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COVID-19: THE PLAGUE THAT STRIKES BEHIND THE EAR

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ABSTRACT

Nontypeable Haemophilus Influenzae (NTHI) is a major cause of invasive disease worldwide. Viral infections in patients colonized with NTHI may be at risk for serious complications as specific viruses, like SAR-CoV-2, on top of a bacterial infection significantly enhances the risk for excessive inflammation and upregulation of ICAM-1. ICAM-1 is elevated in COVID-19 patients with mild disease and dramatically elevated in severe cases. C-C chemokine receptor CCR5 is also upregulated in COVID-19 patients. Incidentally, ICAM-1 and CCR5 upregulation are both implicated in the pathogenesis and progression of HIV. Like the HIV, SARS-CoV-2 gains cellular entry through CD4 T-cells. A NTHI / SARS-CoV-2 co-infection causes LFA-1 binding to ICAM-1. LFA-1 activation on target CD4 T-cells enhances SARS-CoV-2 infectivity and transmission by promoting virus binding and cell to cell spread via the CCR5 coreceptor. These mechanisms allow SARS-CoV-2 cellular access to multiple cellular systems inducing a cytokine storm in some patients. LFA-1also increases the cell susceptibility to bacterial toxin LtxA that preferentially targets active LFA-1. Leukotoxin (LtxA; Leukothera), is a protein toxin secreted by the oral bacterium Aggregatibacter actinomycetemcomitans, which specifically kills white blood cells. Interestingly, Aggregatibacter actinomycetemcomitans and NTHI are two species under genus Pasteurellaceae. Throughout history, plagues have been associated with divine punishments from God caused by bacterias. Prophet Muhammad ﷺ told us over 1400 years ago that when fornication becomes widespread new diseases like COVID-19 would increase. A holistic approach including Spiritual, Physical, Emotional, and Mental interventions must be employed to treat COVID-19 as well as to prevent the next pandemic.

Keywords: NTHI , Plague, COVID-19, CCR5, ICAM-1, HIV/AIDS

INTRODUCTION

For Muslims, Islam is a complete way of life that promotes homeostasis in the Spiritual, Physical, Mental, and Emotional domains of wellness. COVID-19 has thrust this generation into a very precarious time where understanding and exploring Islamic pathways to wellness is obviously more relevant now than ever. For example, key principles to promote wellness during COVID-19 include; social distancing which entails refraining from handshaking, an emphasis on physical cleanliness through frequent handwashing, and covering the face and hands, which are all fundamental acts performed daily by billions of Muslims all over the world as religious obligations.

The Islamic approach to medicine is "holistic" as it puts forth that Spiritual, Physical (to include the use of whole plant medicine), Mental, and Emotional causes of disease must be identified and properly treated in order to open the pathway for a complete cure. Treating symptoms is

a common approach that may slow one dis-ease progression while acting as a catalyst for another thus, it does not lead to a complete cure. This can be exemplified in the case of the overprescription of antibiotics for diseases like STDs. The overprescription of antibiotics for diseases like STDs led to antibiotic resistant bacteria such as NTHI and Candida albicans. This can also be evidenced in the decrease in the incidence of invasive Hib diseases due to widespread use of the Hib vaccine. Consequently, NTHi strains have taken the lead in becoming the most common cause of invasive disease in all age groups with routine Hib vaccination (1).

Prophet Muhammadسلى الله عليه و سلم, (may the peace and blessings of Allah be upon him) told us the reasons why we would experience new diseases like COVID-19;

"...If fornification should become widespread, you should realize that this has never happened without new diseases befalling the people which their forebears never suffered." (2).

We are indeed living in a time where fornication has become widespread and deemed morally acceptable by a majority. Results from a 2002 U.S. survey revealed that by age 20, 75% of all respondents had premarital sex. It further revealed that by age 44, 95% of respondents (94% of women, 96% of men, and 97% of those who had ever had sex) had had premarital sex. The conclusions of this survey by the National Survey of Famiy Growth indicated that almost all Americans have sex before marrying (3).

According to a 2019 Pew Research Study, 62% of respondents in the U.S. said casual sex between consenting adults who aren't in a committed relationship is acceptable at least sometimes (4).

