Prevalence and Outcomes of COVID-19 Pneumonia and Bacterial Pneumonia Co-Infection Among COVID-19 Patients Admitted in Cebu Velez General Hospital: A Cross-sectional Study

Joana Marie E. Gantuangco, MD,[1] Shayne Julieane L. Morales, MD,[2,3] Lalaine M. Mayol, MD,[2] Concordio John T. Toring, MD,[2] Noridja C. Yusop, MD,[2] Bayani Pocholo T. Maglinte, MD,[2] and Jeremyjones F. Robles, MD[2,4]

Abstract

Background. Studies on previous viral pandemics showed poorer outcomes of patients with concomitant bacterial infection. During the early period of COVID-19 pandemic, empiric antibiotic therapy is commonly given among COVID-19 patients despite lack of strong recommendations for its use.

Objectives. We determined the prevalence of bacterial co-infection and of empiric use of antibiotics among COVID-19 admissions. We also determined association between COVID-19 severity, ICU admissions, length of hospital stay, and mortality outcomes of those with and without bacterial co-infection.

Methods. A total of 159 patients hospitalized with COVID-19 from April 2020 to April 2021 were analyzed in this cross-sectional chart review study. Data on empiric antibiotic administration and cultures taken within 3 days of admission were collected. Chi-square, Fischer-Exact, and T-tests were used to analyze the data.

Results. Empiric antibiotics were given in 94.97% of COVID-19 admissions with azithromycin as the most common agent. The prevalence of bacterial co-infection among COVID-19 admitted patients was 10%. There were higher ICU admissions and longer hospital stay among those with bacterial co-infection although it did not reach statistical significance. No mortality was seen among patients with bacterial co-infection.

Conclusion. There was a high use of empiric antibiotic treatment in hospitalized COVID-19 patients despite the low prevalence of bacterial co-infection among these cases. This warrants development of strategies for antimicrobial stewardship programs especially during the COVID-19 pandemic.

Keywords: COVID-19 pneumonia, bacterial pneumonia co-infection, empiric antibiotic, pneumonia

Introduction

Since COVID-19 was declared a pandemic by the World Health Organization on March 2020, there was a rapid pace of scientific developments on its management and prevention. It has been a common practice to empirically treat hospitalized COVID-19 patients with antibacterial agents. There are over 200 million COVID-19 confirmed cases worldwide with about 70% of hospitalized patients receiving empiric antibiotics. Studies show that a consistent value of only <4% of these admissions were associated with bacterial infections with usual isolates of *S. aureus, S. pneumoniae*, and *H. influenzae*.[1,2]

The wide disparities between the proportion of admitted COVID-19 patients who are empirically treated with antibiotics and the proportion of patients who have documented bacterial co-infection highlights the unnecessary use of antibacterial agents in COVID-19. Bacterial co-infection in COVID-19 may be rare, however it may be associated with longer length of hospital stay (median 7 days vs 5 days; *p=0.003*) and increased in-hospital mortality (48% vs 18%; *p<0.001*).[2]

[1] Department of Internal Medicine, Cebu Velez General Hospital
[2] Department of Internal Medicine, Cebu Velez General Hospital
[3] Section of Infectious Diseases, Cebu Velez General Hospital
[4] Section of Endocrinology, Cebu Velez General Hospital
Corresponding Author: Joana Marie E. Gantuangco, MD eMail: jmegantuangco@gmail.com

Table I. Demographic Characteristics of COVID-19 Cases with and without Bacterial Co-infection

Parameter	With Bacterial Co-Infection (N=16)	Without Bacterial Co-infection (N=143)	p Value
Age, Mean (SD)	64.6 (18.6)	61.6 (16.3)	0.031
Sex, Male, N (%)	9 (56.3)	87 (55.8)	0.665
Hypertension, N (%)	12 (75.0)	100 (64.1)	0.058
Diabetes, N (%)	3 (18.8)	60 (38.5)	0.371
Asthma, N (%)	3 (18.8)	15 (9.6)	0.606
COPD, N (%)	1 (6.3)	4 (2.6)	0.563
COVID-19 Severity			0.753
Moderate, N (%)	11 (68.8)	84 (58.74)	
Severe, N (%)	3 (18.8)	27 (18.89)	
Critical, N (%)	2 (12.5)	32 (22.38)	
Length of Hospital Stay, Days, Median, (SD)	11.0 (18.6)	9.0 (7.2)	-
ICU Admission, N (%)	2 (12.5)	11 (7.1)	-
Mortality, N (%)	0 (0)	29 (20.27)	-

