Austin Journal of Pulmonary & Respiratory Medicine

Open Access

Austin Publishing Group

Review Article

SARS-CoV-2 Interacts with Mucosal Dysbiosis to Cause the Wide Range of Disease Seen in Covid-19

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Received: February 24, 2022; **Accepted:** March 19, 2022; **Published:** March 26, 2022

Abstract

Hypothesis: SARS-CoV-2 amplifies pre-existing dysbiosis induced mucosal inflammation and this can cause a severe systemic inflammatory disease. The microbial flora perturbation can persist long after the virus has been eliminated leading to a wide range of long Covid symptoms.

Evidence: Dysbiosis induced mucosal inflammation increases with age and is strongly associated with the metabolic syndrome (obesity, type 2 diabetes mellitus, ischaemic heart disease, hypertension, and depression). These are risk factors for the conversion of mild to severe Covid-19. Certain common strains of *Staphylococcus aureus*, which is commonly carried in pharyngeal mucosa, can trigger a cytokine cascade as seen in severe Covid-19. Blood group A and vitamin D deficiency, which are risk factors for hospitalisation in Covid-19 are also associated with increased *S. aureus* pharyngeal carriage rates. Multi-inflammatory syndrome in children is a post Covid condition which resembles toxic shock syndrome and Kawasaki disease (the former is known to be caused by staphylococcal pyrogenic toxins). A number of studies have shown dysbiosis of the oral mucosa and rectal mucosa in patients who progress to severe Covid-19. The wide range of pathology seen during and following SARS-CoV-2 infection is more in keeping with dysbiosis induced inflammation (multiple pathogenic bacteria at multiple sites) than with an otherwise simple viral induced respiratory tract infection.

Implication: Optimization of the microbial flora, prior to encountering the virus, could have reduced the severity of the pandemic. The consumption of fermented foods, especially yoghurt, holds the most promise for reducing dysbiosis induced mucosal inflammation and preventing a wide range of complications. Reduced mucosal inflammation brings not only health but also happiness in which oxytocin has a key role.

Keywords: SARS-CoV-2; Covid-19; Dysbiosis induced mucosal inflammation; Staphylococcal pyrogenic toxaemia; Periodontitis; Yoghurt

Introduction

SARS-CoV-2 causes a mild respiratory tract infection in the majority of young healthy adults. But in the elderly and in those with metabolic syndrome (obesity, ischaemic heart disease, hypertension and type 2 diabetes mellitus) it can cause a severe disease which can prove fatal. In severe Covid-19 there is an initial phase of mild respiratory tract symptoms followed by the development of severe systemic inflammation as the virus is undergoing immune mediated elimination. Severe inflammation in the lung can lead to acute respiratory distress syndrome (ARDS). Severe systemic inflammation can lead to clinical features that resemble toxic shock syndrome or sepsis [1-3].

At the height of the epidemic there were a few cases of multi-system inflammatory syndrome in children with features similar to toxic shock syndrome and Kawasaki syndrome [4,5]. There was also an increase in the number of children presenting with type 1 diabetes mellitus [6,7]. Another complication, occurring in younger people following mild Covid-19 is chronic fatigue syndrome with recurrent bouts of fatigue occurring over many months [8,9].

It seems highly unlikely that the virus acting alone could be responsible for such a wide range of possible outcomes. In this article, the hypothesis proposed, is that the virus interacts with mucosal dysbiosis to cause the various conditions that are observed.

Mucosal Dysbiosis

There are ten trillion bacteria growing on our epithelial surfaces. These bacteria have co-evolved with humans. The bacteria derive their energy from surface secretions. Mucus in the respiratory and enteric tract feeds surface bacteria, as does keratin produced by the skin. The surface cells of non-keratinized stratified squamous epithelium, which line the oral cavity, pharynx, oesophagus and vagina, contain glycogen, which feeds surface lactobacilli. The lactobacilli convert the glycogen to lactic acid and this suppresses the growth of bacterial pathogens. This specific epithelium plays a major role in the development of the hypothesis proposed in this article [10,11].

