ORIGINAL ARTICLE

Bacterial Superinfection Pneumonia in Patients Mechanically Ventilated for COVID-19 Pneumonia

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Abstract

Rationale: Current guidelines recommend patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia receive empirical antibiotics for suspected bacterial superinfection on the basis of weak evidence. Rates of ventilator-associated pneumonia (VAP) in clinical trials of patients with SARS-CoV-2 pneumonia are unexpectedly low.

Objectives: We conducted an observational single-center study to determine the prevalence and etiology of bacterial superinfection at the time of initial intubation and the incidence and etiology of subsequent bacterial VAP in patients with severe SARS-CoV-2 pneumonia.

Methods: Bronchoscopic BAL fluid samples from all patients with SARS-CoV-2 pneumonia requiring mechanical ventilation were analyzed using quantitative cultures and a multiplex PCR panel. Actual antibiotic use was compared with guideline-recommended therapy.

Measurements and Main Results: We analyzed 386 BAL samples from 179 patients with SARS-CoV-2 pneumonia requiring mechanical ventilation. Bacterial superinfection within 48 hours of intubation was detected in 21% of patients. Seventy-two patients (44.4%) developed at least one VAP episode (VAP incidence rate = 45.2/1,000 ventilator days); 15 (20.8%) initial VAPs were caused by difficult-to-treat pathogens. The clinical criteria did not distinguish between patients with or without bacterial superinfection. BAL-based management was associated with significantly reduced antibiotic use compared with guideline recommendations.

Conclusions: In patients with SARS-CoV-2 pneumonia requiring mechanical ventilation, bacterial superinfection at the time of intubation occurs in <25% of patients. Guideline-based empirical antibiotic management at the time of intubation results in antibiotic overuse. Bacterial VAP developed in 44% of patients and could not be accurately identified in the absence of microbiologic analysis of BAL fluid.

Keywords: COVID-19; community-acquired pneumonia; ventilator-associated pneumonia; bronchoalveolar lavage; guideline therapy

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A complete list of the NU COVID Investigators may be found in the online supplement.

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At a Glance Commentary

Scientific Knowledge on the Subject: Current guidelines recommend patients with severe cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia receive empirical antibiotics for suspected bacterial superinfection on the basis of weak evidence. The actual frequency of bacterial superinfection in mechanically ventilated patients with SARS-CoV-2 pneumonia is unclear.

What This Study Adds to the Field: On the basis of BAL cultures and multiplex bacterial PCR results, 21% of patients with SARS-CoV-2 pneumonia have bacterial superinfection pneumonia at the time of intubation. Antibiotic management based on an accurate diagnosis of bacterial superinfection resulted in significantly less antibiotic use than guideline recommendations. Subsequently, 44% of all mechanically ventilated patients with SARS-CoV-2 pneumonia developed ventilator-associated pneumonia.

The contribution of bacterial superinfection to outcomes of severe severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia is unclear. Autopsy studies from patients with pneumonia caused by other viral pathogens, most notably influenza, suggest that bacterial pneumonia contributes significantly to the risk of death (1, 2). Autopsy studies of patients with severe SARS-CoV-2 pneumonia demonstrate evidence of bacterial superinfection in at least 32% of patients (3). In contrast, clinical trials of immunosuppressive therapies to treat SARS-CoV-2 pneumonia either do not report the rates of VAP or report rates that are unexpectedly low. For example, in the recent REMAP-CAP trial of the anti-IL-6 receptor antibodies tocilizumab and sarilumab (4), only one secondary bacterial infection was identified in 803 trial participants (0.1%) despite 29.4% requiring invasive mechanical ventilation at time of enrollment, whereas the highest rate of serious infection in other trials of IL-6 receptor antagonists was 25.9% (5).

