Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents?

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Abstract Co-infection has been reported in patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome, but there is limited knowledge on co-infection among patients with coronavirus disease 2019 (COVID-19). The prevalence of co-infection was variable among COVID-19 patients in different studies, however, it could be up to 50% among non-survivors. Co-pathogens included bacteria, such as *Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumonia*, *Legionella pneumophila* and *Acinetobacter baumannii*; *Candida* species and *Aspergillus flavus*; and viruses such as influenza, coronavirus, rhinovirus/enterovirus, parainfluenza, metapneumovirus, influenza B virus, and human immunodeficiency virus. Influenza A was one of the most common co-infective viruses, which may have caused initial false-negative results of real-time reverse-transcriptase polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Laboratory and imaging findings alone cannot help distinguish co-infection from SARS-CoV-2 infection. Newly developed syndromic multiplex panels that incorporate SARS-CoV-2 may facilitate the early detection of co-infection among COVID-19 patients. By contrast, clinicians cannot rule out SARS-CoV-2 infection by ruling in other respiratory pathogens through old syndromic multiplex panels at this stage of the COVID-19 pandemic. Therefore, clinicians must have a high index of suspicion for coinfection among COVID-19 patients. Clinicians can neither rule out other co-infections caused by respiratory pathogens by diagnosing SARS-CoV-2 infection nor rule out COVID-19

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by detection of non-SARS-CoV-2 respiratory pathogens. After recognizing the possible pathogens causing co-infection among COVID-19 patients, appropriate antimicrobial agents can be recommended.

Introduction

The coronavirus disease 2019 (COVID-19) was first recognized in Wuhan, China, in December 2019. It rapidly spread across mainland China and became a global threat. As of May 7, 2020, the causative pathogen, namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected 3,672,238 people and caused 254,045 deaths globally.[1,2] A striking aspect of COVID-19 is that the disease became a pandemic in less than 3 months.[1] Advances in modern medicine facilitated the early recognition of SARS-CoV-2, previously known as 2019 novel coronavirus, and identification of potential treatments, such as lopinavir/ritonavir, chloroquine/hydroxychloroquine, and remdesivir for SARS-CoV-2.[2-4] However, several issues, such as a useful strategy to prevent disease spread, collection of appropriate clinical specimens, transmission route, viral dynamics, and effective drug treatments, remain unclear. In addition, the possibility of co-infection with other respiratory pathogens remains unknown. However, this should be an important concern for clinicians in the management of COVID-19.

Co-infection in influenza, SARS, and Middle East respiratory syndrome

The recent community-acquired pneumonia (CAP) guidelines by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) recommended initial antibacterial treatment for adults with CAP who test positive for influenza, because bacterial co-infections are a common and serious complication of influenza and it is difficult to exclude the presence of bacterial co-infection in a patient with CAP who tested positive for influenza virus.[5] Based on previous studies on severe coronavirus infections, serological evidence among SARS patients indicated incidences of acute or recent *Chlamydophila pneumoniae* (30%) or *Mycoplasma pneumoniae* (9%) infection, respectively.[6] Furthermore, SARS and human metapneumovirus co-infection were reported during a major nosocomial SARS outbreak in Hong Kong.[7] Moreover, co-infection of the Middle East respiratory syndrome coronavirus (MERS-CoV) with influenza and tuberculosis has been reported.[8,9] A multicenter retrospective cohort study of critically ill patients with MERS-CoV demonstrated that 18% and 5% had bacterial and viral co-infections, respectively.[10] These findings indicate the possibility of co-infection with coronaviruses and other respiratory pathogens. However, there are limited studies reporting this clinical phenomenon.

Co-infection in COVID-19

The recognition of SARS-CoV-2 infection is important as it enables the implementation of appropriate infection control measures and possible promising antiviral therapy, but clinicians should not neglect the possibility of SARS-CoV-2 co-infection. Therefore, this study aimed to better understand the prevalence of co-infection among COVID-19 patients.