The majority of bacteria growing on the body surface does not invade body tissue and do not cause disease. But a tiny fraction of surface bacteria can invade tissue and can cause disease. These pathogenic bacteria grow within the tissues, close to the surface. They

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Citation: Morris JA, Shepherd RF, Diep P-T, Gatheral T, Wray M and Rigby RJ. SARS-CoV-2 Interacts with Mucosal Dysbiosis to Cause the Wide Range of Disease Seen in Covid-19. Austin J Pulm Respir Med. 2022; 9(1): 1086.

damage cells and provoke inflammation. These bacteria have genetic mechanisms which allow them to grow in tissue and to resist immune mediated elimination. There is an uneasy truce between these bacteria and the immune system which persists throughout life [12,13].

A tiny fraction of trillions is billions. Thus, there are billions of these pathogenic bacteria, present in tissues, feeding off blood glucose, priming and maintaining immunity from infancy to old age. The bacteria maintain their potency as we gradually lose ours. The result is that low grade inflammation gradually increases as we age and we will succumb to the bacteria in the end [14,15].

There are probably in excess of 500 species of bacteria growing on the surface, with over 1000 different strains in total. The number of pathogenic species growing within tissues, however, is less, with probably fewer than 100 strains. Thus, specification of the bacterial flora within is a more tractable problem than analysis of the flora without. Dysbiosis is a flora which is less than optimal, and this is also more easily ascertained than for the bacterial flora without. We need to meet a wide range of bacterial pathogens early in life, in low dose, on the mucosal surface in order to develop an appropriate immune response. We also need to be continually or continuously exposed to the pathogens throughout life in order to maintain the response. But once again in low dose and close to the mucosal surface [14].

A number of gram-negative anaerobic bacteria grow in the tissues of the gum and slowly erode the cementum that holds the teeth firmly in their sockets. These periodontal pathogens can invade blood vessels and are carried around the body to establish foci of chronic infection elsewhere. These bacteria are associated with Alzheimer's disease, the metabolic syndrome, and with cancer of the oesophagus, colon, pancreas, breast and prostate. *Porphyromonas gingivalis* is a periodontal pathogen that has been implicated in the cause of Alzheimer's disease and of rheumatoid arthritis. *Fusobacterium nucleatum* has a pathogenic role in ulcerative colitis, colonic cancer and oesophageal cancer [16-21].

Pharyngeal bacterial pathogens include *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and occasionally *Escherichia coli*. These bacteria can cause life threatening infections following viral respiratory tract infection. It is these bacteria in particular that are relevant to the complications seen in Covid-19.

Clinical Syndromes

Anosmia

SARS-CoV-2 is a respiratory tract pathogen. The virus is inhaled and enters the lining epithelial cells using the ACE2 receptor. Olfactory receptor cells are functional nerve cells that are present at the surface and SARS-CoV-2 can directly enter and replicate within them. This can cause varying degrees of loss of smell and taste sensation.

Mild respiratory tract infection

SARS-CoV-2 has surface spike proteins with receptor binding domains which have a high affinity for the enzyme angio-converting enzyme 2 (ACE2). Angio-converting enzyme 1 (ACE1) converts angiotensin 1 to angiotensin 2. ACE1 is present on the luminal surface of endothelial cells and most of the conversion of angiotensin 1 to 2 occurs in the lung, because all the blood flows through the lung. ACE2 is concerned with the breakdown of angiotensin 2.

The original SARS virus (SARS-CoV-1), caused acute interstitial pneumonia. It, too, entered cells by the ACE2 receptor. This has led some to assume that the SARS-CoV-1 replicates within endothelial cells in the lung. But, of course, a respiratory pathogen cannot transmit efficiently by endothelial replication alone. In the case of SARS-CoV-1 and SARS-CoV-2 the viral replication is in ciliated respiratory epithelial cells which have ACE2 receptors on their apical surface [22,23]. The virions enter and leave by the apical surface. The viruses might replicate in type 1 and 2 pneumocytes, but there is no convincing evidence of endothelial replication [22]. SARS-CoV-2, unlike SARS-CoV-1, transmits easily from person to person, often with few or even no symptoms.

Interstitial pneumonia

In a minority of adults infected with SARS-CoV-2 the respiratory infection progresses to a severe interstitial pneumonia which can prove fatal. In this condition the inflammatory process extends from the bronchi and bronchioles to involve the interstitial tissue of the alveolar walls. This development of severe inflammation is associated with a decreasing viral load [3]. At autopsy viral particles are seen in type 1 and type 2 pneumocytes, but not in endothelial cells [22]. In the most severe cases there is desquamation of type 1 and type 2 pneumocytes with fibrin exudation leading to acute respiratory distress syndrome (ARDS) [1-3].