Another survey conducted by The Pew Research Center in 2014 compared global views of premarital sex found that respondants in predominantly Muslim countries like Indonesia, Jordan, Turkey and Egypt overwhelmingly agreed that premarital sex is morally wrong. Western countries such as Europe mainly found premarital sex morally acceptable (4).

What is a Plague?

According to the Merriam Webster Dictionary, the word plague has several meanings. For one, it can mean a disastrous evil or affliction. It can also mean a virulent contagious febrile disease that is caused by a bacterium (Yersinia pestis) and that occurs in bubonic, pneumonic, and septicemic forms.

Islam is a complete way of life. The Qur'an (The Speech of Allah) and Sunnah (legal ways of Prophet Muhammad سلى الله عليه و سلم) provide mankind with knowledge needed to achieve wellness and a cure Spiritually, Physically, Mentally, and Emotionally. When mankind accepts this knowledge given by Allah and then acts upon it, they are given the opportunity to achieve holistic wellness. When societies act in opposition to the Qur'an and Sunnah it opens the pathways to sickness and ultimately death which is brought on by widespread calamities, fitna and trials.

Allah سُبْحَانَهُ وَتَعَالَى says in The Qur'an;

يَٰٓأَيُّهَا ٱلَّذِينَ ءَامَنُواْ ٱسْتَجِيبُواْ لِلَّهِ وَلِلرَّسُولِ إِذَا دَعَاكُمْ لِمَا يُحْيِيكُمْ ۖ وَٱعْلَمُوٓاْ أَنَّ ٱللَّهَ يَحُولُ بَيْنَ ٱلْمَرْءِ وَقَلْبِهِۦ وَأَنَّهُۥٓ إِلَيْهِ تُحْشَرُونَ

وَٱتَّقُواْ فِتْنَةً لَّا تُصِيبَنَّ ٱلَّذِينَ ظَلَمُواْ مِنكُمْ خَآصَّةً ۖ وَٱعْلَمُوٓاْ أَنَّ ٱللَّهَ شَدِيدُ ٱلْعِقَابِ

"Oh you who believe! Answer Allah (by obeying Him) and (His) Messenger ﷺ when He calls you to that which will give you life, and know that Allah comes in between and person and his heart (i.e. He prevents an evil person from deciding anything). And verily, to Him you shall (all) be gathered.
And fear the Fitnah (affliction and trial) which affects not in particular (only) those of you who do wrong (but it may afflict all the good and the bad people), and know that Allah is Severe in punishment." **Surah Al-Anfal, 8:24-25** (The Noble Qur'an) (5).
Ibn Qiyyum رَحِمَهُ ٱللَّهُ a renowned scholar in Islam stated in his book; "Medicine of The Prophet": "Although the plague describes every infection that sends septic blood to the heart, becoming fatal sometimes, it particularly describes the infection that attacks the soft tissues of the body. Since the infected blood is septic, the various organs reject the blood, except those that have become weak. The worst types of plague are those that strike behind the ears and under the arms, because they are closer to the essential organs of the body." (6).
According to the CDC, there are three types of plague: bubonic, septicemic, and pneumonic. In pneumonic plague patients develop fever, headache, weakness, and a rapidly developing pneumonia with shortness of breath, chest pain, cough, and sometimes bloody or watery mucus. Pneumonic plague may develop from inhaling infectious droplets or may develop from untreated bubonic or septicemic plague after the bacteria spread to the lungs. The pneumonia may cause respiratory failure and shock. Pneumonic plague is the most serious form of the disease and is the only form of plague that can be spread from person to person (by infectious droplets) (7).
Symptoms presented by COVID-19 patients strongly resemble symptoms of pneumonic plague to include shortness of breath, fever, headache, tiredness, cough, and
Pneumonia (8).

