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The Jounced Entrails-Intestine in COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19), initiated by contemporary coronavirus is a pandemic which engenders severe respiratory disease. SARS-CoV-2 preponderantly transmits through airborne particles and mammoth respiratory droplets additionally, gastrointestinal symptoms are manifested as anorexia, diarrhoea, vomiting, nausea, abdominal pain, hepatic involvement and gastrointestinal haemorrhage. SARS-CoV-2 employs receptors for Transmembrane Protease Serine 2 (TMPRSS2) in order to infect cells in order to engender modifications of Angiotensin Converting Enzyme II (ACE2) within the gut which enhances probability of intestinal inflammation and diarrhoea. Comorbidities such as asthma, hypertension, smoking, Alzheimer's disease, dementia or disease occurrence in male subjects are associated with disease severity, concurrent complications and mortality in COVID-19.

Preface

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) commenced in Wuhan (China) in 2019. The syndrome, additionally designated as 2019-nCoV, engenders severe respiratory disease. Coronavirus disease 2019 (COVID-19), initiated by contemporary coronavirus is a pandemic which influences global health and socioeconomic parameters. Respiratory symptoms are potent and pertinent manifestations of SARS-CoV-2 infection and human-to-human transmission is a pertinent methodology of viral dissemination within the community. The virus depicts a significant ability for transmission through airborne particles

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and massive respiratory droplets. Although SARS-CoV-2 infection is frequently asymptomatic, incriminated individuals may disseminate the virus. Additionally, asymptomatic subjects eliminate the virus in the absence of typical symptoms of COVID-19, thereby indicating the contribution of a competent immune system. COVID-19 frequently affects the gastrointestinal system with implication of intestinal immune system. Thus, occurrence of antecedent gastrointestinal symptoms such as diarrhoea may indicate a possible SARS-CoV-2 infection which mandates preliminary discernment and adequate treatment. Infected subjects represent a varied spectrum of clinical manifestations wherein respiratory symptoms such as cough and fever are characteristic of COVID-19 and appear in a majority of individuals. Gastrointestinal symptoms are consistently manifested and appear as anorexia, diarrhoea, vomiting, nausea, abdominal pain, hepatic involvement and gastrointestinal haemorrhage.

Physiology and Pathogenesis

Gastrointestinal symptoms of COVID-19 demonstrate intestinal inflammation or degeneration. Integrity of intestinal barrier is decimated and gut microbes activate innate and adaptive immunity thereby releasing pro-inflammatory cytokines into the circulation with consequent occurrence of systemic inflammation [1,2]. Certain intestinal signalling pathways regulate intestinal inflammation through dendritic cells. Commensal gastrointestinal microbiome configures a dynamic environment which is variable and engenders intestinal dysbiosis due to viral infection [1,2]. Viral shedding of SARS-CoV-2 in stool samples occurs in around 54% of incriminated subjects. Identification of coronavirus RNA within the faecal samples may indicate expunging infectious viral load or viral transmission. Median duration of viral shedding in survivors of SARS-CoV-2 infection is 20 days with a range between 8 days to 37 days. Also, SARS-CoV-2 may be viable and elicited from faecal or urine specimens for a duration exceeding > 4 weeks. Detection of SARS-CoV-2 within the faeces of asymptomatic individuals indicates viral transmission through the faecal route, a feature discernible for a duration longer than nasopharyngeal swabs [1,2]. Faecal microbiota transplant donors mandate appropriate evaluation for SARS-CoV-2 in order to decimate possible risk of transmission. Viral particles of SARS-CoV-2 are detectable in faecal samples during second phase of COVID-19 along with decimation of intestinal inflammation. Therefore, it may be posited that inflammatory diarrhoea observed in COVID-19 is associated with declining levels of faecal SARS-CoV-2 RNA [1,2]. SARS-CoV-2 employs receptors for Transmembrane Protease Serine 2 (TMPRSS2) in order to ingress and infect cells as the enzyme is also discerned in small intestinal epithelial cells. Activity of SARS-CoV-2 may engender modifications of Angiotensin Converting Enzyme II (ACE2) within the gut which enhances probable intestinal inflammation and diarrhoea. Elevated co-expression of ACE2 and TMPRSS2 is enunciated in enterocytes of small intestine, colon and the oesophagus, as evaluated by single-cell ribonucleic acid (RNA) sequencing of the gastrointestinal tract. Besides inducing intestinal inflammation,

