EMPIRIC ANTIBACTERIAL THERAPY AND COMMUNITY-ONSET BACTERIAL CO-INFECTION IN PATIENTS HOSPITALIZED WITH COVID-19: A MULTI-HOSPITAL COHORT STUDY

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ARTICLE SUMMARY

In 38 Michigan hospitals, early empiric antibacterials were prescribed to 56.6% (965/1705) of patients hospitalized with COVID-19 while 3.5% (59/1705) had a confirmed community-onset bacterial co-infection. Among hospitals, empiric antibacterial use varied from 27% to 84%.

ABSTRACT

Background: Antibacterials may be initiated out of concern for bacterial co-infection in patients with COVID-19. We determined prevalence and predictors of empiric antibacterial therapy and community-onset bacterial co-infections in hospitalized patients with COVID-19.

Methods: Randomly sampled cohort of 1705 patients hospitalized with COVID-19 in 38 Michigan hospitals between 3/13/2020-6/18/2020. Data were collected on early (prescribed within 2 days of hospitalization) empiric antibacterial therapy and community-onset bacterial co-infections (positive culture or diagnostic test within 3 days). Poisson generalized estimating equation models were used to assess predictors of empiric antibacterial use.

Results: Of 1705 patients with COVID-19, 56.6% were prescribed early empiric antibacterial therapy; 3.5% (59/1705) had a confirmed community-onset bacterial infection. Across hospitals, early empiric antibacterial use varied from 27%-84%. Patients were more likely to receive early empiric antibacterial therapy if they were older (adjusted rate ratio [ARR]: 1.04 [1.00-1.08] per 10 years), had a lower body mass index (ARR: 0.99 [0.99-1.00] per kg/m^2), had more severe illness (e.g., severe sepsis, ARR: 1.16 [1.07-1.27]), had a lobar infiltrate (ARR: 1.21 [1.04-1.42]), or were admitted to a for-profit hospital (ARR: 1.30 [1.15-1.47]). Over time, COVID-19 test turnaround time (returned ≤1 day in March [54.2%, 461/850] vs. in April [85.2%, 628/737], P<.001) and empiric antibacterial use (ARR: 0.71 [0.63-0.81] April vs. March) decreased.

Conclusion: The prevalence of confirmed community-onset bacterial co-infections was low. Despite this, half of patients received early empiric antibacterial therapy. Antibacterial use varied widely by hospital. Reducing COVID-19 test turnaround time and supporting stewardship could improve antibacterial use.

KEYWORDS: SARS-CoV, COVID-19, antibiotic stewardship, viral pneumonia, pneumonia, co-infection

INTRODUCTION

COVID-19, the disease caused by the SARS-CoV2 virus, frequently presents as a febrile respiratory illness that may progress to pneumonia and respiratory failure.[1-3] In the absence of bacterial co-infection, antibacterial therapy has no known benefit in patients with COVID-19. However, patients with COVID-19 may be at risk for concomitant bacterial infections that would require antibacterial treatment.[4] Data on bacterial co-infections are sparse and variable, with reports of co-infections occurring in 3-30% of patients with COVID-19.[5-10] Specifically, patients with COVID-19 are often started empirically on antibacterials when first hospitalized.[2,11] However, it's unclear if bacterial co-infections are present early during hospitalization or develop later, after additional hospital exposures. To guide efforts to improve antibiotic therapy, more data are needed on the prevalence of community-onset bacterial co-infections.

In a multi-center cohort study of hospitalized patients with COVID-19 at 38 Michigan hospitals, we aimed to determine patterns and predictors of early empiric antibacterial therapy and community-onset bacterial co-infection.

METHODS

MI-COVID19

MI-COVID19 is a statewide multi-institutional collaborative quality initiative (CQI) sponsored by Blue Cross Blue Shield of Michigan and Blue Care Network[12] to improve care for hospitalized patients with COVID-19. Institutional participation in MI-COVID19 is voluntary.

The data abstraction and collection templates were adapted from the Michigan Hospital Medicine Safety Consortium (HMS).[13] Of the 92 non-critical access, non-federal hospitals in Michigan, 38 (41.3%) elected to participate in MI-COVID19. Hospitals participating in MI-COVID19 were diverse in terms of size, teaching status, and ownership structure (**Table 1**). Trained abstractors collected data via medical record review; data collection and quality assurance procedures have been previously described.[14]

Inclusion/Exclusion Criteria

Our primary cohort of interest was hospitalized adults with positive COVID-19 PCR (polymerase chain reaction) testing during the 2020 COVID-19 surge in the state of Michigan. Patients were excluded if they were pregnant, <18 years-old, left against medical advice, were comfort care within 3 hours of hospitalization, or were transferred from another hospital. For patients with multiple hospitalizations, only the first was included.

Sampling

A pseudo-random sample of COVID-19 positive cases discharged between 3/13/2020 and 6/18/2020 from each hospital was included. When hospitals had abstractor capacity to include all eligible patients, they did. Hospitals unable to abstract all cases (e.g. due to high COVID-19 volumes) followed a pseudo-randomization procedure in which daily eligible cases were sorted by timestamp of discharge and included in order of smallest minute value until abstraction capacity was reached.

Data Collection

Similar to prior studies,[15,16] data on included patients were collected from 90-days prior to admission until death or hospital discharge. Data collected included demographics, comorbidities, antibacterial use (daily inpatient utilization), daily signs and symptoms (e.g.,

laboratory results, vital signs, organ support), radiographic results, and microbiologic data. Data were collected from medical records using a standardized data dictionary and operations manual and entered into the MI-COVID19 registry using a structured data collection template.