Table II. Antibiotic Utilization Among COVID-19 Cases (n, %)

	With Bacterial Co-Infection (N=16)	Without Bacterial Co-infection (N=143)	Total (N=159)
Without Empiric Antibiotic	0 (0)	8 (5.59)	8 (5.03)
With Empiric Antibiotic	16 (100)	135 (94.4)	151 (94.97)
Azithromycin	14 (87.5)	102 (75.55)	116 (72.96)
Piperacillin-Tazobactam	7 (43.75)	43 (31.85)	50 (31.45)
Ceftriaxone	6 (37.5)	71 (52.59)	77 (48.43)
Co-amoxiclav	1 (6.25)	3 (2.22)	4 (2.51)
Meropenem	1 (6.25)	16 (11.85)	17 (10.69)
Cefepime	1 (6.25)	1 (0.74)	2 (1.26)
Levofloxacin	0 (0)	1 (0.74)	1 (0.63)
Clindamycin	0 (0)	3 (2.22)	3 (1.89)

The unnecessary use of antibiotics increases the risk of antibiotic resistance however, the long-term impact of antibiotic overuse during COVID-19 pandemic remains to be seen.[3,4] The study aimed to determine the prevalence and outcomes of bacterial pneumonia co-infection among admitted patients with COVID-19 and to present the local antibiogram in this population. The findings of this study may help promote and improve antimicrobial stewardship programs as these strategies have been shown to optimize antibiotic use, improve patient outcomes, and reduce harms from excess use including antibiotic resistance.[3] Improving antimicrobial stewardship programs in the hospital may lead to reduction in avoidable cost, prioritization of limited resources, and decreased rates of antibiotic resistance.

Methodology

Design and Population. In this retrospective, descriptive, cross-sectional chart review study, we reviewed a total of 221 charts of individual patients admitted in Cebu Velez General Hospital from April 2020 to April 2021. A total of 62 charts were excluded and the remaining 159 charts were analyzed. The protocol was reviewed by the Research Committee of Cebu Velez General Hospital and was approved by the CIM-CVGH Institutional Review Board.

All charts were anonymized and identified by their chart numbers. Data privacy and confidentiality were maintained. Included charts reviewed were patients aged 21-99 years with laboratory-confirmed COVID-19 by RT-PCR. The parameters taken for the chart review were all disclosed in the chart including sex, presence of comorbidities, whether respiratory and/or blood samples for culture were taken within 3 days of admission, COVID-19 severity, length of hospital stay, and status upon discharge.

COVID-19 pneumonia in this study was operationally defined as cases positive for SARS-CoV-2 upon admission with pneumonia noted on imaging and/or presence of rales on physical examination notes. On the other hand, bacterial pneumonia co-infection was defined as cases with COVID-19 pneumonia as previously defined, with bacterial growth on blood culture and/or sputum culture taken within 3 days of hospitalization.

Charts with missing data were excluded in the study. Charts of mild and asymptomatic COVID-19 cases, patients of ages below 18 years, with RT-PCR for SARS-CoV-2 not done in an accredited laboratory or with no blood or sputum cultures taken were likewise excluded from the study.

Statistical Analysis. Descriptive statistics for all variables were taken. Statistical analyses were performed by the statistical software *IBM SPSS* version 22.0 (IBM Corp, Armonk, NY USA). Significance of association between bacterial co-infection and mortality and severity of COVID-19 were determined through *chi-square analysis* and *Fisher Exact Test*. Significance of difference in terms of length of hospital stay were determined through *t-test. predictive analysis*

Results

Of the 221 charts initially screened, 62 (28%) did not have blood nor respiratory samples taken for culture or had missing details for profiling, thus were excluded. One hundred fifty-nine (159) charts were included in the final analysis.

