Do Empiric Antibiotics Improve Outcomes in Patients Admitted with COVID-19?

Alexander Lawandi, Jeffrey R. Strich, Xiaobai Li, Christina Yek, Sarah Warner, Sameer S. Kadri

Critical Care Medicine Department, National Institutes of Health Clinical Center, Bethesda, MD

Background

Secondary bacterial infections in patients with viral pneumonias:
- Have long been recognized,
- Commonly seen with respiratory syncytial virus and influenza (1).

The pathophysiology is not fully understood, but evidence (2) suggests that:
- Local immune dysfunction and,
- A distorted pulmonary architecture allows for local invasion by bacteria.

Clinicians faced with patients presenting with symptomatic COVID19 often prescribe empiric antibiotics to treat potential bacterial co- infections, despite:
- Numerous studies suggesting a low prevalence (3),
- Without any study suggesting benefit.

We sought to assess the impact of empiric antibacterial therapy on the outcomes of patients admitted for COVID19 without signs of concomitant bacterial infections on admission.

Methods

A retrospective cohort study using the Premier HealthCare Database.

Inclusion criteria:
- Adult patients (≥18 yrs old)
- Admitted between March 1 and December 31, 2020,
- With positive SARS-CoV-2 PCR test and ICD9/10 coding for COVID19

Exclusions criteria:
- ICD10 coding for extrapulmonary bacterial infections, or
- Positive bacterial cultures from extrapulmonary sites drawn within 3 days of admission, and/or,
- ICDO10 coding for septic shock and/or
- Receipt of vasopressors, and/or
- Requiring mechanical ventilation within 3 days of admission

Patients were grouped according to the receipt of empiric antibacterial therapy within 3 days of admission. Baseline patient and clinical characteristics for the encounters were recorded.

Outcomes:
- Primary = in-hospital mortality or discharge to hospice,
- Secondary =
  - Need for mechanical ventilation rate beyond day 3 of admission
  - Acute kidney injury rate using overlap weight matching and binomial regression

Statistical analysis:
- Two groups were created using overlap weight propensity scores
- Outcomes were compared using binomial regression with downstream adjustment for covariates

Adjustment variables included in the overlap weighting propensity score were:
- Age
- Gender
- Ethnicity
- Month of Admission
- Elixhauser score
- Presence of any AOFS organ failure score
- Receipt of corticosteroids
- Receipt of tocilizumab
- Receipt of Remdesivir
- Need for ICU admission within 2 days of presentation
- Hospital Surge Index

Results

- 53,071 patients met inclusion criteria
  - 39,157 (73.8%) receiving empiric antibacterial therapy
- Mortality rate: 12.2% for patients receiving empiric therapy vs 10.9% for controls
- In the adjusted analysis of patients who survived beyond admission day, the mortality was:
  - 11.57% (95% CI 11.24-11.90%) in the empiric antibiotic group vs 11.23% (95% CI 10.72-11.74) in controls
  - Difference of 0.34% (95% CI -0.23-0.91%, p = 0.24)
- Mechanical ventilation occurred similarly between groups (p=0.83)
- Rate of AKI: 2.47% (95% CI 2.31-2.64%) in empiric antibiotic group vs 3.04% (95%CI 2.74-3.35%) in controls, for a difference of -0.57% (95% CI -0.92-0.22%, p = 0.0014)

Table 1. Baseline patient and encounter characteristics

	Empiric Antibiotic Therapy Group	Control Group
N	**39517**	**13914**
Patient Characteristics		
Age (median [IQR])	64.0 [52.0, 76.0]	65.0 [53.0, 76.0]
Male	21885 (55.4)	7552 (54.3)
Race/Ethnicity		
Hispanic	8116 (20.5)	2052 (14.7)
Non-Hispanic Asian	1173 (3.0)	434 (3.1)
Non-Hispanic Black	6987 (17.7)	2393 (17.2)
Other or Unknown Race	2712 (6.9)	1068 (7.6)
Non-Hispanic White	20529 (51.9)	7967 (57.3)
Comorbidities - Present on Admission		
Cancer	1507 (3.8)	435 (3.1)
Stage 3 Chronic Kidney Disease	3815 (9.7)	1206 (8.7)
Immunocompromised	529 (1.3)	156 (1.1)
Overweight/Obese	12332 (31.2)	4513 (32.4)
Pregnant	254 (0.6)	95 (0.7)
Sickle Cell Disease	120 (0.3)	27 (0.2)
Thalassemia	43 (0.1)	22 (0.2)
Diabetes	15549 (39.3)	5452 (39.2)
Asthma	1299 (3.3)	536 (3.9)
Interstitial Lung Disease	451 (1.1)	126 (0.9)
Heart Failure	7244 (18.3)	2675 (19.2)
Cerebrovascular Disease	1990 (5.0)	685 (4.9)
Liver Disease	21 (0.1)	5 (0.0)
COPD	4866 (12.3)	1599 (11.5)
Admission Characteristics		
ICU Admission POA	4840 (12.2)	1573 (11.3)
Steroid Administration	31291 (79.2)	10941 (78.6)
Remdesivir Administration	15043 (38.1)	5884 (42.3)
Tocilizumab Administration	2430 (6.1)	498 (3.6)

IQR = Interquartile range; POA = Present On Admission; COPD = Chronic Pulmonary Obstructive Disorder.

