

Bacterial coinfections in COVID-19: an underestimated adversary

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Abstract

Current literature shows that secondary bacterial infections, although less frequent than in previous influenza pandemics, affect COVID-19 patients. *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella pneumophila*, *Streptococcus pneumoniae*, *Haemophilus* and *Klebsiella* spp. are the main species isolated. Of note, *Mycobacterium tuberculosis*-COVID-19 coinfections are also reported. However, bacterial coinfection rates increase in patients admitted in the intensive care units, and those diseases can be due to superinfections by nosocomial antibiotic-resistant bacteria. This highlights the urgency to revise frequent and empiric prescription of broad-spectrum antibiotics in COVID-19 patients, with more attention to evidence-based studies and respect for the antimicrobial stewardship principles.

Key words

- COVID-19
- bacterial coinfections
- superinfections
- antibiotics
- therapy
- intensive care units

INTRODUCTION

Secondary bacterial infections associated with influenza pandemics are well described in the literature, with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* being reported as the most common causes, and rates ranging between 11 and 35% of cases in a meta-analysis [1]. Most deaths associated with influenza pandemic of 1918 were not caused by influenza virus alone, but by subsequent bacterial pneumonia, particularly caused by *S. pneumoniae*. More recently, secondary bacterial infections were also reported in the 2009 swine influenza pandemic [1] and during the 2002 severe acute respiratory syndrome (SARS) [2] and the 2012 Middle East respiratory syndrome (MERS) [3], both caused by the coronavirus of zoonotic origin SARS-CoV and MERS-CoV, respectively. Secondary bacterial infections can be complications of viral respiratory diseases, and lead to increase in pneumonia severity [1]. Here, we explored current literature on bacterial coinfections reported in the 2020 coronavirus pandemic.

SECONDARY INFECTIONS ASSOCIATED WITH THE 2020 PANDEMIC

Data regarding secondary respiratory infections in the severe disease caused by the SARS-CoV-2 coronavirus (COVID-19) are limited due to the still ongoing spread of the disease worldwide. However, some reports showed that secondary infections significantly decreased survival of COVID-19 patients, particularly when they were admitted to the Intensive Care Units

(ICU). In the studies of Huang and Zhou *et al.* [4, 5] involving 41 and 191 COVID-19 patients, respectively, performed in Wuhan, China, secondary infections were observed in 10% and 15%, respectively, of patients, with 31% of them requiring mechanical ventilation in ICU care and 0% in no-ICU care. A secondary infection was reported in 50% of non-survivors and only 1% of survivors [5]. Respiratory specimens (nasal and pharyngeal swabs, sputum, bronchoalveolar lavages, bronchial aspirates) and blood were tested for routine bacterial and fungal examinations and for common respiratory viruses and COVID-19 virus, using real-time PCR or next-generation sequencing (NGS) methods. Secondary infections were diagnosed when patients showed clinical symptoms or signs of pneumonia or bacteremia, and had a positive culture of a new pathogen [4, 5].

In another study, Zhang *et al.* [6] reported that in 221 COVID-19 patients in Wuhan, those with severe illness were 14.2, 18.2 and 2.9 times more likely to have coinfections with bacteria, fungi and other viruses, respectively, than those not severely ill. Furthermore, deaths associated with coinfections by bacteria, fungi and other viruses occurred in 55.6, 44.4 and 44.4%, respectively, of patients in the ICU, and in 26.1, 13.0 and 8.7%, respectively, of patients transferred from ICU to the general wards. In COVID-19 patients coinfecting with bacteria in the ICU-death group, carbapenem-resistant *Acinetobacter baumannii* was isolated. This nosocomial, antibiotic-resistant pathogen is known to pose challenges in antibiotic therapy, and to increase the death-risk [6].

COMMON SPECIES INVOLVED IN COVID-19 COINFECTIONS

The species of the microorganisms identified in COVID-19 positive specimens are reported in Table 1 [7-19]. Overall, the 13 studies performed on a total of 733 patients showed that viral coinfections, including mainly influenza virus and rhinovirus/enterovirus, occurred in 17.2% of patients (126/733), while bacterial coinfections due to both Gram-positive and Gram-negative species and *Mycoplasma pneumoniae* occurred in 11.7% (86/733) patients, and fungal coinfections in 1.8% (13/733) patients. The bacterial species more frequently isolated were, in ranking order, *M. pneumoniae*, *S. aureus*, *Legionella pneumophila*, *Haemophilus* spp., *Klebsiella* spp., *Pseudomonas aeruginosa*, *Chlamydia* spp., *S. pneumoniae*, *A. baumannii*. Patients in the ICU were 522/733 [8, 10, 14-16, 18, 19], and 1.3% of them (7/522) developed nosocomial super-infections with antibiotic-resistant *S. aureus*, *Klebsiella pneumoniae*, *P. aeruginosa*, or *A. baumannii*. Apparently, no antibiotic-resistant strains were isolated outside the ICU.

