Microbial co-infections and pathogenic consortium with SARS-CoV-2 in COVID-19 patients: A contingent review

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Abstract

The emergence of novel coronavirus infectious disease-2019 (COVID-19) in December 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has traumatized the whole world with the ongoing devastating pandemic. After droplet mediated transmission of infectious virus particle, and subsequent tissue tropism through the upper and lower respiratory tract, the acute clinical disease is manifested by severe respiratory illness accompanied by shortness of breath, progressive pneumonia, multi-organ dysfunction and ultimate death in SARS-CoV-2 infected patients. The involvement of other microbial co-infections leading to extortionate ailment in critically ill patients has not been significantly reviewed along with conclusive reporting on underlying molecular mechanisms in COVID-19 patients. Although the incidence of co-infections could be up to 94.2% in laboratory-confirmed COVID-19 cases, the fate of co-infections among SARS-CoV-2 infected hosts often depends on the balance between the host's protective immunity and immunopathology. The cross-talk between co-pathogens (especially lung microbiomes), SARS-CoV-2 and host is an important factor that ultimately increases the difficulty of diagnosis, treatment, and prognosis of COVID-19, and even increase the symptoms and mortality of the disease. Simultaneously, co-infecting microorganisms may use new strategies to escape host defense mechanisms (by altering both innate and adaptive immune responses) to further aggravate SARS-CoV-2 pathogenesis. This review of literature suggests that clinicians should rule out SARS-CoV-2 infection by ruling in other respiratory co-pathogens, and must have a high index of suspicion for co-infection among COVID-19 patients. Thus, after recognizing the possible pathogens causing co-infection among COVID-19 patients, and the underlying molecular mechanisms of co-infections appropriate curative and preventive interventions can be recommended.

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Abstract

The emergence of novel coronavirus infectious disease-2019 (COVID-19) in December 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has traumatized the whole world with the ongoing devastating pandemic. After droplet mediated transmission of infectious virus particle, and subsequent tissue tropism through the upper and lower respiratory tract, the acute clinical disease is manifested by severe respiratory illness accompanied by shortness of breath, progressive pneumonia, multi-organ dysfunction and ultimate death in SARS-CoV-2 infected patients. The involvement of other microbial co-infections leading to extortionate ailment in critically ill patients has not been significantly reviewed along with conclusive reporting on underlying molecular mechanisms in COVID-19 patients. Although the incidence of co-infections could be up to 94.2% in laboratory-confirmed COVID-19 cases, the fate of co-infections among SARS-CoV-2 infected hosts often depends on the balance between the host's protective immunity and immunopathology. The cross-talk between co-pathogens (especially lung microbiomes), SARS-CoV-2 and host is an important factor that ultimately increases the difficulty of diagnosis, treatment, and prognosis of COVID-19, and even increase the symptoms and mortality of the disease. Simultaneously, co-infecting microorganisms may use new strategies to escape host defense mechanisms (by altering both innate and adaptive immune responses) to further aggravate SARS-CoV-2 pathogenesis. This review of literature suggests that clinicians should rule out SARS-CoV-2 infection by ruling in other respiratory co-pathogens, and must have a high index of suspicion for co-infection among COVID-19 patients. Thus, after recognizing the possible pathogens causing co-infection among COVID-19 patients, and the underlying molecular mechanisms of co-infections appropriate curative and preventive interventions can be recommended.

Key Words: COVID-19, SARS-CoV-2, microbial co-infections, virus, bacteria, archaea, fungi, and molecular pathogenesis.

Introduction

The novel coronavirus infectious disease-2019 (COVID-19) is a rapidly transmissible pneumonia-like disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China in December 2019, and is currently circulating throughout the world (Hoque, Chaudhury, Akanda, Hossain, & Islam, 2020; Rahman et al., 2020) (Hoque, Chaudhury, et al., 2020; Rahman et al., 2020). The SARS-CoV-2 is an enveloped RNA virus which is genetically significantly different from the previously known coronaviruses, such as SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) (Hoque, Chaudhury, et al., 2020; Rahman et al., 2020; N. Zhu et al., 2020). Immediately its first outbreak in China, this fearsome SARS-CoV-2 has emerged as one of the deadliest human pathogens in the last hundred years after the Spanish Flu in 1918-20 (Li et al., 2020; Reid, Fanning, Hultin, & Taubenberger, 1999). The deadly outbreaks of SARS in 2003 and MERS in 2012, with case fatality rate 9.6% and 34.4%, respectively were successfully contained within six months. However, the SARS-CoV-2 infection has become a public health challenge for all over the world, and thus, the World Health Organization (WHO) has declared this disease as a public health emergency of international concern (Hoque, Chaudhury, et al., 2020; Rahman et al., 2020). The COVID-19 disease affected total 217 countries and territories until November 25, 2020, and more than 60,150,606 cases have been confirmed globally with 14,15.746 deaths. Therefore, this quickly spreading COVID-19 pandemic highlights the critical need for rapid development of vaccines and antiviral treatments to reduce the number of hospitalizations and deaths by this disease (Mirzaei et al., 2020).

Co-infections and superinfections are common in any respiratory viral infectious diseases (Mirzaei et al.,

2020; Paget & Trottein, 2019). Secondary or bacterial co-infections can significantly increase the mortality rate in patients infected with any viral infections (Jia et al., 2017; Mirzaei et al., 2020; Quah, Jiang, Tan, Siau, & Tan, 2018). Bacterial co-infections were also reported in MERS-CoV patients receiving intensive care (Memish, Perlman, Van Kerkhove, & Zumla, 2020). The co-infection of the SARS-CoV-2 with other microorganisms is a very important factor in COVID-19 disease that may complicate proper diagnosis, treatment, prognosis of COVID-19, and even increase the mortality of the patients (Hoque, Rahman, et al., 2020) (Ruuskanen et al., 2011). Clinical trials and metagenomic investigations indicate the co-presence of other viruses, bacteria, archaea, fungi with SARS-CoV-2 in COVID-19 patients (N. Chen et al., 2020; Hoque, Rahman, et al., 2020; Shen et al., 2020). About 50% of the patients who died of COVID-19 had secondary bacterial infections (N. Chen et al., 2020; Zhou et al., 2020) which further intensifies the patho-physiological progressions of COVID-19 diseases. Better understanding of co-infections in COVID-19 is critical for the effective patient management, treatment and containment of SARS-CoV-2. It is therefore, necessary to strengthen the investigation of the co-infection in COVID-19 patients. In the case of COVID-19 disease, several issues such as useful strategies to prevent disease spread, collection of appropriate clinical specimens, transmission route, viral dynamics and effective drug treatments are still largely unknown. Although, the possibility of co-infection with other respiratory pathogens including bacteria, archaea, viruses (other than beta coronavirus) and fungi are not clearly understood, the association of these secondary pathogens to causing co-infections should be an important concern for the clinician in the management of COVID-19 cases. The Centers for Disease Control and Prevention (CDC, USA) endorsed testing for other respiratory pathogens, suggesting that evidence of another infection could aid the evaluation of patients with potential COVID-19 in the absence of widely available rapid testing for SARS-CoV-2 (CDC, 2020).

