

Superadded Coinfections and Antibiotic Resistance in the Context of COVID-19: Where do We Stand?

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ABSTRACT

Purpose of review: Poor outcomes in the current coronavirus disease 2019 (COVID-19) pandemic have been attributed to superadded bacterial coinfections. The World Health Organization has reported overzealous usage of broad-spectrum antibiotics during this current pandemic raising concerns of increasing antimicrobial resistance? Therefore, the knowledge of coinfection and the common pathogens during these challenging times is essential for antibiotic stewardship practices.

Recent findings: The incidence of reported superimposed bacterial and viral coinfections in COVID-19 patients is around 0.04 to 17%. However, more than 70% of patients have received broad-spectrum antibiotics. The presence of a simultaneous coinfection can be suspected in patients with neutrophilic lymphocytosis and elevated procalcitonin in the setting of COVID-19. Multiplex polymerase chain reaction (PCR) panels, with its short turnaround time, aid in the definitive diagnosis of possible coinfection. *Acinetobacter baumannii*, *Mycoplasma pneumonia*, influenza virus, *Aspergillus*, *Candida*, etc., are commonly implicated pathogens.

Summary: Rapid characterization of coinfection and avoidance of overzealous use of broad-spectrum antibiotics in COVID-19 patients are the key to prevent antibiotic resistance during this pandemic.

Keywords: Antibiotic resistance, Coinfections, COVID-19—coronavirus disease 2019, SARS-CoV-2—severe acute respiratory syndrome coronavirus-2.

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INTRODUCTION

Patients with respiratory viral infections are generally predisposed to bacterial coinfections. While a superinfection is attributed to resistant microorganisms or new-onset resistance to the previously used antibiotics, a coinfection is defined as an infection that occurs simultaneously with the initial agent. The difference is chiefly temporal.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease is a global concern in view of endemicity, mortality, and an unprecedented burden on the current health-care system. SARS-CoV-2 is an enveloped, single-stranded RNA betacoronavirus. The clinical features mimic the previous outbreaks of SARS-CoV in 2002, and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012.¹

The prevalence of bacterial coinfections in the previous influenza epidemics ranges between 20 and 30%.^{2,3} They usually occurred within the initial 6 days of influenza infection and were leagued with increased morbidity and mortality. The most common organism implicated during the influenza epidemic was *Streptococcus pneumoniae*.⁴

Coinfections with *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have also been reported during the 2003 SARS-1 epidemic. The incidence of coinfection was 4 to 25%.⁵ During the MERS-CoV outbreak, the coinfection rates were even lower ranging from 1 to 1.4%. Atypical bacteria like *Legionella pneumophila*, *C. pneumoniae*, and *M. pneumoniae* had been implicated. However, a study reported that treatment with macrolides did not improve the outcome in MERS-CoV patients with the said bacterial coinfections.⁶

The majority of the studies in this current pandemic have focused primarily on SARS-CoV-2, while associations with coinfecting organisms have been comparatively overlooked. The

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extent to which SARS-CoV-2 is complicated by bacterial or fungal infections remains unclear. Envisioning the concerns of increased fatality of bacterial superinfections during previous influenza pandemics, pragmatic use of antibiotics in SARS-CoV-2 infection has been advocated.^{7,8} However, the incidence of coinfection in the previous coronavirus epidemics was much lower with little implications on mortality. Thus, overzealous use of antibiotics and consequently increasing bacterial resistance have become a serious concern. Therefore, the awareness about the usual organisms causing acute respiratory coinfection in patients already infected with SARS-CoV-2 is important for implementing antibiotic stewardship practices.

PATHOGENESIS

Studies on the influenza epidemic suggest that coinfection predominantly occurred during periods of high viral shedding within the first 6.2 (range, 1.3–11) days of infection.⁴ The susceptibility of the influenza virus to bacterial coinfections had been attributed

to the viral enzyme neuraminidase and a proapoptotic influenza protein, PB-F2.⁹ As the viral replication accelerates, endothelial barrier disruption occurs leading to impaired alveolar–capillary oxygen transmission. Viral shedding is maximum from 7 days before to 3 days after symptom onset.¹⁰

The virus proliferation in the respiratory system affects the mucociliary clearance of bacteria from the lower airway. The deceased epithelial cells uncover the basal cell layer, resulting in bacterial adherence and invasion. The decrease of lymphocytes and host immune function further contribute. There is a delayed release of cytokines and chemokines from the respiratory epithelium, dendritic cells, and macrophages in patients with coronavirus disease 2019 (COVID-19). This hyperactive immune response, called the cytokine storm, is further worsened by coinfections or secondary infections.¹¹

ORGANISMS

Several studies have reported superadded bacterial, fungal, and even viral coinfections in COVID-19 patients (Table 1). A recent systematic review on 3,338 patients with COVID-19 has reported that 14.3% of patients are affected with secondary bacterial infection, and it is more common in critically ill patients. *Mycoplasma*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* are the most commonly reported organisms.¹²