Another study [20] reported bacteremia by clinical pathogens in 21/643 blood cultures (3.3%) from COVID-19 patients, with respiratory sources being confirmed in two cases (a community acquired *K. pneumoniae* and a ventilator associated *Enterobacter cloacae*). All other bacteremias were attributed to non-respiratory sources. No pneumococcal, legionella or influenza infections were detected.

Overall, bacterial infections reported in COVID-19 patients were less frequent and different from those causing lower respiratory tract infections in influenza pandemics [1], with *S. pneumoniae* being rarely isolated. It must be noted that bacteria were mainly cultured from nasopharyngeal samples, while lower respiratory samples were less available also due to safety concern for performing bronchoalveolar lavage. Bacterial diagnosis was performed by routine methods (not detailed in the papers), and by multiplex PCR kits for rapid detection of a wide range of respiratory pathogens, mostly viruses. Thus, coinfections by bacterial species not included in multiplex PCR kits [7-9], or not searched during emergency, could have been under-estimated, so as to undervalue their contribution in COVID-19 severity and mortality. Early and rapid diagnosis and drug susceptibility testing of mixed bacterial infections by culture-independent approaches such as, for instance, NGS methods and Nanopore metagenomics [21], could better guide/adjust antibiotic therapy so as to prevent fatal outcomes, particularly in case of Multi Drug Resistant (MDR) bacteria.

Rapid detection of bacterial infections may also limit development of virus super-spreaders, defined as patients infecting ≥ 10 persons each. For instance, in Singapore, during the SARS-CoV outbreak, two patients hospitalized with bacterial infections were co-infected with SARS-CoV, and caused 76% of SARS-CoV infections in a healthcare facility [2]. Thus, to contain current COVID-19 pandemic it is important to triage and isolate patients with known bacterial infections in designated wards, and to apply efficient infection control measures, in order to limit virus super-spreading.

MYCOBACTERIUM TUBERCULOSIS-COVID COINFECTIONS

During the SARS and MERS epidemics, few coinfections involving *Mycobacterium tuberculosis* (Mtb) were reported [22, 23]. However, in the COVID-19 pandemic the World Health Organization and other institutions published several documents including sustainability of tuberculosis (TB) services [24] and information on similarity, differences and interactions between these two dangerous respiratory pathogens, to anticipate the impact of COVID-19 on TB patients and TB control programmes [25, 26]. These publications were important to better tackle TB and COVID-19 pandemics worldwide. Indeed, clinical data were reported in studies regarding TB-COVID coinfections [27, 28] and characterization of patients who died with Mtb and COVID-19 [29].

For instance, Stochino *et al.* [27] reported TB-COVID coinfections in 20/24 TB patients admitted to the phthisiology unit of the hospital of Sondalo (Northern Italy). In the 3-4 weeks following COVID-19 diagnosis, the clinical course of TB and COVID-19 coinfection was generally benign, but follow-up was limited to a few weeks, not allowing assessment of longer-term outcomes. Following analysis of the dynamics of the infection spread in the hospital, it was apparent that the outbreak was due to insufficient control practices associated with a higher vulnerability of TB patients. No patient was admitted in the ICU. Furthermore, Tadolini *et al.* [28] reported TB-COVID infections in 49 patients with current or former TB occurring in 8 countries (Belgium, Brazil, France, Italy, Russia, Singapore, Spain, Switzerland). Patients were treated with first-line TB drugs and, in case of MDR-TB, with second-line drugs. Medications for COVID-19 included anti-viral drugs (lopinavir/ritonavir, darunavir/cobicistat) and antibiotics (azithromycin). Diagnosis, treatment and outcome details of the 49 COVID-19 patients showed various clinical profiles, thus larger studies are necessary. Finally, after preliminary analysis of 8 deaths occurring in the 69 TB-COVID coinfections reported by Stochino *et al.* [27] and Tadolini *et al.* [28], Motta *et al.* [29] concluded that i) higher mortality was likely to occur in elderly patients with comorbidities, ii) TB might not be a major determinant of mortality, iii) migrants had lower mortality, probably because of their younger age and lower number of comorbidities.

TREATMENT OF BACTERIAL INFECTIONS IN THE COVID-19 PANDEMIC

The respiratory symptoms of patients with COVID-19 pneumonia admitted to hospital with fever and dry cough can mimic those of atypical bacterial pneumonia, making difficult to distinguish patients with hospital acquired and ventilator associated pneumonia (VAP). A biomarker used to differentiate bacterial from viral infections is procalcitonin [4-6, 8, 10, 11, 14, 16-18], a peptide whose serum levels increase during bacterial but not viral infections.