ACE2 is pertinent in the composition of intestinal microbiota [1,2]. Downregulated tissue levels of ACE2 appear to be concurrent with effective viral replication and pathogenicity along with an unequivocal regulation of Renin- Angiotensin System (RAS). Imbalanced RAS-ACE2 activity arising within COVID-19 may significantly exacerbate tissue inflammation with unfavourable outcomes, especially when appearing in association with diverse comorbid conditions [1-3]. ACE2 is related to transport of neutral amino acids, gut homeostasis, regulation of intestinal epithelium along with composition and function of gastrointestinal microbiota engendering microbial dysbiosis. Emergence of around > 20 proteins in circulation is contingent to severity of COVID-19 and configures the blood proteomic risk score (PRS) which can suitably analyse severity of infection. Diverse proteins appear within the circulation which are immune factors augmented during systemic inflammation such as the C-Reactive Protein (CRP). Aforesaid risk score in concordance with intestinal microbiota can be associated with severity of COVID-19 [1,3]. Profile of gut microbiome in severe COVID-19 and altered faecal shedding of SARS-CoV-2 may be associated wherein the gastrointestinal bacteria appearing within infected individuals are diverse from healthy control subjects. However, live faecal SARS-CoV-2 may be absent from subjects infected with COVID-19. Also, infected individuals demonstrate an abundant gut microbiome, albeit composed of a significantly decreased bacterial diversity [3,4]. Enhanced mortality associated with COVID-19 infection usually arises in individuals above > 80 years, possibly due to variable contributory factors such as inability to combat infection, decimated immune system and declining diversity of the microbiome. Gut microbiota in the elderly population depicts a decreased diversity with augmented intestinal dysbiosis along with associated cognitive deficits, depression and elevated inflammatory markers [3,4]. Obesity or a distinctive dietary pattern is concurrent with altered intestinal flora and probably augments severity of COVID-19. Adipose tissue acts as a reservoir of SARS-CoV-2 and is involved in virus clearance and systemic immune activation. Mature adipocytes in obese individuals depict elevated values of ACE2. Besides, decline or elimination of inflamed adipose tissue may decimate viral ingress, systemic viral dissemination and prolonged pathogenicity. In obese individuals, significant dysregulation of myeloid and lymphoid genesis and cytokine secretion occurs within the adipose tissue [3,4]. Pro-inflammatory adipokines, leukotrienes or chemerin may be elevated with exacerbated possibility of emerging “cytokine storm syndrome” which subsequently engenders disease associated mortality. Altered immune system and coronavirus infection modifies the intestinal flora which modulate the gut-brain axis. Intestinal microbiota also regulate neurological functions and may induce depression or anxiety [4,5]. Diverse genes appear associated with immune pathways and cytokine signalling such as interferon-gamma signalling, features which concur with discernment and severity of COVID-19 [4,5].

Keywords

COVID-19; Pathogenicity; Infection; Gastrointestinal Symptoms

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Symptoms and Significance

Incrimination of gastrointestinal tract with COVID-19 as an emerging infection is of uncertain significance although severity of infection is concurrent to profile of intestinal microbiota. The viral infection alters intestinal permeability with consequent enterocyte dysfunction and frequently engenders diarrhoea (40%) along with associated gastrointestinal symptoms. Tissue specimens of ileum and terminal colon may demonstrate the presence of SARS-CoV-2 virus. Although the pathophysiology remains undetermined, gastrointestinal disease with SARS-CoV-2 is associated with digestive manifestations such as anorexia, diarrhoea, nausea, vomiting or abdominal pain [4]. Gastrointestinal symptoms enhance with increasing severity and progression of disease. Gastrointestinal symptoms may precede characteristic clinical manifestations of fever and respiratory symptoms as dry cough [4,5]. Diarrhoea is an initial, frequently observed gastrointestinal symptom. Anorexia is discerned in adults whereas vomiting is prominent in children. SARS-CoV-2 infection can unusually represent singular, gastrointestinal symptoms in the absence of cogent respiratory symptoms. Certain subjects may demonstrate diarrhoea due to unrelated conditions or medication, in contrast to infection with COVID-19 [4,5]. Gastrointestinal manifestations are augmented in delayed stage and with enhanced disease severity of COVID-19 infection. Individuals unaware of COVID-19 infection may serve as carriers, especially during onset of pertinent gastrointestinal symptoms [5,6]. Majority of gastrointestinal symptoms associated with COVID-19 are resistant to medications and specific treatment. Diarrhoea and anorexia are commonly discerned. Additionally, nausea, vomiting, abdominal pain and gastrointestinal haemorrhage may ensue [5,6]. Haemorrhage and abdominal pain are exemplified in severely infected subjects. Gastrointestinal symptoms such as hyperbilirubinemia, upper gastrointestinal haemorrhage and dysentery are exceptional [5,6]. No age group is exempt from SARS-CoV-2 infection although the elderly population, adults and individuals with comorbid conditions are particularly prone to severe infection. Possibly, absence of microbial diversity in the elderly and enhanced susceptibility to intestinal inflammation is implicated in emergence of pertinent gastrointestinal symptoms [5,6]. Comorbidities such as asthma, hypertension, smoking, Alzheimer's disease, dementia or disease occurrence in male subjects are associated with severity of disease, concurrent complications and eventual mortality in COVID-19. Altered gastrointestinal microbiome is associated with aforesaid comorbidities wherein the dysregulation may modulate immune system and enhance disease susceptibility, severity, complications and morbidity in COVID-19 [5,6]. Occurrence of diabetes is associated with disease severity and complications of COVID-19 on account of emerging systemic inflammation and gut-metabolite dysfunction [5,6]. Individuals with cardiovascular disease and coinfection of SARS-CoV-2 delineate an adverse prognosis and occurrence of cardiovascular complications such as myocardial infarction, arrhythmia, stroke, heart failure or myocardial suppression. Cardiovascular disease is associated with imbalanced gastrointestinal microbiota with reduced microbial diversity [6,7]. Hypertension is concurrent to dietary or lifestyle factors and profile of gut microbiome [7].

