Impact of COVID-19 on the Gut: A Review of the Manifestations, Pathology, Management, and Challenges

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ABSTRAK

Virus SARS-CoV-2 merupakan suatu virus yang dapat memasuki sel penjamu melalui reseptor Angiotensin Converting Enzyme–2 (ACE2). ACE2 banyak diekspresikasn pada saluran cerna seperti epitelial esofagus, dan enterosit dari ileum-kolon. COVID-19 memiliki gejala klinis yang bervariasi dan berbeda disetiap individu yang menderitanya, mulai dari yang tidak ditemukan gejala klinis apapun, hingga pada spektrum klinis yang sedang dengan gambaran klinis pneumonia ringan, dan sampai spektrum klinis yang berat dengan klinis dyspnea dan hipoksia sampai mungkin menuju kematian akibat gagal nafas ataupun kegagalan multiorgan. Pada kenyataannya infeksi COVID-19 ini tidak saja berhubungan dengan masalah respirasi, namun juga dapat bermanifestasi dengan gejala klinis saluran cerna seperti diare, muntah, nausea, dan nyeri perut. Hal terburuk yang dapat terjadi sehubungan saluran cerna adalah terjadinya perdarahan atau perforasi pada saluran cerna dan inflamasi berat, yang dapat kemudian berdampak pada gangguan sistem imunitas jaringan intenstinal, dan lebih lanjut dapat mempengaruhi sistem imunitas tubuh penjamu. Pada traktus gastrointestinal, COVID-19 dapat mempengaruhi homeostasis mikrobiota didalam saluran pencernan. Namun demikian, sesungguhnya hingga kini belum ada penjelasan yang jelas mengenai mekanisme patofisiologi dari infeksi SARS-CoV-2 berhubungan dengan gejala klinis saluran cerna, mekanisme terdeteksinya virus RNA pada faeces, dan adanya kemungkinan transmisi fecal-oral pada SARS-CoV-2. Artikel ini diharapkan dapat membahas pengaruh infeksi SARS-CoV-2 pada saluran pencernaan, mikrobiota saluran cerna dan paru, dan kemungkinan terjadinya transmisi fecal-oral pada COVID-19.

Kata kunci: *virus SARS-CoV-2, ACE-2, COVID-19 pada saluran cerna, mikrobiota, transmisi fecal-oral.*

ABSTRACT

SARS-CoV-2 is a virus that can enter its hosts through the Angiotensin Converting Enzyme-2 (ACE2) receptor. ACE2 is mainly expressed in cells of the gastrointestinal tract, such as the esophageal epithelium and enterocytes from the ileum-colon. Coronavirus Disease 2019 (COVID-19) has varying clinical symptoms and presents differently in individuals, ranging from asymptomatic carriers to moderate clinical spectrum with mild pneumonia clinical features, and to a severe clinical presentation with dyspnea and hypoxia, leading to death due to respiratory or multi-organ failure. COVID-19 infection can also manifest themselves in the form of gastrointestinal symptoms

such as diarrhea, vomiting, nausea, and abdominal pain. Severe complications of gastrointestinal COVID-19 infections include hemorrhage or perforation of the gastrointestinal tract and severe inflammation, which can adversely affect the intestinal immune system, and therefore the systemic immune system of the host. Furthermore, COVID-19 has also shown to affect microbiota homeostasis in the digestive tract. To date, no clear explanation is available regarding the pathophysiology of gastrointestinal SARS-CoV-2 infection, fecal RNA detection, and the possibility of fecal-oral transmission of SARS-CoV-2. This review aims to discuss the effects of SARS-CoV-2 infection on the digestive tract, microbiota, and lung, and the possibility of fecal-oral transmission in COVID-19.