Outcomes

The primary outcome was the percentage of patients prescribed early empiric antibacterial therapy (any intravenous or oral antibacterial on day 1 or 2 of hospitalization). Antibacterial therapy started after day 2 was not considered empiric as it may have been aimed toward hospital-onset infection. Empiric antibacterials were categorized as targeting a) community-acquired organisms only (defined using 2019 American Thoracic Society and Infectious Diseases Society of America guidelines to include ampicillin/sulbactam, cefotaxime, ceftriaxone, moxifloxacin, levofloxacin, ceftaroline; please see **Appendix** for details),[17] b) methicillin-resistant *Staphylococcus aureus* (MRSA), or c) *Pseudomonas aeruginosa*. Azithromycin in the absence of other antibacterial treatment was not included as many MI-COVID19 hospitals recommended its use as COVID-19 specific therapy.[18] We also calculated antibiotic duration based on daily administration and discharge prescriptions.

The secondary outcome of interest was community-onset bacterial co-infection. Co-infections were identified by a) blood or respiratory culture positive for a typically pathogenic bacterium (for a list of excluded contaminants, see **Appendix**), b) positive *Legionella pneumophila* or *Streptococcus pneumonia* antigen, or c) positive *Mycoplasma pneumonia* or *Chlamydophila pneumonia* PCR test. We also report how many patients had a community-onset viral infection based on respiratory virus PCR testing. Co-infections were

considered community-onset if the positive culture or test was collected in the first three days of hospitalization.

Predictor Variables

Variables of interest included: a) patient demographics; b) comorbidities; c) symptoms (e.g., cough); d) disease severity on admission (admission to intensive care, highest mode of respiratory support on day 1 or 2 of hospitalization, sepsis, severe sepsis, septic shock); and e) features potentially indicating bacterial infection (chest imaging showing lobar infiltrate, sputum production, elevated procalcitonin, elevated white blood cell count, elevated c-reactive protein [CRP]). Hospital-level variables included bed size, profit-type, and self-reported teaching status.

Statistical Analysis

Descriptive statistics (percentages and medians with interquartile range [IQR]) were used to characterize the cohort. To evaluate individual predictors associated with empiric antibacterial use or community-onset bacterial co-infection, we performed bivariable analyses using general estimating equation (GEE) Poisson models with robust standard errors and compound symmetry correlation structure, accounting for hospital clustering. We used Poisson models rather than logistic regression because the odds ratio only approximates the rate ratio when the outcome is rare.[19] For multivariable analysis, we used Poisson GEE models with backwards elimination starting with all variables that had a P-value of <0.10 in bivariable analyses and eliminating variables until all had P-value <0.050. CRP and procalcitonin were not missing at random (both variables were linked to hospital test availability and practice) and thus could not be imputed and were not included in the multivariable model. When describing hospital variation in empiric antibacterial use, we

included hospitals with at least 10 included COVID-19 positive patients (N=32 hospitals). All statistical tests were 2-sided; P-values <0.050 significant. SAS version 9.4 was used for analyses. We followed EQUATOR reporting guidelines (STROBE in **Appendix**).

IRB Approval

This project received non-regulated status prior to data collection by the University of Michigan Institutional Review Board.

RESULTS

3412 patients with COVID19 were eligible for inclusion. After pseudo-randomization, a total of 1705 patients from 38 hospitals were included. Patient characteristics are shown in **Table 1**.

Early Empiric Antibacterial Therapy

The majority 56.6% (965/1705) of hospitalized patients with COVID-19 were prescribed early empiric antibacterial therapy (**Table 2**). The most commonly prescribed empiric antibacterials were ceftriaxone (38.9% [663/1705]), vancomycin (13.8% [235/1705]), doxycycline (10.9% [185/1705]), and cefepime (10.4% [177/1705]). Of patients who received empiric antibiotic therapy (N=965), the majority (63.4%, 612) were only prescribed antibacterials targeting community-acquired pathogens; however, 25.8% (249) received antibacterials targeting MRSA, and 26.3% (254) received antibacterials targeting pseudomonas. In those who received empiric antibacterial therapy, the median inpatient duration was 3 days (IQR 2-6). Only 11.4% (110/965) of those prescribed antibiotics were prescribed antibiotics at discharge (median 4 days [IQR 3-5] duration after discharge). Total days of inpatient, post-discharge, and total antibacterial therapy were 4158 days/1000 patients, 484 days/1000 patients, and 4628 days/1000 patients, respectively.

Bacterial Co-infections in COVID-19 Positive Patients

Community-onset bacterial co-infections were confirmed in 3.5% (59/1705) of all patients, including 1.8% (31/1705) who had a positive blood culture and 1.7% (29/1705) who had a bacterial respiratory pathogen identified (from respiratory culture or non-culture diagnostic test). Community-onset bacterial infections occurred in 4.9% (47/965) of patients who received early empiric antibacterial therapy vs. 1.6% (12/740) of those who did not (P<.001), of which 33.3% (4/12) were subsequently started on antibiotics. Patients were more likely to have a community-onset bacterial infection if they were older, had a lower body mass index, had kidney disease, were admitted from a skilled nursing facility, were more severely ill (e.g., admitted to intensive care), or had more signs of a bacterial infection (e.g., higher white blood cell count; see **Table 3** for details). Though 55.9% (19/34) of patients with a community-onset bacterial co-infection had a procalcitonin >0.5 ng/mL, so did 21.2% (186/876) of those without a community-onset bacterial co-infection. Thus, the positive predictive value of a procalcitonin >0.5 ng/mL was 9.3% for community-onset bacterial co-infection. In contrast, the negative predictive value of a procalcitonin ≤0.1 ng/mL was 98.3%. Compared to patients without a confirmed community-onset bacterial infection, those with a confirmed infection had a longer length of stay (median 7 [IQR 4-10] vs. 5 days [3-8], P=0.003) and had higher in-hospital mortality (47.5% [28/71] vs. 18.0% [297/1634], P<.001).