Table I shows the demographic characteristics of admitted COVID-19 patients. The mean age was 64.6 years and was higher in those with bacterial co-infection. This reached statistical significance. There was a slight male predominance in both groups. Among the 159 patients, only 16 (10.06%) had bacterial co-infection. There was a higher rate of hypertension (75% vs 64%), asthma (18.8% vs 9.6%), and COPD (6.3% vs 2.6%) in those with bacterial co-infection compared to those without co-infection. Diabetes on the other hand was more prevalent in those without bacterial co-infection (38.5% vs 18.8%).

Most patients for both groups had moderate COVID-19 and were unvaccinated. Length of hospital stay, and ICU admissions were higher in those with bacterial co-

infection but did not reach statistical significance. Among those with bacterial co-infection, none expired, while the mortality reached 29 (20.27%) among those without bacterial co-infection.

Table II shows the antibiotic utilization among the COVID-19 admitted patients. Among the 159 patients, 151 (94.96%) were started empiric antibiotic treatment upon admission. Among the 151 patients with empiric antibiotics, only 16 (10.6%) had bacterial co-infection. The most used agents were azithromycin (72.96%) and ceftriaxone (48.43%). Only 8 of 159 (5.03%) COVID-19 admissions did not receive empiric antibiotic treatment. Other empiric antibiotics used were piperacillin-tazobactam, co-amoxiclav, meropenem, cefepime, levofloxacin, and clindamycin.

Table III shows the microbial isolates from blood and respiratory samples of COVID-19 patients with bacterial co-infection. The predominant microorganism isolated were *Klebsiella pneumoniae* followed by *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Other isolates from sputum and tracheal aspirate specimens included *Moraxella catarrhalis*, and *Enterobacter cloacae*.

Table III. Microbial Isolates of COVID-19 Cases with Bacterial Co-Infection (n, %)

	Sputum or Tracheal Aspirate Culture (N=13)	Blood Culture (N=3)	Total (N=16)
S. aureus	2 (15.38)	0 (0)	2 (12.5)
P. aeruginosa	2 (15.38)	2 (66.67)	4 (25)
K. pneumoniae	7 (53.85)	1 (33.33)	8 (50)
E. cloacae	1 (7.69)	0 (0)	1 (6.25)
M. catarrhalis	1 (7.69)	0 (0)	1 (6.25)

Discussion

Viral infections in nature do not warrant antibiotic therapy. However, data from the 1918 and 2009 Influenza A H1N1 pandemic showed that 25-50% of hospitalized patients with influenza, also a viral infection, had a bacterial infection resulting in increased mortality.[5] The high frequency and clinical significance of bacterial co-infections in influenza and other novel coronaviruses raised concern that bacterial co-infection could be an important complication of SARS-CoV-2 infection.[2] Additionally, the typical symptoms of COVID-19 pneumonia such as fever, cough, and dyspnea are not distinguishable from bacterial pneumonia, posing a challenge to clinicians whether to start empiric antibiotic treatment upon presentation.[6] The past studies did not clarify whether bacterial co-infection implied co-infection throughout hospital admission including hospital-acquired bacterial infections. In our study, we use the term bacterial co-infection implying that the co-infection is community-acquired with samples taken within 3 days of admission.

There has been a substantial increase in antibiotic utilization during the early period of the pandemic with the largest increase seen in the use of empiric antibiotic therapy for community-acquired pneumonia. We found that empiric antibiotic therapy was administered to 94.07% among COVID-19 admissions which is markedly higher compared to other studies (56.6% to 71.9%).[7,8] The most commonly prescribed empiric antibiotics were targeting community-acquired pathogens with a significantly increased use of ceftriaxone and azithromycin during the early period of the pandemic which is consistent with the findings of our study showing that azithromycin and ceftriaxone were the most commonly used agents for empiric antibiotic treatment.[7,9] Other commonly used antibiotics in our study include piperacillin-tazobactam (31.45%) and meropenem (10.69%) empirically covering for *Pseudomonas aeruginosa* which is also targeted for in 26.3% of COVID-19 admissions in other literatures.[7] Most studies show that empiric coverage for MRSA was also common (25.8%) but was only seen in 1.89% in our study.

