COVID-19 and the digestive system

Lynn Cooper M.D.
Robert J. Smith M.D.
Great Yarmouth, UK.

REVIEW

GASTROENTEROLOGY

OPEN ACCESS

Abstract: Since December 2019 a global epidemic of the novel coronavirus disease (Covid19) started, caused by the severe acute respira-tory syndrome coronavirus 2 (SARS-CoV-2). Unfolding the natural history of the disease proved that although the predominant site of infection is the lungs, about one third of Covid19 patients present extrapulmonary symptoms especially in the gastrointestinal (GI) system such as anorexia, diarrhea, vomiting, and abdominal pain. SARS-CoV-2 can actively infect and replicate in the GI tract through its entry receptor angiotensin converting enzyme 2 (ACE2) that is highly expressed in both alveolar and GI epithelial cells. These find-ings imply the possible involvement of the gut microbiota, which is known to influence the effectiveness of lung immunity. The aim of this rapid-review is to provide an update of the impact of Covid19 infection on the GI tract with a special focus on the microbiome. A better understanding of the relationship between Covid19 and the digestive system may explain why the virus results in severe complications in some patients and mild responses in others.

Keywords
Covid19; Gastrointestinal System; Microbiome; ACE2

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), or coronavirus 2019 (Covid-19) disease is been causing a major outbreak worldwide that has led to exceptional measures including social isolation and population confinement. The World Health Organization declared a Global Public Health Emergency on the 30th of January 2020. Initially the viral replication rate and lethality were underestimated leading to a pandemic. As of June 23nd, it has infected over 8,860,000 people worldwide and caused over 470,000 deaths globally [1]. The most recent measures of containment is improving greatly the health and death rate, but has a negative impact from an economic point of view. SARS-CoV-2 is a positive-sense single-stranded RNA virus that belongs to the Betacoronavirus genus. The first detectable marker after contagion is viral RNA determined by PCR from nasopharynx and sputum swabs. Viral specific IgM class antibodies begin to appear 5 – 7 days after the infection while IgG class antibodies are produced 14 days after [2]. So far the best strategy to contain the spread is mass diagnosis by rapid antigen tests of the population, but its efficacy is limited by its low sensitivity [1]. An increasing number of studies has demonstrated that the gastrointestinal (GI) system is invaded by SARS-CoV-2 and is possible that the GI can be evolved into an alternative source of infection. The aim of this rapid-review is to provide an update on the importance of the gastrointestinal aspects of Covid19 infection.

Gastrointestinal symptoms in Covid-19 infection

Human coronavirus family include the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS). About one third of the SARS patients present GI symptoms and active viral replication in both small and large intestines suggesting a viral tropism in the GI tract [3,4]. Typically, the general symptoms of Covid19 disease include fever, cough, shortness of breath, dyspnea and major asthenia. Based on the evolutionary similarity to SARS-CoV and MERS, it was proposed that although the predominant site of infection is the lungs, Covid19 patients have extrapulmonary symptoms especially in the GI system, such as anorexia, diarrhea, nausea, vomiting and abdominal pain, elevated liver enzymes, as well as anosmia and ageusia [5,6]. Diarrhea can be one initial symptom and may even occur earlier than pyrexia or respiratory symptoms but many times is being misregarded as a symptom because it is self-limited [7,8]. Early studies presented a low incident of GI symptoms in Covid19 disease (1-3.8%) but others are now showing a much higher rate (11 - 24%) [7,9-13]. One study reported the diarrhea rate up to 35.6% in a cohort of 73 patients stressing the variability of the clinical presentation of the disease [14]. Abdominal pain was presented in 2.2 - 5.8% in patient cohorts [8,15]. In another study that investigated viral shredding in pediatric Covid-19 patients, diarrhea was observed in 3 out of the 10 infected children [12]. Notably, although Covid-19 children manifest different clinical features, such as a milder disease

 DOI 10.17605/OSF.IO/6QJX5

course and less respiratory symptoms, the GI symptoms appear to be similar [12].