Keywords: *SARS-CoV-2, ACE-2, COVID-19, gastrointestinal tract, microbiota, transmission.*

INTRODUCTION

The SARS-COV-2outbreak, causing the Coronavirus Disease 2019 (COVID-19), has led to a global pandemic.[1] This COVID-19 infection was initially identified in Wuhan, Hubei Province, China.[2,3] On January 30, 2020, the World Health Organisation (WHO) declared COVID-19 a global health emergency, based on the data of its spread, which continues to increase exponentially.[4]

SARS-CoV-2 virus is a single stranded virus of Betacoronavirus genus.. Mechanically, the virus enters host cells through the Angiotensin Converting Enzyme-2 (ACE2) receptor.[5] ACE2 is mainly expressed in gastrointestinal cells, such as esophageal epithelial cells and enterocytes from the ileum and colon. Presentation of COVID-19 varies greatly in relation to the spectrum of symptoms, ranging from asymptomatic (often found in young patients without comorbidities or underlying diseases), moderate spectrum conditions with mild pneumonia as the defining clinical feature, to a syndrome of severe symptoms, including dyspnea and hypoxia, that leads to death caused by respiratory or multi-organ failure.[6]

While COVID-19 infection primarily affects the respiratory system, it can also manifest itself with clinical gastrointestinal symptoms such as diarrhea, vomiting, nausea, and abdominal pain.[7] Therefore, through this article, we wish to review the impact of SARS-CoV-2 infection on the digestive tract, gastrointestinal and lung microbiota, and the probability of fecal-oral transmission of COVID-19.[8]

EPIDEMIOLOGY OF GASTROINTESTINAL DISEASE IN COVID-19

COVID-19 is most commonly associated with a majority of respiratory problems, such as pneumonia, hypoxia, and acute respiratory distress syndrome (ARDS). Currently, a subgroup of COVID-19 patients has been defined which include (1) patients with gastrointestinal symptoms such as diarrhea, anorexia, vomiting, and nausea that occur along with respiratory symptoms, (2) patients with early gastrointestinal symptoms, followed by respiratory symptoms, (3) patients with only respiratory symptoms, and (4) patients with only gastrointestinal.[7-14]

Data obtained from a systematic review conducted by Zhao et al. of 93 studies consisting 25.210 patients, the incidence of gastrointestinal symptoms in COVID-19 patients was found to be 18.6% (95% CI 15.7-21.6%).[15] Pooled results of the various studies showed that anorexia and diarrhea were two major clinical symptoms occuring in patients infected with COVID-19 with incidences of 26.1% (95% CI:17.6-34.5%) and 13.5% (95% CI:10.8-16.1%), respectively. Other gastrointestinal symptoms observed included nausea (7.5%, 95% CI: 5-10%), vomiting (6%, 95% CI: 4.4-7.6%), and occasional abdominal pain (5.7%, 95% CI: 3.2-8.1%).[15]

In a cohort study conducted by Fang D, et al (2020) it was found that diarrhea often occurred on day 1-8 (median 3.3 days) after disease onset and would last about 1-14 days. Defecation stimulation reached a frequency of 9 times per day, with a median of 3.3 SD 1.6 episodes per day. In most cases, feces excreted by the patients had a liquid consistency (34.3%).[13,16]

PATHOGENESIS OF CORONA VIRUS IN HUMANS

Virology of COVID-19

Coronavirus is a family of RNA viruses with the Nidovirales order and is a significant

pathogenic agent in humans and animals. SARS-CoV-2 is a single-chain RNA virus and is composed of 4 structure proteins, including spike glycoproteins (S), small envelope glycoproteins (E), glycoproteins membrane (M), nucleocapsid (N), and other accessory proteins. Glycoprotein S is a transmembrane protein found in the outer portion of the virus body. Protein S, which appears on the surface of the virus, facilitates the binding of the viral cell to host cells through the ACE2 receptor.

After entering the cell, this S protein will be split into 2 sub-units, S1 and S2. S1 and S2 will ultimately be in charge of mediating the virus to undergo fusion and allow the transmission process into the host cell. Protein N is a structural component of the virus that is localized in the Endoplasmic Reticulum-Golgi Apparatus and is structurally bound to nucleic acid components. N protein is involved in the process of viral replication and the cellular response of host cells to viral infections. Meanwhile, M protein is the most structurally significant component and has a role in determining the shape of the virus envelope.[4] The life cycle of the SARS-CoV-2 virus, beginning from the transmission into the host's body, its replication, transcription, translation, and until its release, is illustrated in **Figure 1**.

Pathogenesis of SARS-CoV-2

COVID-19 has a pre- or asymptomatic incubation phase that ranges from 2-14-day time intervals. The most common symptoms that appear are fever, cough, dyspnea, and weakness.