1. Nontypeable Haemophilus Influenzae (NTHI): The Bacteria Behind the New Plague

According to research on emerging pathogens published by the National Institutes of Health in 2015, Nontypeable Haemophilus Influenzae (NTHI) is a major cause of invasive disease worldwide (9). It is believed that this emergence may be partly due to increased NTHi colonization in children which might contribute to increased transmission to persons susceptible to developing invasive NTHi disease. Over the last 25 years in the U.S., the elderly have accounted for 89% of all invasive NTHI infections. Much like SARS-CoV-2, pre-existing diseases such as COPD, cancer, chronic renal failure, and diabetes place people at greater risk for contracting invasive NTHI (10, 11). However, it has been found that NTHI infections are not just found in persons with immunocompromising conditions or co-existing conditions but in almost half the cases in persons who were otherwise in good health (11).
Viral infections in patients colonized with NTHI may be at risk for future exacerbations as specific viruses, like SAR-CoV-2, on top of a bacterial infection may significantly enhance the risk for excessive inflammation. In a 2015 study, it was found that Nontypeable Haemophilus influenzae (NTHI) can enhance expression of the cellular receptor intercellular adhesion molecule 1 (ICAM-1) on airway epithelial cells, which in turn increases the binding of major group human rhinoviruses (HRVs) for attachment (12).

Major group human rhinoviruses or HRVs are members of the Picornaviridae family. Like Coronaviruses or CoVs, they are a large family of single stranded RNA viruses. These viruses can cross species barriers and can cause, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS (13).

Many COVID-19 patients experience symptoms that are similar to symptoms presented by those who have COPD including frequent coughing, excess phlegm, shortness of breath, and trouble breathing (8). Recent studies have focused on the role of viral and bacterial coinfection in patients with COPD. This coinfection is associated with incidences of intensified respiratory disease and more inflammation (14). The most common co-infection is with rhinovirus (RV) and NTHI in COPD (15-16). NTHI also has significant and scientifically noted high morbidity risks for patients who smoke, or have Bronchiectasis, Cystic Fibrosis, Pneumonia, and Intestinal Lung Disease (17). These factors and diseases are also associated with increased risk of severe complications from COVID-19 (10).

NTHI is a very common gram-negative coccobacillus that colonizes the nasopharyngeal region in up to 80% of humans (18). It is present in the nose and throat of 50% of all children and is usually harmless until it moves to the middle ear or the lungs where it can cause the most damage. NTHI is a frequent cause of otitis media (chronic middle ear infections) (19) in children and acute bronchitis and pneumonia in patients with chronic obstructive pulmonary disease (20). Non-typeable Haemophilus influenzae (NTHI) has been associated with early pregnancy loss and in a 2020 report it was deemed an emerging neonatal and maternal pathogen (21).

This bacterium needs an iron rich environment to survive. Once NTHI has moved into the lungs and middle ear, heme iron is sequestered as part of the body's immune response. Instead of dying, the bacterium is kept alive by using clever hacks of the host's immune response (22).

Scientists Kevin M. Mason, PhD and Sheryl S. Justice, PhD, principal investigators in the Center for Microbial Pathogenesis figured out how NTHI was able to maintain a relatively low profile amongst clinicians with respiratory/pulmonary backgrounds and not be considered an important pathogenic bacterium. Their research shows that NTHI uses the body's own immune system to its advantage. Once the immune system is alerted of a bacterial invasion in the lungs, middle ear, and other parts of the body, the immune system cuts off access to nutrients the bacteria need to survive- including heme iron. This process is known as nutritional immunity. This immune response triggers a series of additional immune defenses to include inflammation, which involves the release of chemicals that are designed to find and sequester NTHI and bring in white blood cells to the site of infection to destroy the invading bacterium (22).

The scientist developed a lab experiment designed to imitate the immune response to NTHI infection in the middle ear and to further observe how NTHI responds to the body's immune responses. The research results showed that in the body's immune response a serum designed to carry disease fighting chemicals and white blood cells to the site of the infection includes heme-iron. They further observed that when NTHI was re-exposed to heme-iron the bacteria underwent structural changes that allowed it to divide much more slowly and become elongated and spaghetti-like in appearance. As a result, the NTHI was ignored by the disease fighting white blood cells as they usually target rapidly dividing shorter cells. Thus, NTHI was left alone to replicate and thrive. "This clearly shows that NTHI is changing to become more fit in

the host," says Dr. Justice, who also is an assistant professor of pediatrics and urology at the Ohio State University College of Medicine (23).

Much like NTHI, SARS-Co-V-2 also has the ability to block the host innate immune response through its links to the function of structural and non-structural proteins (24) which makes co-infection with invasive NTHI and SARS-Co-V-2 a severe threat to host morbidity. In three separate studies it was found that COVID-19 patients were co-infected with Haemophilus Influenzae (96-98).