Firstly, 13 studies reported the prevalence of COVID-19 co- and secondary infections (Table 1), and all of them were cross-sectional studies.[11-24] Nine of the above-mentioned studies were conducted in China.[11,12,14-16,18,19,21,22] Meanwhile, three of these studies were conducted in the United States (US),[13,20,22] one each in Singapore[17] and Italy.[24] Only laboratory-confirmed COVID-19 cases were identified from these studies, and the study population ranged from 21 to 5700 cases. In the study of 18 patients in Singapore, none had co—or secondary infections.[17] By contrast, Zhou et al. showed that 27 (50%) of 54 non-survivors had secondary infections in a study of 191 patients in China.[18] Among the other 10 studies, the prevalence of COVID-19-associated co- and secondary infection ranged from 0.6% to 45.0%. Six studies reported the occurrence of bacterial co-infection, and *M. pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, and C. pneumoniae* were identified as co-pathogens. Eight studies reported viral co-infections; rhinovirus/enterovirus and influenza A were the commonest co-pathogen, and coronavirus, respiratory syncytial virus, parainfluenza, metapneumovirus, and influenza B virus were also reported as co-pathogens. In Chen et al.'s study of 99 COVID-19 patients, 4 (4.0%) had fungal co-infections, including *Candida albicans* (n = 3) and *C. glabrata* (n = 1).[12] Secondary bacteremia can develop in 37% (27/73) of patients with acute respiratory distress syndrome, however, whether organisms causing bacteremia were related to bacterial pneumonia or were they typical hospital acquired infection was not reported.[24]

Secondly, 12 patients showed COVID-19 co-infections based on the literature search of case report or small case series (Table 2).[25-33] Their ages ranged from 10 years to 80 years, and 11 of them were men. Two patients had diabetes mellitus, and one had thyroid cancer, while the rest had no underlying disease. The patients showed varying radiographic results, and bilateral involvement was common. Six patients had COVID-19 co-infection with influenza A, and two of these (patients 3 and 4) had initial negative real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) results for SARS-CoV-2. The other co-pathogens included HIV, *M. pneumoniae*, *Staphylococcus aureus, L.*

Table 1 Summary of studies that reported the incidence of co- and secondary infection among COVID-19 patients.

Study	City, country	No. of patients with COVID-19 reported	No (%) of co—or secondary infection			
			Virus	Bacteria	Fungus	Total
Huang et al.[11]	Wuhan, China	41	Not mentioned			4 (9.8)
Chen et al.[12]	Wuhan, China	99	0	1 (1.0%)	4 (4.0): *Candida albicans* (n = 3) and *C. glabrata* (n = 1)	5 (5.1)
Arentz et al.[13]	United States	21 (critically ill)	3 (14.3)	1 (4.8)	0	4 (19.0)
Chen et al.[14]	Wuhan, China	29	0	1 (3.4)	0	1 (3.4)
Wang et al.[15]	Wuhan, China	104	6 (5.8): coronavirus (n = 3), influenza A virus (n = 2), rhinovirus (n = 2), and influenza A virus subtype H3N2 (n = 1)	0	0	6 (5.8)
Wu et al.[16]	Wuhan, China	201 (acute respiratory distress syndrome)	1 (0.6): influenza A virus	0	0	1 (0.6)
Young et al.[17]	Singapore	18	0	0	0	0
Zhou et al.[18]	Wuhan, China	191	27 (50) of 54 non-survivors with secondary infections			
Ding et al.[19]	Wuhan, China	115	5 (4.3): influenza A virus (n = 3) and influenza B virus (n = 2)	0	0	5 (4.3)
Kim et al.[20]	Northern California, United States	116	24 (20.7): rhinovirus/ enterovirus (n = 8), RSV (n = 6), other coronaviridae (n = 5), parainfluenza (n = 3), metapneumovirus (n = 2), and influenza A (n = 1)	0	0	24 (20.7)
Xing et al.[21]	Qingdao and Wuhan, China	68	Influenza A (n = 18), influenza B (n = 16), and RSV (n = 1)	*Mycoplasma pneumoniae* (n = 8) and *Legionella pneumophila* (n = 6)	0	25 (36.8)
Li et al.[22]	Wuhan, China	40 (children)	4 (10.0): influenza A or B virus (n = 3) and adenovirus (n = 1)	14 (35.0): *M. pneumoniae* (n = 13) and *Streptococcus pneumoniae* (n = 1)	0	18 (45)
Richardson et al.[23]	New York, United States	5700	39 (1.95): Rhinovirus/ enterovirus (n = 22), other coronaviridae (n = 7), RSV (n = 4), parainfluenza 3 (n = 3), metapneumovirus (n = 2), and influenza A (n = 1)	3 (0.15): *Chlamydophila pneumoniae* (n = 2) and *M. pneumoniae* (n = 1)	0	42 (2.1)
Zangrillo et al.[24]	Milan, Italy	73 (acute respiratory distress syndrome)		Bacterial pneumonia (n = 9, 17.2%) and secondary bacteremia (n = 27, 37.0%)		

Table 2 Summary of case reports with detailed descriptions of COVID-19 co-infections.