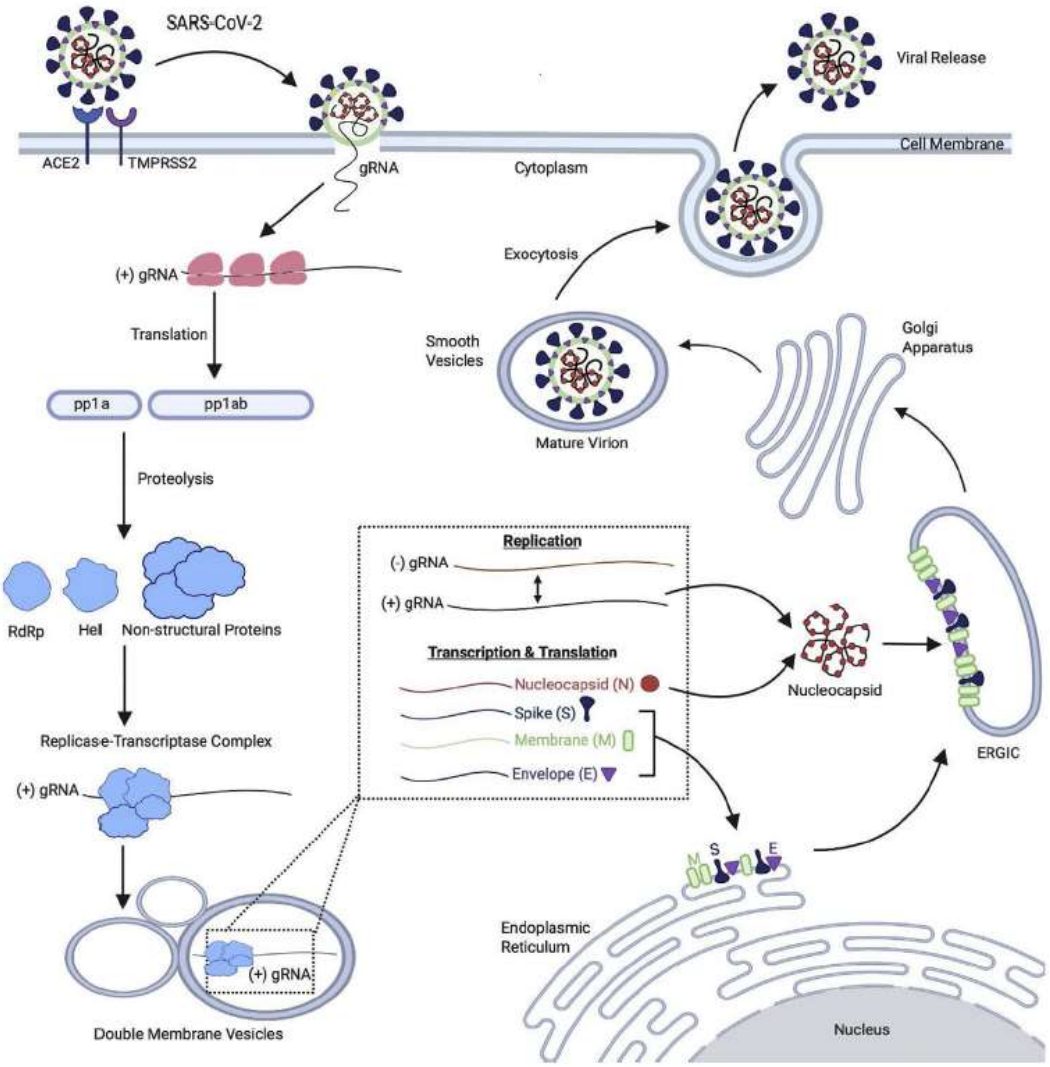

Figure 1. Virology of COVID-19.[4]

Lymphocytopenia is also found in most patients. The increasing severity of the disease, is indicated by high levels of pro-inflammatory cytokines such as IL-2 IL-7, IL-10, G-CSF, and TNF-alpha. Septic shock is therefore possible due to altered hemodynamics and multi-organ failure.[4]

