Review Article

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TANAFFOS

SARS-CoV-2 Related Viral Respiratory Co-Infections: A Narrative Review

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Background: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the new coronavirus originating from Wuhan, China, responsible for the illness known as coronavirus disease 2019 (COVID-19). Early experience and the recent literature have shown that co-infection of SARS-CoV-2 with another respiratory virus might occur. Similar symptoms of acute respiratory infections (ARIs) and COVID-19 represent a challenge for diagnostic and therapeutic efficacy and may modify COVID-19 outcomes.

Materials and Methods: We reviewed the literature on the epidemic pattern and major learning points on important aspects of SARS-CoV-2-related viral respiratory co-infections during the COVID-19 pandemic. Databases such as PubMed, Scopus, Science Direct, and Google Scholar were used to conduct a comprehensive search.

Results: The circulation of respiratory viruses changed as the COVID-19 epidemic continues. Phenomena like viral interference, resource competition, and differences in virus-host range might explain why simultaneous viral respiratory infections have seemed to vanish with the spread of SARS-CoV-2.

Conclusion: Key research to be conducted during this pandemic should include the simultaneous screening of other respiratory pathogens with many available commercial platforms for transmission containment and appropriate clinical management.

Keywords: Co-infection; COVID-19; Respiratory viruses; SARS-CoV-2

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which originated in Wuhan, China. It has been declared a global threat (1). A striking aspect of COVID-19 is that the disease became a pandemic in less than 3 months and rapidly spreads worldwide (2, 3). In addition, SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) as the first and second lethal coronaviruses emerged in 2002 and 2012 in China and Saudi Arabia, respectively (4).

The human respiratory tract hosts a diverse community of co-circulating respiratory pathogens that provides the opportunity for virus–virus, and bacteria–virus interactions (5). Early experience and recent literature have shown that co-infection of SARS-CoV-2 with other respiratory viruses might occur (2, 6-8). The most common viral agents causing respiratory tract infection are influenza viruses (IFVs), adenoviruses (AdVs), parainfluenza viruses (PIVs), respiratory syncytial virus (RSV), and rhinoviruses (RVs) (9-12). In addition, intensive investigations have led to the identification of new human respiratory viruses including human metapneumovirus (hMPV), human boca virus (HBoV), human polyomavirus KI (KIV), human polyomavirus WU (WUV), and new human CoVs (13-15). Phenomena like physical damage to

the respiratory tract epithelium, disruption of mucociliary clearance, damage to the immune system especially B cells, T cells, and NK cells may cause increase in respiratory tract co-infections (6, 16, 17).

The comparable symptoms of acute respiratory infections (ARIs) and COVID-19 pose a challenge in accurately diagnosing and treating the conditions, which could potentially impact the outcomes of COVID-19 cases. Therefore, identifying the causative agent and epidemiological patterns of respiratory pathogens may be relevant for stopping the epidemic spread (reducing transmission) of COVID-19, reducing the duration of patient isolation, providing information for the development of optimal diagnosis, treatment strategy, and health policies (18).

There are numerous published articles describing varying rates of co-infections in patients with COVID-19. We did not intend to write a comprehensive review on this topic; instead, we aimed to summarize and highlight the epidemic pattern and major learning points on important aspects of SARS-CoV-2 related viral respiratory co-infections during COVID-19 pandemic. Databases such as PubMed, Scopus, Science Direct, and Google Scholar were used to conduct a comprehensive search. In the next section of this review, we will first take a look at co-infection status of SARS-CoV-1 and MERS-CoV. This is followed by an overview of the prevalence of SARS-CoV-2 co-infection with other respiratory viruses, how viral respiratory pathogens have been impacted during the COVID-19 pandemic, and clinical outcomes of co-infection of SARS-CoV-2 with IFV. The latter will include the issue of combination therapy and concomitant infection of SARS-CoV-2 and MERS-CoV in the endemic area.

Looking at Co-Infection Status in SARS-CoV-1 and Mers-CoV: A Lesson from Previous Outbreaks

Co-infections occurred in few patients infected with SARS-CoV-1, including HMPV, *Chlamydia pneumoniae* and *Mycoplasma pneumonia* (19-22). Moreover, Co-infections of MERS-CoV with other respiratory pathogens have been documented to be low as IFV A, RSV, HMPV, PIV, *Streptococcus pneumoniae*, RV, and *Mycobacterium tuberculosis* which have been reported infrequently in previous studies (23-25). The SARS-CoV-1 epidemy infected a total of 8098 people and caused 774 deaths across 29 countries and the outbreak died out on its own. Also, there are 2519 confirmed MERS-CoV cases and 866 deaths across 27 countries which still has ongoing reports of sporadic cases (24).