Nearly half (45.9%, 783/1705) of patients had respiratory PCR testing while only 0.5% (9/1705) had an identified community-onset viral co-infection. There was no difference in early empiric antibiotic use in those with an identified community-onset viral co-infection vs. those without (66.7% vs. 56.5%, P=0.74).

Variation in Empiric Antibacterial Therapy in Patients with COVID-19

Thirty-two hospitals had at least 10 patients with COVID-19 included in MI-COVID19. Within these sites, the percentage of patients with COVID-19 who were prescribed empiric antibacterials varied from 27%-84%. Similarly, the percentage of patients receiving antibacterial therapy targeting community-acquired vs. anti-MRSA and/or anti-pseudomonal coverage also varied widely by hospital (**Figure 1**).

Predictors of Empiric Antibacterial Therapy in Patients with COVID-19

Bivariable predictors of empiric antibacterial therapy are shown in **Table 1**. On multivariable analysis, patients were more likely to receive early empiric antibacterial therapy if they were older, had a lower body mass index, had more severe disease (e.g., respiratory support, severe sepsis), had a lobar infiltrate, or were admitted to a for-profit hospital; patients admitted at a later date in the surge were less likely to receive empiric antibacterials (see **Table 4**).

Empiric Antibacterial Therapy and COVID-19 PCR Tests

Of patients with COVID-19 who were prescribed empiric antibacterials and had their COVID-19 test return before the end of their hospitalization, 453/832 (54.4%) had their antibacterials stopped within 1 day after COVID-19 tests returned positive. Of the 379 that had antibacterials continued, only 28 (7.4%) had a confirmed community-onset bacterial co-infection. Of those who had antibacterials continued and did NOT have a confirmed community-onset bacterial co-infection, 35.9% (126/351) had <5 days total inpatient antibacterial duration; 39.6% (139/351) had 5 to 7 days; and 24.5% (86/351) had >7 days.

Excluding 4 patients with missing COVID-19 test dates, the percentage of patients who had a COVID-19 PCR test turnaround time of ≤1 day was 64.9% (624/962) in patients who received

early empiric antibacterial therapy vs. 76.4% (565/739) in patients without early empiric therapy (P<.001). Antibacterial therapy was often given prior to clinicians knowing the results of COVID-19 tests. For example, 13.6% (131/962) of patients who received early empiric therapy did not have COVID-19 tests return until after discharge. Furthermore, about half (52.5%) of antibacterial treatment duration occurred prior to COVID-19 PCR tests turning positive. Turnaround times decreased over time (54.2% [461/850] returned ≤1 day in March; April: 85.2% [628/737]; May: 89.2% [91/102]; June: 75.0% [9/12]; P<.001 for month trend). Similarly, the percentage of patients with COVID-19 who were treated empirically with antibacterials decreased over time (March: 66.7% [95% CI:63.4-69.9]; April: 46.7% [95% CI: 43.1-50.4]; May: 46.9% [95% CI: 37.3-56.6]; June: 60.0% [95% CI: 32.3-83.7], P<.001 for month trend).

DISCUSSION

In this large, multicenter cohort of patients hospitalized with COVID-19, we found 56.6% were treated with early empiric antibacterial therapy. Despite concerns that patients with COVID-19 might be at high risk for bacterial co-infections, we found only 3.5% of COVID-19 positive patients had a confirmed community-onset bacterial co-infection. Early empiric antibacterial use varied from 27% to 84% across hospitals and decreased over time.

Similar to other studies,[4,9,11,20] we found patients hospitalized with COVID-19 were often treated with early empiric antibacterials. Notably, we saw wide variability between hospitals in early empiric antibacterial use suggesting a need for a standardized approach to antibiotic use, diagnostic testing, and antibiotic stewardship in patients with COVID-19. Though the reasons for variation in empiric antibiotic use are unclear, variability could relate to existing antibiotic stewardship infrastructure or hospital culture. Supportively, we found for-profit

hospitals had more empiric antibacterial use even after adjustments. Other studies have found for-profit hospitals to have more variable quality of care;[21,22] however, this has not been seen previously with hospitalized patients with pneumonia in HMS hospitals.[15] The fact that empiric antibacterial use was low in some hospitals suggests that unnecessary antibacterial use can be reduced even during pandemics; for example, by fast-moving, responsive, and well-supported antibiotic stewardship programs.[23]

