamin D, and mast cell stabilization medications to at-risk individuals. Most importantly, additional research should be initiated in order to determine if our hypothesis continues to hold true. We will not know for certain until these studies can be done.

Mast Cell Activation Syndrome affects a large minority of the population, but it is a disease that most people have never heard of. If MCAS is indeed the key to the COVID-19 mystery, there may be no better time than this moment to raise the profile of this important disease.