Figure 1: Gastrointestinal infection in COVID-19 demonstrating receptors for transmembrane protease serine 2 (TMRPSS2) and angiotensin converting enzyme II (ACE2) which abet viral ingress into host cell.

Figure 2: Gastrointestinal infection in COVID-19 displaying viral ingress into host cell and alteration of intestinal microbiota engendering specific gastrointestinal symptoms.

Figure 3: Gastrointestinal infection in COVID-19 infection exemplifying viral entry into host cell via receptors for transmembrane serine protease II (TMRPS2) and angiotensin converting enzyme II (ACE2) and development of specific gastrointestinal symptoms due to altered microbiome.

Figure 4: Gastrointestinal infection in COVID-19 due to viral ingress into enterocytes with consequent emergence of intestinal inflammation and microbial dysbiosis.

Assay and Analysis

Faecal detection of coronavirus is possible for around ~12 days following disease onset and the virus may be discernible in stool samples despite being absent in respiratory secretions. Also, subjects with gastrointestinal infection display an extended duration of onset of clinical

symptoms and clearance of viral load with detectable virus in the faeces [6,7]. Incriminated COVID-19 subjects with intestinal symptoms require concurrence with contributory factors such as age, gender or associated comorbid conditions. However, intestinal deterioration may follow the emergence of respiratory symptoms [6,7]. Elevated levels of faecal calprotectin in subjects with COVID-19 indicate a possible contribution of SARS-CoV-2 infection towards intestinal inflammation. Calprotectin values and serum interleukin 6 (IL-6) concentrations are significantly enhanced in diarrhoea associated COVID-19 subjects. Thus, adequate discernment and monitoring of COVID-19-related diarrhoea may be achieved by assessing calprotectin concentrations. Also, diarrhoea may appear secondary to virus-induced intestinal inflammation on account of infiltration of inflammatory cells such as neutrophils and lymphocytes into the intestinal mucosa along with discordance of gut microbiota [6,7]. Around 50% of SARS-CoV-2 infected subjects display a reactive reverse transcription polymerase chain reaction (RT-PCR), employed for detection of SARS-CoV-2 RNA in faecal samples in addition to intestinal microbial dysbiosis, indicating infectivity of samples with viral strains. Possibility of faecal-oral route of viral transmission of SARS-CoV-2 requires evaluation along with cogent isolation strategies [7,8]. Subjects of faecal microbiota transplantation and healthy donors necessitate pertinent viral screening. Gastrointestinal microbiome and faecal transplantation from healthy donors may depict a contributory role in therapeutic strategies adopted for treating severely infected COVID-19 individuals, a manoeuvre which is of immediate benefit in critically ill individuals demonstrating a decrepit immune system [7,8]. Pertinent perception and discernment of gastrointestinal symptoms is crucial as prompt diagnosis can appropriately curb viral dissemination. Diagnostic manoeuvres such as endoscopy and colonoscopy may be employed to demarcate clinical symptoms of COVID-19 infection from associated diseases such as inflammatory bowel disease or carcinomas of the gastrointestinal tract [8,9].