COVID-19 CAUSES GASTROINTESTINAL DISORDERS

ACE2 receptors are ubiquitously found in the epithelial cells of the human small intestine. ACE2 physiologically expresses type II epithelial cells. Many studies have proven that COVID-19 patients can experience clinical symptoms related to the gastrointestinal tract, indicating that SARS-CoV-2 can invade the target organs of the gastrointestinal tract through the ACE2 receptor, which then causes primary damage to the invaded organs. A study found that angiotensin II was accumulated in patients with COVID-19, and the high levels of angiotensin II were significantly associated with the patient's clinical improvement.[17]

ACE2 directly regulates the homeostasis of amino acids in the gastrointestinal tract, expresses antimicrobial peptides, and maintains the balance of microbiota in the intestine. Animal studies have shown that suppression of ACE2 in mice models resulted in decreased serum tryptophan. Tryptophan is essential for the synthesis of niacin in the body, and a deficiency of niacin or tryptophan in the body can lead to pellagra. Tryptophan is absorbed through the ACE2 transport route, which is on the lumen of the intestinal epithelial cell surface. It can therefore be hypothesized that binding of SARS-CoV-2 to ACE2 receptors in the gastrointestinal tract can cause a decrease in the number of free receptors, which in turn results in reduced tryptophan absorption and ultimately destabilizes the microbiota in the intestine (marked by diarrhea).[17]

RELATIONSHIP BETWEEN GI AND RESPIRATORY DISORDERS IN COVID-19

Changes in the composition and function of the normal flora in the gastrointestinal system can affect the respiratory tract through the mucosa of the immune system. Disorders of normal flora in the respiratory tract can also simultaneously affect the digestive system through the regulation of the immune system. This effect is called the gut-lung axis.

Based on research report by Ye et al., it can be speculated that the clinical gastrointestinal symptoms may not be directly caused by viral damage to the gastrointestinal tract. CD4 effector T cells that enter the intestinal mucosa are the key to impaired immunity to the gastrointestinal mucosa and the occurrence of chronic enteritis. The CC chemokine receptor type 9 is a chemokine receptor for CD4 T cells that acts as a mediator to the small intestine, as described in **Figure 2**.[17] Small intestinal epithelial cells can express CCL25, which can then initiate the call for CCR9 CD4 cells into the small intestine, and cause damage to the immune system, homeostasis, and microbiota in the intestine. Disruption of the normal flora in the intestine will provoke the polarization of Th17 cells in the small intestine. Excessive production of IL-17A will induce the arrival of neutrophils, causing damage to the immune system in the digestive tract, diarrhea, and other gastrointestinal symptoms.[17]

Damage to the intestinal mucosa and imbalance of the gut microbiota can also affect the gut-liver axis, which is the bidirectional relationship between the intestine, microorganisms, and the liver through the portal vein. In the intestine, the host and the metabolic products of the microbiota will be transferred to the liver through the portal vein, resulting in damage to the liver function. Simultaneously, the

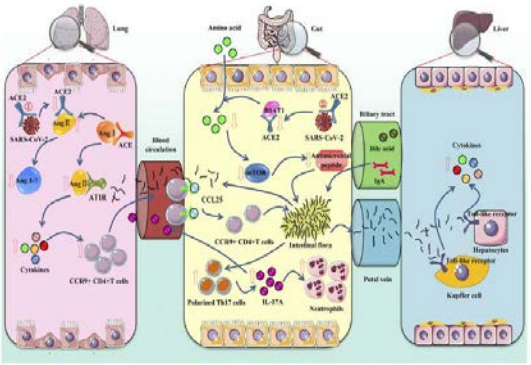

Figure 2. Gut-Lung Axis and Gut-Liver Axis in relation to clinical symptoms of the respiratory tract, gastrointestinal tract, and liver disorders of COVID-19 patients.[17]

liver can also transport its metabolic products into the intestine through the biliary tract.