2. Upregulated ICAM-1 in COVID-19 Patients Could be Due to NTHI + SARS-CoV-2 Co-Infections

To date it is believed that SARS-CoV-2 via its surface spike glycoprotein interacts with Angiotensin-converting enzyme 2 (ACE2) and invades host cells. ACE2 is expressed in human vascular endothelium, respiratory epithelium, and other cell types (25). Endothelial cells play an important role in virtually every system in the body. These cells form the inner lining of the cardiovascular and lymphatic systems. They make up the inner layer of blood and lymphatic vessels and organs including the brain, lungs, skin and heart. Epithelial cells provide biochemical barriers by synthesizing and secreting substances meant to trap or destroy bacteria like NTHI (26). However, NTHI is able to allow its binding to epithelial cells. There is also evidence that NTHI may thrive in the respiratory tract by surviving inside of epithelial cells (27).

Though ACE2 is thought to be the main point of cellular entry for SARS-CoV-2, it is well known that viruses often use a variety of mechanisms for attachment. The most common cell adhesion molecules are CAMs which are routinely exploited by viruses to gain cellular entry (28). A retrospective study of COVID-19 patients in China found that serum levels of fractalkine, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and vascular adhesion protein-1 (VAP-1) were elevated in patients with mild disease, dramatically elevated in severe cases, and decreased in the convalescence phase (29).

Much like Human herpesvirus 8 (HHV-8), HIV, and AIDS, NTHI can inhibit epithelial host defense proteins (30-33). Once compromised, airway epithelial cells respond to the invasion of NTHI by secreting inflammatory acute-phase reactants such as IL-6, IL-8, and TNF-ą (31,32). NTHI then increases the expression of ICAM-1 by airway epithelial cells which increases the susceptibility of viruses binding to the cells (34).

ICAM-1 or Intercellular Adhesion Molecule 1, also known as CD54 (Cluster of Differentiation) is a protein that in humans is encrypted by the ICAM-1 gene. The ICAM-1 gene is coded by a cell surface glycoprotein which is expressed on endothelial cells and cells of the immune system (35). An NTHI and SARS-CoV-2 co-infection that originates from the middle ear might allow these pathogens cellular access to the respiratory system as scientists have discovered that there is a similar allergic inflammation in the middle ear and the upper airway suggesting the middle ear may be a part of the united airways concept (36). The major leading cause of death in patients with COVID-19 is respiratory failure from acute respiratory distress syndrome (ARDS) (37).

3. Comparing the Pathophysiology of COVID-19 to that of HIV/AIDS for better understanding of the disease and to develop treatments

Many receptors for cytokines/chemokines have recently been identified by a group of scientists as upregulated in COVID-19 patients including; C-C chemokine receptor (CCR) 1 (CCR1), CCR2, and CCR5. These same scientists claim; "our work highlights opportunities for clinical trials with existing or under development CCR5 drugs to treat high risk or severe COVID-19 cases" (38). ICAM-1 and CCR5 upregulation are both implicated in the pathogenesis and progression of HIV (39, 40).

It has been previously established that HIV's replication is facilitated by ICAM-1 which is believed to increase infection of CD4 T-cells (41). Plasma biomarkers of endothelial injury such as higher levels of cICAM-1, lower levels of cICAM2, an increase in cB2 microglobulin levels, and the decrease in CD4 T-cell counts are well established predictive biomarkers in HIV1-infected patients used to determine disease progression and prognosis for AIDS progression (39). These same markers may be useful in determining disease progression and prognosis in asymptomatic COVID-19 patients and further identifying potential therapeutic candidates.

Due to the similarities between COVID-19 and HIV disease infection and progression, a closer look at the mechanisms of HIV infection is warranted. HIV gains entry into the cells via gp120 and CD4. This allows for binding to the chemokine receptors CCR5 or CXCR4, which act as coreceptors for the virus for which CD4 antibodies have been identified as effective therapeutic targets (42). It is important to note that a 2008 research study found that HIV transfer between CD4 T-cells did not require LFA-1 binding to ICAM-1 and is governed by the interaction of HIV envelope glycoprotein with CD4. The researchers discovered that HIV transmission between infected and uninfected primary CD4 T-cells was stopped by inhibitors of gp120 binding to CD4 by not blocking LFA-1 binding to ICAM-1 or ICAM-3. Further, it was noted that LFA-1 and ICAM-3 monoclonal antibodies (MoAb) actually enhanced HIV transfer (43). Recent research noted that CCR5 receptor and chromosome 3 gene clusters contribute to susceptibility to COVID-19 and the development of severe complications. Additionally, □32 allele , a polymorphism in CCR5 that regulates its expression has been identified as a partial to full protection against HIV infection and acts as a foundational basis for gene deletion studies aimed at achieving a permanent cure to HIV (44-45). It should be noted that a positive correlation between COVID-19 mortality rate and the □, 32 allele (n African population was found (46).