Signs, symptoms, and laboratory abnormalities in patients with SARS-CoV-2 pneumonia are identical to those of bacterial community-acquired pneumonia (CAP). Hence, most patients with severe SARS-CoV-2 pneumonia receive empirical antibiotic treatment to avoid undertreatment of superinfecting bacterial pathogens. This approach is supported by recommendations from the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) CAP guidelines for documented viral pneumonia despite the acknowledged weak evidence for the recommendation (6). The World Health Organization and Surviving Sepsis guidelines specifically recommend empirical antibiotic treatment for severe SARS-CoV-2 pneumonia (7, 8). Later in the disease course, the persistence of fever, hypoxemia, radiographic infiltrates, and elevated inflammatory biomarkers over the unusually long duration of mechanical ventilation among patients with SARS-CoV-2 pneumonia (9–18 d) (9–11) puts these patients at risk for both undertreatment of unrecognized VAP and overtreatment of clinically suspected VAP with empirical broad-spectrum antibiotic therapy (12).

Because clinical signs and symptoms of SARS-CoV-2 and bacterial pneumonia largely overlap, an accurate microbiologic diagnosis is critical to diagnose bacterial superinfection pneumonia in intubated patients with severe coronavirus disease (COVID-19). Sampling of the alveolar space by BAL is the gold standard for the detection of respiratory pathogens. BAL has been shown to be superior to nasopharyngeal swab or endotracheal aspiration (13–16), but BAL procedures in patients with SARS-CoV-2 pneumonia have been avoided in many centers because of concerns regarding operator safety (17). Hence, although as many as 90% of patients with SARS-CoV-2 pneumonia requiring mechanical ventilation receive antibiotics, the prevalence of both initial bacterial superinfection and subsequent VAP among patients with severe SARS-CoV-2 pneumonia are unclear (12, 18, 19). Moreover, the spectrum and antibiotic susceptibility of superinfecting pathogens remains undefined.

Clinical teams in our ICU routinely obtain BAL fluid from mechanically ventilated patients at the time of intubation and when VAP is clinically suspected to manage antibiotics. With the initial COVID-19 surge in Chicago, we modified the standard bronchoscopic BAL technique to minimize operator exposure to infectious aerosols (20). Serendipitously, our clinical laboratory had validated and approved a multiplex PCR assay to detect respiratory pathogens in BAL fluid (BioFire Pneumonia panel) shortly before the first surge. The BioFire panel accurately detects respiratory pathogens and antibiotic resistance genes (21–24), provides results to clinicians within 3 hours, and can be used to safely discontinue or narrow antibiotics in patients with severe CAP requiring mechanical ventilation (24). Routine use of BAL and molecular diagnostics to diagnose pneumonia and manage antibiotics in our ICU allows us to present a robust and accurate analysis of the entire spectrum of bacterial superinfection in severe SARS-CoV-2 pneumonia, from the time of intubation for CAP or hospital-acquired pneumonia (HAP) through subsequent bacterial VAPs, and to report our experience using these tools to manage antibiotic therapy.

Some of the results of these studies have been previously reported in preprint form (https://doi.org/10.1101/2021.01.12.20248588).

Methods

Patient Cohort

We conducted this retrospective, observational study at Northwestern Memorial Hospital, a quaternary acute care hospital in Chicago, Illinois. Consecutive patients admitted to ICUs with PCR-confirmed SARS-CoV-2 pneumonia–induced respiratory failure who received mechanical ventilation and were discharged from the hospital or died between March 1 and June 30, 2020, were included in the cohort. SARS-CoV-2–positive patients intubated for reasons other than pneumonia (surgical procedures, intoxication, etc.) were excluded by adjudication by at least two critical care physicians. Pertinent details of patient management are included in the online supplement. The Northwestern University Institutional Review Board (STU00212283) approved this study.

Clinical teams in our ICU routinely obtain BAL fluid from patients within 24–48 hours after endotracheal intubation and whenever VAP is suspected. To accommodate patients with suspected or confirmed COVID-19, we modified the standard diagnostic bronchoscopic BAL

technique to minimize aerosol generation during the procedure (20). Further details are included in online supplement. We defined bacterial superinfection as the detection by quantitative culture or multiplex PCR of a respiratory pathogen known to cause pneumonia on a BAL specimen. Persistence was defined as the detection of the same bacterial pathogen in serial BAL samples after more than 4 days of appropriate antibiotics. BAL fluid PCR results were available to the clinical teams less than 3 hours after the completion of the procedure. Quantitative culture results were reported 48–72 hours after the completion of the procedure.