The two earlier coronaviruses (SARS-CoV-1 and MERS-CoV), influenza virus, and SARS-CoV-2 show highly similar respiratory symptoms, including high fever, cough, headache and even pneumonia (Assiri et al., 2013; Cao et al., 2020; Zahariadis et al., 2006; T. Zheng et al., 2019). Recent clinical and *in silico* studies showed that virus co-infection mainly includes respiratory viruses such as entero/rhinovirus (hRV), human metapneumovirus (hMPV), respiratory syncytial virus (RSV),*Siphovirus* , *Alphapapillomavirus* , *Myovirus* ,*Tombusvirus* , *Victorivirus* , *Partitivirus* ,*Chrysovirus* , *Totivirus* , and other coronaviruses (non-COVID-19) (Hoque, Rahman, et al., 2020; X. Lin et al., 2020). Concurrent co-infection in COVID-19 can also change the respiratory microbiome homeostasis, and thus triggers the infection and stimulates immune cells to produce more severe inflammation (Hoque, Rahman, et al., 2020; X. Lin et al., 2020). The gut bacterial diversity of the COVID-19 patients is also reduced with the increased relative abundance of opportunistic pathogens, and the lower relative abundance of the beneficial symbionts (Guan et al., 2020). Recent metagenomic studies reveal the concurrent association of bacteria, archaea and non-COVID viruses in nasal swabs of COVID-19 patient (Hoque, Rahman, et al., 2020). In the two earlier coronaviruses (SARS-CoV-1 and MERS-CoV) epidemics, patients receiving invasive mechanical ventilation were easily developed co-infections, and had higher mortality rates (Assiri et al., 2013; Zahariadis et al., 2006). Therefore, bacterial co-infection might be a key element that promotes severities of the disease and mortality rates (McCullers, 2014). In a recent COVID-19 study, focusing on deceased patients showed that sepsis (100%) acted as one of the main complications (X. Chen et al., 2020), indicating that co-infection is of great importance to prognosis and subsequent treatment of COIVD-19 patients. Furthermore, co-infection has been associated with more severe outcomes in pandemic and seasonal influenza (Lansbury, Lim, Baskaran, & Lim, 2020). It has been suggested that influenza-related bacterial infections overall may account for up to 30% of community-acquired pneumonia (CAP) cases (Joseph, Togawa, & Shindo, 2013). Several studies of hospitalized patients with COVID-19 note the empiric use of antibiotics in a majority of patients (Lansbury et al., 2020; D. Wang et al., 2020; X. Wu et al., 2020). However, there is an evidence of increased inflammatory serological markers associated with bacterial infections including procalcitonin and C-reactive protein in patients with COVID-19 without a corresponding bacterial co-infection (Lansbury et al., 2020; Wan et al., 2020). Meanwhile, several descriptive studies showed that the ecosystem of commensal microbiota can both regulate and be regulated by invading viruses, facilitating either stimulatory or suppressive effects (X. Chen et al., 2020; Kalantar-Zadeh, Ward, Kalantar-Zadeh, & El-Omar, 2020; Netea et al., 2020). More importantly, the coinfected microorganisms may also be a new strategy for the development of new treatment of SARS-CoV-2 infection. Despite increasing

evidence for its salience to COVID-19 outcomes, the effect of co-infection clearance on SARS-CoV-2 load has not yet been systematically reviewed or critically discussed. This systematic review updates our knowledge on the microbial co-infections associated with SARS-CoV-2 pandemic, and the possible molecular mechanisms of co-infections in COVID-19 to emphasize that microbial co-infection.

Rationale and review methodology

To date, thousands of reports on genomics, origin, genome evolution, molecular diagnosis and vaccine and/or therapeutics of SARS-CoV-2 have been published. However, a comprehensive review on microbial (virus, bacteria, fungus, archaea) co-infections associated with COVID-19 and the impact of its on COVID-19 patients, characterization of co-infections and underlying molecular mechanisms of co-infections in COVID-19 patients are lacking. Therefore, we conducted a rigorous literature survey on the co-infections, identifying of co-infecting microorganisms and their pathogenesis. The concept and evidence of co-infection with COVID-19 disease and a rationale of this comprehensive review are described in the introduction section. Later sections of this review were arranged coherently from the literature available in the PubMed central, Google Scholar, ResearchGate, bioRxiv, MedRxiv, Preprints archives, World Health Organization (WHO) COVID-19 blog, National Institute of Health (NIH), Centers for Disease Control and Prevention (CDC, USA), Clinical Trials Registry databases, and COVID-19 vaccine and therapeutics tracker (https://biorender.com/covid-vaccine-tracker). The original research articles that discussed the evidence and significance of co-infections amid COVID-19, detection and possible molecular mechanisms of co-infections were considered for the content of this review. This literature survey also included case studies, case series and observational studies published from the very beginning of COVID-19 outbreak in Wuhan city in China in late December, 2019 to November 15, 2020. The literature search was done through screening of titles, abstracts and full articles for eligibility. Proposed molecular mechanisms of co-infections concurrent in SARS-CoV-2 infections have been represented in Figure 1.

Microbial co-infections in hospitalized patients with COVID-19

Co-infection refers to the concurrent infection of a cell or host by two or multiple pathogen species and/or strains, whereas, superinfection is a scenario where one pathogen infects the host some time before infection by the second pathogen (Salas-Benito & Nova-Ocampo, 2015). For both of these cases, the fate of the infected host often depends on a balance between the host's protective immunity and immunopathology (Makoti & Fielding, 2020). The universal pervasiveness or incidence of co-infection among humans is unknown, but it is thought to be commonplace, sometimes more common than single infection (E. C. Griffiths, Pedersen, Fenton, & Petchey, 2011). Coinfecting pathogens can alter the population of the primary pathogen, as for example, Van der Hoek et al. (2004) reported that in respiratory co-infections, the human coronavirus (hCoV) load was much lower than for a single infection (Van Der Hoek, Pyrc, & Berkhout, 2006). Co-infections may occur by multiple infectious agents of viral, bacterial, archaeal and fungal origin (Figure 1), and appear to occur simultaneously with the initial onset of illness (Bengoechea & Bamford, 2020). Co-infection morbidity has previously been studied within certain cohorts (e.g., age and sex), and is often reported to be worse than single infections (E. Griffiths, Pedersen, Fenton, & Petchey, 2015). Recently, several observational and cohort studies reported that pulmonary complications occurred in 51·2% COVID-19 patients, of which 82.6% accounted for deaths, and independent risk factors for mortality were male sex, age 65 years or older (Nepogodiev et al., 2020). However, the occurrence of co-infection in death across age and sex cohorts of COVID-19 patients has not been studied yet. We assume that co-infection associated death may be more common in early adulthood, but it is not known whether younger adults are more susceptible to co-infection per se, or more susceptible to fatal co-infection. Therefore, better understanding of the risk factors and biological interactions associated with higher case-fatality may help efforts to predict and combat co-infection mortality.