Further, there is a correlation between the progression of HIV and invasive NTHI infections. A study designed to evaluate increases in invasive NTHI infection from 2017-2018 among homosexual HIV infected men in Atlanta, Georgia found the incidence of invasive NTHI infection increased signigicantly from 2017-2018 compared with 2008-2016. Additionally, two unique but genetically connected strains were observed and associated with septic arthritis among homosexual black men who lived in geographic proximity (47).

On a spiritual level, it makes sense that there are such similarities between COVID-19 and HIV/AIDS as both have causes tied to fornication.

4. COVID-19 Pathophysiology may be much like HIV/AIDS with Distinct Characteristics

Like HIV, SARS-CoV-2 gains cellular entry via CD4 T-cells. However, different mechanisms lead to SARS-CoV-2 infection.

Asymptomatic people may be super spreaders of COVID-19 due to high levels of NTHI. SARS-CoV-2 rarely causes serious disease super spreader populations yet, the virus causes severe disease progression in others. This may be due to the condition of the innate immune system. Several groups have found that the binding of IgM to the bacterial surface might play a role in the innate defense against NTHI infections. Another study found that patients with hyper-IgM syndrome were less susceptible to NTHI colonization, a finding that emphasizes the role of IgM in the immune system defense against NTHI. The percentages of IgM-producing CD27+ memory B cells in the peripheral blood of children are low but increases to almost 20% in adults and declines again in the elderly. This might address the question of whether a diminished protective immunoglobulin level in the elderly contributes to susceptibility to invasive NTHI disease (9).

The COVID-19 Model

1. A person with increased NTHI colonization becomes infected with SARS-CoV-2.
2. Due to a weakened immune system (lower IgM levels) the body pushes harder against the co-infection through mounting an excessive inflammatory response.
3. ICAM-1 becomes upregulated.
4. ICAM-1 acts as a ligand to LFA-1.
5. LFA-1 becomes activated on CD4 T-cells.
6. LFA-1 activation on target and infected CD4 T-cells enhance SARS-CoV-2 infectivity and transmission by promoting virus binding and cell to cell spread via the CCR5 coreceptor.
7. LFA-1also increases the cell susceptibility to bacterial toxin LtxA that preferentially targets active LFA-1 (48).

a. Leukotoxin (LtxA; Leukothera), a protein toxin secreted by the oral bacterium Aggregatibacter actinomycetemcomitans, specifically kills white blood cells (WBCs). LtxA binds to the receptor known as lymphocyte function associated antigen-1 (LFA-1), a ß2 integrin expressed only on the surface of WBCs (49).

b. NTHI and Aggregatibacter actinomycetemcomitans are two species under genus Pasteurellaceae thus closely related (50).

c. A. actinomycetemcomitans is associated with oral and non oral diseases (51).

8. LtxA binds to the active form of LFA-1 and nominally affects cells that express resting-state LFA-1 (52-54). The mechanism of cellular killing by LtxA has been studied in HL-60 monocytes. It has been found that LtxA causes necrosis at high doses by forming pores in the host cell membrane, while at low doses LtxA induces apoptosis (55-56). This might explain why persons with increased NTHI and Aggregatibacter actinomycetemcomitans colonization would be at a higher risk of severe complications from COVID-19.

6. Intestinal Disease as a Marker for COVID-19 Disease Progression

Prophet Muhammad, may peace and blessings be upon him, said, "The son of Adam cannot fill a vessel worse than his stomach, as it is enough for him to take a few bites to straighten his back. If he cannot do it, then he may fill it with a third of his food, a third of his drink, and a third of his breath." (57) It is well known that overeating (gluttony), particularly on unhealthy foods, can cause an array of stomach and intestinal diseases. Eating Disorders (ED) including Binge Eating (BE) has been associated with imbalances in the gut flora compromising gut health and immune defense maintenance. These imbalances are negatively correlated with anxiety and depression scores (58).