Endpoints

We examined the following two primary endpoints: *1*) the prevalence of bacterial superinfection within 48 hours of intubation and *2*) the incidence rate of subsequent VAP over the entire duration of mechanical ventilation. Bacterial CAP, HAP, and VAP were defined using standard nomenclature (6, 13, 25). Bacterial CAP was defined as bacterial pneumonia (in addition to known SARS-CoV-2 pneumonia) suspected and diagnosed within the initial 48 hours of admission (6). Bacterial HAP was defined as a bacterial pneumonia newly suspected and diagnosed after 48 hours of hospitalization. Bacterial VAP was defined as a bacterial pneumonia newly suspected and diagnosed after 48 hours of endotracheal intubation (13, 25). Secondary endpoints included the emergence of pathogens demonstrating resistance to antimicrobial therapies, clinical outcomes based on infection status, and the use of antibiotics.

For each day of mechanical ventilation, we measured the spectrum and number of antibiotics using a Narrow Antibiotic Treatment (NAT) score developed for CAP treatment studies (26). Briefly, standard CAP treatment of ceftriaxone and azithromycin was assigned a score of 0, monotherapy with either was assigned a score of −1, and no antibiotic therapy was assigned a score of −2; broader spectrum antibiotics were assigned progressively higher positive scores (*see* Table E2 and Figure E1 in the online supplement). A difficult-to-treat pathogen was defined by the need for a carbapenem to treat gram-negative pathogens (27) rather than standard first-line β-lactam HAP antibiotics (25) or vancomycin or linezolid for *Staphylococcus aureus*.

Statistical Analysis

Data were analyzed using custom scripts in R 4.0.2 using tidyverse 1.3.1 (The R Foundation for Statistical Computing; http://www.R-project.org). All plotting was performed using ggplot2 3.3.2. Cohort characteristics are reported as median and interquartile range (IQR) for quantitative variables and percentages for categorical variables. Median NAT scores were compared with guideline-recommended therapy using nonparametric methods (Wilcoxon Rank-Sum test). Other comparisons between groups used Kruskal-Wallis, Wilcoxon Rank-Sum, and Fisher's Exact tests, as appropriate. In cases of multiple testing, *P* values were corrected using false discovery rate correction. Adjusted *P* values of less than 0.05 were considered significant. Two-sided statistical tests were performed in all applicable cases.

Results

Clinical Features of the Cohort

From March 1, 2020, to June 30, 2020, the 4-month period encompassing most of the initial COVID-19 surge in Chicago, we cared for 196 patients intubated for severe SARS-CoV-2 pneumonia; the 179 who were discharged from the hospital or died by June 30 were included in the analysis (Figure E2). Characteristics at the time of ICU admission and outcomes are described in Table 1. Patients transferred from an external hospital constituted 18% of the population and were more likely to be managed with extracorporeal membrane oxygenation (ECMO), had higher mortality, and had a shorter duration of mechanical ventilation. No patient receiving ECMO was off mechanical ventilation before decannulation.

Bacterial Superinfection at the Time of Intubation

The majority (74.3%; 133/179) of patients underwent an early BAL (occurring within the initial 48 h of intubation). Of the 133 patients undergoing an early BAL, 43 (32.3%) had been hospitalized for more than 48 hours, thus meeting the definition of suspected HAP. Of patients receiving antibiotics at the time of initial BAL, the mean (± SD) duration of antibiotics before sampling was 2.03 (1.67) days for cases with positive bacterial detections and 2.17 (1.33) days for those with no bacterial detection. Women were less likely to have an early BAL, as were patients transferred directly to our ICU from another hospital (48.4% vs. 80.1% in nontransfer patients; $P < 0.001$). The median duration of ventilation among external transfer patients at the time of transfer was 2 days, and therefore many were outside the window for an early BAL by our definition. We found only minimal differences in some other baseline characteristics of the population that did not undergo an early BAL.