Case	Author	Age (year, month)/ gender	Underlying disease[a]	Laboratory findings	Image	Co-pathogens	Remarks
1	Zhu et al.[25]	61 year/M	DM and smoker	Lymphocyte: 1100/μL	Multiple bilateral ground-glass opacities in the lungs	HIV	HIV was firstly diagnosed
2	Fan et al.[26]	36 years/M	N/A	Lymphocytopenia and moderate thrombocytopenia	N/A	*Mycoplasma pneumoniae*	Blood smear showing cold agglutination and Rouleaux formation
3	Wu et al.[27]	68 years/M	No	WBC, 5700/μL; lymphocyte, 2180/ μL	A ground-glass consolidation in the right inferior lobe	Influenza A virus	Initially negative rRT-PCR for SARS-CoV-2
4	Li et al.[28]	10 months/M	No	WBC, 9320/μL; lymphocyte, 6412/ μL; CRP, 11 mg/L	Diffuse ground-glass opacities in both lungs	Influenza A virus	Initially negative rRT-PCR for SARS-CoV-2
5	Khodamoradi et al.[29]	74 years/F	Hypertension and stroke	WBC, 4300/μL; lymphocyte, 300/ μL; CRP, 24 mg/L	Diffuse infiltrates in both lungs	Influenza A virus	
6		40 year/M	No	WBC, 4100/μL; lymphocyte, 1900/ μL; CRP, 10 mg/L	Diffuse and bilateral infiltration in the lungs	Influenza A virus	
7		64 year/M	No	WBC, 6200/μL; lymphocyte, 1100/ μL; CRP, 45 mg/L	Diffuse and bilateral infiltration in the lungs	Influenza A virus	
8		50 year/M	No	WBC, 4000/μL; lymphocyte, 600/ μL; CRP, 55 mg/L	Diffuse infiltrates in both lungs	Influenza A virus	
9	Arashiro et al.[30]	80 year/M	DM	WBC, 5300/μL; lymphocyte, 991/ μL; CRP, 5.05 mg/L	bilateral, patchy, peripheral ground-glass opacity	*Legionella pneumophila*	From Nile cruise, died
10	Duployez et al.[31]	?/M	No	N/A	A parenchymal consolidation of the left upper lung without ground-glass opacities	Panton-Valentine leukocidin-secreting *Staphylococcus aureus*	Died
11	Liew et al.[32]	53 year/M	Metabolic syndrome and spinal spondylosis	WBC, 10,400/μL; CRP, 199 mg/L	Mixed ground-glass airspace opacities, patchy consolidation, and a "crazy paving" appearance	*Klebsiella pneumoniae*	
12	Lescure et al.[33]	80 year/M	Thyroid cancer	WBC,8,000/μL; CRP, 123 mg/L	bilateral alveolar opacities	*Acinetobacter baumannii* and *Aspergillus flavus*	Died

[a] DM, diabetes mellitus; N/A, not applicable.

Table 3 Summary of recommendations on the use of non-anti-SARS-CoV-2 agents for the treatment of COVID-19.