When mild viral respiratory tract infections turn nasty the commonest cause is secondary bacterial infection by pharyngeal bacterial pathogens [24]. This can lead to bronchopneumonia and or septicaemia. It is possible that secondary bacterial infection is a contributing factor in the development of ARDS in some cases [25]. But in the majority blood cultures have been negative when the disease first deteriorated and high dose antibiotic therapy, given early, has not led to definite improvement. Furthermore, steroids have proved to be beneficial [26]. The appearance of the lungs at post mortem, in most cases, has been that of interstitial pneumonia rather than bronchopneumonia. But secondary bacterial infection with positive blood cultures has not been uncommon [25], and most severely ill patients did receive high dose antibiotic therapy at some stage in the course of their disease.

One possible explanation for severe interstitial inflammation that has not been excluded is staphylococcal pyrogenic toxaemia [27]. *S. aureus* is commonly carried in the upper airways and in the pharynx. All strains produce alpha-haemolysin, which is a perforin (it inserts a channel in cell membranes and leads to cell lysis). Some strains produce pyrogenic toxins which are superantigens. Toxic shock syndrome toxin (TSST), and staphylococcal enterotoxins (SEs) stimulate the proliferation of T cells, which secrete pro-inflammatory cytokines. This leads to marked tissue inflammation. This process can occur in the absence of septicaemia; therefore, negative blood cultures. Staphylococcal pyrogenic toxaemia is less likely to respond to antibiotics once the cytokine cascade has been triggered, and the bacteria in tissues often form bio-films which protect them from antibiotic action. Steroid therapy will help, however, as this suppresses the inflammation which is only serving to cause damage.

Failure to grow *S. aureus* from nasal, pharyngeal and bronchiolar

secretions does not exclude staphylococcal pyrogenic toxaemia. Nor do negative blood cultures. The simplest method is to perform selective culture of faeces for *S. aureus*, count the colonies and assess the genetic profile of the isolates [28].

It is of note, however, that in one study [25] *S. aureus* was one of the common isolates from positive blood cultures in hospitalized patients with Covid-19 and was a bad prognostic sign.

Systemic hyperinflammatory syndrome in adults

A systemic cytokine cascade leads to multi-system hyperinflammatory syndrome with damage to kidneys, heart and brain. These systemic features are similar to those seen in septicaemia or staphylococcal pyrogenic toxaemia. The cytokine storm in Covid-19, however, is more attenuated than that seen in other forms of sepsis. Cytokines with a short half-life are at lower levels but markers such as ferritin and d-dimers are markedly increased. The degree of disseminated coagulation is a particular feature of this condition [29].

Toxic shock syndrome was first described in 1978 [30]. The authors describe seven children, aged 8 -17 years, presenting with fever, headache, confusion, conjunctival hyperaemia, a scarlatiniform rash, subcutaneous oedema, vomiting, watery diarrhoea, oliguria, and a propensity to acute renal failure, hepatic abnormalities, disseminated intravascular coagulation, and severe prolonged shock. *S. aureus* was isolated from mucosal surfaces, mainly the nasopharynx, but not blood. The essential clinical picture was that of life-threatening bacterial sepsis or bacterial septicaemia but with negative blood cultures. The authors then inferred that the likely cause was bacterial toxaemia. This clinical insight was treated with some scepticism initially but was then confirmed a few years later when an epidemic of toxic shock syndrome in menstruating females was shown to be caused by a heavy growth of *S. aureus* in tampons [31]. Identification of the molecular structure of TSST and SEs (SEA, SEB, SEC, etc) followed.

Multi-system inflammatory syndrome in children (MIS-C)

Multi-system inflammatory syndrome in children shows features of staphylococcal toxic shock syndrome and Kawasaki disease. The epidemiological link between this condition and SARS-CoV-2 was made because of increased diagnosis of Kawasaki like conditions occurring at the peak of the SARS-CoV-2 epidemic [4,5].

Todd and colleagues, who first described toxic shock syndrome, expressed the opinion in the original publication that "similarities between toxic shock syndrome and Kawasaki disease raise the possibility of a common aetiology" [30]. This observation is prescient in view of the re-appearance of the two conditions in the current pandemic.