Of patients who underwent an early BAL, 21.1% (28/133) had a documented bacterial superinfection pneumonia. The median duration of hospitalization before intubation was 1 day (IQR, 2 d) for both those with superinfection bacterial pneumonia and those with only severe SARS-CoV-2 pneumonia. Forty-three (32%) patients in our early BAL cohort met guideline definitions for suspected HAP, whereas the remaining 90 met guideline definitions for CAP. The rate of superinfection bacterial pneumonia among patients with suspected HAP was 11.6% compared with 25.6% in those with suspected CAP ($P = 0.11$). Superinfection bacterial pneumonia was diagnosed in only two patients undergoing an early BAL on the basis of a positive PCR result but negative culture results. Both patients had positive PCR results for methicillin-susceptible *S. aureus* (MSSA), one of whom also had *Streptococcus agalactiae* detected. Although one-third of patients met the guideline definition for suspected HAP, etiologies of early postintubation superinfection bacterial pneumonia were typical of CAP. *Streptococcus* species and MSSA combined accounted for 79% (22/28) of cases. Polymicrobial infections were common, with 51 pathogens detected in 28 early BAL fluid samples. Only three patients (all previously treated with antibiotics) had pathogens resistant to standard CAP antibiotics—one *Stenotrophomonas maltophilia* and two methicillin-resistant *S. aureus* (MRSA). *Pneumocystis* was codetected in one patient with HIV that was well-controlled on antiretroviral treatment. Pneumococcal and/or *Legionella* urinary antigen tests were obtained on 64 patients each and were all negative.

At the time of BAL, neither standard clinical measures nor blood biomarkers distinguished patients with SARS-CoV-2

Table 1. Demographics, Clinical Characteristics, and Outcomes by Early BAL Status at the Time of ICU Admission