The high rate of empiric antibacterial use seen in patients hospitalized with COVID-19 must be considered in the context of the low prevalence of confirmed community-onset bacterial co-infection (3.5% in all patients; 4.9% in those who received antimicrobials). For every patient we identified as having a bacterial infection, nearly 20 without an identified infection also received empiric antibacterial therapy. These findings are similar to a two-hospital study in the United Kingdom, which noted 3.2% of patients with COVID-19 had early confirmed bacterial infections (rising to 6.1% later during hospitalization),[7] and a study in New York which identified 3.6% of hospitalized patients with COVID-19 who had bacterial or fungal co-infections.[8] Other studies with systematic sampling have found bacterial co-infections in up to 30% of patients with COVID-19; though it is unclear the clinical significance as only 4% were severely or critically ill.[6]

As with all retrospective studies of bacterial infection, we were limited by the poor sensitivity and incomplete use of diagnostic tests for bacterial infections. In particular, there was very low use of respiratory cultures in our cohort: only 7.7% of patients had a respiratory culture performed in the first three days of hospitalization. This is much lower than a prior study of patients hospitalized with pneumonia in HMS hospitals where 32.3% had respiratory cultures.[15] There are two potential reasons for the lack of respiratory

cultures. First, it is likely that fewer respiratory cultures—specifically more sensitive tests, such as induced sputum or bronchoalveolar lavage—were ordered due to concerns regarding aerosolization (and therefore healthcare worker safety) in patients with COVID-19. This may explain why we found other tests that do not create aerosols were used at similar or higher levels than in prior studies. For example, 54.8% of patients had non-culture respiratory pathogen testing (e.g., urine legionella antigen) compared to 15.9% in our prior study of patients hospitalized with pneumonia in HMS hospitals.[15] Second, respiratory cultures may be difficult to obtain in patients with COVID-19 due to the nature of their coughs—only 13.1% of patients in our cohort had documented sputum production vs. 51.6% in a historical sample of HMS patients with pneumonia.[15] This deficiency in diagnostic testing is a critical barrier to co-infection detection and antibiotic stewardship. Regardless, because patients with COVID-19 have a known viral pathogen (SARS-CoV2) that explains their infectious symptoms, more judicious antibacterial use may be necessary in the absence of other signs of bacterial infection.

Our findings suggest some potential ways to improve antibacterial use and point to continued need for investigation. First, diagnostic uncertainty caused by delays in the turnaround time for COVID-19 PCR testing may have contributed to antibacterial use, highlighting the need for more testing capacity and faster COVID-19 turnaround times. We found that over half (54.3%) of COVID-19 positive patients had antibacterial therapy stopped within a day of testing returning positive. As the turnaround time for COVID-19 decreased, early empiric antibacterial use decreased. Second, we found patients who were more severely ill had more empiric antibacterial treatment. In a subset of patients with severe COVID-19, a cytokine storm rather than bacterial sepsis may be responsible for early

decompensation.[24] Further studies are needed to aid clinicians in distinguishing the two. For example, stewardship programs could help guide antibacterial de-escalation and cessation for critically ill patients who have a negative work-up for bacterial pathogens. Similarly, biomarkers have a theoretical role in distinguishing patients who have vs. do not have bacterial infection, though it is unclear if they would truly change clinical practice: we found procalcitonin values of <0.1 ng/mL to have a negative predictive value of 98.3%, yet nearly a third of patients treated empirically with antibacterials had procalcitonin values this low.

Our study represents a diverse look at early empiric antibacterial therapy across multiple hospitals. However, our findings must be considered in the context of limitations. First, we do not have complete data on secondary bacterial infections which may develop later during hospitalization. It is likely that, for some patients, bacterial co-infections develop later in hospitalization.[25] Second, we have limited data on patient outcomes given insufficient time since most were discharged, limiting our ability to assess the effect of early empiric antibacterial use on outcomes. Larger or prospective studies are needed to help determine who would benefit from empiric antibacterial therapy. Third, as noted above, we were limited by lack of systematic diagnostic testing. Fourth, we excluded azithromycin as an "antibacterial" because we were unable to distinguish between azithromycin use as an antibacterial vs. targeted therapy for COVID-19; thus, we likely underestimate the true prevalence of antibacterial overuse. Study strengths include data from multiple, diverse hospitals across a state that was surging at the time of data collection. Furthermore, the existing infrastructure from our prior pneumonia quality improvement work[13-15] allowed us to rapidly but rigorously collect and analyze data with experienced abstractors and analysts.

Our findings have important implications. The known risks associated with unnecessary antibacterial use and the low rate of confirmed early bacterial co-infection in patients with COVID-19 suggest against routinely prescribing antibacterial therapy to patients with COVID-19 pneumonia who present without other risk factors or signs of bacterial infection. Second, the variation in antibacterial use across hospitals suggests an imperfect response to limited data. Key will be understanding whether existing stewardship or quality infrastructure may also help hospitals make better treatment decisions during pandemics. Third, our findings suggest that faster testing turnaround is imperative to help inform empiric treatment decisions, including antibacterial therapy. Notably, antibacterials were stopped after COVID-19 tests returned positive at higher rates than in other viral pneumonias.[26] Finally, we need better training and understanding of how to incorporate imperfect tests and diagnostic uncertainty into decision making.[27]

In conclusion, we found high use of early empiric antibacterial therapy in patients hospitalized with COVID-19, despite low prevalence of confirmed community-onset bacterial co-infections. Given the potential harms to patients and society from unnecessary antibacterial use—plus the additional burden on staff use and PPE required for antibacterial administration—it is imperative that we develop strategies to help clinicians prescribe antibacterials judiciously to hospitalized patients with COVID-19.

