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RESEARCH ARTICLES

COVID-19: the gut to lung hypothesis

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Abstract

Increasingly COVID-19 is being recognised as a multisystem disease, with viral replication within the gastrointestinal tract now being well accepted. This article collates evidence pointing to possible gastrointestinal transmission as well as outlining possible mechanisms for intra-institutional or cruise ship spread and explores the possible impact of gastrointestinal replication on disease course.

Key words: COVID-19, transmission, fecal aerosols

At the time of writing, the cause of mortality with COVID-19 is respiratory failure in the context of a viral pneumonia. Prior to this outbreak, the coronavirus family, to which SARS-CoV-2 belongs, was known to cause respiratory disease through SARS-1 and other more benign coronaviruses such as the "common cold" subtypes 229E and OC43.

However, the idea of COVID-19 existing as a multi-systems disease is increasingly gaining traction. The ACE2 receptor, used by SARS-CoV-2 to enter cells, has widespread expression within the human body. Independent virus replication has been demonstrated in cells in the nasopharynx and lungs (1), and SARS-CoV-2 RNA has been detected in gastric, duodenal and rectal glandular epithelia (2). ACE2 receptors are present in cells composing blood vessels, and autopsies of COVID-19 patients have revealed widespread potential SAR-CoV-2 infiltration, including in kidneys (3) and myocardium (4). Most recently, a COVID-19 induced coagulopathy is being explored as a potential cause of mortality (5).

With COVID-19 initially being conceived as a respiratory disease, the unspoken assumption has been that this is its preferred and usually first site of proliferation, as well as its source of viral shedding for transmission.

It is well accepted that direct placement of SARS-CoV or SARS-CoV-2 onto the respiratory tract is capable of causing respiratory infection (6). But should we be open to the idea that respiratory disease could be caused by spread from the gastrointestinal tract? And could the gastrointestinal tract be responsible for transmission in a significant way?

That SARS-CoV-1 could be spread by the fecal route via air aerosols was demonstrated in the Amoy Gardens outbreak in 2003. A patient with SARS had diarrhea in an apartment building where sewage airflow was connected between apartments. The explosive outbreak within the complex caused 321 patients to become infected in the space of approximately 3 weeks, including in surrounding buildings in a pattern consistent with airflow, demonstrating both the route and potency of fecal aerosol transmission (7). SARS-CoV-2 has both been demonstrated to be present in large volumes in feces and maintain infectivity while suspended in aerosols for 16 hours (8). In a recent study of two hospitals in Wuhan, aerosolised SARS-CoV-2 RNA was located at low levels in regular isolation rooms and rooms with intubated COVID patients, and at high levels in toilet spaces (9).

The proposed mechanism that allowed viral aerosols to travel between apartments in Amoy Gardens was the failure of the replenishment of water traps and is not a phenomenon unique to Hong Kong. Water traps are used worldwide to prevent sewage aerosols from re-entering bathroom spaces. They are simple turns in pipes (an S-turn, U-turn, etc.) which allow water to accumulate and prevent the backflow of air. For a trap seal to function, it must be filled with water, as occurs with use. A dry trap is by definition not a functioning one. The apartment buildings in the Amoy Gardens complex perhaps connected the greywater (bath, floor drains, sink, etc.) and blackwater (sewage) outflows early on, allowing blackwater aerosols to emerge from the floor (greywater) drains. This opens the possibility of blackwater aerosols generated in one apartment emerging through blackwater drains of empty apartments with dry traps. In other words, a bathroom left unused has the potential to act as a source of infectious SARS-CoV-2 aerosols, if a nearby one is being used by someone infected with COVID-19. Airborne transmission of fecal aerosols through faulty sanitary plumbing systems has been studied and identified as short burst transient events (10). Could this represent the effect of flushing toilets causing a sudden rush of air backflow into adjacent pipes, where no back pressure is present from a functional trap?

Could this have contributed to the intense outbreaks of COVID-19 on cruise ships? Or outbreaks in other institutions, such as nursing homes or hospitals, where high rates of infection persist despite quarantine and other measures being implemented? Empty cabins unused for periods allowing the blackwater traps to dry would allow blackwater aerosols to enter the bathroom

space. If such transmission routinely exists, does this also present a risk of apartment buildings presenting an increased risk of infection when, as case numbers grow in a city, and through sickness or eviction, apartments are left empty long enough for traps to dry? This would also have implications for protocols regarding keeping crew or staff aboard cruise ships after the identification of a COVID-19 outbreak or hospitals with COVID-19 patients (11). Additionally, given the demonstrated ability of high energy flush toilets (the common flushing mechanism) to generate toilet plume (12), could the bathroom be responsible for some part of the high spread within households?

The study of COVID-19 clusters has shown features that might be consistent with spread via fecal aerosols, and potentially toilet plume (the aerosols generated by flushing toilets). In an outbreak in a Chinese mall, the initial outbreak occurred on the office level, with workers from that level noted to visit the shops and bathrooms in the mall below. The subsequent outbreak in the commercial section was exclusively female, including the toilet janitor, which might be explained by use of the female bathroom (13). The clusters are often long events (2 hour church services, conferences) during which there is an expectation that people will use the bathroom. In the first cluster in Germany, a physician who saw 132 patients, saw all his contacts tested. Despite the high number of contacts, the two people subsequently infected were his partner, and a co-worker (14), both people with whom he might be expected to share a home or staff toilet.