Circulating anti-toxin IgG antibodies which recognize the staphylococcal toxins are universally present [32]. Thus, free toxins will not occur in the blood in the absence of immune complexes. Kawasaki disease is complicated by coronary arteritis which is presumed to be immune complex mediated.

Type 1 diabetes mellitus

An increased number of children with type 1 diabetes mellitus were diagnosed at the peak of the SARS-CoV-2 epidemic [6,7]. Type 1 diabetes mellitus is an autoimmune disease caused by waves of immune destruction of the insulin producing beta cells of the pancreas. The penultimate wave of destruction leads to presentation with diabetic ketosis. There is then a honeymoon period before final waves of destruction causes a complete loss of insulin production. These waves of destruction commonly follow episodes of viral respiratory tract infection, but it is important to note that the virus causing the infection is different each time.

It has been suggested previously that the sequence of viral respiratory tract infection followed by pharyngeal bacterial overgrowth might be the key factor leading to type 1 diabetes mellitus [33]. There are a number of features that suggest that the process of molecular mimicry that underlies autoimmunity is provided by bacterial rather than viral antigens.

- Viral antigens change with each infection but the bacterial flora is constant.
- The genetic diversity of the bacterial flora is enormous and cross reaction of bacterial antigens with human antigens is to be expected.

Long covid

Many patients take a long time to recover from Covid-19. This applies to those hospitalized with severe infection but also to some who have suffered only a mild infection. Severe systemic inflammation involving kidneys, heart and brain can take months to resolve. If there is residual fibrosis in organs such as the lungs then there could be permanent deficit. All this is relatively easy to understand. But what is more difficult to explain is the common occurrence of symptoms resembling chronic fatigue syndrome seen particularly in young women who suffered only a mild infection [8,9].

The concept that "functional disorders" such as anorexia nervosa, chronic fatigue syndrome, anxiety neurosis and irritable bowel syndrome are due to an autoimmune response provoked by molecular mimicry with bacteria of the microbial flora has been proposed previously [34]. This fits with the age incidence and female prevalence of the conditions. Thus, chronic fatigue syndrome seen in long Covid is probably no different than chronic fatigue syndrome seen following other viral infections. Autoantibody production is common in patients with severe Covid-19; it would not be surprising if some patients with otherwise mild disease also developed antibodies to self-proteins in the course of fighting the infection [35].

Mechanisms of Disease

Viral respiratory tract infection - mucosal dysbiosis interaction

Viral respiratory tract infections always interact with the respiratory tract microbial flora and it is a mistake to ignore the possible consequences of this interaction. In the case of influenza, secondary bacterial infection is a common cause of severe disease and death [24]. But although pneumonia and septicaemia are relatively easy to diagnose, conditions such as toxic shock syndrome are not.

The importance of this interaction is evident to students of sudden infant death syndrome (SIDS). In the 1980s this condition commonly occurred in the winter months following viral respiratory tract infections [36]. But it was a different virus each year, and the

specificity did not lie with the virus but with the nasopharyngeal bacterial flora. Even otherwise healthy infants with a viral respiratory tract infection have increased carriage of *S. aureus* in the nasopharynx, increased carriage in the faeces and increased production of staphylococcal toxins, detected in urine [28]. Infants with a viral URTI sleeping prone have increased nasopharyngeal carriage of a number of bacterial pathogens including *S. aureus*. A simple action of putting infants to sleep on their backs led to decreased carriage of nasopharyngeal bacteria and a marked decrease in the number of deaths - from 1500 deaths in England and Wales in the mid-1980s to less than 500 per annum in the mid-1990s [37].

Type 1 diabetes mellitus shows a seasonal pattern of presentation, and commonly follows viral infection. But the evidence in this case points to multiple episodes of viral induced autoimmune attacks on the pancreatic beta cells. Once again, the specificity does not lie with the virus. It is more likely that the vast number of antigens presented by the mucosal bacterial flora leads to an autoimmune attack provoked by molecular mimicry [33].

Many of the features of Covid-19 and of long Covid can be understood in terms of a viral respiratory tract infection and an interaction with the microbial flora. Dysbiosis induced mucosal inflammation increases with age, as does the risk of severe Covid-19 [38,39]. Dysbiosis induced mucosal inflammation is also a feature of the metabolic syndrome (obesity, type 2 diabetes mellitus, hypertension, and ischaemic heart disease). Severe systemic inflammation in Covid-19 follows viral elimination [3], therefore an explanation in terms of amplification of dysbiosis induced mucosal inflammation makes sense. As does a continuation of symptoms of inflammation long after the virus has gone, as in long Covid.