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Disclaimer

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Potential Conflicts of Interest

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Table 1. Patient Characteristics and Bivariable Predictors of Early Empiric Antibacterial Therapy in Patients with COVID-19, N=1705

	Total, N (%) N=1705	Received Early Empiric Antibacterials,[a] N=965	Did Not Receive Early Empiric Antibacterials, N=740	Rate Ratio (95% CI)	P-value
Hospital Characteristics					
Teaching hospital	1560 (91.5%)	891 (92.3%)	669 (90.4%)	1.06 (0.85-1.33)	0.59
Ownership					
Non-profit	1470 (86.2%)	779 (80.7%)	691 (93.4%)	REF	
For profit	235 (13.8%)	186 (19.3%)	49 (6.6%)	1.46 (1.32-1.62)	<.001
Bed size (per 100 bed)	391 (250-537)	404 (250-537)	391 (250-632)	0.98 (0.96-1.01)	0.24
Admission Month					
March	834 (48.9%)	556 (57.6%)	278 (37.6%)	REF	
April	745 (43.7%)	348 (36.1%)	397 (53.6%)	0.73 (0.65-0.81)	<.001
May	111 (6.5%)	52 (5.4%)	59 (8.0%)	0.75 (0.57-0.98)	0.04
June	15 (0.9%)	9 (0.9%)	6 (0.8%)	0.86 (0.65-1.16)	0.32
Demographics					
Age (years); median (IQR); rate ratio reported per 10 year increase	64.7 (53.0-76.7)	66.3 (54.5-78.1)	62.8 (51.3-74.1)	1.05 (1.02-1.09)	0.001
Women; N (%)	820 (48.1%)	471 (48.8%)	349 (47.2%)	1.02 (0.94-1.10)	0.65
Race; N (%)					
White	732 (42.9%)	394 (40.8%)	338 (45.7%)	Ref	Ref
Black	802 (47.0%)	473 (49.0%)	329 (44.5%)	1.05 (0.90-1.21)	0.56
Other	171 (10.0%)	98 (10.2%)	73 (9.9%)	1.06 (0.92-1.22)	0.40
Comorbidities					
Body Mass Index; kg/m^2	29.8 (25.5-35.9)	29.4 (25.4-35.6)	30.4 (25.7-36.7)	0.99 (0.98-1.00)	0.06
Charlson Comorbidity Score; median (IQR)	1 (0-3)	2 (0-3)	1 (0-3)	1.03 (1.01-1.05)	0.003
COPD; N (%)	200 (11.7%)	121 (12.5%)	79 (10.7%)	1.06 (0.94-1.20)	0.33
Asthma; N (%)	215 (12.6%)	112 (11.6%)	103 (13.9%)	0.91 (0.77-1.08)	0.27
Moderate or severe chronic kidney disease; N (%)	449 (26.3%)	275 (28.5%)	174 (23.5%)	1.12 (1.02-1.22)	0.02
On dialysis; N (%)	57 (3.3%)	30 (3.1%)	27 (3.6%)	0.94 (0.77-1.15)	0.57
On immune	166 (9.7%)	98 (10.2%)	68 (9.2%)	1.08 (0.97-1.20)	0.16

suppressive medications; N (%)					
Admission from skilled nursing or sub-acute rehabilitation facility	236 (13.8%)	155 (16.1%)	81 (10.9%)	1.18 (1.05-1.32)	0.006
Severity of Illness					
Initial admission to intensive care unit	185 (10.9%)	132 (13.7%)	53 (7.2%)	1.31 (1.20-1.44)	<.001
Highest mode of respiratory support on day 1 or 2 of hospitalization					
No supplemental oxygen	595 (34.9%)	278 (28.8%)	317 (42.8%)	Ref	Ref
Low flow oxygen	937 (55.0%)	554 (57.4%)	383 (51.8%)	1.24 (1.12-1.36)	<.001
Heated high-flow nasal cannula	44 (2.6%)	33 (3.4%)	11 (1.5%)	1.58 (1.35-1.85)	<.001
Non-invasive positive pressure ventilation	13 (0.8%)	9 (0.9%)	4 (0.5%)	1.50 (1.16-1.95)	0.002
Mechanical ventilation	116 (6.8%)	91 (9.4%)	25 (3.4%)	1.61 (1.35-1.92)	<.001
Sepsis on day 1 or 2 of hospitalization[b]	1260 (73.9%)	748 (77.5%)	512 (69.2%)	1.23 (1.11-1.36)	<.001
Severe sepsis on day 1 or 2 of hospitalization[b]	481 (28.2%)	319 (33.1%)	162 (21.9%)	1.25 (1.15-1.36)	<.001
Septic shock on day 1 or 2 of hospitalization[b]	138 (8.1%)	101 (10.5%)	37 (5.0%)	1.35 (1.19-1.53)	<.001
Signs/Symptoms potentially indicating bacterial infection					
Highest white blood cell count on day 1 or 2 of hospitalization, K/uL; median (IQR)	6.8 (5.2-9.2)	7.0 (5.3-9.8)	6.6 (4.9-8.6)	1.01 (1.00-1.01)	0.11
Initial Chest X-ray or Chest CT was normal; N (%)	196 (11.5%)	74 (7.7%)	122 (16.5%)	0.66 (0.57-0.76)	<.001
Initial Chest X-ray or Chest CT showed lobar infiltrate; N (%)	87 (5.1%)	63 (6.5%)	24 (3.2%)	1.29 (1.14-1.47)	<.001
Initial procalcitonin value, ng/mL; N=910[c]					
0-0.1; N (%)	288 (31.6%)	133 (26.7%)	155 (37.7%)	Ref	Ref
0.1-0.25; N (%)	278 (30.5%)	144 (28.9%)	134 (32.6%)	1.15 (0.97-1.35)	0.11
0.25-0.5; N (%)	139 (15.3%)	76 (15.2%)	63 (15.3%)	1.22 (1.02-1.46)	0.03
>0.5; N (%)	205 (22.5%)	146 (29.3%)	59 (14.4%)	1.57 (1.39-1.77)	<.001
Initial C-reactive	18.8 (7.2-	22.8 (8.9-	15.2 (5.4-67.5)	1.001 (1.000-	0.001