Viral co-infections in hospitalized patients with COVID-19

Co-infections with other viruses are very common in the viral infections of respiratory diseases. The prevalence of respiratory virus co-infection varies from 3.0% to 68.0% (X. Lin et al., 2020; Nickbakhsh et al.,

2019). Several clinical studies indicated that viral co-infections of SARS-CoV-2 occurred with other virus from different countries (X. Chen et al., 2020; D. Wang et al., 2020). Lin et al. (2020) reported that in Shenzhen Third People's Hospital, 3.2% SARS-CoV-2 patients suffered from viral co-infections. Association of other viruses, bacteria, fungi, with SARS-CoV-2 infection has been reported (Shen et al., 2020). Bacteriophages are naturally occurring viruses that use bacteria as hosts, and play an extremely important part in allowing relatively harmless bacteria to become pathogens (Hoque et al., 2019; T. Zheng et al., 2019). The bacteriophages are overlooked human pathogens that imply in triggering and worsening of a number of human diseases (T. Zheng et al., 2019). The COVID-19 causing SARS-CoV-2 strains show neighboring relationship to human classic coronavirus, the SARS coronavirus isolate Tor2 (SARS-CoV Tor2) corroborating with the recent findings of Konno et al. (2020) (Konno et al., 2020). In a recent metagenomic study, Hoque et al. (2020b) reported that COVID-19 samples have sole association with 16 viral genera (other than*betacoronavirus*), and of them, *Tombusvirus* ,*Victorivirus* , *Partitivirus* , *Chrysovirus* and*Totivirus* were the most abundant genera associated with SARS-CoV-2 co-infections (Hoque, Rahman, et al., 2020).

SARS-CoV-2 and influenza: the disarray

Influenza is an acute and highly contagious respiratory disease that is responsible for significant morbidity and mortality worldwide. Annually, influenza can affect approximately 9% of the world's population, with up to 1 billion infections, 3 to 5 million severe cases, and 0.3 to 0.65 million deaths (Lambert & Fauci, 2010). The current COVID-19 pandemic caused by SARS-CoV-2 demonstrates similar symptoms of influenza such as fever, headache, sore throat and so on. Although, at the early stage of COVID-19 pandemic, the co-infection of SARS-CoV-2 and influenza did not draw any significant attention, the first report of influenza and SARS-CoV-2 co-infection (X. Zheng et al., 2020) indicated that only 0.4% influenza positive patients were infected with SARS-CoV-2 in January, 2020. The incidence of co-infection by influenza viruses in COVID-19 patients have been reported frequently from different countries other than China (X. Wu et al., 2020). A case report of a 78-year old woman in Japan, showed the presence of Influenza A co-infection with SARS-CoV-2 (Azekawa, Namkoong, Mitamura, Kawaoka, & Saito, 2020) which intensified the necessity for specific and accurate detection of etiologic agents considering the travel history and medical condition of the patients. Another study showed 4.35% presence of influenza co-infection in hospitalized COVID-19 positive patients (Ding, Lu, Fan, Xia, & Liu, 2020). Although no anomalies in hematology screening were reported, all coinfected patients were clinically cured after treatment with oxygen inhalation, oseltamivir and antimicrobial agents without any invasive ventilator, ICU care and extracorporeal membrane oxygenation treatment (Ding et al., 2020). In another retrospective study in Jiangsu Province in China demonstrated that 94.2% of laboratory-confirmed COVID-19 patients had co-infection, specifically 31% of them had viral co-infections with influenza virus (X. Zhu et al., 2020). In a recent retrospective cohort study on COVID-19 patients in a hospital in Barcelona showed that only 0.4% patients were co-infected with community-acquired influenza A virus, whereas 3.1% patients infected with community-acquired bacterial infections, 4.7% of which were hospital-acquired superinfections (Garcia-Vidal et al., 2020). However, the concomitant outbreak of influenza and COVID-19 in the winter season confirmed the presence of co-infection in multiple cases and inevitably emphasized the simultaneous laboratory diagnosis facilities for both SARS-CoV-2 and influenza viruses. The amphipathic symptoms of both COVID-19 and typical influenza have necessitated the co-diagnosis of influenza in COVID-positive patients, specifically with recent travel in influenza-endemic areas.

Hepatitis-B co-infections in COVID-19 patients

Hepatic complications associated with COVID-19 are particularly concerning among people living with hepatitis B virus (HBV) co-infection with pre-existing liver complications (e.g., cirrhosis, liver failure, hepatocellular carcinoma) (Kunutsor & Laukkanen, 2020; Zhang, Shi, & Wang, 2020). Co-infections among COVID-19 patients with hepatitis symptoms before developing the respiratory syndromes have been documented in several studies (Alqahtani & Schattenberg, 2020; Wander, Epstein, & Bernstein, 2020). While our understanding of SARS-CoV-2's pathogenesis continues to grow, initial studies suggest that the virus could lead to liver injury mainly by binding to angiotensin-converting enzyme 2 (ACE2) receptors on hepatocytes

or causing an immune-mediated hepatic injury through activation of cytokine storm (Mehta et al., 2020). It is now clear that COVID-19 could lead to liver injuries and elevate alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, particularly among the severe COVID-19 cases who need ICU (Huang et al., 2020; Khinda et al., 2020; G. Zhang et al., 2020). Abnormal liver functions in COVID-19 patients have also been associated with increased disease severity and risk of mortality. Interestingly, viral co-infections caused by non-respiratory infectious agents have been reported from the Wuhan city in China, which stated the co-incidence of hepatitis B virus infections in 12.2% patients with acute COVID-19 (X. Chen et al., 2020). The significant rate of liver cirrhosis and abnormally higher liver functions in severe COVID-19 patients corroborated with the findings of co-infection with hepatitis B including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) levels accompanied by moderately elevated prothrombin time (PT), and total bilirubin (TB) levels in COVID-19 patients (Ali, 2020; Cai et al., 2020). The possibilities of liver impairment in severe COVID-19 patients have been suggested due to viral tropism to hepatic tissues, drug toxicity and systemic inflammation (G. Zhang et al., 2020). Therefore, extensive screening for hepatitis B infections in critical COVID-19 patients can be more useful for disease progression analysis, and effective treatment plan application in patients with remarkable diagnostic indications of abnormalities in liver functions.