Another meta-analysis in this regard has found 7% of hospitalized COVID-19 patients had a bacterial coinfection "(95% CI, 3–12%; $n = 2183$; $I^2 = 92.2\%$)," and 3% of them had a viral coinfection "(95% CI, 1–6; $n = 1014$; $I^2 = 62.3\%$)." *M. pneumoniae*, *P. aeruginosa*, *H. influenzae*, and *Klebsiella pneumoniae* are the commonest bacteria, and respiratory syncytial virus and influenza A are the commonest virus associated with. Fungal coinfection with *Candida albicans*, *Aspergillus fumigatus*, and *flavus* was also reported.¹³

CLINICAL PRESENTATIONS

The presence of coinfection may lead to confounding and misleading diagnosis. Suspicion, identifying, and distinguishing them from colonization remain a challenge. COVID-19 is usually associated with lymphopenia. On the contrary, lymphocytosis has been reported in cases of coinfection with *M. pneumoniae*.¹⁴ A possible bacterial coinfection can be suspected when patients present with neutrophilic lymphocytosis in the setting of COVID-19.

An increased level of procalcitonin has been associated with the severity of SARS-CoV-2 infection. It is identifiable in 2 to 4 hours, tops at 12 to 24 hours, with a half-life of 25 to 30 hours.¹⁵ Thus, the elevated procalcitonin level may be beneficial in identifying the presence of a superadded bacterial coinfection, as it is non specific and also raised in patients with end-stage renal disease, cardiogenic shock, and multiorgan failure.¹⁶

The computed tomography patterns of pneumonia are generally related to the pathogenesis of infection. In comparison to other viral pneumonia, COVID-19 tends to have a more peripheral distribution, lower lobe predominance, with rounded ground-glass opacities, increased vascular enlargement, and a "reverse halo" sign, central ground-glass opacities with an interrupted peripheral ring of consolidation.¹⁷ Bacterial or viral superinfection can complicate these findings. The presence of mediastinal lymphadenopathy, a tree in bud appearance, pleural effusion, cavitation, and pneumothorax should raise concern for probable coinfection.^{18,19}

It is, however, difficult to determine the specific type and the number of coinfecting pathogens based on imaging findings and medical history alone. Therefore, for early and definitive diagnosis of associated coinfection and to detect a broad range of potential pathogens, multiplex polymerase chain reaction (PCR) panels are required. They have a shorter turnaround time of 1 to 2 hours, higher sensitivity for viral pathogens, and help in the detection of a broad panel of a virus, and coinfections.²⁰ The respiratory panel can spot 17 viruses and 3 bacteria simultaneously with an overall sensitivity and specificity of 95 and 99%, respectively. The respiratory tract sample (tracheal aspirate, BAL, or sputum) can be collected as soon as COVID-19 is confirmed or when a coinfection is suspected, and the results will aid in initiating or de-escalating appropriate antibiotic therapy as indicated. Multiplex PCR panels have been used in earlier outbreaks of infective diarrhea and have been effective in detecting coinfections at a lesser time in comparison to conventional diagnostics.²¹

IMPLICATIONS

The clinical evidence so far shows that the bacterial, viral, or fungal coinfection rate of COVID-19 patients is lower than that of influenza viral infection. However, 70% of patients have received fluoroquinolones, third-generation cephalosporins, and other broad-spectrum antibiotics.²²

Antibiotic prescriptions are becoming extensive and excessive during this pandemic, and 90% of patients are being prescribed empirical antibiotics. The World Health Organization has also reported widespread usage of azithromycin in the current scenario despite the absence of any clinical guidelines. Oral doxycycline is also being widely used for its spectrum against *M. pneumoniae* and *Staphylococcus aureus*.²²⁻²⁴

At present, there is no consensus regarding the use of antibiotics in the background of COVID-19. While in China, broad-spectrum antibiotics covering all possible pathogens have been used in >90% of patients, some countries abutted the use of antibiotics in mild to moderate SARS-CoV-2 patients (Table 2).

Antimicrobial resistance requires urgent attention and action. A survey conducted by the Infectious Disease International Research Initiative involving participants from 23 countries also revealed widespread broad-spectrum antibiotic use during this epidemic.²⁵ Interruption of routine health services during the pandemic also has caused interruption to treatment, especially of tuberculosis and HIV, which can further contribute to antimicrobial resistance.²⁶ During the first SARS-CoV outbreak, the incidence of methicillin-resistant *S. aureus* (MRSA) significantly increased from 3.53% pre-SARS to 25.30% during the SARS outbreak.²⁷

CONCLUSION

The ramification of COVID-19 on antimicrobial resistance remains unclear. In the absence of a definitive therapeutic and preventive modality, we should look ahead and prevent a larger hidden threat from rising upon us. Thus, further studies regarding the rapid characterization of coinfection and avoiding overzealous use of antibiotics in patients with mild to moderate COVID-19 are the need of the hour, keeping in mind the likelihood of secondary bacterial or fungal pneumonia in a patient with worsening respiratory failure or sepsis.