Recommendation	Anti-bacterial agent	Anti-fungal agent	Anti-non-SARS-CoV-2 antiviral agent	Comments
National Institutes of Health[42]	Insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication			For critically ill patients
Infectious Diseases Society of America[43]	N/A	N/A	N/A	No
Surviving Sepsis Campaign[44]	Daily assessment for de-escalation and re-evaluation of the duration of therapy after initiating empiric antimicrobials, and spectrum of coverage based on the microbiology results and the patient's clinical status			In mechanically ventilated patients with COVID-19 and respiratory failure, empiric antimicrobials/ antibacterial agents were suggested.
Canada[46]	Empirical antibiotic should be based on the clinical diagnosis, local epidemiology, and susceptibility data.	N/A	Empiric therapy with a neuraminidase inhibitor should be considered for the treatment of influenza virus infection in patients with or at risk for severe disease under influenza endemic.	Empiric antimicrobials should be used in the treatment of all likely pathogens causing severe acute respiratory infection and sepsis within 1 h of initial patient assessment for COVID-19 patients with sepsis.
Unites Kingdom[48]	An oral antibiotic is indicated in the following scenarios: (1) The likely cause is bacterial (2) It is unclear whether the cause is bacterial or viral and symptoms are more concerning (3) They are at high risk of complications Doxycycline is used as first-line treatment, whereas amoxicillin is used as alternative treatment.	N/A	N/A	Antibiotics are not used as treatment for or to prevent pneumonia if the infection is likely caused by SARS-CoV-2 and symptoms are mild. Dual antibiotics are not routinely used.
China[49]	Mild patients use antibiotics, such as amoxicillin, azithromycin, or fluoroquinolones, as treatment against CAP; severe patients use empirical antibiotics to treat all possible pathogens.	NA	NA	Blind or inappropriate use of antibacterial drugs should be avoided.

pneumophila, Klebsiella pneumoniae, Acinetobacter baumannii and *Aspergillus flavus*.

In this study, we established that COVID-19 can cause co-infections with bacteria, viruses, and fungus. The prevalence of COVID-19-associated co-infections varied; however, the prevalence of secondary infections could be as high as 50% among non-survivors. Three of the four patients with secondary infection in Huang et al.'s study had procalcitonin levels greater than 0·5 ng/mL (0·69, 1·46, and 6·48 ng/mL), which may suggest bacterial infections,[11] but the clinical utility of procalcitonin alone in the differential diagnosis of co-infection between bacteria and SARS-CoV-2 infection needs further validation. Like the findings of previous studies that showed an association between influenza and invasive pulmonary aspergillosis,[34] one COVID-19 patient had *Aspergillus* co-infection was reported.[33] Furthermore, we were unable not obtain other laboratory findings or imaging studies on the characteristic information to distinguish bacterial co-infection from COVID-19. Therefore, these findings suggest the need to conduct comprehensive microbiologic surveys and clinical evaluation other than those conducted for SARS-CoV-2, especially in COVID-19 patients at high risk of mortality. Table 3.

In this study, influenza A virus was one of the common viral pathogens causing co-infection among patients with SARS-CoV-2 infection, and two of the reported patients showed false-negative results for SARS-CoV-2 on rRT-PCR; therefore, false-negative results for SARS-CoV-2 can occur

in COVID-19 patients co-infected with influenza A virus. Ruling out SARS-CoV-2 by ruling in another pulmonary pathogen, such as influenza viruses, carries a significant risk. By contrast, ruling out co-infection with influenza by ruling in SARS-CoV-2 could confer a risk in the period of seasonal influenza. Besides the influenza A virus, other viruses, including coronavirus, rhinovirus/enterovirus, parainfluenza, metapneumovirus, and influenza B virus, have been reported to cause pneumonia[35-37] and can cause co-infections with SARS-CoV-2.

Rapid laboratory methods for identifying co-infection

Before the emergence of COVID-19, the US Food and Drug Administration approved the use of many multiplex PCR panels, including Luminex xTAG RVP v1 (Luminex Corporation), Luminex xTAG RVP Fast (Luminex Corporation), FilmArray respiratory panel (BioFire Diagnostics), eSensor RVP (GenMark Diagnostics), Verigene Respiratory Pathogens Flex test (Luminex Corporation), Luminex NxTAG respiratory pathogen panel (Luminex Corporation), and ePlex respiratory pathogen panel (GenMark Diagnostics), to help in the early diagnosis of possible respiratory pathogens.[38,39] However, these tests should be carefully used because ruling in one respiratory pathogen cannot rule out SARS-CoV-2. Two patients (patients 3 and 4) in the present study (Table 2) initially tested positive for influenza and negative for SARS-CoV-2 rRT-PCR[27,28]; however, repeated testing showed positive results for SARS-CoV-2 and confirmed a co-infection of COVID-19 and influenza A. Therefore, during this COVID-19 pandemic, the above-mentioned tests should only be used for the detection of possible non-SARS-CoV-2 infections in COVID-19 patients. Fortunately, SARS-CoV-2 has been rapidly incorporated into preexisting syndromic multiplex panels, such as QIAstat-Dx® Respiratory 2019-nCoV Panel (Qiagen, the Netherlands) and BioFire FilmArray RP-2.1 (BioFire FilmArray Respiratory Panel-2 plus SARS-CoV-2; bioMérieux, France). In addition to SARS-CoV-2, many other common respiratory pathogens, including bacteria and viruses, can be simultaneously identified using the QIAstat-Dx® Respiratory 2019-nCoV Panel. Using this SARS-CoV-2 containing syndromic/co-infection test, the risk of under-diagnosis of co-infection can be largely reduced during the COVID-19 pandemic.

