Procalcitonin levels and antibiotic use associations with COVID-19 disease severity in the absence of bacterial co-infection of Hospitalized Adults: An observational cohort investigation

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Abstract

Elevated procalcitonin levels guide clinicians in antibiotic use for suspected bacterial infections. Early in the pandemic, these levels were also used with regularity in COVID-19 patients to assess for co-infection. Electronic medical records were interrogated in a cohort of hospitalized adults with COVID-19 (n=78) who experienced moderate and severe disease as defined by the Yale Impact Score (NCT05603677). Antibiotics were administered to 47.4% of all patients enrolled while the rate of bacterial co-infection in this patient population was 18.7%. Hospitalized patients with severe COVID-19 had significantly higher procalcitonin levels than those with moderate disease. Of the 55 participants with procalcitonin levels, 30 (55%) were given antibiotics while 25 (45%) were not, and only 8 patients had clinical documentation of bacterial co-infection, confirmed by blood, respiratory, or urine culture positivity . The results from this study show that in the setting of COVID-19 infection, procalcitonin is more closely linked to viral disease severity and less associated with bacterial co-infection. Procalcitonin as a prognostic tool for bacterial infection and COVID-19 disease severity warrants further investigation to ensure therapeutic measures and antibiotic stewardship are appropriately applied. More data are needed to set standardized clinical guidelines regarding procalcitonin use to ensure appropriate treatment is maintained.

Objectives

To better understand the connection between procalcitonin elevation and COVID-19 disease course, this study examined the procalcitonin levels of hospitalized COVID-19 patients during acute stages of infection and for correlations with disease severity, antibiotic use, and rate of bacterial co-infection.

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Methods

Data for this study were obtained from hospitalized participants who were admitted during the acute stage of infection and enrolled in the Northern Colorado Coronavirus Biorepository.

The primary study endpoint was the relationship between procalcitonin elevation and disease severity. Procalcitonin elevation was defined as any value greater than 0.15 ng/mL (per UCH lab reference range). We tested for independent correlations between procalcitonin and body mass index (BMI), and age. ANOVA was used to test for differences in procalcitonin across BMI groups: underweight/normal, overweight and obese [30].

The secondary study endpoint was the incidence of bacterial coinfection in the setting of primary SARS-CoV-2 infection. Diagnosis of bacterial co-infection was determined by any indication of bacterial growth in blood, respiratory or urine cultures or stool culture for *C.diff* Colitis. Continuous data were checked for the distributional assumption of normality. A natural log transformation was applied to procalcitonin which improved the distribution and was designated as LnProcalcitonin. If procalcitonin was < 0.06 then procalcitonin was assigned a value of 0.059 so that a natural log transformation could be performed. Independent samples T-tests were applied to continuous variables. Independent T-tests were used to test for a difference in procalcitonin levels between those with moderate disease and those with severe disease. ANOVA was used to test the relationship of procalcitonin with BMI groups and a Tukey-Kramer p-value adjustment was used to see which groups differed. $P < 0.05$ was considered significant. ANCOVA was used to adjust for covariates such as age, sex and BMI. It was determined that the sample size N =66 would provide 93% power to detect a medium effect size of 0.5 with a two-sided alpha = 0.05. However, we used all samples available at the time of abstraction. Chi Square Test of Independence or Fisher's Exact were used for the analysis of categorical variables. Data were presented as Mean ± SD, Geometric Mean and 95% CI, or frequency and percent. $P < 0.05$ was considered significant. All analyses were performed using SAS 9.4 (Cary, NC).

Results

Table 1: Level of Procalcitonin in patients categorized by COVID-19 Disease Severity

	Moderate (N = 27)	(95% CI)	Severe/Fatal (N = 28)	95% CI	P-value
Procalcitonin (ng/ml)	0.14 ± 0.11	(0.10-0.18)	0.31 ± 0.40	(0.15-0.46)	0.0380
Ln Procalcitonin (ng/ml)	0.12	(0.09-0.15)	0.18	(0.12-0.26)	0.0480

Table 2: Procalcitonin levels in the presence and absence of bacterial Co-Infection

	No Co-infection (N = 46)	(95% CI)	Co-infection (N = 8)	95% CI	P-value
Procalcitonin (ng/ml)	0.22 ± 0.32	(0.12-0.31)	0.27 ± 0.22	(0.09-0.45)	0.6310
Ln Procalcitonin (ng/ml)	0.13	(0.11-0.17)	0.20	(0.10-0.41)	0.2129

Table 3: Association of co-infection, elevated procalcitonin, complications, and the use of antibiotics (N = 55)

	No Antibiotics (N = 25)	Antibiotics (N = 29)	Chi Square or Fisher's Exact P-value
No Co-infection (N = 46)	24 (52%)	22 (48%)	0.0561
Co-infection (N = 8)	1 (12.5%)	7 (87.5%)	
Procalcitonin Not Elevated (N = 34)	18 (53%)	16 (47%)	0.1559
Elevated procalcitonin (N = 21)	7 (33%)	14 (67%)	
No Complication (N = 44)	22 (50%)	22 (50%)	0.3095
Complication (N = 10)	3 (30%)	7 (70%)	

Discussion

- There were significant differences in procalcitonin and Lnprocalcitonin (natural log) levels between those with moderate and severe disease ($p = 0.0380$ and $p = 0.0480$, respectively). The rate of confirmed co-infections was 7(12.7%) out of N = 55. Six out of the 7 with confirmed co-infections received antibiotics
- We also evaluated the presence of any bacterial coinfections in COVID-19 patients and the subsequent prescription of antibiotics.
- The rate of co-infection in this patient population was low (12.7%) while over half of the cohort received an antibiotic (52%). Out of an N=55, 24 (50%) of patients without a documented coinfection received an antibiotic The data show that only a small number of patients present with bacterial co-infections in the setting of COVID-19 and that many patients (50%) are prescribed antibiotics in the absence of laboratory confirmed co-infections.

Conclusions

- Our data suggests that procalcitonin may have prognostic value in determining disease severity and subsequent oxygen requirements and/ or need for intubation.
- Our findings are consistent with the previously observed overuse of antibiotics in hospitalized COVID-19 patients. This core finding supports the use of antibiotic stewardship during admission and hospitalization of COVID-19 patients. Although antibiotics are a life-saving therapy in cases of bacterial infection, unnecessary usage can place the patient at risk for opportunistic infections, which may further complicate the disease course
- Procalcitonin is typically a helpful diagnostic measure in predicting bacterial infection, though the findings described herein demonstrate that this may not be the case for COVID-19 patients. Thus, the prescription of antibiotics in this patient population should consider procalcitonin levels within a broader clinical picture that includes temperature curve, white blood cell count, blood cultures, patient history, and physical exam.