GASTROINTESTINAL CLINICAL SYMPTOMS CAUSED BY TREATMENT SIDE EFFECTS

Diarrhea is a common side effect of antibiotics, especially after the use of macrolides, cephalosporins, and beta-lactam antibiotics. A study by Leung WK, et al. (2003) with a sample of 138 SARS-CoV patients, showed that 38% of the subjects experienced diarrhea after using the antibiotics mentioned above, with a median duration of 3.7 days after antibiotic use. This suggests that some diarrhea symptoms experienced by COVID-19 patients may be related to the use of antibacterial drugs.[18]

Anti-viral drugs, such as oseltamivir and arbidol, which are widely used as a therapeutic option for COVID-19, are also known to cause diarrhea in users. The incidence of diarrhea in patients using thesedrugs was approximately 55.2%. Other anti-viral drugs that could cause diarrhea include chloroquine phosphate, lopinavir, and remdesivir, as well as the traditional Chinese medicine lianhuaqingwen.[17]

GASTROINTESTINAL MICROBIOTA DISORDERS IN COVID-19

In patients with COVID-19 infection, the balance of microbiota in the intestine is disturbed, causing a condition known as dysbiosis. It has been proven that patients with COVID-19 develop dysbiosis in the gastrointestinal tract, which is characterized by a decrease in probiotic agents such as *Lactobacillus* and *Bifidobacterium*.[19,20] Nutrition and prebiotics or probiotics administration is hypothesized to restore the balance of microbiota in the gastrointestinal tract and reduce the risk of infection due to bacterial translocation. Gou et al, through their study, found that administration of probiotics or prebiotics can be a preventive agent or treatment option, especially for patients who are susceptible to or are infected with SARS-CoV-2.[21]

Another therapy that can also be considered for COVID-19 patients is fecal microbiota transplantation (FMT) therapy. It is hypothesized that this therapy delivery strategy can improve the balance of both microbiota in the gastrointestinal tract of COVID-19 patients.[22]

MANAGEMENT OF COVID-19 RELATED TO UPPER GASTROINTESTINAL PROBLEMS

Anorexia is one of the most common symptoms in COVID-19 patients, followed by nausea and vomiting. This symptom can be a response of the gastrointestinal tract to SARS-CoV-2 infection or a side effect of the anti-viral medication administration. The recommended therapy involves drug side effect management and/or psychotherapy. Metoclopramide, domperidone, or 5-hydroxytryptamine receptor antagonists can be considered in COVID-19 patients who experience ongoing nausea and vomiting.[23]

Furthermore, it has been found that COVID-19 can induce metabolic stress in the patient's gastrointestinal tract, which in turn causes mucosal damage to the digestive tract resulting in gastrointestinal bleeding and erosive gastritis. Provision of proton pump inhibitors and administration of gastroprotective drugs as a therapeutic option may be considered.[23]

MANAGEMENT OF DIARRHEA IN COVID-19

Diarrhea caused by side effects of anti-viral medications usually resolves spontaneously without the need for additional therapy. However, in cases where diarrhea occurs more than four times a day, pharmacological treatment should be considered. To date, there are no specific guidelines regarding the management of diarrhea in COVID-19 patients. Prescribing probiotics or prebiotics and dioctahedral montmorillonite is thought to be a therapeutic option for COVID-19 patients who experience diarrhea. Provision of probiotic preparations containing the microorganism *Lactobacillus* is thought to be used in COVID-19 patients with diarrhea, although further research is still required to assess efficacy.[17]

MANAGEMENT OF LIVER DYSFUNCTION IN COVID-19

Impaired liver function in patients with COVID-19 can be caused by systemic

inflammation or the direct effect of SARS-CoV-2 on the ACE2 receptor on cholangiocytes. However, it also needs to bit must be noted that administration of drugs used in COVID-19 therapy, including anti-viruses such as lopinavir, antipyretics, antibiotics, or traditional herbal medicines from China, can cause damage to the liver function. In most cases, impaired liver function is characterized by an increase in the AST / ALT value but not more than twice the normal value. In this condition, what can be done is dynamic observation without the need for special therapy for the COVID-19 patient. However, in severe conditions, where the AST / ALT value increases to more than twice the normal value, cessation, or dose reassessment of anti-viral drugs need to be considered. Administration of hepatoprotectors such as glutathione, polyene phosphatidylcholine, or glycyrrhizic acid, can also be considered.[17]