Staphylococcus aureus

The hypothesis proposed in this article is that SARS-CoV-2 interacts with respiratory (and upper enteric) tract dysbiosis to cause the wide range of clinical features observed in Covid-19. Furthermore, it is suggested that a prime suspect for a major role in this process is *S. aureus*.

***S. aureus* is toxigenic:** The majority of strains produce alpha haemolysin, which is a perforin. Some strains also produce pyrogenic toxins which are super-antigens. Toxic shock syndrome toxin (TSST) and the staphylococcal enterotoxins (SEs) are pyrogenic toxins. They cause proliferation of T cells leading to the secretion of pro-inflammatory cytokines. *S. aureus* grows in tissues and at first sight it seems paradoxical that they carry toxins which can induce inflammation. But it is a targeted immune response that the host generates to eliminate bacteria, with maximum damage to the bacteria and minimum damage to the surrounding host tissue. Staphylococcal pyrogenic toxins cause the inverse, the immune response is not targeted on the bacteria but is generalized. The result is maximal damage to surrounding tissue with less damage to the bacteria. An uneasy truce then develops between the host and the bacteria and *S. aureus* defends itself and its immediate surroundings (its niche) against immune attack [27].

Viral respiratory tract infections lead to increased carriage of *S. aureus* and to increased toxin production [28]. In the case of SARS-CoV-2 the initial respiratory tract infection is mild, but if severe inflammation does develop it follows the mild phase and rises as the virus is eliminated. Thus, viral particles replicating within epithelial cells and causing cell lysis lead to mild inflammation, but when the cytotoxic T cells start to eliminate infected epithelial cells, *S. aureus*, if present in sufficient dose, will defend its niche and cause a severe non-directed inflammatory response.

There are two important risk factors for complications in Covid-19 which are associated with increased *S. aureus* carriage. These are blood group A and low serum levels of vitamin D [40-44]. These factors don't increase the risk of mild or asymptomatic Covid-19, but they do increase the risk of admission to hospital in the case of blood group A and a fatal outcome in the case of low levels of vitamin D.

Periodontitis

Marouf and colleagues [45] studied 588 patients from Qatar who developed Covid-19. Cases were defined as patients who suffered the complications of death, ICU admission or assisted ventilation. Controls were patients with Covid-19 who were discharged without major complications. Periodontal conditions were assessed in all patients using national electronic health records. Periodontitis was associated with Covid-19 complications including death (OR = 8.81, 95% CI, 1-77.7). ICU admission (OR = 3.54, 95% CI, 1.39-9.05) and need for assisted ventilation (OR = 4.57, 95% CI, 1.19-17.4).

The advantage of this study is that degree of periodontitis was ascertained from health records and therefore it represents dysbiosis prior to development of Covid-19. Periodontitis is a form of dysbiosis with pathogenic bacteria growing within tissues of the gum and causing inflammation. But the bacteria also cause systemic disease and systemic inflammation by various methods including spread of bacteria to distant sites, release of extracellular vesicles containing toxins [46], and spread of pro-inflammatory cytokines within the blood. The pathogenic bacteria can also spread to other mucosal surfaces. Finally, it is likely that if a lack of diversity of the commensal flora has allowed periodontitis to develop then dysbiosis at other mucosal surfaces will be present.

Studies of the gut microbiome have also revealed differences between patients with Covid-19 who develop severe disease and those who do not [47]. However, it is not possible to determine cause and effect as the gut microbiome changes might be contributing to the severity of the disease, be a consequence of the severe disease or be associated with dysbiosis at other mucosal surfaces.

Discussion

Covid-19 has protean clinical manifestations and it stretches credulity to imagine that SARS-CoV-2 is the sole cause of every variant [1-3]. Indeed, the concept that each disease has a single specific cause is dated. The biopsychosocial model of disease, which has gained prominence in recent years, indicates that multiple factors interact to cause disease [48]. A host of social, cultural and psychological factors interact with physical factors forming a complex causative pathway to disease. For instance, smoking raises the risk of many diseases, but we do not make the mistake of regarding this habit as the sole cause of any one disease. There are many different diseases but relatively few pathological processes that lead to disease. The latter interact to generate the wide range of disease that we observe. This means causative pathways are complex and that individual causative factors

are more common than the diseases they cause.