Accumulating evidence from endoscopy examinations of Covid-19 patients also showed that SARS-CoV-2 is present in the GI tract while it has been successfully isolated from anal/rectal and stool specimens [12,15,16]. Interestingly, a number of studies revealed that Covid-19 patients were persistently tested positive on rectal and stool samples days after showing negative in their respiratory swabs [12,14]. This suggested that viral shedding from the gastrointestinal tract is abundant and can last long after the resolution of the clini-cal symptoms. Indeed, a previous study of SARS-CoV indicated that viral RNA could still be detected after 30 days in the stools of SARS patients [5]. The main receptor for SARS-CoV-2 and its viral nucleocapsid, is angiotensin converting enzyme 2 (ACE2) that mediates viral entry into the cells. ACE2 expression positively correlates with viral infectivity [8,9] and its expression predominates in lung cells, the absorptive intestinal epithelial cells in the ileum and colon as well as in the esophageal upper and stratified epithelial cells [15]. Xiao., et al. dem-onstrated abundant ACE2 expression in biopsies of gastric, duodenal and rectal mucosa of Covid19 infected patients [14]. SARS-CoV-2 nucleocapsid protein was also detected in the cytoplasm of gastric, duodenal, and rectal epithelium [17].Nevertheless, the presence of SARS- CoV-2 in the stool has not proven to correlate with the GI symptoms [7]. The coexistence of GI and respiratory manifestations may entail greater disease severity as compared to patients with exclusively respiratory symptoms. Further-more, the digestive symptoms can appear without respiratory symptoms, which has important epidemiological implications [11]. More cohort studies are required to address whether there are diagnostic and prognostic values of GI symptoms in Covid-19 disease. On the top of shedding some light into the receptor-mediated entry of SARS-CoV-2 into the host cells, these findings imply that SARS-CoV-2 possible transmission through the fecal-oral-route although there is no solid evidence yet to support this notion.

The impact of Covid19 infection in gut microbiota

The evidence that some Covid19 patients present GI symptoms, viral RNA is found in their stools and ACE2 is abundantly expressed in the intestine suggests the involvement of gut microbiota, which is also known to influence lung immunity [5,18]. Germ free mice, without a gut microbiota have been shown to have impaired pathogen clearance capacity in the lung [19].A healthy balanced gut microbiota is essential for the maintenance of an competent immune system able to control excessive immune reactions and cytokine storm that eventually become harmful to lungs and vital organ systems [20]. Clearly, a balanced immune response instead of an over reactive one can magnify clinical complications such as pneumonia in Covid-19 disease. Furthermore, Covid19 is notori-ous for being severe in the older and immune-compromised patients that are also reported to have gut dysbiosis. Gut microbiota composi-tion can be a major factor in determining the course of Covid19 disease. For example, the removal of beneficiary gut bacteria by antibiotic treatment was shown to induce increased susceptibility to influenza virus infection in the lungs [21]. Also, several bacterial metabolites and fragments are known to modulate lung immune response [22]. It can therefore be deducted that a personalized diet that can shift the microbiota composition towards a balanced gut microbiota, can potentially improve prophylaxis and can improve clinical outcomes in Covid19 patients.

Conclusion

Today SARS-CoV-2 presents a serious threat to health and economy worldwide. As our understanding on the disease advances, we now know that SARS-CoV-2 has a tropism to the GI tract and gut dysbiosis may be influencing the clinical manifestation of the disease. Since, gut microbiota can be modulated by diet we can develop personalized diet strategies to use them as a supplement to current routine therapies. In order to do so, the microbiota composition of Covid19 patients should be assessed and modulated by changing the patients' diet to include prebiotics, probiotics, such as FOS, GOS, and various lactobacilli strains to improve gut dysbiosis to the end of minimiz-ing excessive immune responses. This may improve and accelerate recovery in Covid19 patients especially in patients that are severely affected. More studies must be conducted to understand the role of the gut and lung microbiota in Covid19 disease and to develop such effective nutritional strategies. A better understanding of this relationship may explain why the virus results in severe complications in some patients and mild responses in others.