protein; mg/dL; N=999[c]	92.3)	107.7)		1.002)	
Sputum production; N (%)	223 (13.1%)	131 (13.6%)	92 (12.4%)	1.04 (0.93-1.16)	0.51

Abbreviations: CI (confidence interval); IQR (inter-quartile range); CT (computed tomography)

[a] Empiric antibacterial therapy was defined as any intravenous or oral antibacterial therapy prescribed on day 1 or 2 of hospitalization. Does not include patients who received azithromycin only.

[b] Sepsis was defined as ≥2 of the following: temperature >38 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min, and leukocyte count >12 × 109 cells/L or <4 × 109 cells/L or >10% immature bands. Severe sepsis was defined as sepsis plus evidence of organ dysfunction, defined as any of the following: systolic blood pressure <90 mm Hg (or initiation of vasopressors), lactate level >2 mmol/L, platelet count <100 × 109 cells/L, bilirubin level >2 mg/dL (without documentation of moderate or severe liver disease), creatinine level >2 mg/dL (without documentation of moderate or severe chronic kidney disease) or ventilatory support (i.e., non-invasive positive pressure ventilation or
mechanical ventilation). Septic shock included any vasopressor requirement (vasopressors include angiotensin II, dobutamine, epinephrine, norepinephrine, phenylephrine, or vasopressin).

[c] Not missing at random. 910 patients had a procalcitonin and 999 had a CRP.

Missing data: 86 patients were missing body mass index, 23 patients were missing white blood cell count.

Table 2. Diagnostic Testing, Co-infection, and Antibacterial Use in Hospitalized Patients with COVID-19, N=1705

Cultures obtained within first 3 days of hospitalization	N (%)
Blood or respiratory culture obtained	1095 (64.2%)
Blood culture	1063 (62.3%)
Respiratory culture	131 (7.7%)
Non-culture testing performed	934 (54.8%)
Respiratory PCR Test	783 (45.9%)
Urine legionella antigen	413 (24.2%)
Urine pneumococcal antigen	304 (17.8%)
Had a community-onset bacterial co-infection[a]	59 (3.5%)
Positive blood or respiratory culture	55 (3.2%)
Positive blood culture	31 (1.8%)
Positive respiratory culture	25 (1.5%)
Had a community-onset viral co-infection[b]	9 (0.5%)
Influenza A or B	1 (0.1%)
Other viral pathogen	8 (0.5%)
Empiric Antibacterial Therapy	
Empiric antibacterial therapy;[c] N (%)	965 (56.6%)
Community-acquired empiric coverage only[d]	612 (35.9%)
Ampicillin/sulbactam	41 (2.4%)
Cefotaxime	5 (0.3%)
Ceftriaxone	663 (38.9%)
Moxifloxacin	4 (0.2%)
Levofloxacin	20 (1.2%)
Ceftaroline	1 (0.1%)
Empiric anti-MRSA therapy[e]	249 (14.6%)
Vancomycin	235 (13.8%)
Empiric anti-pseudomonal therapy[f]	254 (14.9%)
Cefepime	177 (10.4%)
Piperacillin/ tazobactam	72 (4.2%)
Empiric anti-MRSA AND anti-pseudomonal therapy[e,f]	184 (10.8%)
Turnaround time for COVID-19 PCR test; days; median (IQR)	1 (0-2)
Length of hospital stay; days; median (IQR)	5 (3-9)

Abbreviations: IQR (inter-quartile range); MRSA (methicillin-resistant *Staphylococcus aureus*); PCR (polymerase chain reaction)

[a] Community-onset bacterial co-infection include any positive blood or respiratory culture or microbiological test obtained in the first three days of hospitalization (contaminants excluded).

[b] Community-onset viral co-infection include any viruses identified on a respiratory PCR obtained in the first three days of hospitalization (contaminants excluded).

[c] Empiric antibacterial therapy was defined as any intravenous or oral antibacterial therapy prescribed on day 1 or 2 of hospitalization. Does not include patients who received azithromycin monotherapy. May add up to more than 100% as patients may be in multiple rows.
[d] Includes patients who received antibacterials recommended for empiric community-acquired pneumonia treatment in 2019 CAP guidelines[17] (i.e., ampicillin/sulbactam, cefotaxime, ceftriaxone, moxifloxacin, levofloxacin, ceftaroline) and did not receive empiric anti-MRSA or anti-pseudomonal coverage.
[e] Anti-MRSA antibacterials include: vancomycin, linezolid, sulfamethoxazole/trimethoprim, or clindamycin.
[f] Anti-pseudomonal antibacterials include: piperacillin/tazobactam, aminoglycosides, ceftazidime, aztreonam, meropenem, imipenem, ceftolozane/tazobactam, polymixin B, colistin, ciprofloxacin, cefepime, ceftazadime-avibactam, or meropenem-vaborbactam.