It is possible that the low number of simultaneous infections with SARS-CoV-1 and MERS-CoV was due to the outbreaks being short-lived and resulting in a small number of cases.

Lessons Learned About Viral Respiratory Co-Infections During the SARS-CoV-2 Pandemic

The prevalence and importance of SARS-CoV-2 co-infection with other respiratory viruses

The first systematic review of 16 studies and 1,014 patients arising from the earliest cases of SARS-CoV-2 showed that co-infection with another respiratory virus occurs in 3% of hospitalized COVID-19 patients. Moreover, RSV and IFV were the most common viral pathogens identified (26). The prevalence of co-infection with other respiratory viruses was variable among COVID-19 patients from less than 5 (26-28) to 27% (29, 30) in different studies. Such variations could be explained according to the study period, the geographical area, and the age range of participants.

It is worth mentioning that co-infection by two genetically distinct SARS-CoV-2 lineages was also reported which contributed to the severe disease and prolonged viral shedding (31). Co-infections in COVID-19 can change the respiratory microbiome homeostasis and thus, triggers the infection and stimulates immune cells to produce more severe inflammation (32).

A recent study on deceased patients showed that sepsis acted as one of the main complications, indicating that co-infection is of great importance to prognosis and subsequent treatment of COIVD-19 patients (33). Another

report that is worth mentioning is a fatal case of viral pneumonia caused by HCoV-229E with Rhinovirus co-infection causing ARDS with thrombotic microangiopathy during COIVD-19 pandemic. It implies that not all respiratory deaths in the COVID-19 pandemic are attributed to SARS-CoV-2 and emphasize on the pathogen surveillance (34). In a comprehensive review of co-infection in COVID-19 patients (32), the authors concluded that although the specific molecular events of co-pathogenesis in SARS-CoV-2 pathophysiology is yet unknown, the co-infecting pathogens may participate to damage the respiratory airway, cell loss, goblet cell hyperplasia, alteration of mucus secretion, reduced ciliary beat frequency, function and clearance, reduced oxygen exchange, and damage the immune system. Furthermore, viral co-infection facilitates bacterial adhesion, disrupts the tight junction and epithelial barrier integrity favoring paracellular transmigration of bacteria, and alters both innate and adaptive immune responses that render the lung more vulnerable to SARS-CoV-2 infections.

What happened to viral respiratory pathogens in SARS-CoV-2 pandemic period?

In this section, we will describe how viral respiratory pathogens have been impacted during the COVID-19 pandemic. During the early time of the COVID-19 outbreak in Wuhan (12 January-21 February 2020), co-infection of SARS-CoV-2 and IFVs was highly prevalent (57.3%) (35). But, the circulation of respiratory viruses changed as the COVID-19 epidemic continues. One Italian study indicated that soon after the onset of the global SARS-CoV-2 epidemic, the presence of other respiratory viruses and bacteria declined and even disappeared (36). In a large cohort of French patients tested for SARS-CoV-2 and other respiratory viruses, the occurrence of co-infections decreased by 3.5 times during two months of the study period (30).

Phenomena like viral interference, resource competition, and differences in virus host range might explain why simultaneous viral respiratory infections have seemed to vanish with the spread of SARS-CoV-2. The possibility of a viral interference phenomenon is reminiscent of interruption of the influenza A (H1N1) pdm09 virus spread in European countries by the autumn rhinovirus epidemic (37-39). It has been hypothesized that infection by one respiratory virus limits the replication of another virus. Moreover, induction of inflammatory response by the primary virus infection, makes the respiratory tract refractory to another virus (40).

Several descriptive studies have reported minimal co-infection of SARS-CoV-2 and IFV (41, 42). It has been reported that there was a significant decrease in the prevalence of SARS-CoV-2, as well as other respiratory viruses and non-viral pathogens in Australia. This decline occurred over a span of 11 weeks following the implementation of public health interventions. The downturn from 32% in week 1 to 3-4% in week 8 could be explained by the implementation and success of public health control measures on respiratory infection transmission (43). Control measures established to contain COVID-19 infection also seem to be effective in reducing influenza activity in Singapore, New York, and China (44-47); it also displaced usual community acquired respiratory viruses within only 3 weeks in Switzerland (48). In countries such as Brazil, Taiwan, and Japan, the same effect was also reported for reducing the spread of viral respiratory diseases, particularly IFV (49-51).

