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Polymicrobial pathogenesis in Covid-19 with emphasis on oral manifestations: A review

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Abstract

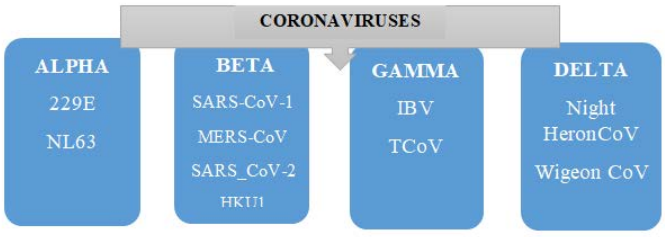
The novel coronavirus infectious disease-2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has devastated the physical, mental, emotional and socioeconomic wellbeing of the society. Severe COVID-19 is associated with involvement of other microbial co-pathogens including viruses, bacteria and fungi that alter the course of the disease. For successful patient management, treatment and containment of SARS-CoV-2, understanding the pathogenesis of co-infections, superinfections and opportunistic infections is essential. This review article summarizes the role of co-pathogens and their clinical and oral manifestations in COVID-19.

Keywords: COVID-19, microbial pathogenesis, coinfection, superinfections, opportunistic infection, oral manifestations

Introduction

Outbreak of Pneumonia of unknown etiology was reported in Wuhan, Hubei Province of China in December 2019[1]. Bronchoalveolar lavage fluid from patients was inoculated into the human respiratory tract epithelial cells and Vero E6 and Huh7 cell lines which led to the isolation of a novel coronavirus, SARS-CoV-2[2].

Coronaviruses belong to the family of Coronaviridae and are enveloped positive strand mRNA viruses. They are divided into four genera of which alpha and beta infect humans [2].



Transmission of virus occurs either via droplet, fomite, and aerosol or feco-oral route and from asymptomatic individuals. Its clinical spectrum is quite broad from common cold to severe pneumonia[3].

As was noticed in the past during the outbreak of Influenza virus in 1918-19 and H1N1 2019 pandemic most deaths were due to secondary bacterial infections than the virulent virus itself and the novel Coronavirus is no exception[4]. Hence we look at the definitions given by Centers for Disease Control and Prevention (US), which defines coinfection as one occurring concurrently with the initial infection, while superinfections are those infections that follow on a previous infection, especially when caused by microorganisms that are resistant, or have become resistant, to the antibiotics used earlier[5,6].

About 50% of the patients who die of COVID-19 had secondary bacterial infections. Concurrent co-infections in COVID-19 can also change the respiratory and gut microbiome homeostasis, and triggers infection and stimulates immune cells to produce severe inflammation.[7] Severe COVID-19 disease is associated with an increase in pro-inflammatory markers, such as IL-1, IL-6, IL-8, and tumor necrosis alpha, inflammatory serological markers procalcitonin and C Reactive Protein, less CD4 interferon gamma expression, and fewer CD4 and CD8 cells, ; this, therefore, increases the susceptibility to bacterial and fungal infections[8]. (Figure 1)

Risk factors for co-infections [9,10]

1. Prolonged hospitalizations
2. Use of empirical broad spectrum antibiotics
3. Inappropriate use of immunosuppressants
4. Improper isolation and antiseptic precautions
5. Weakened immunity and nutrition
6. Pre-existing medical conditions

Pathogenesis of co-infection: SARS-CoV-2 with other microbes

The fate of the infected host in both co-infection and super infection is determined by a balance between the host's protective immunity and immunopathology. Studies have shown that coinfections were reported in 12% of COVID-19 patients and 14% superinfections[11]. Viral infection can destroy the respiratory epithelium allowing bacterial invasion and infection leading to pneumonia, as well as upregulate bacterial binding receptors(due to the action of viral neuraminidase) [12]. Release of interferon gamma by the viral particles reduces the phagocytic activity of neutrophils and macrophages. this results in increased bacterial colonization, transmission, and progression of disease. Downregulation of IFN-α/β-inducible and cathepsin/proteasome genes, TLR/TLR-signalling, cytokine/cytokine, chemokine/chemokine receptor-related, lysosome-related and MHC/chaperon-related genes are differentially regulated by SARS-CoV all of which favors secondary bacterial infections. [13]. In patients with severe COVID-19, disruption of the gut microbiota may be a factor that influences disease outcome [4]. This immunosuppressed state leads to activation of passive bacteria, such as the pneumococcus, H. influenzae and S. aureus[4]

Recognition of viral single stranded RNA by platelet Toll-like receptor 7 (TLR7) results in platelet activation and aggregation due to upregulation of adhesion molecules P selectin, integrin and mobilization of alpha and dense granules which further activate the release of TGFβ, IL-1β and other pro-inflammatory chemokines and pro-thrombotic factors[14,15].