	Total	Early BAL		No Early BAL	*P* Value
		With Superinfection	Without Superinfection		
Number	179	28	105	46	—
Age, median (IQR), yr	62.4 (22.5)	63.8 (19.9)	62.1 (21.9)	59.9 (22.0)	0.96
Sex, M, *n* (%)	110 (61.5)	22 (78.6)	69 (65.7)	19 (41.3)	0.003
Race/ethnicity, *n* (%)					0.74
White	37 (20.7)	5 (17.9)	25 (23.8)	7 (15.2)	
Hispanic	63 (35.2)	8 (28.6)	38 (36.2)	17 (37.0)	
Black	60 (33.5)	13 (46.4)	31 (29.5)	16 (34.8)	
Asian	8 (4.5)	0	5 (4.8)	3 (6.5)	
Other	11 (6.2)	2 (7.14)	6 (5.7)	3 (6.5)	
External transfers, *n* (%)	33 (18.4)	5 (17.9)	11 (10.5)	17 (37.0)	0.001
Admission BMI, *n* (%)					0.22
$<$24.9 kg/m^2	28 (15.6)	6 (21.4)	14 (13.3)	8 (17.4)	
25–29.9 kg/m^2	48 (26.8)	7 (25.0)	29 (27.6)	12 (26.1)	
30–39.9 kg/m^2	71 (39.7)	6 (21.4)	47 (44.8)	18 (39.1)	
$>$40 kg/m^2	32 (17.9)	9 (32.1)	15 (14.3)	8 (17.4)	
SOFA score, median (Q1–Q3)	7 (4–9)	8 (3.75–10)	7 (3–9)	7.5 (6–9)	0.43
Comorbidities, *n* (%)					
Diabetes	80 (44.7)	13 (46.4)	49 (46.7)	18 (39.1)	0.71
Hypertension	105 (58.7)	17 (60.7)	65 (61.9)	23 (50.0)	0.42
Atrial fibrillation	16 (8.9)	3 (10.7)	12 (11.4)	1 (2.2)	0.15
Coronary artery disease	21 (11.7)	6 (21.4)	10 (9.5)	5 (10.9)	0.22
Heart failure	24 (13.4)	3 (10.7)	13 (12.4)	8 (17.4)	0.68
COPD	16 (8.8)	2 (7.1)	10 (9.5)	4 (8.7)	1
Asthma	11 (6.2)	2 (7.1)	3 (2.9)	6 (13.0)	0.044
Obstructive sleep apnea	26 (14.5)	5 (17.9)	16 (15.2)	5 (10.9)	0.66
Solid organ transplant	11 (6.2)	0 (0)	10 (9.5)	1 (2.2)	0.11
BMT/heme malignancy	3 (1.7)	0 (0)	3 (2.9)	0 (0)	0.73
Other cancer	15 (8.4)	2 (7.1)	10 (9.5)	3 (6.5)	0.93
Chronic hemodialysis	14 (7.8)	1 (3.6)	12 (11.4)	1 (2.2)	0.12
Chronic kidney disease	30 (16.8)	4 (14.3)	22 (21.0)	4 (8.7)	0.16
PE/DVT	12 (6.7)	1 (3.6)	7 (6.7)	4 (8.7)	0.77
CVA	8 (4.5)	1 (3.6)	5 (4.8)	2 (4.3)	1
Cirrhosis	3 (1.7)	0 (0)	2 (1.9)	1 (2.2)	1
Active smoker	4 (2.4)	1 (3.6)	3 (3.0)	0 (0)	0.63
Charleson comorbidity index, median (IQR)	2 (4)	1 (2.3)	2 (5)	1.5 (2.8)	0.66
Biomarkers, median (IQR)*					
C-reactive protein, mg/L	16.9 (5.7)	19.4 (11.7)	17.6 (13.9)	14.3 (15.3)	0.077
Procalcitonin, ng/ml	0.43 (1.83)	0.54 (1.92)	0.43 (1.63)	0.40 (2.49)	0.98
White blood cell count, $\times$1,000/μl	8.60 (5.65)	10.05 (5.70)	9.20 (5.70)	7.60 (6.0)	0.16
Absolute lymphocytes, $\times$1,000/μl	0.90 (0.60)	1.10 (0.70)	0.90 (0.73)	0.95 (0.40)	0.74
Absolute neutrophils, $\times$1,000/μl	7.60 (5.7)	10.00 (6.45)	7.50 (5.17)	6.50 (5.28)	0.027
D-dimer, ng/ml	601 (820)	542 (1,474)	590 (649)	719 (1,999)	0.65
Ferritin, ng/ml	8,556 (1,235)	1,110 (867)	902 (1,482)	718 (850)	0.36
Troponin I, ng/ml	0.03 (0.06)	0.03 (0.07)	0.03 (0.05)	0.03 (0.05)	0.73
Management, *n* (%)					
Proning	89 (49.7)	14 (50.0)	51 (48.6)	24 (52.2)	0.93
ECMO	17 (9.5)	2 (7.1)	7 (6.7)	8 (17.4)	0.13
Anti-IL6r study†	17 (9.5)	2 (7.1)	12 (11.4)	3 (6.5)	0.72
Anti-IL6r off-label	30 (16.8)	2 (7.1)	20 (19.0)	8 (17.4)	0.40
Remdesivir study‡	15 (8.4)	3 (10.7)	7 (6.7)	5 (10.9)	0.56
Remdesivir EUA	18 (10.1)	1 (3.6)	10 (9.5)	7 (15.2)	0.30
HCQ	40 (22.1)	5 (17.9)	20 (19.0)	15 (32.6)	0.16
Corticosteroids§	58 (32.0)	11 (39.3)	29 (27.6)	18 (39.1)	0.26
Hospital course					
Ventilation duration, median (IQR), d‖	13.0 (18.5)	16.7 (22.3)	13.0 (18.7)	13.2 (12.6)	0.11
ICU LOS, median (IQR), d¶	16.0 (18.0)	17.3 (21.6)	16.9 (18.1)	13.7 (14.2)	0.13
Hospital LOS, median (IQR), d	25.7 (19.0)	30.2 (17.7)	26.9 (18.8)	21.1 (17.6)	0.03**
VAP, *n* (%)	72 (40.2)	14 (50.0)	38 (36.2)	20 (43.5)	0.37
Difficult-to-treat pathogen, *n* (%)	19 (10.6)	6 (21.4)	9 (8.6)	4 (8.7)	0.15
Tracheostomy, *n* (%)	48 (26.8)	11 (39.3)	27 (25.7)	10 (21.7)	0.25
Chronic respiratory support on discharge, *n* (%)††	20 (11.2)	6 (21.4)	11 (10.5)	3 (6.5)	0.15