Therapeutic Options

Contemporary treatment options include modulation of intestinal microbiota and strategies pertaining to restoration of gastrointestinal microbiome within infected individuals and appear as optimal manoeuvres in decimating SARS-CoV-2 initiated systemic inflammation, intestinal damage or neuronal deterioration following incrimination of brain-gut axis [8,9]. Subjects infected with SARS-CoV-2 display cogent, preliminary digestive symptoms, such as diarrhoea which can be managed with adequate hydration therapy and monitoring serum electrolytes although efficacy of antidiarrheal drugs remains ambiguous. Subjects with diarrhoea demonstrate enhanced possible requirement of respiratory assistance and intensive care [9,10]. Prebiotics and probiotics can be gainfully employed to regulate intestinal bacterial flora, a strategy which is efficacious in reducing possible emergence of bacterial and viral infections. Probiotics interact with intestinal microbiota and modulate the immune system. However, emerging clinical symptoms or duration of hospitalization may remain unaltered. Adequate ingestion of probiotics results in significant decimation of inflammatory response to SARS-CoV-2 infection and declining disease severity. Adopting an anti-inflammatory diet may be a

suitable preventive measure [9,10]. Immunomodulation of innate host immunity through stimulation of epithelial receptors may be achieved, a phenomenon which may be beneficially adopted as a contemporary therapeutic measure in order to exterminate the SARS-CoV-2 virus within the preliminary, infective phase [10,11]. ACE2 receptors can be targeted for treating COVID-19 infection and associated comorbidities. ACE2 depletion within SARS-CoV-2 infection with associated comorbidities is accompanied by adverse outcomes. Primary stimulants of intestinal inflammation release cytokines and specific microbial products with consequent microbial dysbiosis which inculcates an inflammatory environment [11,12]. Circulation of intestinal cytokines augments systemic inflammation associated with COVID-19 which can evoke a damaging immune reaction. Contemporary therapeutic options may be developed with amalgamation of host cytokine pathways and interaction of gut microbiota with cytokines accumulated in SARS-CoV-2 infection. Concurrence of intestinal bacteria to SARS-CoV-2 infection require extended evaluation [11,12]. Intestinal microbiota may be altered by dietary modifications and ingestion of probiotics. An optimal immune response is contingent to adequate nutrition and a balanced, protein- rich diet which is necessary for production of antibodies to adequately control SARS-CoV-2 infection. Malnutrition compromises the immune response thus mounting an inadequate reaction to COVID-19 infection. Competent dietary and nutritional components strengthen the immune system which is necessitated to circumvent potential infections [11,12]. Reduced serum levels of vitamin A or zinc may enhance the risk of infection. Branched-chain amino acids, omega-3 fatty acids, anti-inflammatory and antioxidant molecules such as vitamin C, vitamin E and phytochemicals such as carotenoids and polyphenols are beneficial in mounting a cogent immune response. Adequate nutrients can suitably decimate inflammatory and oxidative stress with consequent melioration of the immune system and minimize severity of COVID-19 infection [12]. Serum levels of vitamin D is concurrent to precise immune response to COVID-19 infection, severity and associated mortality. Elderly individuals with pre-existing comorbidities and declining vitamin D levels are accompanied by enhanced mortality due to COVID-19 [12,13]. Adequate intake of fibre reduces possible mortality from infectious and respiratory diseases. Intake of whole grains favours the composition of intestinal microbiome with subsequent reduction of intestinal and systemic inflammation along with decreasing levels of C-Reactive Protein (CRP), Interleukin 6 (IL-6) and Tumour Necrosis Factor alpha (TNF- α) [13]. Dietary fibre obtained from fruits, vegetables or legumes delineates anti-inflammatory properties and configures beneficial compounds through metabolism and fermentation by gastrointestinal microbiome [12,13]. Subjects with gastrointestinal infection with COVID-19 exhibit enhanced duration of hospitalization with inferior prognostic outcomes [12,13].

Conclusion

Faecal detection of coronavirus is possible for around ~12 days following disease onset. Elevated levels of faecal calprotectin indicate a possible contribution of SARS-CoV-2 infection towards intestinal inflammation. A reactive Reverse Transcription Polymerase Chain Reaction (RT-PCR), employed for detection of SARS-CoV-2 RNA in faecal samples is observed in

roughly 50% individuals infected with the virus. Modulation of intestinal microbiota and restoration of gastrointestinal microbiome are optimal manoeuvres in decimating SARS-CoV-2 initiated systemic inflammation and intestinal damage. Prebiotics and probiotics can be employed to regulate intestinal bacterial flora. ACE2 receptors can be targeted for treating COVID-19 infection and associated comorbidities. Adequate nutrition, balanced protein- rich diet with antioxidants such as vitamin C, vitamin E, carotenoids and Vitamin D is beneficial. Immunomodulation of innate host immunity through stimulation of epithelial receptors or faecal transplantation from healthy donors may be advantageously adopted in treating severely infected individuals.

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