Platelets and their inflammatory mediators, particularly reactive oxygen species, HMGB1, IL-8, and CD62P, leads to formation of neutrophil extracellular traps (NETs), which are major contributors in the development of

SARSCoV-2-associated Acute Respiratory Distress Syndrome and cardiac problems[16,17].

Patients who are at increased risk of developing opportunistic infections such as mucormycosis, due to decrease in the number of lymphocytes, CD4+ and CD8+ T cells, high levels of inflammatory mediators IL-1, 6, TNFα etc with low levels of interferon gamma, high blood glucose levels and long term consumption of steroids all of which leads to a severely immunocompromised state[18,19].

Table 1: Microbial co-pathogens commonly found in COVID-19, their likely mechanism and outcomes [1-20]

Type of Organism	Pathogen	Probable mechanism of co-infection	Probable outcomes
Viruses	Influenza	Influenza virus induced IFN triggers overexpression of ACE aiding SARS CoV 2 infection	Induces a hyper-inflammatory state in COVID-19 with increased risk of cardiac injury
	HBV and HCV	SARS-CoV-2 may reactivate pre-existing HBV and HCV infection by Overexpressing host cell receptors, causing increased liver damage and inflammation.	Elevation of ALT, AST, TBIL, ALP, and γ-GT.
	HIV	Immunocompromised state leads to increase in disease severity and mortality, due to delayed antibody response to Covid-19.	High and prolonged body temperature, Prolonged improvement time of chest CT image.
	Rhinovirus	HRV-A16 infection increases the expression of ACE2 and TMPRSS2 in epithelial cells by generating IFNb1.	Critical illness
Bacteria	Streptococcus pneumoniae	Normal Opportunistic flora of upper respiratory tract	Pleural effusion and necrotizing pneumonia , higher mortality rate
	Staphylococcus aureus	Normal Opportunistic flora of upper respiratory tract, gut and skin	Necrotizing pneumonia. Bacteremia Higher mortality rate
	Klebsiella pneumoniae	Opportunistic normal flora of mouth, skin, and intestine	Fatal sepsis
	Mycoplasma pneumoniae	Not determined	Severe pneumonia

	Clamydia pneumoniae	Not determined	Severe pneumonia
	Legionella pneumophila	Not determined	Altered LFT, elevates C Reactive Protein
	Neisseria meningitides	Not determined	Convulsions , headache, neck stiffness, rigors, elevated C-reactive protein and a new purpuric rash over hands and feet
	Mycobacterium tuberculosis	Covid-19 induced cytokine storm may reactivate latent TB or initiate the development of active TB. Previous lomg damage due to TB may also increase the disease severity of Covid 19	Directly associated with disease severity, progression and death rate
Fungal	Aspergillus species	Production of cytokines (particularly IL-6 and IL-10) during COVID-19 causes tissue necrosis and ARDS, making the patient susceptible to Aspergillosis	Invasive pulmonary aspergillosis, higher case fatality rate (64.7% reported)
	Candida species	Opportunistic pathogen of human skin and mucosa.	Candidemia, increased mortality rate
	Mucormycetes	lymphopenia, increased neutropjil count and high cytokine storm	High mortality rate, involvement of multiple organs associated with aggressive clinical course of the fungus
	Cryptococcus species	depressed T-cell function and lymphopenia	Meningoencephalitis

List of Abbreviations Used

IFN: Interferon; ACE2: Angiotensin-Converting Enzyme 2; SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus Disease 2019; 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-Glutamyl Transferase; CT: Computed Tomography; HRV-A16: Human Rhinovirus A16; TMPRSS2: Transmembrane Protease, Serine 2; Ifnb1: Interferon Beta

1; ARDS: Acute Respiratory Distress Syndrome; TB: Tuberculosis; IL-6: Interleukin 6; IL-10: Interleukin 10.