The disease evolution of COVID-19 shows that a proportion of patients present with gastrointestinal symptoms before respiratory ones. One study showed 10% of patients with COVID-19 initially presented with diarrhea (15), and another showed 18% presented with either diarrhea, vomiting or abdominal pain but on questioning 34% of all COVID-19 admission had diarrhea at presentation (16). Additionally, worsening respiratory symptoms were often in parallel with worsening gastrointestinal ones (17). Patients with digestive symptoms showed a longer time from onset to hospital admission than those without symptoms (16), a timeframe that would be consistent with subclinical gastrointestinal disease in those without overt gastrointestinal symptoms. That other CoVs primarily cause gastrointestinal disease is true for other species, with some CoVs presenting as enteritis in pigs and cows (while being mainly an upper respiratory disease in chickens) (18). In 2016, a coronavirus was identified as the causative agent behind a gastrointestinal outbreak in swine, aptly named swine acute diarrhea syndrome coronavirus (SADS-CoV). This outbreak occurred 100km from the index case of SARS, and shared 98.48% of the genome of coronaviruses found in Horseshoe bats (19). Given how common gastrointestinal symptoms are across species and coronavirus types, have we considered that asymptomatic patients may be transmitting through subclinical gastrointestinal disease?

If further examination supports the general thesis here that COVID-19 has a significant gastrointestinal route of pathogenesis and transmission and may in cases be a gut first disease, then it is possible that other avenues to consider for treatment might be in decreasing the viral replication within the gastrointestinal tract.

Seeking clues wherever we can, it should be noted that several countries appear to be less affected by COVID-19. South Korea, Japan and Germany were early examples of low total fatality from COVID-19. Worldwide, one of the undoubtedly proven methods of control has been high levels of testing, which allow quarantining of infected patients and contact tracing. However, Japan proves to be an outlier. In early May, total deaths equalled 536, despite low testing numbers and no lockdown. Japan has an unusually high number of positives. At May 4th, Japan had tested 185,000 people, with a total of 15,000 positive cases (20). This represents a positive rate of 8%. A possible explanation is testing limited to already unwell people, and with such high positives it is possible there is a much larger spread in the community than is reported. It should be surprising that proportional to population, South Korea and Japan have equal per population mortality rates, despite vastly different testing and tracing regimes. South Korea has a population of 51 million and a mortality of 254, and Japan roughly proportionally doubles both numbers with a population of 125 million and a mortality of 536. At these low numbers, neither country has exceeded its capacity to ventilate, as such this has not yet played a role. It is not impossible that another feature common to both countries that affects the course of COVID-19 has affected these mortality rates.

About 47% of deaths occur in diabetics (21), who have impaired immune systems, but also higher levels of sugar in their blood stream. Is it possible that a virus creating an extremely high viral load (1000x that of SARS-1) (1) is highly responsive in its growth to the environment it is put in? In other words, is it possible that the correlation with diabetes is a reflection that in viral replication, sugar is a limiting growth factor, i.e. what constrains the virus at such high replication rates, is it access to sugar?

And lastly, and only for completion in taking each thought to its possible conclusion, I offer this connection. When thinking about other gastrointestinal diseases that are unable to be cured with antibiotics, I am reminded of C. difficile, a bacteria causing a severe colitis which can become immune to treatment with oral vancomycin. An unusual, but highly successful proven treatment has been stool transplants. The mechanism is understood to be that the introduction of greater gut bacteria creates a competitive environment for resources, where C. difficile is unable to grow. If COVID-19 was in fact disease where its course was impacted by a capacity to replicate in the gastrointestinal tract, a strange, but not entirely impossible connection could be that countries with lower rates of COVID-19 have high consumption of fermented food rich in microbes, be it kimchi, sauerkraut or miso, possibly naturally replicating the effect of increasing bowel flora. By inhibiting viral growth in the gut, could

this process be decreasing spread to the lung? Currently, very little research exists, beyond a study from South Korea in 2012, showing increased survival of chickens infected with avian influenza when fed extracts from kimchi and these extracts causing a decrease in replication of avian influenza in egg substrate (22), and subsequent studies exploring antimicrobial peptides generated by lactic acid bacteria which exhibit antiviral properties, including against influenza A (23). Whether through decreasing the availability of substrate for virus reproduction or directly through antimicrobial peptides, could certain gut bacteria decrease viral loads generated by COVID-19, and the subsequent disease course? Public health measures and testing are extremely important determinants of epidemic growth, but gut pathogenesis may be an additional factor.

In this fast paced and high stakes environment, it is imperative we consider all options. A gut to lung pathway for COVID-19, if it forms a significant route of transmission or impacts on viral replication, would open the door to new preventative and treatment options to explore.

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