To decrease chances of VAP in the ICU, most COVID-19 patients were empirically treated with antibiot-

ics. The principles of antibiotic stewardship should be considered, but in the case of severely ill patients, the concern surrounding the pandemic forced clinicians to start treatment with antibiotics. Indeed, *Table 1* shows that 88.3% of COVID-infected patients (476/539) were treated with broad-spectrum antibiotics including third-generation cephalosporins, quinolones, carbapenems. The choice of empiric regimens should take into account possible side effects (e.g. QT prolongation, diarrhoea), local epidemiology of drug resistance, and impact of drug resistance on the patient. In some countries, bacteria are resistant to at least one antibiotic class, therefore empiric broad-spectrum therapy could have limited effect particularly in hospital-acquired infections. In case of sepsis, inadequate antibiotic therapy may increase mortality [30].

Overall, since COVID-19 pandemic is still ongoing, and transfer of patients in the ICU continues, the use of antibiotics will steady raise and increase development and transmission of MDR strains in the health-care systems. Thus, when the probability of a bacterial infection is low, antibiotic treatment of COVID-19 patients should be re-evaluated, and stopped if not necessary. Antibiotics should be reserved for patients with the most severe respiratory presentations [20, 31].

CONCLUSION

From current reports, incidence of bacterial coinfections in COVID-19 cases is lower than in previous influenza pandemics. However, coinfection rates increase in patients admitted to the ICU. Super-infections by antibiotic-resistant bacteria occur in 1.3% of patients in

Table 1

Review of recent literature describing the species involved in COVID-19 coinfections

N of bacterial or fungal coinfections / N of COVID-19 patients (pts) tested (%)	N of viral coinfections* / N of COVID-19 pts tested (%)	Clinical sample	Diagnostic methods	N of pts treated with antibiotics (AB), antifungals (AF), antivirals (AV) / N of total pts treated (%). [AB resistances (AB-R)]	Pts treated in the ICU (%)	Country	Reference
<i>Mycoplasma pneumoniae</i> : 1/67 (1.5); <i>Staphylococcus aureus</i> : 1/49 (2); <i>Haemophilus influenzae</i> : 3/49 (6.1) <i>Escherichia coli</i> : 1/49 (2)	REV: 12/67 (17.9) OCV: 10/67 (14.9) IAV: 3/67 (4.5) RSV, ADV, H1N1: 3/67 (4.5)	Nasopharyngeal swabs	Routine diagnosis, BioFire Film Array Respiratory Panel 2 plus (17 viruses, 4 bacteria) (BioMerieux)	AB (doxycycline, moxifloxacin): 8/9 (88.9) AV (oseltamivir): 1/9 (11.1)	NR	United Kingdom	[7]
<i>M. pneumoniae</i> : 1/42 (2.4); <i>Chlamydia pneumoniae</i> : 2/42 (4.8)	REV: 22/42 (52.4) OCV: 7/42 (16.7) IAV: 1/42 (2.4) RSV: 4/42 (9.6) H1N1: 2/42 (4.8) PIV: 3/42 (7.1)	Nasopharyngeal samples	RT-PCR (Respiratory panel)	NR	14.2	USA	[8]
<i>Haemophilus parainfluenzae</i> : 4/20 (20.0); <i>Klebsiella aerogenes</i> : 1/20 (5); <i>Candida albicans</i> : 1/20 (5)	REV: 2/20 (10) IAV, IBV: 2/20 (10) RSV: 1/20 (5)	Nasopharyngeal swabs	RT-PCR, NGS, ResPlex II V2.0 kit Respiratory panel (17 viruses, 3 bacteria) (Qiagen)	NR	NR	China	[9]
<i>Acinetobacter baumannii</i> + <i>Klebsiella pneumoniae</i> + <i>Aspergillus flavus</i> : 1/99 (1); <i>Candida spp</i> : 4/99 (4)	Not found	Throat-swab specimens, sputum, endotracheal aspirates	Real time RT-PCR	AB (cephalosporins, quinolones, carbapenems, tigecycline): 70/99 (70.7); AF: 15/99 (15.2); AV (oseltamivir, ganaciclovir, lopinavir/ritonavir): 75/99 (75.8). [AB-R: 1 <i>A. baumannii</i>]	23	China	[10]
<i>M. pneumoniae</i> : 4/20 (20)	IAV, IBV: 3/20 (15) RSV, CMV: 2/20 (10)	Pharyngeal swabs from pediatric patients	Nucleic acid tests	NR	NR	China	[11]
<i>Legionella pneumophila</i> : 6/68 (8.8); <i>M. pneumoniae</i> : 8/68 (11.8)	IAV, IBV: 34/68 (50)	Acute phase serum	IgM antibodies by indirect immunofluorescence	NR	NR	China	[12]
<i>Enterobacter cloacae</i> : 2/29 (6.9); <i>C. albicans</i> : 2/29 (6.9); <i>A. baumannii</i> : 1/29 (3.4); <i>Chlamydia</i> : 2/28 (7.1), by IgG	RSV, ADV: 2/28 (7.1)	Sputum, serum	Culture, IgG and IgM antibodies in blood	AB (mostly moxifloxacin): 66/67 (98.6); AF: 8/67 (11.9); AV (mostly umifenovir): 66/67 (98.6);	NR	China	[13]