Combination therapy with non-anti-SARS-CoV-2 agents in suspected COVID-19 patients

For influenza, the original recommendations in the in the ATS/IDSA CAP treatment guidelines were made for the treatment of potential bacterial co-infections.[5] As similar clinical entity of co-infection is possible with SARS-CoV-2 infections, this recommendation has been applied in the treatment of COVID-19 and has been reported in the previous studies on SARS-CoV-2 infections in China. In the first series of 41 patients infected with SARS-CoV-2, all patients received empirical antibiotic treatment, while 93% (n = 38) received antiviral therapy.[11] The second case series of 99 COVID-19 patients reported that antibiotic, antiviral, and antifungal agents were administered in 71%, 76%, and 15% of patients, respectively.[12] A third case series of 138 COVID-19 patients requiring intensive care unit admission reported that most patients received antiviral therapy (oseltamivir, 124 [89.9%]), and many received antibacterial therapy (moxifloxacin, 89 [64.4%]; ceftriaxone, 34 [24.6%]; and azithromycin, 25 [18.1%]).[40] Even in a large series of 1099 patients, the majority of patients (58.0%) received intravenous antibiotic therapy, and 35.8% received oseltamivir therapy.[41] Finally, according to the recommendation of National Institutes of Health, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication in patients with COVID-19 and severe or critical illness.[42] In addition, the Infectious Diseases Society of America guidelines did not mention this issue.[43] By contrast, the Surviving Sepsis Campaign suggested the use of empiric antimicrobials/antibacterial agents, over no antimicrobials, in mechanically ventilated patients with COVID-19 and respiratory failure, although they are weak recommendations with low level of evidence based on the data extrapolated from previous studies on other types of viral pneumonias, particularly influenza.[44,45] In Canada and Taiwan, empiric antimicrobials used in treating all likely pathogens causing severe acute respiratory infection and sepsis should be administered within 1 h, and the choice of antimicrobial agents should be based on the clinical diagnosis (CAP, healthcare-associated pneumonia, or sepsis), local epidemiology, and susceptibility data.[46,47] Moreover, anti-influenza agents should be considered in patients with or at risk for severe disease when there is ongoing local circulation of influenza.[46] In UK, antibiotic should only be offered to adult patients in the community with suspected or confirmed COVID-19 if the likely cause is bacterial. It remains unclear whether the cause is bacterial or viral or whether the patients are at high risk of complications.[48] In this condition, oral doxycycline is preferred because of its broader spectrum, particularly against *M. pneumoniae* and *S. aureus* [48]. In China, for COVID-19 patients in whom co-bacterial infection cannot be ruled out, empirical antibiotic, such as amoxicillin, azithromycin, or fluoroquinolones, was recommended for mild cases but broad-spectrum antibiotic covering all possible pathogens was suggested for severe cases.[49] Based on the limited data of the present work, it remains unclear which antimicrobial agents should be empirically prescribed in patients with suspected COVID-19. In addition, antimicrobial stewardship program should be implemented to prevent the rising rates of antimicrobial resistance could be caused by an increase in inappropriate antibiotic use for viral pneumonia.[50]

Conclusion

Co-infection is possible among COVID-19 patients. Clinicians cannot rule out co-infection with other respiratory pathogens when diagnosing SARS-CoV-2 infection nor rule out COVID-19 by detecting non-SARS-CoV-2 respiratory pathogens. However, our findings were based on a limited number of observational studies. Further large-sample, well-designed studies are warranted to investigate the

prevalence of COVID-19 co-infection, risk of co-infection, microbiological distribution, and impact of co-infection on the clinical outcomes of COVID-19 patients. After obtaining more data regarding co-infection with SARS-CoV-2, empirical antimicrobial agents in suspected COVID-19 cases can be recommended.

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Declaration of Competing Interest

None declared.

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