Cytokine induced changes in mucin expression and O-glycosylation are likely involved in the pathogenesis and progression of inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease. Disrupted gut barrier integrity is at the heart of all inflammatory bowel diseases (59-60).

A recent study performed by researchers Giron, Dweep and others revealed severe COVID-19 is fueled by disrupted gut barrier Integrity. These researchers found that hospitalized COVID-19 patients had higher plasma levels of zonulin, (the only known physiological conciliator of tight junction permeability in the digestive tract), and were more likely to die. This progression of disease was due to the ability of microbes to enter into the bloodstream causing systemic inflammation. The researchers also pointed that systemic inflammation caused by a lung infection can lead to a disruption of the gut barrier integrity leading to microbial translocation. Upon examining plasma glycomes, their research uncovered that translocation of glycan-degrading enzymes alter extraintestinal circulating high-mannose glycoform (HM-ICAM-1) (61). Further, in the inflamed gut of Crohn's Disease and Ulcerative Colitis patients, 1CAM-1 is enhanced. Research points to HM-ICAM-1, ICAM-1 as a key therapeutic target for controlling leukocyte trafficking and endothelial inflammation (62,63).

7. Candida albicans: a Therapeutic Target

Some bacteria in the normal intestinal microbiome are opportunistic. Opportunistic bacteria like Candida albicans can overgrow due to prolonged treatment with broad-spectrum antibiotics (64). Broad-spectrum antibiotics are often prescribed to target pathogens sensitive to antimicrobial agents. However, other organisms such as Candida albicans that are resistant to the therapeutic intervention invate the unoccupied space and multiply rapidly. This occurrence is called Candidiasis or superinfection (65). In 2019 the CDC listed drug resistant Candida species in its Antimicrobial Resistance Threats Report, stating that many are resistant to antifungals used to treat them (66).

When Candida albicans overgrowth and the normal lining of the intestinal tract is damaged, the body can absorb yeast cells, particles of yeast, and various toxins (67). Candida accounts for 70-90% of all invasive fungal infections in hospitalized patients and is a leading cause for sepsis in critically ill patients. Additionally, administration of broad-spectrum antibiotics, central vascular catheters, diabetes mellitus, parenteral nutrition, mechanical ventilation, renal insufficiency, hemodialysis, colonization, antifungal prophylaxis, surgery, pancreatitis, and treatment with corticosteroids and chemotherapy were the most frequently identified risk

factors for sepsis in patients with Candidiasis (68). Researchers have increasingly become aware of COVID-19 fungal co-infections. The main fungal pathogens for fungal co-infections in severe COVID-19 patients are Aspergillus and Candida albicans (69).

On April 24, 2020 a 67 year old COVID-19 patient presented oral mucosal lesions resembling late state herpetic recurrent oral lesions associated with candidiasis. He was admitted to the ICU for supplemental oxygen therapy. The patient's symptoms worsened and doctors suspected pneumonia. The patient was placed on antibiotic regimens. On the twenty fourth day of hospitalization, dentists discovered white patches on the patient's tongue. He was prescribed antifungal medications and the patches cleared up. The patient was released from ICU two weeks later and was discharged from the hospital after forty-four days.

It should be noted that Acute Acquired Haemolytic Anaemia has been associated with Herpes Simplex Infection (70-71). Hemolytic anemia is a blood disorder that occurs when your red blood cells are destroyed faster than they can be replaced. Severe hemolytic anemia can cause fever, chills, back pain, shock, irregular heartbeat, and cardiomyopathy in which the heart grows larger than normal (72).

8. NTHI, SARS-CoV-2, Intestinal Disease & Inflammation: Making Sense of MIS in Children

Inflammation can modify the glycosylation pattern of glycolipids and glycoproteins. It is well known that the glycosylation of acute-phase proteins is subjected to marked changes during acute and chronic inflammation (73). The inflammatory response caused by ICAM-1 Upregulation and COVID-19 can lead to increased levels of pro-inflammatory cytokines in response to pathogens lead to a constant NF-κB activation resulting in an increased synthesis of pro-inflammatory cytokines, which contributes the vicious inflammatory cycle seen in patients with Kawasaki disease and other systemic inflammation presentations (74-75).