SARS-CoV-2 anddengue: the deadly duo

The spread of SARS-CoV-2 in temperate countries such as Switzerland and France, where arboviral dengue fever is endemic, has been described with a contemporary travel history (Epelboin, Blonde, Nacher, Combe, & Collet, 2020). In France, the first diagnostic test of SARS-CoV-2 RT-PCR revealed negative with a flu-like syndrome in patients, which became positive a week later with severe clinical onsets of COVID-19 symptoms like fever, fatigue, loss of appetite and diarrhea (Epelboin et al., 2020). The appearance of diffuse maculopapular exanthema made the clinicians to screen for *Leptospira* spp., Rift Valley fever virus, dengue virus and Chikungunya virus infections which indicated that RT-PCR for type-1 dengue virus was positive. Another report of two patients from Singapore revealed that rapid serological tests for dengue can generate false positive results accelerating the respiratory complications in patients who later became positive for SARS-CoV-2 (Yan et al., 2020). The initially worsening fever, increasing thrombocytopenia and sero-positivity for dengue misguided the clinicians who lately found the absence of dengue specific immunoglobulins, but with positive results from RT-PCR test of nasopharyngeal swab for SARS-CoV-2. In several countries of South America, a significant numbers of dengue cases were reported along with a gradual increase of COVID-19 cases. A study from Brazil depicted the possibility of under-reporting of dengue cases due to extensive mobilization of epidemiological sero-surveillance response team for COVID-19 emergency response, which may indirectly affected the reporting and treatment of dengue during COVID-19 outbreak (Lorenz, Bocewicz, et al., 2020). That study urged the robust integrated national strategy for combined surveillance, treatment and prevention plan for dengue and COVID-19 management in Brazil. Another study from Columbia analyzed the dual epidemiological features of dengue and SARS-CoV-2 in the first 20 weeks of COVID-19 pandemic (Cardona-Ospina et al., 2020). The viral interference resulting in blocking entry and replication of dengue during SARS-CoV-2 infection may also have contributed to decreased onset of clinical dengue in subclinically or, mildly COVID-19 infected population (Pinky & Dobrovolny, 2016). Contemporary reports from Ecuador revealed that the eco-epidemiological dynamics and high endemic-epidemic transmission of dengue in large coastal areas can drastically affect the mitigation campaign and COVID-19 containment measures through extensive loads of patients on public health facilities for diagnosis, treatment and preventive actions (Navarro, Arrivillaga-Henriquez, Salazar-Loor, & Rodriguez-Morales, 2020). These reports indicated the urgency of sero-surveillance for dengue virus infections in dwellers and travelers from temperate endemic areas. It has also been stated that the physical distancing and reduced public mobility may contribute to the containment of dengue infections amid COVID-19 (Lorenz, Azevedo, & Chiaravalloti-Neto, 2020).

COVID-19 patients with chronic viral diseases: HIV and HCV

The triple burden of COVID-19, human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is one of the major and persistent global health challenges of the twenty-first century. The HIV, HCV and newly

emerging infectious diseases such as coronavirus epidemics are expected to overlap in high HIV and HCB or HCV burden countries (Tamuzi et al., 2020). How COVID-19 will manifest itself in persons co-infected with HIV/HCV is still unclear (Tamuzi et al., 2020). Populations infected with HIV and HCV may be at elevated risk for severe responses if they are infected with COVID-19. In the future, lung lesions associated with COVID-19 may increase the risk of HIV or HCV, which induces a truly vicious circle of HIV-HCV-COVID-19 co-infections (Soriano & Barreiro, 2020; Tamuzi et al., 2020). While COVID-19 continues to spread across the world, many areas face the risk of infection with SARS-CoV-2 and the obstacles and challenges to sustaining the continuum of HIV and HCV treatment in high-burden HIV/HCV countries are increasing (Tamuzi et al., 2020). In fact, the pathogenicity of COVID-19 could be accelerated in people living with HIV, who have compromised immunity (Soriano & Barreiro, 2020). Recent evidence has indicated a substantial association between coronavirus-related lower respiratory tract infections (LRTIs) and increased risk of death in immuno-compromised individuals (Tamuzi et al., 2020). Co-infections of HIV and SARS-CoV-2 in five individuals—three male and two transgender patients in Spain has been reported (Makoti & Fielding, 2020). Interestingly, the HIV/SARS-CoV-2 patients had similar clinical, laboratory and radiographical features to the HIV-negative patients infected with SARS-CoV-2. During the current SARS-CoV-2 pandemic, this lack of information is a concern in countries with high HIV cases, especially in Sub-Saharan Africa, where 70% of people living with HIV infection (Makoti & Fielding, 2020). As the patient had the history of co-infection with HIV-1 and HCV before 4 years, the follow-up study of anti-SARS-CoV-2 immune response revealed the delayed antibody response but with repeatedly negative RT-PCR test for SARS-CoV-2 RNA (Tang et al., 2020). However, the compromised immune status of the patient caused the delayed humoral response development against the SARS-CoV-2, but the anti-HIV therapeutics and elevated level of activated IFN-γ due to anti-HIV agents may be suppressed to SARS-CoV-2 infection leading to persistently undetectable RNA in RT-PCR tests (Tang et al., 2020). Therefore, history of viral co-infection with immuno-compromised status and antiviral therapeutics may lead to delayed antibody response along with indistinct COVID-19 diagnosis.

SARS-CoV-2 with hCoV-HKU1

The endemic human coronaviruses (hCoVs) have been known to cause co-infections, sequential infections or can be co-detected with each other or with other respiratory viruses, including influenza A/B, respiratory syncytial virus (RSV), metapneumovirus, enterovirus, and adenovirus (Chaung, Chan, Pada, & Tambyah, 2020). A critical case of co-infection by human coronavirus HKU1 in a COVID-19 patient, reported from Indonesia, indicated the sequential infections by hCoV-HKU1 and SARS-CoV-2, which was confirmed by a FilmArray Respiratory Panel (RP) test (Chaung et al., 2020). Thus, clinicians need to be aware of hCoV co-infections among COVID-19 patients. A high degree of suspicion in this rapidly evolving outbreak is required to make the diagnosis, and thereby, to contain and control the spread of the COVID-19.

Bacterial, archaeal and fungal co-infections in hospitalized patients with COVID-19

Like other well studied respiratory viral infections including the 1918 influenza outbreak (Reid et al., 1999), and 2009 H1N1 pandemic (MacIntyre et al., 2018), the current pandemic outbreak of SARS-CoV-2 is also reported to associate with secondary microbial infections (N. Chen et al., 2020; Hoque, Rahman, et al., 2020; Manna, Baindara, & Mandal, 2020). Bacterial co-infections were previously reported for respiratory diseases including SARS-CoV, MERS-CoV and influenza patients receiving intensive care (Langford et al., 2020; Memish et al., 2020). Several retrospective studies showed that during the 1918 Spanish flu pandemic, bacterial pneumonia was a major cause of morbidity and mortality (Morens, Taubenberger, & Fauci, 2008). In a previous study, the prevalence of bacterial co-infections during the pandemic of influenza A (H1N1) between 2009 to 2012 was 23.0% (MacIntyre et al., 2018). Recent study reported that about 65% of laboratory-confirmed cases of influenza infection are known to be complicated by bacterial co-infections (Klein et al., 2016).

Bacterial co-infections develop in patients amid or after the primary infection initiated by an infectious agent. Bacterial co-infections also play a significant role during COVID-19 and are associated with an increasing rate of disease severity and case fatality (Bengoechea & Bamford, 2020). However, till now a limited number

of studies have been reported the prevalence/incidence of bacterial co-infections with confirmed cases of severe respiratory illness caused by SARS-COV-2 infection. The prevalence rate of bacterial co-infections in critically ill hospitalized COVID-19 patients was around 14% revealed by a meta-analysis (Bassetti, Kollef, & Timsit, 2020). Co-infections with *Streptococcus pneumoniae, Staphylococcus aureus* , or other colonizing bacteria during the patho-physiology of COVID-19 impairs both innate and adaptive antibacterial host defenses and temporarily compromise the physical and immunological barrier to cause secondary bacterial pneumonia, leading to severe and deadly disease in people with pre-existing comorbidities and previously healthy people (Ginsburg & Klugman, 2020). Data regarding bacterial co-infections in COVID-19 pneumonia are still emerging, but an association has been made between the detection of bacterial pathogens in samples with disease severity in COVID-19 patients. The incidence of co-infection associated with bacterial pneumonia ranged between 11% and 35% among the patients who had been infected with respiratory viruses (Klein et al., 2016). Recently, Fu et al. (2020) reported that among ICU admitted COVID-19 patients, 13.9% were suffering from bacterial co-infections. Despite having a varying rate of bacterial co-infections among COVID-19 patients, the rate of prevalence could be as high as 50% among the non-survivors (Fu et al., 2020). A series of retrospective case studies on SARS-COV-2 confirmed that severely and non-severely ill patients had 7.7% and 3.2%, bacterial and fungal co-infections, respectively (G. Zhang et al., 2020). In Italy, a study conducted among 16,654 patients with critical condition, who died of SARS-CoV-2 infection depicted that 11% of those cases were associated with bacterial and fungal co-infections (Lai, Wang, & Hsueh, 2020).