SUPPLEMENTATION THERAPY IN COVID-19

Zinc

A single layer of gastrointestinal mucosal epithelial cells, bound or joined together by tight junctions, can provide a defense between the external environment and the body. Zinc is considered to be an important factor in maintaining the structural integrity of the gastrointestinal defense system. Any mechanism and any stress that causes damage to the integrity of the defense tract can alter the health level of the gastrointestinal mucosa.[24]

Several clinical studies have shown the efficacy and safety of zinc supplementation as an therapy and immune system enhancer for viral infectious diseases, especially those induced by viral RNA. A meta-analysis of randomized clinical trials showed positive results for oral zinc (elemental zinc dosage ranges from 80-92 mg/day) in relieving flu symptoms. The study found that 70% of subjects experienced recovery on the fifth day of treatment, without side effects, compared to 27% of subjects who received placebo.[24]

Based on existing in vitro studies, it was found that zinc can induce the production of IFN-alpha and IFN-gamma, which can potentially act as an anti-viral. In healthy individuals, zinc supplementation can decrease the production of TNF-alpha and interleukin-1 beta. Zinc can also induce changes in the capillary epithelium by inhibiting translocation of plasma proteins and reducing local edema, inflammation, exudation, and mucus secretion. Therefore, zinc can protect or stabilize the cell membrane, which can inhibit the entry of viruses into cells.[25]

Nidoviruses are a large group of positive chain viruses included in the criteria for infectious agents in humans, including SARS-CoV and other coronaviruses, arteriviruses (equine arteritis virus), and porcine reproductive and respiratory syndrome virus (PRRSV). Zinc can effectively inhibit the synthesis of RNA from nidovirus in vitro, which is mediated by changing the activity of the RNA-dependent RNA polymerase (RdRp) virus, especially in the RNA synthesis phase. It is hypothesized that in the corona virus, zinc can inhibit both the proteolytic process of polyprotein replicase and the activity of RdRp.[25]

Probiotics

Probiotics are live microorganisms that, when given in adequate doses or quantities, can provide health benefits. Some clinical evidence has shown that probiotics can help prevent bacterial and viral infections, including gastroenteritis, sepsis, and respiratory infections.[26]

A meta-analysis involving 8,000 preterm infants in a randomized study showed that administration of probiotics decreased the incidence of enterocolitis, nosocomial sepsis, and all causes of death.[27] Another meta-analysis of 12 randomized studies involving 3,720 adult and child subjects stated a 2-fold decrease in the incidence of upper respiratory tract infections after probiotic administration.[26]

The microbiota present in the intestine has a major influence in regulating the immune response inside the intestine and mucosa in other organs such as the lungs. Probiotics have shown increase Interferon type I, increasing the number and activity of antigen-presenting cells, NK cells, T cells, and specific antibodies present in the gastrointestinal mucosa and lung. Apart from that, the microbiota can also maintain a balance between pro-inflammatory and anti-

inflammatory cytokines which can regulate viral clearance but can also minimize the immune response that does not damage the surrounding tissue, which could be related to the prevention of ARDS in COVID-19.[26]

OUTPATIENT CARE FLOW DURING THE COVID-19 OUTBREAK

SARS-CoV-2 is generally transmitted via droplets and direct contact. However, the current study studies suggest that fecal-oral transmission may be of concern. Self-protection and prevention in the outpatient care of COVID-19 patients are needed, including a special gastrointestinal patient care flow, was made for COVID-19 patients as shown in **Figure 3**. Indirect history taking, such as via telephone, can be done before the patient comes and meets the health worker. Patients who want to come to an outpatient clinic should have a strict screening from an assessment of body temperature, respiratory symptoms related to COVID-19, travel history or previous contact with COVID-19 patients. Patients who are confirmed or suspected to have COVID-19 can then be treated immediately in an isolation room and transferred to a COVID-19 infection room.[23]

FLOW OF GASTROINTESTINAL ACTION IN A PANDEMIC

Prevention and control of the transmission of SARS-CoV-2 during this pandemic on gastrointestinal procedural measures such as endoscopy and other invasive procedures need to be evaluated regarding the transmission of infections to the working health personnel, as illustrated in **Figure 4**. Recommendations to postpone or cancel these procedures in patients who are suspected of being infected with COVID-19, especially in elective cases. However, in emergency situations, endoscopic procedures may still have to be performed. It should be noted that COVID-19 screening must be done before action can be taken.