Using a mathematical model, it was found that SARS-CoV-2 has a slower growth rate than other respiratory viruses. So, another possible explanation for the low number of co-infections involving SARS-CoV-2 was attributed to the suppression of SARS-CoV-2 infection when initiated concomitantly or after infection with other respiratory viruses (52). In one study in Japan, even though no co-infection with SARS-CoV-2 and other viruses was observed, respiratory viruses remained prevalent after implementing preventive measures (53). In addition, during the fight against the COVID-19 pandemic, when the schools reopened in Guangzhou, rhinovirus remains prevalent in school teenagers (54). This data provides

insights into how containment measures can help limit the spread of other respiratory viruses while combating the COVID-19 pandemic. Social lockdown, travel ban, wearing face masks, screening of close contacts, and screening for fever cases are some instances of public health policies directed against COVID-19.

Co-infecting pathogens can be detected at variable intervals

Ma L et al. showed that the co-infecting pathogens could be detected from very early, from symptom onset to later or even during the recovery stage the of COIVD-19 disease course. Indeed, co-infecting pathogens were detected in a third of co-infected patients during the first week after symptom onset. While in another third of patients, co-infecting pathogens were detected more than three weeks after symptom onset (55). Also, Zhu et al. noticed that a high co-infection rate occurred 1–4 days after the onset of the disease in COVID-19 patients (56).

Co-infection of SARS-CoV-2 with Influenza: clinical outcome

Patients co-infected with SARS-CoV-2 and IFV did not show a more severe condition based on similar clinical and laboratory findings, imaging studies, and prognosis compared with the patients infected only by SARS-CoV-2 (55, 57). Other studies showed that symptoms and clinical outcomes of COVID-19 patients co-infected with IFV were similar to those with a single SARS-CoV-2 infection (58, 59). Interestingly, in an investigation from china, a protective effect of co-infection with IFV for COVID-19 patients was reported. The results showed that the fatality rate was significantly higher in the non-influenza group (60). However, this theory needs to be further investigated until it shows any surprising outcome. Meanwhile, recent data from Iran support higher mortality of COVID-19 patients as a result of IFV co-infection (22.3%) (61). The result of one study in china confirmed that a high proportion of critically ill COVID-19 patients were co-infected with IFV. The co-infection induced more and earlier cytokine storms in critically ill COVID-19 patients and they were more prone to cardiac injury than those without IFV (62).

Co-infections among COVID-19 patients: A need for combination therapy?

Among COVID-19 guidelines, only Canadian and Turkish guidelines recommend adding oseltamivir as a neuraminidase inhibitor to deal with IFV (2, 63). Neuraminidase inhibitors should be considered in COVID-19 patients with or at risk for severe disease when there is the local circulation of IFV. The effectiveness of neuraminidase inhibitors is related to the timing and should be initiated rapidly before the onset of respiratory failure (63). In a retrospective matched-pair cohort study, among COVID-19 patients with IFV co-infection, those treated with lopinavir/ritonavir exhibited faster pneumonia resolution (37%) compared to the patients in the control group (3.1%) (64). In the case of other respiratory viruses such as RSV, treatment options are limited.

Concomitant infection of SARS-CoV-2 and MERS-CoV in the endemic area

In an initial cohort of 99 hospitalized COVID-19 patients, none had coinfection with MERS-CoV in the largest academic hospital in the Kingdom of Saudi Arabia (65). In the follow-up to this study, the same group has not detected MERS-CoV co-infection among hospitalized patients during the peak months of the pandemic (66). Several factors have been proposed by Ebrahim SH (67) on the lack of concurrent infections of MERS-CoV and SARS-CoV-2 in Barry M et al . studies (65, 66). The small sample size, the seasonality of MERS-CoV sero-prevalence as observed among camels, the highest being in winter months, and the low circulation of MERS-CoV in the Saudi population were among the proposed factors. It was significant to note that among the patients admitted to the ICU, 8 (12%) had contracted both SARS-CoV-2 and MERS-CoV infections, providing valuable new information to the medical community (68). However, the combined infection was not associated with an increased risk of death compared to mono-infection by MERS-CoV in that small case series.

CONCLUSION

Concluding from the above-mentioned studies, it is clear that we should be aware of the co-infection of other respiratory viruses during the outbreak of COVID-19. Nowadays, more attention is paid to SARS-CoV-2 and it is important to note that comprehensive pathogen surveillance during the pandemic such as the use of respiratory panels is necessary. It is necessary to strengthen the examination of the co-infection in COVID-19 patients for accurate prevention, treatment of infectious complications, enhancing patients' outcomes, and evaluating the effectiveness of the intervention. Some issues that remained to be addressed are: "is there a specific vulnerable population to viral co-infection?", describing co-infection status in children with COVID-19 infection, the relationship of viral coinfection in COVID-19 patients with the morbidity and mortality, and the outcome differences in patients with co-infections vs mono-infection. Key research to be conducted during this pandemic should include the simultaneous screening of other respiratory pathogens with many available commercial platforms for transmission containment and appropriate clinical management.

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