References

1. An Overview of the Rapid Test Situation for COVID-19 Diagnosis in the EU/EEA (2020).
2. Jin Yujiao., et al. "Diagnostic Value and Dynamic Variance of Serum Antibody in Coronavirus Disease 2019". International Journal of Infectious Diseases 94 (2020): 49-52.
3. Leung Wai K., et al. "Enteric Involvement of Severe Acute Respiratory Syndrome-Associated Coronavirus Infection". Gastroenterology125.4 (2003): 1011-1017.

4. Hung IFN., et al. "Viral Loads in Clinical Specimens and SARS Manifestations". Emerging Infectious Diseases 10.9 (2004): 1550-1557.
5. Chan Jasper Fuk Woo., et al. "A Familial Cluster of Pneumonia Associated with the 2019 Novel Coronavirus Indicating Person-to-Person Transmission: A Study of a Family Cluster". The Lancet 395.10223 (2020): 514-523.
6. Gu Jinyang., et al. "COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission". Gastroenterology 158.6 (2020): 1518-1519.
7. Lin Lu., et al. "Gastrointestinal Symptoms of 95 Cases with SARS-CoV-2 Infection". Gut 69.6 (2020): 997-1001.
8. Wang Jun., et al. "ACE2 Expression by Colonic Epithelial Cells Is Associated with Viral Infection, Immunity and Energy Metabolism". Med Rxiv (2020)
9. Chen Yun., et al. "Structure Analysis of the Receptor Binding of 2019-NCoV". Biochemical and Biophysical Research Communications525.1 (2020): 135-140.
10. Lu Xiaoxia., et al. "SARS-CoV-2 Infection in Children". New England Journal of Medicine 382.17 (2020): 1663-1665.
11. Guan Wei-jie., et al. "Clinical Characteristics of Coronavirus Disease 2019 in China". New England Journal of Medicine 382.18 (2020): 1708-1720.
12. Xu Yi., et al. "Characteristics of Pediatric SARS-CoV-2 Infection and Potential Evidence for Persistent Fecal Viral Shedding". Nature Medicine 26.4 (2020): 502-505.
13. Mao Ren., et al. "Implications of COVID-19 for Patients with Pre-Existing Digestive Diseases". The Lancet Gastroenterology and Hepa-tology 5.5 (2020): 426-428.
14. Xiao Fei., et al. "Evidence for Gastrointestinal Infection of SARS-CoV-2". Gastroenterology 158.6 (2020): 1831-1833.
15. Zhang Jin jin., et al. "Clinical Characteristics of 140 Patients Infected with SARS-CoV-2 in Wuhan, China". Allergy: European Journal of Allergy and Clinical Immunology (2020).
16. Holshue Michelle L., et al. "First Case of 2019 Novel Coronavirus in the United States". New England Journal of Medicine 382.10 (2020): 929-936.
17. Harmer Dan., et al. "Quantitative MRNA Expression Profiling of ACE 2, a Novel Homologue of Angiotensin Converting Enzyme". FEBS Letters 532.1-2 (2002): 107-110.
18. Bingula Rea., et al. "Desired Turbulence? Gut-Lung Axis, Immunity, and Lung Cancer" (2017).
19. Fagundes Caio T., et al. "Transient TLR Activation Restores Inflammatory Response and Ability To Control Pulmonary Bacterial Infec-tion in Germfree Mice". The Journal of Immunology 188.3 (2012):1411-1420.
20. Koumbi Lemonica. "Gut Microbiota Alterations in Liver Diseases". EC Gastroenterology and Digestive System 5 (2018).
21. Looft Torey and Heather K Allen. "Collateral Effects of Antibiotics on Mammalian Gut Microbiomes". Gut Microbes 3.5 (2012).22. Dhar Debojyoti and Abhishek Mohanty. "Gut Microbiota and Covid-19- Possible Link and Implications". Virus Research 285.1 (2020): 198018.

Lynn Cooper
79 Peachfield Road
Yarmouth, UK.
Coopermdlynn@gmail.com.uk

DOI 10.17605/OSF.IO/6QJX5