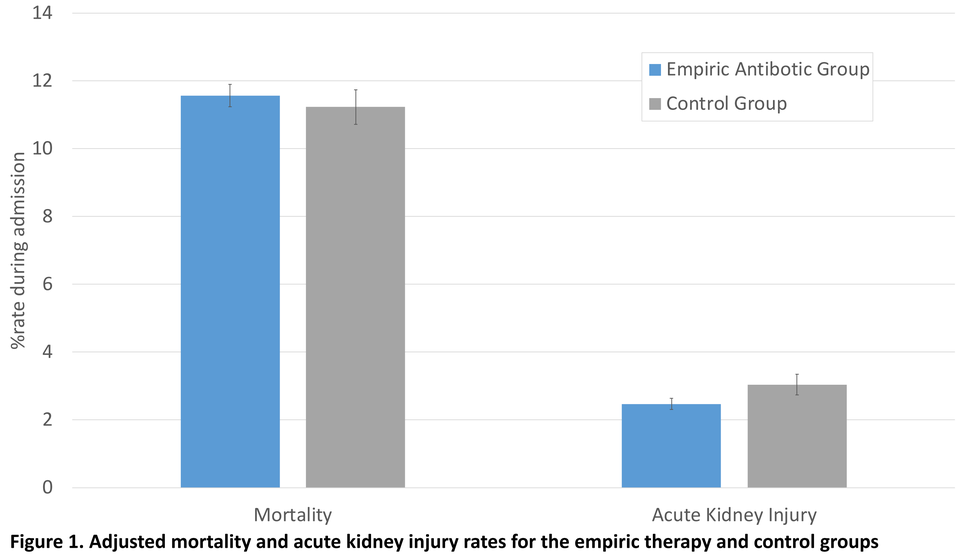

Figure 1. Adjusted mortality and acute kidney injury rates for the empiric therapy and control groups

Discussion

The results presented suggest that empiric antibiotic therapy in non-intubated patients presenting with COVID19 pneumonia without evidence of extra-pulmonary bacterial co-infections were not associated with:
- Improved mortality.
- Reduced need for mechanical ventilation during admission.
- Clinically significant reduced rates of acute kidney injury.

Our findings are consistent with:
- A recent meta-analysis (3) identifying a co-infection rate of 5.62% over the course of admission.
- Clinical guidelines suggesting not to treat empirically with antibacterial therapy.

The strengths of this study include:
- The large sample size.
- The use of overlap weighting to create matched study groups.
- Adjustment for clinical severity and treatment characteristics.

The limitations of this study include:
- The risk of confounding by indication.
  - The use of overlap weighted propensity scores minimized this risk.
- Only patients who were hemodynamically stable and did not require initial mechanical ventilation on admission were included.
- The results of respiratory bacterial cultures was not available for all patients due to differences in sampling rates across institutions and therefore we were unable to distinguish empirical vs targeted treatment.

Conclusion

Patients presenting with COVID19 pneumonia, without suspicion for extrapulmonary bacterial infections, who are hemodynamically stable and not in need of mechanical ventilation on admission, should not receive empiric antibacterial therapy

References

1. Hedberg, P., Johansson, N., Ternhag, A. *et al.* Bacterial co-infections in community-acquired pneumonia caused by SARS-CoV-2, influenza virus and respiratory syncytial virus. *BMC Infect Dis* **22**, 108 (2022). https://doi.org/10.1186/s12879-022-07089-9
2. McCullers, J. The co-pathogenesis of influenza viruses with bacteria in the lung. *Nat Rev Microbiol* **12**, 252–262 (2014). https://doi.org/10.1038/nrmicro3231
3. Alshaikh FS, Godman B, Sindi ON, Seaton RA, Kurdi A. Prevalence of bacterial coinfection and patterns of antibiotics prescribing in patients with COVID-19: A systematic review and meta-analysis. PLoS One. 2022 Aug 1;17(8):e0272375. doi: 10.1371/journal.pone.0272375. PMID: 35913964; PMCID: PMC9342726.

Contact Information

Alexander Lawandi, MDCM, MSc, FRCPC
Division of Infectious Diseases, Department of Medicine
McGill University Health Centre
1001 Boul Decarie, E05.1709
Montreal, Qc
H4A3J1
Alexander.Lawandi@mcgill.ca