NTHi strains cause mucosal infections, including otitis media, conjunctivitis, sinusitis, bronchitis, and pneumonia. Less commonly, these strains cause invasive disease in children but account for half of the invasive infections in adults which may explain why children are less likely to become severely ill from COVID-19 (76).

On August 7, 2020 a report on Multisystem Inflammatory Syndrome in Children (MIS-C) was released by the U.S. Department of Health and Human Services and the CDC. Clinical symptoms of patients included in this report included; fever, rash, conjunctivitis, peripheral edema, gastrointestinal symptoms, shock, and elevated markers of inflammation and cardiac damage.

This report found that of the 570 children with COVID-19 related MIS-C, 25% of them were obese. 90% of them experienced gastrointestinal symptoms including abdominal pain, vomiting, and diarrhea. About 71% of them experienced dermatologic and mucocutaneous presentations including rash (55.3%) and mucocutaneous lesions (35.3%). Furthermore, 60.4% of these children had Elevated D-dimer levels indicating significant formation and breakdown of blood clots in the body. Researchers further found that it is often difficult to distinguish MIS-C from other conditions like severe COVID-19 and Kawasaki disease. Hispanic and Black children made up 73% of this study (75).

DISCUSSIONS

Male children who are more prone to chronic ear infections may be more likely to be the asymptomatic superspreaders of COVID-19. High COVID-19 morbidity rates among men may be explained by a lifetime overuse of antibiotics (for chronic ear infections and other diseases) which may have led to imbalance in gut flora specifically candida albicans infection, and a disrupted gut barrier. Generally, Men are underdiagnosed for candida albicans infection. Men become more susceptible to this infection by using testosterone containing products as research strongly suggests that testosterone plays an important role in decreasing resistance to systemic C. albicans infection (77).

Published national and state data shows that persons of color might might be more likely to become infected with SARS-CoV-2, the virus that causes COVID-19, experience more severe COVID-19–associated illness, including that requiring hospitalization, and have higher risk for death from COVID-19 (78) and pre-existing anemia may be a contributing factor. Pre-existing anemias, can worsen the symptoms of NTHI/COVID-19 Infections during the nutritional immunity stage. During this stage iron is sequestered as a first line defense strategy. However, iron is reintroduced to NTHI which causes sharp rises and falls in iron levels which can have severe clinical implications for those who suffer with iron deficient blood. Furthermore, acquired haemolytic anemia may develop after treatment with drugs such as quinine, sulphonamides, para-amino-salicylic acid, or it may follow infections caused by bacteria or viruses (71). In the case of a patient with pre-existing anemias getting infected with NTHI/COVID-19 could be deadly especially when the aforementioned treatments are used. In a 2013 study, it was found that Blacks have moderate to severe anemia almost 3 times more than whites and hispanics (79).

Doctors have reported that after NIV respiratory therapy, there is a sudden, unexpected worsening of symptoms in some patients. This often leads to intubation and invasive mechanical ventilation (13). This may be due in part to the fact that Nontypeable Haemophilus bacteria is an anaerobe. These types of pathogens die quickly when exposed to oxygen. The rapid decline in patients' health after NIV may be explained by the Herxheimer Reaction or "die off effect" of the NTHi bacteria dying quickly.

Infections caused by NTHI are chronic and similar to other bacterial infections that are difficult to treat (23) with antibiotics. Antibiotics further strengthen bacterial resistant microbes which in turns further disrupts the gut barrier integrity. "In essence, antibiotics progress COVID-19 disease manifestations leaving moderate to severe patients open to re-infection. In severe patients, antibiotic therapies can lead to death as in the case of Penicillin. Penicillin is known to cause hemolytic anemia which can lead to hemorrhaging, blood clots, heart failure, and stroke" (80).

What Practitioners Can Do Now:

1. Consider Antiviral therapies using iminosugar derivatives. Since ADCC is thought to play a role in protecting against initial infection and controlling progression of infection in HIV, 2G12 dimmers may be a possible therapy (81). 2G12 is a neutralising human monoclonal antibody that has 3 possible combining sites. It has been identified as a possible antiviral

therapy for various viruses (82). Studies also suggest that " 2G12 competitively inhibits interactions between gp120's V3 loop and the tyrosine sulfate-containing CCR5 amino terminus, thereby reducing assembly of complexes that catalyze entry (83).