Bacterial pathogens which grow within our tissues cause low grade inflammation throughout life. They have genetic mechanisms that resist immune mediated elimination and they form an uneasy truce with the immune system. These bacteria retain their potency but age reduces ours. This leads to an inevitable but slow decline with age in our ability to maintain health and fight disease. The pathogenic bacteria that grow within our upper enteric (oral, pharyngeal, oesophageal) and respiratory tissues are perturbed by viral respiratory tract infection. It is to this interaction between virus and bacteria that we should look for the explanation of the protean manifestations of Covid-19.

Dysbiosis is deviation from the optimal flora. It is a complex state with many variants. But in the specific case of Covid-19 a great deal of circumstantial evidence points to a prime role for *S. aureus*. SARS-CoV-2, when acting alone, appears to cause a mild respiratory tract mucosal infection. Severe inflammation in the lung, and severe multi-system inflammation is associated with a cytokine cascade [3]. The most likely cause is staphylococcal pyrogenic toxaemia [12]. The sudden appearance of a new disease showing features of toxic shock syndrome and Kawasaki disease [4,5] also points to *S. aureus* as the culprit, or at least prime suspect. It surely isn't just coincidence that recognised risk factors for the development of severe disease; including blood group A, low serum vitamin D levels, and type 2 diabetes mellitus are associated with increased *S. aureus* carriage [40-44]. An increase in the number of children presenting with type 1 diabetes mellitus is another intriguing observation, as a role for common bacteria, such as *S. aureus*, has been long suspected [33].

Secondary bacterial infection complicating viral respiratory infection is common. There are reliable techniques to diagnose bacterial pneumonia and septicaemia. In the case of severe Covid-19 there is evidence of secondary bacterial infection in some cases but it does not appear to be the major cause of the cytokine cascade [3,29]. However staphylococcal pyrogenic toxaemia is much more difficult to diagnose and has not been excluded in the current pandemic. Nasal, pharyngeal and bronchiolar secretions have yielded *S. aureus* in a few cases, but there is no record of toxigenic potential [25]. A more reliable approach would be quantitative analysis of faecal specimens (*S. aureus* counts), followed by genotyping of the isolates [28].

There are no commercially available assays for staphylococcal pyrogenic toxins. Lancaster University scientists have developed an ELISA test for alpha-haemolysin, TSST and SEs [49-51]. This has been used to examine a wide range of urine samples in infants and adults. Staphylococcal pyrogenic toxins, in the picogram range, are found in a small proportion of infants in the early weeks of life and a larger proportion of infants who have a viral respiratory tract infection [28]. The ELISA, however, proved negative in 100 adults who had suffered myocardial infarction. Subsequent examination of the same urine specimens by polyacrylamide gel electrophoresis (PAGE) and immunoblotting demonstrated staphylococcal toxins in around 30% of cases [50]. This was in spite of the fact that the PAGE method was much less sensitive, but more specific. The explanation is that staphylococcal toxin production in adults is common, but anti-toxin IgG antibodies are almost universal [32]. Thus, any toxin produced combines with antibody in the circulation to form immune complexes which are in antibody excess. Some of the circulating immune complexes are secreted into the urine [49]. This must be an active process as the complexes are far too large to be passively filtered. The ELISA test does not see the antigen as it is shielded in the complex. But the immune complex partially denatures in the polyacrylamide gel and some of the toxin is released and can be recognised by immunoblotting. In addition, a reverse ELISA can recognize anti-toxin IgG.

The 100 patients with myocardial infarction all had measurable anti-alpha-haemolysin IgG in the urine samples taken immediately on admission [50]. The immune complexes were still present in urines taken six weeks later but the levels were less. A control group of healthy adults had very low levels of anti-alpha-haemolysin IgG. Alpha-haemolysin and other staphylococcal toxins were demonstrated by PAGE and immunoblotting in urines from patients with rheumatoid arthritis and in controls who were attending a fracture clinic [51]. It appears that immune complexes in blood and urine are common in patients with disease and not uncommon in healthy controls. The likelihood that they are present and contributing to the cytokine cascade in patients with severe Covid-19 is high.