Table 1: Summary of studies that have demonstrated coinfection in COVID-19

Sl. No.	Author [doi]	Country	Sample size	Coinfection (n,%)	Organisms identified	Diagnostic modality	Outcome
1	Chen et al. [doi:10.1016/S0140-6736(20)30211-7]	China	99	5 (5.02)	<i>Acinetobacter baumannii</i> <i>Klebsiella pneumoniae</i>	Respiratory NAAT Bacterial and fungal culture	Not specified
2	Wang et al. [doi:10.1093/cid/ciaa272]	China	29	5 (17)	<i>Acinetobacter baumannii</i> <i>Enterobacter cloaca</i>	Sputum culture	Not specified
3	Yu et al. [doi:10.1016/S1473-3099(20)30176-6]	China	7	3 (42)	<i>Legionella pneumophila</i> Influenza H1N1	Sputum culture RT-PCR	Obstetric patients— No ICU admission
4	Chen et al. [doi:10.3760/cma.j.issn.1001-0939.2020.0005]	China	29	1 (3.4)	Organism not reported	Not specified	Patient with bacteremia died
5	Goyal et al. [doi:10.1056/NEJMc2010419]	USA	393	19 (4.8)	Organism not reported	Not specified	Not specified
6	Huang et al. [doi:10.1016/S0140-6736(20)30183-5]	China	41	4 (9.7)	Organism not reported	Not specified	Not specified
7	Zhou et al. [doi:10.1017/ice.2020.156]	China	191	28 (15)	Organism not reported	Not specified	Secondary bacterial infection associated with mortality
8	Zhu et al. [doi:10.1016/j.virusres.2020.198005]	China	257	243 (94.2)	<i>Streptococcus pneumoniae</i> <i>Klebsiella pneumoniae</i> <i>Haemophilus influenzae</i> <i>Escherichia coli</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> <i>Mycoplasma pneumoniae</i> <i>Bordetella pertussis</i>	RT-PCR	Coinfection observed in all severe/critical cases in 1–4 days after onset
9	Kim et al. [doi:10.1001/jama.2020.6266]	USA	116	25 (20)	HRV Human adenovirus Influenza A&B <i>Candida</i>	RT-PCR	Not specified
10	Arentz et al. [doi:10.1001/jama.2020.4326]	USA	21	1 (0.04)	Rhinovirus Influenza A Metapneumovirus Parainfluenza	Not specified	Not specified
11	Liu et al. [doi:10.1097/CM9.0000000000000775]	China	78	0	Organism not reported No organism identified	Respiratory NAAT	Not specified

Table 2: Summary of the various society guidelines regarding antimicrobial therapy for coinfection in COVID-19

Sl. No.	Recommendation	Diagnosis of coinfection and guidance of antibiotic therapy	Treatment modality	Antimicrobial of choice
1	Surviving sepsis campaign of critically ill adults [doi:10.1007/s00134-020-06022-5]	No recommendation	Consider empiric antimicrobials in patients with respiratory failure and mechanically ventilated patients (weak evidence)	No recommendation
2	NICE, UK [https://www.nice.org.uk/guidance/ng173/ Assessing the ongoing need for antibiotic]	<ul style="list-style-type: none"> • Routine culture and sensitivity (sputum, tracheal aspirate, blood) • Chest imaging • Full blood count • Legionella and pneumococcal antigen (urine) • Insufficient evidence for routine procalcitonin testing 	Empirical antibiotics to be started only on clinical suspicion, and within 4 hrs of diagnosis	Symptoms <48 hrs (suspected CAP): Oral: Doxycycline 200 mg on the first day and then 100 mg once a day Intravenous: Co-amoxiclav 1.2 gm three times a day + Clarithromycin 500 mg twice a day Consider Levofloxacin 500 mg once/twice a day in severe pneumonia Symptoms >48 hrs (suspected HAP): Oral: Doxycycline 200 mg on first day and then 100 mg once a day Intravenous: Piperacillin-Tazobactam 4.5 gm three times a day
3	MoHFW, India [https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19.pdf]	No recommendation	Antibiotics not to be prescribed unless there is a clinical suspicion of bacterial infection	No recommendation
4	Infectious diseases Society of America [www.idsociety.org/COVID19 guidelines]	No recommendation	No recommendation	No recommendation
5	Canada [https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/clinical-management-covid-19.html#8]	No recommendation	Empirical antimicrobials to treat all likely pathogens in patients with sepsis and within 1 hr of diagnosis	No recommendation
6	Taiwan Clinical Guidance [doi:10.1016/j.jmii.2018.11.004]	No recommendation	Broad-spectrum antibiotics covering all possible pathogens are suggested due to the higher prevalence of coinfections	Mild: amoxicillin, azithromycin, or fluoroquinolones Moderate to severe: empirical antibiotics to treat all possible pathogens

Author’s Individual Contribution

Dr. Bhavana Kayarat contributed to search strategy and draft the manuscript; Dr. Puneet Khanna contributed to conceptualization and editing; and Dr. Soumya Sarkar contributed to study selection, data extraction, draft the manuscript, and editing.

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