2. Cleanse Patient Gut - consider using enema treatments with antisense oligonucleotides as a short term remedy to reduce intestinal inflammation and downregulate ICAM-1 (84-86). A holistic approach using herbs and lifestyle modifications will be necessary to prevent symptom relapse after therapy.
3. Consider Replenishing Gut Flora via exaggerated probiotic therapy.
4. Consider available therapies using iminosugar derivatives for Candida Albicans overgrowth.
5. Enlist Resident Nutritionists with backgrounds in Vitamin Therapy, microbiology, biochemistry etc to help formulate the appropriate (and available) therapies given the considerations outlined in this research.
6. Non-clinical and Clinical Trials of holistic Islamic Medicine Therapies including Divine Ayats' Fitra30 COVID-19 Protocol.

Divine Ayat's Fitra30 COVID-19 Protocol
(Patent Pending)

RNA viruses, COVID-19 in particular, are highly mutagenic- up to a million times higher than that of their hosts therefore, it is essential to build host resilience and defence mechanisms to ward off entry of this disease into the body. The Fitra30 COVID-19 Protocol consists of natural treatments that stimulate and strengthen defence and healing mechanisms which are intrinsic to the host. These treatments are designed to specifically target COVID-19 by 1) blocking of pathways to SARS-CoV2 cellular entry and 2) Riding the body of COVID-19. Divine Ayats' Fitra30 COVID-19 Protocol is useful for individuals who desire effective natural treatments to

prevent and treat COVID-19 as opposed to (or in conjunction with) vaccines and standard treatments. In Arabic the word "fitra" means "a state of purity and innocence". Muslims believe that all humans were born in this state or "natural disposition". Divine Ayats' Fitra30 COVID-19 Protocol is a 30-day program designed to guide participants back to a state of purity Spiritually, Physically, Mentally, and Emotionally.

This Protocol Consists of Three Features:

1) The Milhu Shamsi Herbal Formulation (MSHF). MSHF is designed to prevent and treat COVID-19 by targeting internal mechanisms which act as conduits for COVID-19 infection such as ICAM-1 and CCR5.

2) Induction of autophagy through herbal medicine and intermittent fasting. The term "autophagy" is Greek, meaning "eating of self". It is a sophisticated way by which the body rids itself of harmful pathogens (bacteria, viral particles, etc.) on a cellular level to restore homeostasis (87). In disease recovery, autophagy can be thought as the body's desperate, self-destructive attempt at survival. Autophagy may in fact be the last immune defense against infectious pathogens that penetrate intracellularly (88). SARS-CoV-2 infection suppresses autophagy (89).

Interventions include Autophagy Jumpstart Herbal Blend (AJHB) and lifestyle modifications (i.e., intermittent fasting, proper diet, exercise, and sleep recommendations). A proven way of inducing autophagy is by food restriction (intermittent fasting), which upregulates autophagy in many organs (90). Fasting plays an important role in Islamic Medicine. Once per year Muslims are obliged to participate in Ramadan in which they fast from sunrise to sundown. Outside of Ramadan, it is encouraged for Muslims to fast at least 11 days during the month, to include; Mondays, Thursdays, and the 13, 14, and 15th of each month (according to the Islamic Calendar). Eating in moderation outside of these times is encouraged and recommended foods include (but are not limited to) Prophetic Foods (i.e., honey- which contains strong antifungal properties against Candida albicans infection (91), grapes - which are high in antioxidant Resveratrol which helps to induce autophagy (92), and pomegranates- which suppresses necrosis (93).

3) Divine Ayat's Spiritual, Emotional, and Mental Rejuvenation Program (SEM-RP) . COVID-19 has greatly affected many lives around the world. The combination of uncertainty and quarantining is causing depression, anxiety, sleep problems, and psychological distress (94). Divine Ayat's SMER Program is a 30-day guided meditation program designed to reduce stress. In a previous study, after 3 weeks of meditation students reported feeling less anxious, stressed, and displayed greater improvements in attentional control (95).

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Taliah Safah Muhammad wrote the manuscript.

Declaration of Competing Interests

The author is the Owner of Divine Ayat, LLC. and patent holder of Divine Ayats' Fitra30 COVID-19 Protocol.

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