(*Continued*)

Table 1. (*Continued*)

	Total	Early BAL		No Early BAL	*P* Value
		With Superinfection	Without Superinfection		
Renal replacement therapy during admission, *n* (%)	49 (27.4)	9 (32.1)	32 (30.5)	8 (17.4)	0.21
New chronic HD on discharge, *n* (%)	5 (2.8)	2 (7.1)	3 (2.9)	0 (0)	0.16
Discharge outcomes, *n* (%)					0.068
Death	34 (19.0)	3 (10.7)	17 (16.2)	14 (30.4)	
LTACH	25 (14.0)	9 (32.1)	13 (12.2)	3 (6.5)	
SNF	11 (6.2)	0 (0)	8 (7.6)	3 (6.5)	
Acute inpatient rehab	25 (14.0)	4 (14.3)	14 (13.3)	7 (15.2)	
Home	84 (46.0)	12 (42.9)	52 (50.5)	19 (41.3)	

Definition of abbreviations: BMI = body mass index; BMT = bone marrow transplant; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; ECMO = extracorporeal membrane oxygenation; EUA = emergency use authorization; HCQ = hydroxychloroquine; HD = hemodialysis; IQR = interquartile range; LOS = length of stay; LTACH = long-term acute care hospital; PE/DVT = pulmonary embolus/deep venous thrombosis; Q = quartile; SNF = skilled nursing facility; SOFA = Sequential Organ Failure Assessment; VAP = ventilator-associated pneumonia.
*Biomarkers at intubation (or date of transfer to Northwestern Memorial Hospital for cases of external transfers).
†Randomized ranged from 4:1 to 2:1.
‡Randomized 1:1.
§Specifically for coronavirus disease.
‖As total time under ventilation, including time in other institutions before transfer, median and IQR.
¶LOS at Northwestern Memorial Hospital system; for external transfers, when exact ICU LOS was not known, date of intubation was used for start of ICU stay.
**Northwestern Memorial Hospital system only, not meaningful comparison.
††LTACH on ventilator, lung transplant, and home ventilation.

pneumonia who had an early bacterial superinfection from those who did not (Table 2). The BAL fluid composition in patients with SARS-CoV-2 pneumonia was enriched for lymphocytes. In a historical cohort of patients with pneumonia attributed to other pathogens in our center, the upper 95% confidence interval (CI) for lymphocytes as a percentage of total BAL cells was 10% (28, 29). In patients with SARS-CoV-2 pneumonia, 55.6% of patients had BAL lymphocytes percentage >10%. Nevertheless, the BAL cellular composition was insufficient to distinguish patients with superinfection from those without.

Analysis of median daily NAT scores relative to performance of an early BAL procedure is shown in Figure 1. Among all patients who received an early BAL procedure, the median daily NAT score in the first 7 days was −1 (95% CI, −1.5 to −0.5), indicating that our clinical teams administered a significantly more narrow spectrum of antibiotics to these patients than would be recommended for empirical therapy on the basis of current guidelines (NAT = 0 for CAP; NAT ⩾ 1 for HAP; $P <$ 0.001 for both comparisons). The median daily NAT score for patients with a positive BAL was −1 (95% CI, −1 to 0), which did not statistically differ from guideline-recommended empirical treatment (Figure 1). In contrast, the median daily NAT score for patients with negative BAL results was significantly lower than guideline-recommended empirical treatment (median, −1.5; 95% CI, −1.5 to −0.5; $P < 0.001$; Figure 1). The median difference between NAT scores for patients with positive and negative BAL results was statistically significant (median difference, −1; 95% CI, −1 to 0; $P = 0.001$). These findings suggest that clinical teams used negative BAL fluid analysis result to discontinue or narrow antibiotic therapy.