CONCLUSION

COVID-19 is a new disease that has become a pandemic. The management of this disease requires additional concern due to its rapid transmission, a high mortality rate that cannot be ignored, and lack of definitive therapy. This review has highlighted that COVID-19 can manifest clinically in the gastrointestinal tract and can cause fecal-oral transmission. However, further studies are needed to answer the current knowledge gaps.

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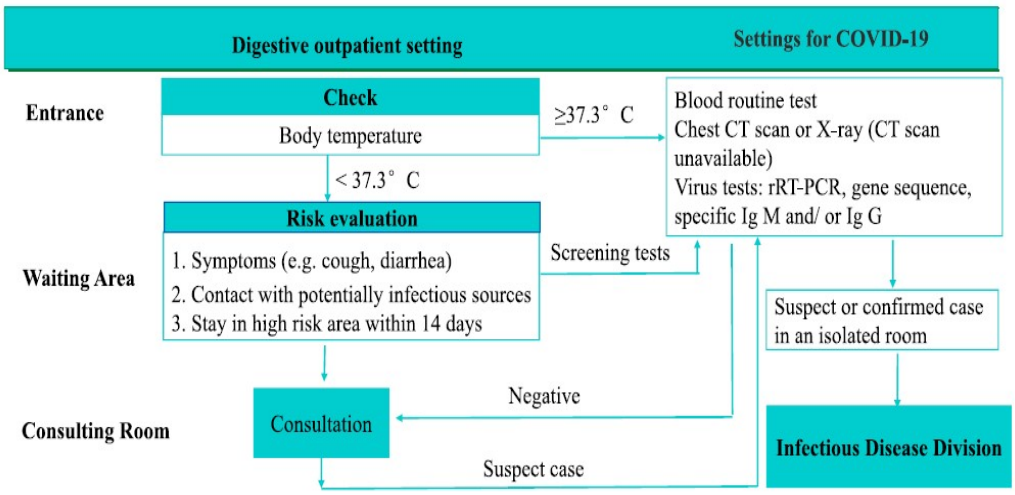

Figure 3. Flow of outpatients in the COVID-19 pandemic condition.[23]

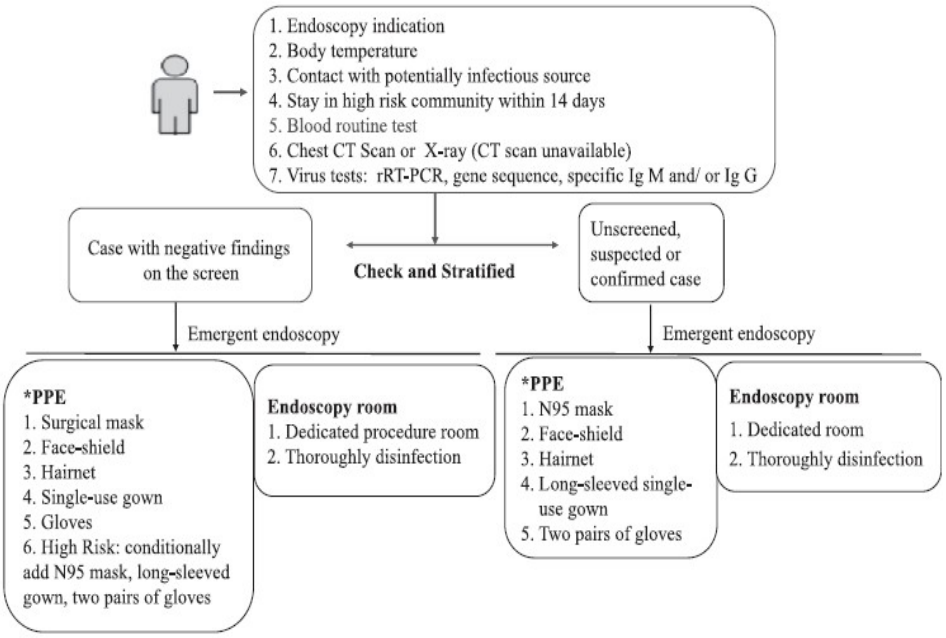

Figure 4. Flow of gastrointestinal action during the COVID-19 pandemic.[23]

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