Viral infections in Covid 19

Viral coinfection occurs in 4% and superinfections in 2% of Covid positive patients. Patients with viral infections of the respiratory system are more likely to develop co-infections, resulting in increased disease severity and mortality[1,20].

SARS-CoV-2 and influenza

Approximately 9% of the world's population is affected by influenza each year. Amphipathic symptoms of COVID-19 and influenza have obligated the co-diagnosis of influenza in COVID-positive patients.[21] Also the influenza virus generates neuraminidase, a protein that aids in bacterial attachment by removing sialic acid. Bacteria such as Streptococci have sialic acid which allows direct attachment with viral hemagglutinin and this is expressed by influenza-infected host cells thus aiding co-infection with bacteria[22].

Hepatitis-B co-infections

There is correlation in the significant rate of liver cirrhosis and unusually high liver functions in COVID patients correlated with the findings of co-infection with hepatitis B including elevated ALT, AST, gamma-glutamyl transferase (GGT), elevated prothrombin time (PT), and total bilirubin (TB) levels in COVID-19 patients. Therefore, extensive screening for hepatitis B infections in critical COVID-19 patients can be more useful for analysis of disease progression, and effective treatment plan[23,24].

HIV and HCV

HIV-related immunosuppression may increase risk of severity of COVID-19 instead confer protection and delayed antibody response along with indistinct COVID-19 diagnosis[25]. Though the study does not show excess morbidity and mortality among HIV. 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[26].

Bacterial infections in Covid 19

Bacterial co-infections occur in 4% and superinfections are 6% in Covid positive patients. The bacterial strains known to coinfect COVID-19 patients include Mycoplasma pneumoniae, Staphylococcus aureus, Legionella pneumophila, Haemophilus influenzae, Klebsiella spp., Pseudomonas aeruginosa, Chlamydia spp., Streptococcus pneumoniae, and Acinetobacter baumannii. These bacteria can be either identified by bacterial culture or thorough PCR tests. Bacterial coinfection is a huge problem as it complicates treatment in COVID-19 patients, worsen the prognosis and increase the fatality rate[27]. 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 sepsis and death of people[28].

Fungal infections in Covid patients

Severe COVID-19 disease is linked with an increase in pro-inflammatory markers, like IL-1, IL-6, IL-8, and tumor necrosis alpha, less CD4 interferongamma, and decrease in CD4 and CD8 cells which can lead to opportunistic fungal infections[8]. Symptoms of some fungal diseases can be similar to those of COVID-19, including fever, cough, and shortness of breath which masks its early diagnosis[29].

Mucormycosis: Previously known as zygomycosis, also known as black fungus in India due to its clinical presentation. Mucormycosis can presents as, gastrointestinal mucormycosis, rhinocerebral mucormycosis, disseminated mucormycosis, pulmonary mucormycosis and cutaneous mucormycosis[29,30] .

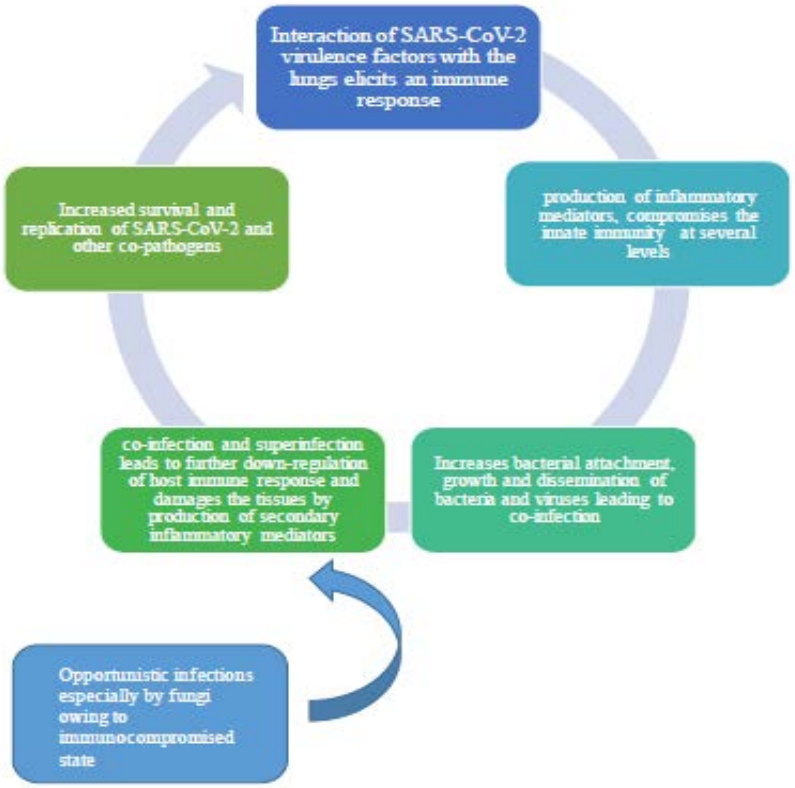
Candidiasis: A fungal infection commonly seen during COVID-19 is C. Auris commonly called as white fungus. The main concern regarding this fungus is it being multi-drug resistant, hard to identify with standard laboratory methods and it is known to have caused various outbreaks in healthcare settings causing invasive candidiasis[29,30].