Table 3. Patient Characteristics and Bivariable Predictors of Community-onset Bacterial Co-infection in Patients with COVID-19, N=1705

	Confirmed Community-Onset Bacterial Co-infection,[a] N=59	No Confirmed Bacterial Co-infection N=1646	Rate Ratio (95% CI)	P-value
Demographics				
Age (years); median (IQR); rate ratio reported per 10 year increase	72.6 (61.9-85.4)	64.5 (52.7-76.5)	1.30 (1.08-1.57)	0.006
Women; N (%)	32 (54.2%)	788 (47.9%)	1.30 (0.70-2.41)	0.41
Race; N (%)				
White	33 (55.9%)	699 (42.5%)	Ref	Ref
Black	22 (37.3)	780 (47.4%)	0.63 (0.33-1.17)	0.14
Other	4 (6.8%)	167 (10.1%)	0.50 (0.17-1.46)	0.21
Comorbidities				
Body Mass Index; kg/m^2	26.6 (22.7-31.1)	30.0 (25.6-36.1)	0.94 (0.90-0.99)	0.009
Charlson Comorbidity Score; median (IQR)	2 (1-5)	1 (0-3)	1.20 (1.10-1.31)	<.001
COPD; N (%)	10 (16.9%)	190 (11.5%)	1.52 (0.67-3.46)	0.31
Asthma; N (%)	5 (8.5%)	210 (12.8%)	0.66 (0.31-1.39)	0.27
Moderate or severe chronic kidney disease; N (%)	26 (44.1%)	423 (25.7%)	2.19 (1.35-3.57)	0.002
On immune suppressive medications; N (%)	8 (13.6%)	158 (9.6%)	1.44 (0.83-2.51)	0.20
Admission from skilled nursing or sub-acute rehabilitation facility	23 (39.0%)	213 (12.9%)	3.96 (2.44-6.43)	<.001
Severity of Illness				
Initial admission to intensive care unit	21 (35.6%)	164 (10.0%)	4.45 (2.87-6.88)	<.001
Highest mode of respiratory support on day 1 or 2 of hospitalization				
No supplemental oxygen	12 (20.3%)	583 (35.4%)	Ref	Ref
Low flow oxygen	29 (49.2%)	908 (55.2%)	1.52 (0.75-3.09)	0.24
Heated high-flow nasal cannula	1 (1.7%)	43 (2.6%)	1.13 (0.15-8.33)	0.91
Non-invasive positive pressure ventilation	1 (1.7%)	12 (0.7%)	3.65 (0.57-23.52)	0.17
Mechanical ventilation	16 (27.1%)	100 (6.1%)	6.74 (3.43-13.25)	<.001
Sepsis on day 1 or 2 of hospitalization[b]	52 (88.1%)	1208 (73.4%)	2.55 (1.28-5.08)	0.008
Severe sepsis on day 1 or 2 of hospitalization[b]	35 (59.3%)	446 (27.1%)	3.62 (2.16-6.07)	<.001
Septic shock on day 1 or 2 of hospitalization[b]	17 (28.8%)	121 (7.4%)	4.60 (2.65-8.00)	<.001
Signs/Symptoms				

potentially indicating bacterial infection				
Highest white blood cell count on day 1 or 2 of hospitalization, K/uL; median (IQR)	10 (5.9-15.8)	6.8 (5.1-9.0)	1.03 (1.01-1.04)	<.001
Initial Chest X-ray or Chest CT was normal; N (%)	7 (11.9%)	189 (11.5%)	1.04 (0.42-2.58)	0.93
Initial Chest X-ray or Chest CT showed lobar infiltrate; N (%)	4 (6.8%)	83 (5.0%)	1.30 (0.44-3.86)	0.64
Initial procalcitonin value, ng/mL; N=910[c]				
0-0.1; N (%)	5 (14.7%)	283 (32.3%)	Ref	Ref
0.1-0.25; N (%)	9 (26.5%)	269 (30.7%)	1.88 (0.70-4.69)	0.22
0.25-0.5; N (%)	1 (2.9%)	138 (15.8%)	0.44 (0.07-2.68)	0.37
>0.5; N (%)	19 (55.9%)	186 (21.2%)	4.99 (1.87-13.33)	0.001
Initial C-reactive protein; mg/dL; N=999[c]	26.2 (14.9-123.0)	18.5 (7.1-90.0)	1.00 (1.00-1.00)	0.15
Sputum production; N (%)	12 (20.3%)	211 (12.8%)	1.69 (0.93-3.08)	0.09

Abbreviations: CI (confidence interval); IQR (inter-quartile range); CT (computed tomography)

[a] Community-onset bacterial co-infections include any positive blood or respiratory culture or microbiological test obtained in the first three days of hospitalization (contaminants excluded).

[b] Sepsis was defined as ≥2 of the following: temperature >38 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min, and leukocyte count >12 × 109 cells/L or <4 × 109 cells/L or >10% immature bands. Severe sepsis was defined as sepsis plus evidence of organ dysfunction, defined as any of the following: systolic blood pressure <90 mm Hg (or initiation of vasopressors), lactate level >2 mmol/L, platelet count <100 × 109 cells/L, bilirubin level >2 mg/dL (without documentation of moderate or severe liver disease), creatinine level >2 mg/dL (without documentation of moderate or severe chronic kidney disease) or ventilatory support (i.e., non-invasive positive pressure ventilation or
mechanical ventilation). Septic shock included any vasopressor requirement (vasopressors include angiotensin II, dobutamine, epinephrine, norepinephrine, phenylephrine, or vasopressin).