The most commonly identified coinfected bacterial pathogens include,*Acinetobacter baumannii, Klebsiella pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae,* and*Clamydia pneumoniae* (Hoque, Rahman, et al., 2020; Khatiwada & Subedi, 2020; Langford et al., 2020; Peddu et al., 2020), while*Aspergillus flavus, Candida glabrata* , and *Candida albicans*are the most common coinfected fungi (Bassetti et al., 2020). In addition, bacterial pathogens such as *Staphylococcus aureus, Haemophilus influenzae, Klebsiella pneumoniae, Streptococcus pneumoniae, Neisseria meningitides* (Khatiwada & Subedi, 2020; Peddu et al., 2020) as well as some genera of *Proteus, Enterobacter, and Citrobacter* species have also been reported in hospitalized COVD-19 patients (Rawson et al., 2020). In a recent microbiome study, Hoque et al. reported 527 and 306 bacterial genera in COVID-19 patients of Bangladesh and China, respectively (Hoque, Rahman, et al., 2020). In the recent outbreaks, *Pseudomonas aeruginosa* and*E. coli* are the most frequently isolated multi-drug resistant (MDR) pathogens to be associated with hospital acquired superinfections (Garcia-Vidal et al., 2020). Remarkably, SARS-CoV-2 RNA has also been detected in fecal samples of COVID-19 patients. It raises the question of gastrointestinal infection of SARS-CoV-2 and a possible fecal-oral route of disease transmission (Gao, Chen, & Fang, 2020; Xiao et al., 2020). Moreover, high expression levels of ACE2 mRNA in the gastrointestinal system revealed a strong interaction of SARS-CoV-2 with the gastrointestinal system that has high microbiome diversity and possible chances of immune suppression and bacterial co-infections (Gao et al., 2020; Xiao et al., 2020). The role of SARS-CoV-2 in modulation of microbiome diversity in the gastrointestinal tracts is an important question for further research.

A study on hospitalized COVID-19 patients with oropharyngeal candidiasis (OPC) showed that *C. albicans* was found to be the most prevalent pathogen, which was counted for 70.7%, followed by other fungi including *C. glabrata* (10.7%), *C. dubliniensis* (9.2%),*C. tropicalis* (3%), and *C. krusei* (1.5%) (Salehi, Abedi, Balakrishnan, & Gholamrezanezhad, 2020). On the other hand, Chen et al. (2020b) reported 5% prevalence of fungal co-infections in 99 COVID-19 patients in China, including one case of *Aspergillus flavus* , one case of *Candida glabrata* and three cases of *C. albicans*(X. Chen et al., 2020). Yang et al. (2020) found that 5.8% (3/52) of the critically COVID-19 patients had fungal co-infections with *A. flavus* , *A. fumigatus* and *C. albicans* (X. Yang et al., 2020). In addition, 8-15% incidence of non-specific co-infections among COVID-19 patients were reported in different studies from China, but it is not clear whether it is bacterial or fungal infections (Huang et al., 2020; Song, Liang, & Liu, 2020). A significant percentage of the SARS-CoV-2 infected patients developed co-infections associated with MDR typically from nosocomial pathogens (Clancy, Buehrle, & Nguyen, 2020). An appreciable minority cases of superinfection, most commonly pneumonia and bacteremia can be developed due to MDR bacterial pathogens and fungus specially *Aspergillus* spp. Fun-

gal originated co-infections including pulmonary aspergillosis and candidiasis were reported to complicate SARS-CoV-2 infection (Garcia-Vidal et al., 2020). To date COVID-19-associated pulmonary aspergillosis (CAPA) has been documented in >30% of the cases (Bassetti et al., 2020).

Until now, most of the reported respiratory tract co-infections are limited to viral, bacterial, and fungal pathogens (Bassetti et al., 2020; Díaz-Muñoz, 2017; Li et al., 2020; Song et al., 2020), while a plethora of other concomitant microbial components including archaea could also be found (Contou et al., 2020; Hoque, Rahman, et al., 2020). Unlike bacteria, the incidence, diversity and composition of these co-pathogens always remain much lower compared to the infectious agent of COVID-19. Metagenomic investigations confirmed presence of *Methanosarcina* ,*Methanocaldococcus* , *Thermococcus* ,*Methanothermobacter* , *Haloarcula* , *Staphylothermus* ,*Natronomonas* , *Ferroglobus* , *Caldivirga* ,*Halobacterium* , *Natrialba* , *Methanosphaerula* and*Picrophilus* as the archaeal genera in samples of COVID-19 (Hoque, Rahman, et al., 2020).

Molecular mechanism of co-infection in COVID-19

Co-infections can augment the pathogenesis, morbidity and mortality in most of the respiratory viral diseases (Bengoechea & Bamford, 2020). The Table 1 discusses the commonly reported microbial co-pathogens amid COVID-19, their transmission pattern, possible mechanism of co-infections and outcomes. Co-infections in COVID-19 patients may also complicate the clinical outcomes of the disease. The SARS-CoV-2 enters human cells by binding to the ACE2 protein of the cells lining the upper and lower airways. Recently, Lee et al. (2020) reported that the ACE2 receptor protein robustly localizes within the motile cilia of airway epithelial cells, which likely represents the initial or early subcellular site of SARS-CoV-2 viral entry during host respiratory transmission. However, the ciliary ACE2 expression in the upper airway is influenced by patient demographics (age, sex and smoking), clinical characteristics, comorbidities/co-infections or medication use (Lee et al., 2020). Remarkably, specific molecular kinetics of these additional infections in COVID-19 patients are still remained unclear although a few studies proposed some models for the co/superinfections in COVID-19 patients in different countries (D. Wang et al., 2020). Based on available literature, we propose a plausible mechanism of co-infection in COVID-19 patients (Figure 1, Table 1).