The assessment of dysbiosis by second generation DNA sequencing techniques is complex and expensive. There is also considerable variation between individuals and rather less variation between groups such as cases and controls etc. In addition, only a tiny proportion of bacteria is pathogenic and has the genetic apparatus that allows them to survive long term within mucosal tissue. Periodontitis, however, is a form of dysbiosis that can be assessed clinically. It is associated with chronic inflammation at other sites and with the conditions that constitute the metabolic syndrome which in turn are associated with severe Covid-19. Periodontitis, dysbiosis, dysbiosis induced inflammation and mortality from Covid-19 also increase with age. Thus, periodontitis is best regarded as a clinical marker of more widespread mucosal dysbiosis involving both periodontal pathogens and other bacterial pathogens.

Dysbiosis is an extremely complex pathological condition with many different bacterial pathogens and many ways in which local and systemic inflammation can be produced. The uneasy truce between bacteria and the immune system, the necessity that bacteria defend themselves and their niche, and the inevitable waning of the potency of immune defense with age all add to this complexity. It is no surprise that the full cornucopia of pathological processes and disease states are represented in the phrase "dysbiosis induced mucosal inflammation".

But although the pathology is complex, prevention, or perhaps more accurately mitigation, might well be simple.

The non-keratinized stratified squamous epithelium, which lines the oral cavity, the pharynx, oesophagus and vagina, is composed of layers of squamous cells. The surface layer contains glycogen which feeds the surface lactose fermenting bacterial flora. The latter includes lactobacilli which convert the glycogen to lactic acid. Lactic acid suppresses the growth of bacterial pathogens, which are adapted to body pH. The bacteria that line epithelial surfaces ultimately enter the body in food and drink or are inhaled. The inhaled bacteria are carried by ciliary action to the pharynx. Thus, all bacteria meet non-keratinized stratified squamous epithelium on their way in to the

body. It is the control and entry point. Mother's milk has evolved to create an optimal flora in the oral cavity. It contains plentiful lactose fermenting organisms and pathogens in low dose. The pathogens prime the immune system and provide continuous or continual exposure throughout life. But the lactose fermenters suppress their growth, lock them down and keep them in check. This is the optimal flora we should try to re-create and maintain throughout life [11]. Unfortunately, our modern diet contains too much processed food in which the bacterial content has been lost. The result is a less diverse microbial flora and fewer lactose fermenters. Something comparable occurs in laboratory mice. They live in ultra clean conditions with sterilized food and filtered air. If mice in these conditions are given yoghurt in food, or lactobacilli in drinking water, they become noticeably healthier [52,53]. Their fur literally glows with health, they show increased grooming and experimentally induced wounds heal more quickly. They change from a pro-inflammatory to an anti-inflammatory state, and the latter condition is associated with increased oxytocin production. Indeed, the production of this neuropeptide has profound pathological, physiological and even philosophical implications. The molecule of love interacts with many aspects of the immune system, has healing properties, and both short-term and long-term influences on our emotional state.

A recent study from Stanford has shown that a diet supplemented with fermented foods, mainly yoghurt, leads to increased microbial diversity and reduced inflammatory cell markers [54]. The simple answer to the mitigation of dysbiosis induced mucosal inflammation might well be the consumption of yoghurt (live, no added sugar) [11].

Key Messages

- SARS-CoV-2 appears to amplify dysbiosis induced mucosal inflammation seen in the elderly and in those with the metabolic syndrome. This inflammation is present prior to viral infection, increases with viral infection and can continue long after viral elimination.
- Dysbiosis involves all mucosal surfaces, not just the gut.
- Pathogenic bacteria growing within tissues, a tiny minority of the microbial flora, cause chronic inflammation and contribute to the wide range of symptoms seen in Covid-19.
- Periodontitis is a clinical manifestation of dysbiosis, it causes systemic disease and indicates dysbiosis at other mucosal surfaces.
- Pharyngeal carriage of *Staphylococcus aureus* is a form of dysbiosis and this organism is a prime suspect in triggering the cytokine cascade seen in severe Covid-19.
- Fermented foods, especially yoghurt, reduce dysbiosis induced mucosal inflammation. They have potential to prevent, or at least mitigate, the severe systemic inflammation seen in some cases of Covid-19.
- The healthy anti-inflammatory state induced by long term yoghurt consumption is associated with oxytocin production; an observation of pathological, physiological, psychological and even philosophical significance.

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