Continues

Table 1
Continued

N of bacterial or fungal coinfections / N of COVID-19 patients (pts) tested (%)	N of viral coinfections* / N of COVID-19 pts tested (%)	Clinical sample	Diagnostic methods	N of pts treated with antibiotics (AB), antifungals (AF), antivirals (AV) / N of total pts treated (%). [AB resistances (AB-R)]	Pts treated in the ICU (%)	Country	Reference
Gram-positive cocci and Gram-negative bacilli (not identified): 1/11 (9.1)	IAV, CMV: 2/11 (18.2), by IgM	Sputum, serum	Culture, IgM antibodies in blood	AB (mostly moxifloxacin): 4/11 (36.4); AF (caspofungin): 1/11 (9.1); AV (mostly umifenovir): 8/11 (72.7).	9.1	China	[14]
<i>A. baumannii</i> + <i>A. flavus</i> : 1/5 (20);	Not found	Upper and lower respiratory tract samples, blood, urine, stools	Culture, multiplex PCR	AB (meropenem, tigecycline, colistin): 1/5 (20); AF (isavuconazole): 1/5 (20); AV (remdesivir): 3/5 (60).	40	France	[15]
<i>Pseudomonas spp</i> 1/21 (4.8)	IAV: 2/21 (9.6) PIV: 1/21 (4.8)	Nasopharyngeal samples	NR	NR	81	USA	[16]
<i>L. pneumophila</i> 1/7 (14.3)	IAV: 2/7 (28.6)	Sputum, endotracheal aspirates	Real time RT-PCR	AB (cephalosporins, macrolides, quinolones): 7/7 (100) AV (oseltamivir, ganciclovir, umifenovir); 7/7 (100)	NR	China	[17]
<i>S. aureus</i> 7/289 (2.4); <i>Streptococcus pneumoniae</i> 4/289 (1.4); <i>Pseudomonas aeruginosa</i> 1/289 (0.3); <i>Klebsiella spp</i> 2/289 (0.7); <i>E. coli</i> 1/289 (0.3); <i>Bordetella holmesii</i> 1/289 (0.3); <i>Stenothrophomonas maltophilia</i> 1/289 (0.3); <i>Aspergillus niger</i> 1/289 (0.3) Oral bacterial flora 15/289 (5.2)	IAB, IBV: 2/289 (0.7) REV 2/289 (0.7) ADV, HMV: 2/289 (0.7)	Upper and lower respiratory tract samples, blood, urine	Culture, respiratory viral panel, PCR	AB (not specified): 271/289 (93.8) AV (remdesivir): 28/289 (9.7) [AB-R: 3 methicillin resistant <i>S. aureus</i>]	36.3	USA	[18]
<i>K. pneumoniae</i> 2/55 (3.6) <i>P. aeruginosa</i> 1/55 (1.8) <i>Serratia marcescens</i> 1/55 (1.8) <i>Aspergillus spp</i> 2/55 (3.6) <i>C. albicans</i> 1/55 (1.8)	NR	Respiratory tract samples, blood	NR	AB (not specified): 49/52 (94.2) AV (remdesivir, lopinavir): 23/52 (44.2) [AB-R: 2 <i>K. pneumoniae</i> , 1 <i>P. aeruginosa</i>]	100	China	[19]

*Influenza A virus (IAV), influenza B virus (IBV), other coronavirus (OCV), rhinovirus/enterovirus (REV), respiratory syncytial virus (RSV), adenovirus (ADV), human metapneumovirus (HMV), parainfluenza 3 virus (PIV), cytomegalovirus (CMV). Not reported (NR).

ICU and 0% in no-ICU care. *M. tuberculosis*-COVID-19 coinfections are also reported. Overall, despite frequent prescription of broad-spectrum antibiotics, antimicrobial stewardship principles should be re-considered to avoid development and transmission of drug resistant organisms in healthcare facilities.

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