Respiratory viruses are frequently collaborated by secondary bacterial infections due to the outgrowth of opportunistic bacterial pathogens. Although the specific molecular mechanisms of co-infections in COVID-19 patients remain unclear, it may include virus-induced airway damage, cell loss, goblet cell hyperplasia, altered mucus secretion, reduced ciliary beat frequency, function and clearance, reduced oxygen exchange, and damage to the immune system (X. Wu et al., 2020; You et al., 2017; X. Zhu et al., 2020). Co-infection increases the levels of C-reactive protein (CRP) and procalcitonin (PCT) (Li et al., 2020). Viral infections damage the respiratory airway both histologically and functionally (Avadhanula et al., 2006; Manna et al., 2020). The co-infection mechanisms include virus-induced airway damage, cell loss, goblet cell hyperplasia, altered mucus secretion, reduced ciliary beat frequency, reduced mucociliary clearance, dis-coordinated mucociliary functions, reduced oxygen exchange, and damage to the immune system (Avadhanula et al., 2006; Manna et al., 2020; Vareille, Kieninger, Edwards, & Regamey, 2011). Viral co-infection can also facilitate bacterial adhesion, disrupt the tight junction and epithelial barrier integrity favoring paracellular transmigration of bacteria, and alter both innate and adaptive immune responses that render the lung more vulnerable to SARS-CoV-2 infections ((X. Lin et al., 2020; Nickbakhsh et al., 2019). Since many viruses can destroy the airway epithelium, which facilitates other viral co-infection (Denney & Ho, 2018). The COVID-19 patient having co-infected with HIV had a longer progression of the disease and slower generation of specific antibody because of the collapse of immune system (Wang, Luo, Bu, & Xia, 2020). SARS-CoV-2 infection may cause liver damage (Li et al., 2020), and thus, drug-induced liver injury (DILI) is more likely to occur in patients who already have certain viral infections including HCV and HIV (X. Chen et al., 2020). Therefore, the development and outcome of SARS-CoV-2 associated co-infections with other viruses are highly dependent on the host immune response, especially in the elderly (X. Chen et al., 2020). The co-infection of viruses is associated with different molecular mechanisms by which the predisposition of the virus occurs in the respiratory tract that promotes simultaneous bacterial infection. The epithelial cells of the respiratory tract help bacterial adherence using different mechanisms during viral infection, while the disease severity varies

upon virus, bacterial strain, other co-pathogens and hosts immunity. Respiratory viruses can up-regulate the expression of host cell membrane protein to facilitate their binding (Manna et al., 2020). Respiratory syncytial virus (RSV) reported to bind directly with *Haemophilus influenzae* and *Staphylococcus pneumonia* , and thus, favoring bacterial proximity to the epithelial monolayer and supplementing attachment to the host cell receptors. Moreover, the expression and localization of the RSV glycoprotein on the host cell membrane during infection can further act as bacterial receptors for pneumococcal binding (Iverson et al., 2011). Previous studies demonstrated that influenza virus can make mice susceptible to pneumonia caused by *S. aureus* where both virus and bacterial load increased during co-infection (Iverson et al., 2011; Smith et al., 2013). Several respiratory viruses such as RSV, parainfluenzavirus-3, and influenza viruses reported to increase the bacterial adherence upon infection, in both primary and immortalized epithelial cells (Manna et al., 2020). The surface glycoprotein adhesion molecule-1 (ICAM-1) expression is upregulated during RSV and adenovirus infection, and thereby, increases adherence for *S. pneumoniae* in human nasopharyngeal cells (HEp-2) and pneumocyte type II cells (A549). The enhanced pneumococcal adherence in epithelial cells results in bacterial accumulation which may facilitates other bacterial co-infections (Manna et al., 2020; Nguyen et al., 2015). Methanogenic archaea coexist and interact closely with anaerobic bacteria (Hoque et al., 2019). Methanogenic archaea utilize low molecular weight compounds, such as H_2 + CO_2, formic acid, or acetate, and therefore, have symbiotic relationships with the producers of these substrates. It is reasonable to assume that the presence or increase in level of methanogenic archaea modulates the composition of the polymicrobial community and changes the virulence property of the microflora (Hoque et al., 2019) (Maeda et al., 2013). Although, several earlier studies stated that archaeal co-infection is frequently detected in viral and bacterial hosts (Díaz-Muñoz, 2017; Roux et al., 2014), the systematic tests of the factors explaining variation in viral co-infection across different taxa and environments are still lacking.

Recent studies suggested that COVID-19 patients having microbial co-infections are characterized by lymphopenia and enhanced levels of proinflammatory cytokines including interleukin-6 (IL-6) and IL-1β as well as MCP-1, IP-10, and granulocyte colony-stimulating factor (G-CSF) in the plasma. It has been proposed that high levels of proinflammatory cytokines might lead to shock as well as respiratory failure or multiple organ failure, and several trials to assess inflammatory mediators are under way (Arunachalam et al., 2020). Cytokine storm, or hypercytokinemia, describes hyperactivation of the immune system that may be provoked or worsened by co-infections. This can lead to devastating and irreparable destruction of lung tissue as proinflammatory cytokines damage the alveoli, tiny sacs in the lungs responsible for gas exchange and oxygenation (Kwon et al., 2020). Damage to lung tissues caused by SARS-CoV-2 may explore the receptors for other pathogenic or opportunistic microorganisms facilitating secondary infections. Specific domains in which viruses play such facilitating role including enhancement of bacterial adhesion by unmasking cryptic receptors and upregulation of adhesion proteins, disruption of tight junction integrity favoring paracellular transmigration of bacteria and loss of epithelial barrier integrity, increased availability of nutrients, such as mucins and iron, alteration of innate and adaptive immune responses, and disabling defense against bacteria, and lastly, changes in airway microbiome that render the lung more vulnerable to pathogens (Rossi, Fanous, & Colin, 2020). Moreover, SARS-CoV-2 infection can damage lymphocytes, especially B cells, T cells, and NK cells, which will lead to the immune system's impairment during the period of disease (D. Wang et al., 2020). The decrease of lymphocytes and host immune function may be the main reason for further super- or secondary infection (Luo et al., 2019). The mortality is more significant in severe cases compared with the non-severe group (Qin et al., 2020) due to the higher co-infection rate in severe patients (Luo et al., 2019; Qin et al., 2020) (Luo et al., 2019; Qin et al., 2020). The mechanistic evidence of influenza and pneumococcal co-infections showed that influenza virus causes a depletion of alveolar macrophage which allows a smaller inoculum of bacteria to establish productive infection (Smith & Smith, 2016), and consequent severity of the bacterial co-infection is exacerbated by preexisting host factors such as obesity (McArdle, Turkova, & Cunnington, 2018). For more severely ill patients, they are more likely to receive treatment with invasive catheters, resulting in increased sensitivity to co-infections with multidrug-resistant pathogens such as*Acinetobacter baumannii, Escherichia coli, Pseudomonas aeruginosa, and Enterococcus* species (Rawson et al., 2020). In addition, during the patho-physiology of COVID-19, SARS-CoV-2 viruses can interact with a large number of cellular proteins (virus-host interactome) and protein-protein interactions between