Pulmonary aspergillosis : Aspergillus fumigatus causes invasive pulmonary aspergillosis, chronic pulmonary aspergillosis, allergic bronchopulmonary aspergillosis, and chronic rhinosinusitis. these super infections are associated with high mortality rate and prolong the acute phase of COVID-19. pulmonary aspergillosis should be considered in severe COVID-19 patients who show worsening of respiratory function or sepsis[29,30].

Pneumocystis pneumonia: Marked lymphopenia and alterations in lymphocyte functions, explains the high-rate of P. jirovecii detection. Sputum culture, RT-PCR, CT chest are recommended to diagnose on time and do a differential between COVID-19 and P. jirovecii[29,30] .

Cryptococcosis: It is caused by C. neoformans has a high risk of mortality within 30 days in Covid patients, hence administration of immunosuppressive drugs should be prescribed with precautions[29,30].

Figure 1: The complex interactions of microbes in Covid-19 with human body [1,15,29]



Oral manifestations in Covid-19

Cells with ACE2 receptor are host cells for the virus and lead to an inflammatory state in the related organs and tissues, such as the oral mucosa and salivary glands. It may impair taste bud sensitivity, which induces dysfunctional taste perception. Other oral manifestations include ulcer, vesicle, erosion, bulla, fissured or depapillated tongue, macule, papule, plaque, whitish areas, pigmentation, hemorrhagic crust, petechiae, swelling, erythema, and spontaneous bleeding. Increase in the level of tumor necrosis factor (TNF)-α in COVID-19 patients may lead to neutrophil chemotaxis in oral mucosa

causes development of aphthous-like lesions. Immunosuppression and stress secondary to COVID-19 infection could also be another reason. Candidiasis due to long-term antibiotic therapy, deficient immune response, and detoriation of oral hygiene may be the cause of white or red patches. Onset of oral symptoms could also be due to a delayed hyperactivate response of the immune system and release of acute inflammatory cytokines rather than direct cytotoxic effects of the virus on the mucosal cells.[31] Thrombocytopenia caused due to SARS-CoV-2 infection or drugs are suggested causes of petechiae. Thrombotic vasculopathy, vasculitis and hypersensitivity associated with COVID-19 could cause mucositis. Post-inflammatory pigmentations may be a result of increased levels of inflammatory cytokines (interleukin-1, tumor necrosis factor-α) and arachidonic acid metabolites (prostaglandins) secondary to production of stem cell factor and basic-fibroblast growth factor from keratinocytes[32].

Rapid laboratory methods for identifying coinfection

Before the COVID-19 pandemic, the US Food and Drug Administration had approved the use of multiplex PCR panels to aid in the early detection of possible respiratory pathogens, The QIAstat-Dx Respiratory 2019-nCoV Panel can simultaneously identify several other common respiratory infections, including bacteria and viruses, in addition to SARS-CoV-2. During the COVID-19 pandemic, the danger of under-diagnosis of co-infection can be greatly lowered by using this SARS-CoV-2 containing syndromic/co-infection test. [1,7]

Conclusion

Understanding the pathogenesis of other microbes in Covid-19 is essential for choosing the appropriate treatment protocol and timely management of co-infections and superinfections which when present will complicate the course of the disease. Further research is needed in this fieldfor early diagnosis and prevention of the same. Improved diagnostic tools which are economical and widely available are required for earlydetection.

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