[c] Not missing at random. 910 patients had a procalcitonin and 999 had a CRP.

Missing data: 86 patients were missing body mass index, 23 patients were missing white blood cell count.

Table 4. Multivariable Predictors of Early Empiric Antibitoic Therapy in Patients with COVID-19, N=1705

	Adjusted Rate Ratio	P-value
Age (for each 10 additional years)	1.04 (1.01-1.08)	0.02
Body mass index (per additional point)	0.99 (0.99-1.00)	0.03
Highest level of respiratory support on day 1 or 2 of hospitalization		
None	REF	
Low flow oxygen (nasal cannula, oxygen mask)	1.18 (1.06-1.31)	0.002
Heated high-flow nasal cannula	1.50 (1.28-1.76)	<.001
Non-invasive positive pressure ventilation	1.35 (0.98-1.85)	0.07
Invasive mechanical ventilation	1.29 (1.07-1.54)	0.007
Severe sepsis on admission[a]	1.16 (1.07-1.27)	<0.001
Initial chest X-ray or chest CT was normal	0.72 (0.62-0.84)	<.001
Initial chest X-ray or chest CT showed lobar infiltrate	1.21 (1.04-1.42)	0.02
Admission month		
March	REF	
April	0.71 (0.63-0.81)	<.001
May	0.76 (0.58-1.01)	0.06
June	0.79 (0.59-1.06)	0.11
Hospital ownership		
Non-profit	REF	
For profit	1.30 (1.15-1.47)	<.001

Abbreviations: CT (computed tomography)

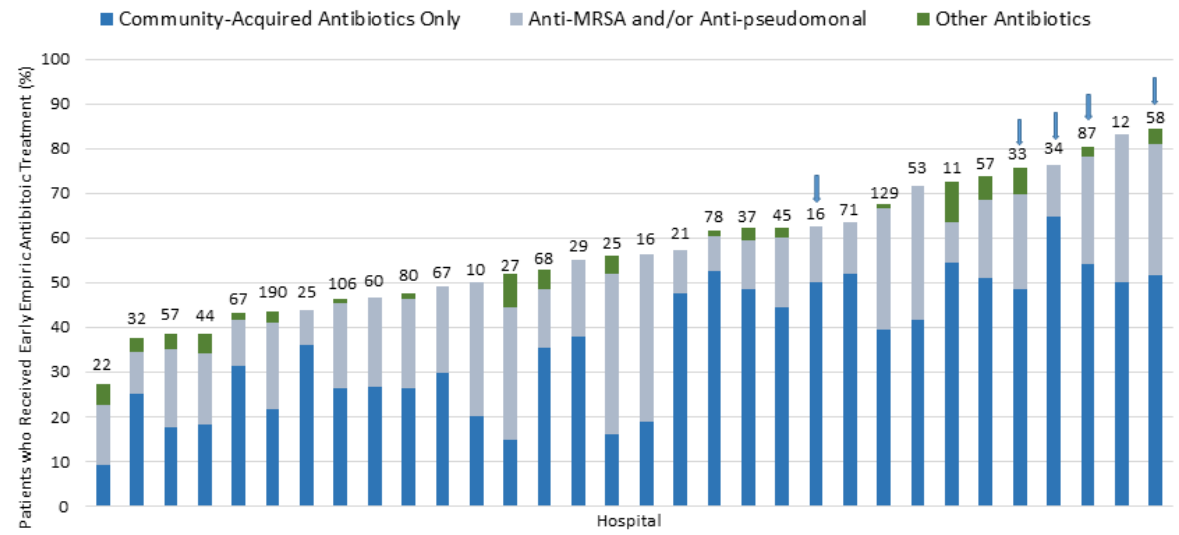
Empiric antibacterial therapy was defined as any intravenous or oral antibacterial therapy prescribed on day 1 or 2 of hospitalization. Does not include patients who received azithromycin only. Multivariable analysis used Poisson GEE models with backwards elimination starting with all variables that had P-value <0.10 in bivariable analyses and eliminating variables until all remaining had P-value <0.050.

[a] Severe sepsis was defined as sepsis plus evidence of organ dysfunction, defined as any of the following: systolic blood pressure <90 mm Hg (or initiation of vasopressors), lactate level >2 mmol/L, platelet count <100 × 109 cells/L, bilirubin level >2 mg/dL (without documentation of moderate or severe liver disease), creatinine level >2 mg/dL (without documentation of moderate or severe chronic kidney disease) or ventilatory support (i.e., non-invasive positive pressure ventilation or mechanical ventilation).

Figure 1. Early Empiric Antibiotic Treatment in Hospitalized Patients with COVID-19, by Hospital (N=32 hospitals)

Each bar represents one hospital. The number of COVID positive cases included per hospital is shown at the top of each bar. Arrows indicate for profit hospitals. Hospitals with <10 included COVID positive cases are not shown (N=6).

Figure 1. Early Empiric Antibiotic Treatment in Hospitalized Patients with COVID-19, by Hospital
(N=32 hospitals; 1,667 patients)



Each bar represents one hospital. The number of COVID positive cases included per hospital is shown at the top of each bar. Arrows indicate for profit hospitals. Hospitals with <10 included COVID positive cases are not shown (N=6).