unrelated viruses, bacteria, archaea and fungi are also possible (Kumar, Sharma, Barua, Tripathi, & Rouse, 2018). Co-infections may result in genetic exchange among heterologous viruses, and/or agents (Roux et al., 2013) leading to the generation of recombinant or chimeric pathogens, and this recombination effects can influence viral evolution, disease dynamics, sensitivity to antiviral therapy, and eventually the fate of the host (Kumar et al., 2018) Though not studied yet, similar mechanistic events may be found in SARS-CoV-2 and associated co-infections aggravating the patho-physiology of COVID-19. In addition, four factors including host ecology, host taxonomy or phylogeny, host defense mechanisms, and the interactions of co-pathogens with SARS-CoV-2 are likely to play vital role in the patho-physiology and severity of COVID-19 disease. The relevance and importance of these are likely to vary for cross-infectivity, culture co-infection, and single-cell co-infection (Díaz-Muñoz, 2017). Overall, due to some risk factors associated including the epithelial lung damage, immune system dysregulation, prolonged period of hospitalization etc., the possible development of superinfections is somewhat expected in severely ill COVID-19 patients (Bassetti et al., 2020). However, the actual scenario of prevalence, incidence and characteristics of microbial co-infections in SARS-CoV-2 infected patients is yet to be elucidated and analyzed. This review highlights that understanding the immunological mechanisms of co-infections underlying the diverse clinical presentations of COVID-19 is a crucial step in the design of rational therapeutic strategies. Therefore, the effect of SARS-CoV-2 replication and induction of innate immune response on the composition of the human or animal upper respiratory tract (URT) microbiome remains to be elucidated and analyzed in depth on a community wide scale. Further extensive investigation is warranted for a better understanding and evaluating the risk factors associated and the disease spectrum of co/secondary and superinfection in critically ill patients suffering from SARS-CoV-2 infection.

Conclusions and perspectives

Co-infections with various microorganisms are commonly found in COVID-19 patients that significantly influences the severity and mortality of COVID-19 patients. However, our understanding about co-infecting organisms and their cross-talks and ultimate interactions with the hosts are poor. The COVID-19 co-infections can be associated with multiple domains of microorganisms including viruses, bacteria, fungi and archaea. Although the specific molecular events of co-pathogenesis in SARS-CoV-2 patho-physiology is yet unknown, the coinfecting pathogens may participate to damage the respiratory airway, cell loss, goblet cell hyperplasia, alter mucus secretion, reduced ciliary beat frequency, function and clearance, reduced oxygen exchange, and damage the immune system. Furthermore, viral co-infection facilitates bacterial adhesion, disrupt the tight junction and epithelial barrier integrity favoring paracellular transmigration of bacteria, and alter both innate and adaptive immune responses that render the lung more vulnerable to SARS-CoV-2 infections. Although this review provides a comprehensive scenario of co-infection in COVID-19 patient, further studies are needed to focus the epidemiology and clinical and laboratory characteristics of coinfecting pathogens among diverse group of COVID-19 patients from different geo-climatic conditions, and assess the effect of co-infecting microorganisms on the outcome of COVID-19 patients.

Figure 1

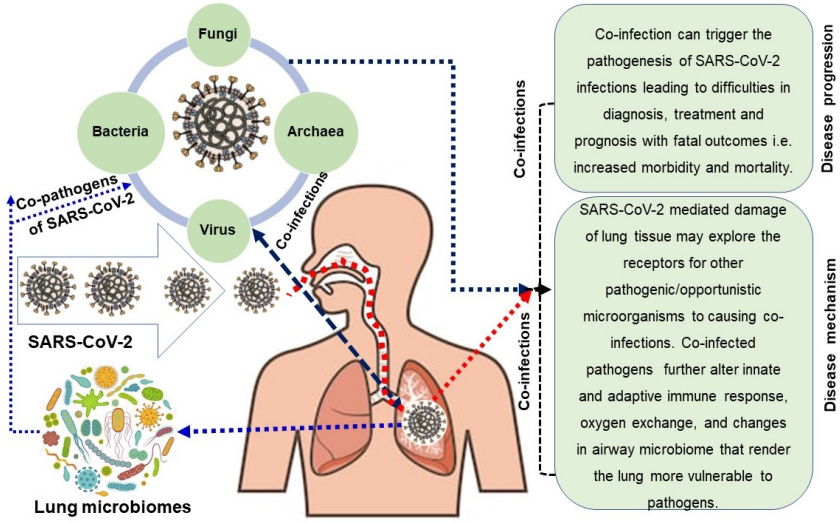

Figure 1 : **Inter-relationship between SARS-CoV-2 and respiratory microbiomes leading to co-infections in CoVID-19 patients** . COVID-19 patients can be co-infected with different microbial domains including viruses (other than SARS-CoV-2), bacteria, archaea and fungi. These diverse microbial communities concurrently complicate the patho-physiology and disease progression of SARS-CoV-2 infections.

Table 1: Commonly reported microbial co-pathogens amid COVID-19, their transmission pattern along with the possible mechanism of co-infections and outcomes.

Type of co-infection	**Co-pathogens**	**Route of transmission**	**Person to person transmission**	**Possible Mechanism of co-infection and pathogenesis**	**Possible Outcomes**
Viral	Influenza	Respiratory	Yes	IFN induced overexpression of ACE2 triggered by influenza virus aids SARS-CoV-2 infection (Suwanwongse & Shabarek, 2020).	Influenza co-infection can provoke COVID-19 hyper-inflammatory states. Higher incidence of acute cardiac injury was reported (Ma, Lai, Chen, Tu, & Qin, 2020)

Type of co-infection	**Co-pathogens**	**Route of transmission**	**Person to person transmission**	**Possible Mechanism of co-infection and pathogenesis**	**Possible Outcomes**
	HBV	Body fluid	Yes	Increased liver tissue damage and inflammatory responses due to COVID-19 may aid HBV co-infection by overexpressing host cell receptors (Wu, Song, Cao, & Li, 2020). It may also fuel the reactivation of pre-existing chronic HBV (Lozano-Sepulveda, Galan-Huerta, Martínez-Acuña, Arellanos-Soto, & Rivas-Estilla, 2020).	Elevation of ALT, AST, TBIL, ALP, and γ-GT. (Zou et al., 2020) Higher risk of liver injury. (Y. Lin et al., 2020)
	Dengue	Mosquito bite	No	NR	Increase the severity of symptoms (Verduyn et al., 2020). Decrease in white blood cell, neutrophils, lymphocytes and platelets count and eventual higher mortality rate (Saddique et al., 2020)

Type of co-infection	**Co-pathogens**	**Route of transmission**	**Person to person transmission**	**Possible Mechanism of co-infection and pathogenesis**	**Possible Outcomes**
	HIV	Body fluid	Yes	Suppression of T lymphocyte mediated immunity (as observed in HIV patients) leads to the prognosis of increased disease severity and higher mortality rate during COVID-19 co-infection (Xu et al., 2020).	HIV Patients under ART exhibits mild COVID-19 symptoms. But ART-naïve patients show acute COVID-19 clinical representation (Hu, Ma, Huang, & Vermund, 2020). Higher maximum body temperatures, longer duration of fever and longer improvement time of chest CT image was reported due to co-infection (R. Yang et al., 2020)