Despite finding only 10% of admitted COVID-19 patients having bacterial pneumonia co-infection in our study, this was still relatively higher than most studies consistently showing <4%.[2,7] Patients with bacterial co-infection had a longer hospital stay (mean 11 days vs 9 days) and more likely to be admitted to the ICU (12.5% vs 7.1%) compared with those without bacterial co-infection which is consistent with the literature.[7]

We found a mortality rate of the total COVID-19 admissions of 20.27% which is higher compared to a meta-analysis with pooled prevalence of 17.62% and to a local study of 18.2%.[10,11] Among those with bacterial co-infection in our study, there was no mortality. This is in stark contrast to a multi-hospital cohort study showing that patients with bacterial co-infection had a higher in-hospital mortality compared to those without bacterial co-infection (47.5%).[7]

The smaller sample size in our study relative to available literature may limit generalizability of our findings. Among the group without bacterial co-infection in our study, there was a higher prevalence of diabetes mellitus, and COVID-19 diabetic patients are at a higher risk of mortality.[12] Presence of diabetes mellitus is likewise considered a risk factor of developing secondary infections that may contribute to increased mortality.[13]

These patients may have initially negative cultures upon admission and thus are considered as without bacterial co-infection in our study. Additionally, this study did not take into consideration partial treatment with antibiotic prior to admission. We think that the presence of bacterial co-infection upon admission may result in physicians veering away from therapeutic inertia leading to more aggressive management and thus reduction in mortality. It is also important to consider that negative cultures do not exclude bacterial co-infection and this study did not include culture of anaerobes, atypical and highly fastidious pathogens, that may have been present in patients that are labelled as without bacterial co-infection – although none of the parameters studied in this case could substantiate such claim.

Among the COVID-19 admissions in our study with cultures taken, 8.17% was positive in respiratory cultures including tracheal aspirate and sputum specimens, and 1.8% was positive in blood cultures which is comparable with the blood culture yield in a study by Vaughn et. al. (1.8%).[7] All patients with positive blood cultures in our study also had positive respiratory cultures with the same organism. In our study, the most common organisms isolated were *K. pneumoniae* (8/16, 50%) followed by *P. aeruginosa* (4/16, 25%) and *S. aureus* (2/16, 12.5%). Most studies also isolate the same organisms, however the most common was *S. aureus* (31%), followed by *S. pneumoniae, H. influenzae, P. aeruginosa*, and *Klebsiella* species.[2] The absence of growth of *H. influenzae* in our findings supports the limitation of inability to culture fastidious organisms in our setting. The varying rates of growth of the isolated organisms compared to other studies may be explained by the differences of the local antibiogram of each institution.

Along with the limitations mentioned above, the following factors limit the generalizability of our results. This study used non-probability sampling design, used total enumeration of all COVID-19 cases in the study setting and randomization may not be achieved, inherent to the cross-sectional design. Although an important innovation during the COVID-19 pandemic, vaccination status was not included in the final analysis due to the lack of homogeneity considering the period considered in the study, limitations of the chart review and limitations in the acquisition of vaccination information including but not limited to recall bias in taking the history of vaccination. The predominant strain of COVID19 likewise cannot be studied at the time of the study.

Conclusion

We found a high use of empiric antibiotic treatment in hospitalized COVID-19 patients within 3 days of admission despite an apparently low prevalence of bacterial pneumonia co-infection. Although the effects of unnecessary antibiotic use are still not largely known in COVID-19, its known potential harms to patients and society, and the additional hospitalization cost warrant development of strategies for antimicrobial stewardship programs that may help guide clinicians for judicious use of antibiotics in admitted COVID-19 patients. Patients with bacterial co-infection did not show an increase in mortality but may be affected by several factors both pre-admission and during hospitalization.

Recommendation

The higher mortality rate among those without bacterial co-infection may have been caused by secondary hospital-acquired infections leading to death. We recommend doing an analysis on the prevalence of hospital-acquired infections among the COVID-19 patients.

Antimicrobial stewardship has been a thrust of many medical societies and with the high use of antibiotic therapy during the COVID-19 pandemic, identifying predictors for bacterial co-infection among COVID-19 patients may be useful for clinicians to guide on whether antibiotics are indeed warranted.

Lastly, institutional protocols promoting antimicrobial stewardship may need to be reviewed and improved.

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