Type of co-infection	Co-pathogens	Route of transmission	Person to person transmission	Possible Mechanism of co-infection and pathogenesis	Possible Outcomes
	HCV	Body fluid	Yes	Both SARS-CoV-2 E and HCV p7 proteins can form similar ion channels which ensure their success in attacking their host and effective replication during co-infection (Alothaid, Aldughaim, El Bakkouri, AlMashhadi, & Al-Qahtani, 2020).	The actual outcome is not reported till date. It has been speculated that some investigational COVID-19 drugs may adversely affect the HCV-related decompensated cirrhosis patients (Reddy, 2020).
	Rhinovirus	Respiratory	Yes	Major disease-causing rhinovirus serotype HRV-A16 infection upregulates ACE2 and TMPRSS2 expression in epithelial cells by inducing by IFNb1. This event facilitates SARS-CoV-2 transmission and further disease severity (Murphy et al., 2020)	One case has been reported in a young patient expressing critical illness as the outcome of co-infection (Orozco-Hernández, Montoya-Martínez, Pacheco-Gallego, Céspedes-Roncancio, & Porras-Hurtado, 2020)

Type of co-infection	**Co-pathogens**	**Route of transmission**	**Person to person transmission**	**Possible Mechanism of co-infection and pathogenesis**	**Possible Outcomes**
	Adenovirus	Respiratory	Yes	Similar ion channel forming capability of SARS-CovV-2 E and Adenovirus 6K proteins facilitates co-infection (Alothaid et al., 2020)	Unfavorable prognostic outcome including ARDS (Motta & Gómez, 2020)
Bacterial	*Streptococcus pneumoniae*	Respiratory	Yes	Opportunistic normal flora of human upper respiratory track	Severe respiratory distress followed by pleural effusion and necrotizing pneumonia (Nieto-Moro et al., 2020), higher mortality rate (Rodriguez-Nava et al., 2020)
	Staphylococcus aureus	Respiratory/ Digestive/ Contact	Yes	Opportunistic normal flora of human upper respiratory track, gut mucosa and skin	Necrotizing pneumonia (Duployez et al., 2020). Bacteremia and higher mortality (Cusumano et al., 2020)
	Pseudomonas aeruginosa	Contact	Yes	Opportunistic pathogen causing HAI mostly related with poor hygiene, mechanical ventilation and urinary catheterization.	NR

Type of co-infection	Co-pathogens	Route of transmission	Person to person transmission	Possible Mechanism of co-infection and pathogenesis	Possible Outcomes
	Acinetobacter baumannii	Contact	Yes	Mechanical ventilation	NR
	Klebsiella pneumoniae	Respiratory/ Contact	Yes	Opportunistic normal flora of human mouth, skin, and intestines	Fatal sepsis (Hosoda et al., 2020)
	Mycoplasma pneumoniae	Respiratory/ contact	Yes	NR	Severe pneumonia (Oliva et al., 2020). Increased morbidity, mortality and disease severity (Amin, McKitish, & Shah, 2020)
	Clamydia pneumoniae	Respiratory/ contact	Yes	NR	Severe pneumonia (Oliva et al., 2020).
	Legionella pneumophila	Digestive/ Respiratory	Yes	NR	Elevated aspartate aminotrans-ferase, blood urea nitrogen, creatinine, lactate dehydrogenase and C-reactive protein (Arashiro et al., 2020)
	Haemophilus influenzae	Respiratory/ contact	Yes	Opportunistic normal flora of human upper respiratory track	NR

Type of co-infection	**Co-pathogens**	**Route of transmission**	**Person to person transmission**	**Possible Mechanism of co-infection and pathogenesis**	**Possible Outcomes**
	Neisseria meningitides	Respiratory/ contact	Yes	NR	Convulsion (Moriguchi et al., 2020), elevated C-reactive protein, headache, neck stiffness, rigors, confusion, and a new purpuric rash over hands and feet (Gallacher & Seaton, 2020)
	Mycobacterium tuberculosis	Respiratory	Yes	Cytokine storm produced by COVID-19 may reactivate latent TB or boost the development of active TB. Lung damages caused by TB may also escalate the disease severity caused by SARS-CoV-2 (Crisan-Dabija et al., 2020).	Co-infection is associated with disease severity and disease progression rate (Liu et al., 2020). 2.17 times higher risk-of-death and 25% lower risk-of-recovery was reported. Also shorter time-to-death and longer time-to-recovery was found (Sy, Haw, & Uy, 2020).

Type of co-infection	**Co-pathogens**	**Route of transmission**	**Person to person transmission**	**Possible Mechanism of co-infection and pathogenesis**	**Possible Outcomes**
Fungal	*Aspergillus* spp.	Respiratory	No	Pro-inflammatory cytokines (especially IL-6 and IL-10 released during COVID-19 results in tissue necrosis and ARDS, which eventually makes patient more vulnerable to Aspergillosis (Lai & Yu, 2020).	Invasive pulmonary aspergillosis, higher case fatality rate (64.7% reported) (Lai & Yu, 2020)
	Candida spp.	Perinatal/ Contact	No	Opportunistic pathogen found in human skin.	Candidemia and increased mortality rate (Al-Hatmi, Mohsin, Al-Huraizi, & Khamis, 2020).

IFN: Interferon; ACE2: Angiotensin-converting enzyme 2; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus disease-19; HBV: Hepatitis B Virus; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; ALT: Alanine transaminase; AST: Aspartate transaminase; TBIL: Total bilirubin; ALP: Alkaline phosphatase; γ-GT: Gamma-glutamyltransferase; ART: Antiretroviral therapy; CT: Computed Tomography; HRV-A16: Human rhinovirus A16; TMPRSS2: Transmembrane protease, serine 2; IFNb1: Interferon Beta 1; ARDS: Acute respiratory distress syndrome; HAI: Hospital Acquired Infections TB: Tuberculosis; IL-6: Interleukin 6; IL-10: Interleukin 10; NR: Not Reported.

Competing Interests

The authors declare no competing interests.

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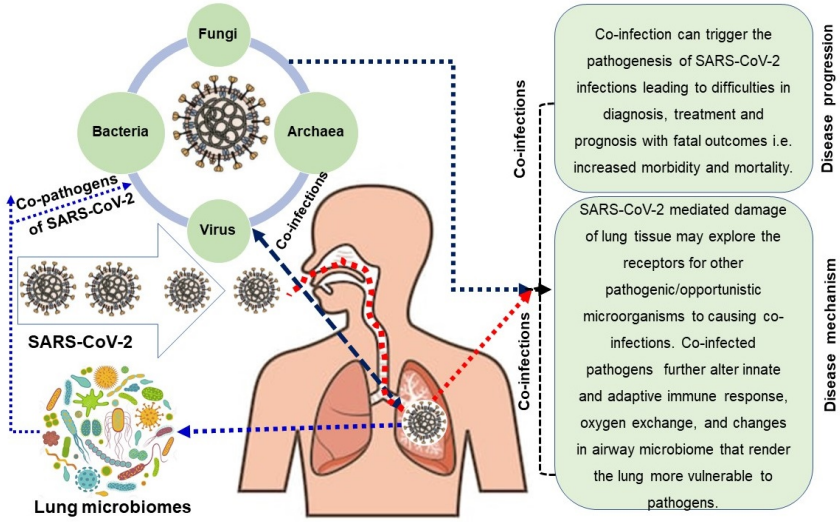

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Table 1.docx available at https://authorea.com/users/469604/articles/562350-microbial-co-infections-and-pathogenic-consortium-with-sars-cov-2-in-covid-19-patients-a-contingent-review