Ventilator-associated Pneumonia

An additional 246 BAL procedures were performed on the 162 patients who remained intubated for more than 48 hours (Figures 2A and E2). Only 18 (11.1%) patients never underwent a BAL procedure for suspected VAP after 48 hours of intubation. Patients with no subsequent BAL had a lower median duration of ventilation (5.0 d; quartile 1 [Q1]–Q3, 3.0–8.5) than those who did (14.0 d; Q1–Q3, 8–27.0; $P <$ 0.001).

At least one episode of new VAP was diagnosed in 120 BAL results from 72 unique patients (44.4% of all patients intubated >48 h), whereas 126 (51.2%) BAL results had no evidence of VAP. The first episode of VAP occurred an average of 10.8 days after intubation. Of patients with diagnosed VAP, 20.8% (15/72) developed a second VAP a median of 9.7 days after the first episode; three patients developed a third episode. Persistence of a previously identified pathogen causing VAP was found in 30 additional BAL results obtained over a range of 1–34 days (median, 10.7) after a previous BAL procedure. Patients with a documented early bacterial superinfection had more VAPs and more VAPs secondary to difficult-to-treat pathogens, although these differences were not statistically significant (Table E3).

At the time of the BAL procedure, clinical characteristics and blood biomarkers in patients with microbiologically proven VAP did not differ from those with clinically suspected VAP but a negative BAL result (Table 3). The cellular composition of the BAL fluid showed a significantly higher percentage of neutrophils and lower percentage of lymphocytes among patients with VAP compared with those without VAP.

Only seven cases of VAP were diagnosed by multiplex PCR in the absence of a positive culture. These included four samples with *S. aureus*, two with *Haemophilus influenzae* and one each with *Streptococcus pneumoniae, Klebsiella pneumoniae*, and *K. aerogenes* (Table E3). Diverse pathogens caused VAP in the cohort (Figure 2B). Monomicrobial VAP was more

Table 2. Early BAL Characteristics and Pathogens at the Time of BAL

	With Superinfection (*n* = 28)	Without Superinfection (*n* = 105)	*P* Value
Maximum temperature before BAL, °F	102.0 (2.8)	100.6 (2.9)	0.41
WBC count, ×1,000/μl	9.4 (6.0)	8.8 (6.0)	0.69
Absolute neutrophil count, ×1,000/μl	8.3 (6.3)	7.1 (5.3)	0.41
Absolute lymphocyte count, ×1,000/μl	0.9 (0.7)	0.9 (0.7)	0.69
NLR*	8 (7.5)	7.1 (5.8)	0.71
C-reactive protein, mg/L†	16.9 (13.1)	17.7 (14.1)	0.99
Procalcitonin, ng/ml	0.4 (1.4)	0.4 (1.8)	0.71
D-dimer, ng/ml‡	630 (1,507)	550 (604)	1.00
Ferritin, ng/ml	1,030 (1,298)	726 (1,331)	0.94
Antibiotics >24 h before BAL, *n* (%)§	5 (20)‖	38 (36)	0.60
Hospitalization >48 h, *n* (%)	5 (18)	38 (36)	0.47
BAL characteristics			
RBC/mm^3¶	27,078 (3,715)	2,375 (6,275)	0.99
WBC/mm^3**	258 (826)	164 (253)	0.41
Neutrophils, *n* (%)††	42 (55)	41 (43)	0.71
Neutrophil % >50%, *n* (%)††	10 (36)	36 (34)	1.00
Lymphocytes, *n* (%)††	11 (20)	14 (19)	0.69
Lymphocyte%>10%, *n* (%)††	14 (50)	60 (57)	0.71
Macrophages, *n* (%)††	7 (18)	14 (26)	0.41
Monocytes, *n* (%)††	8 (15)	9 (12)	0.69
Others, *n* (%)††‡‡	3 (8)	3 (7)	0.71
Amylase, IU/L§§	29 (46)	16 (32)	0.49
Amylase >105 IU/L, *n* (%)§§	2 (7)	2 (2)	0.69
	Microbiology Results [*n* (%)]		
Staphylococcus aureus sensitive	11 (39)‖‖¶¶		
Staphylococcus aureus resistant	2 (7)		
Viridans streptococcus	10 (36)‖		
Streptococcus agalactiae	3 (11)‖‖		
Streptococcus pneumoniae	3 (11)		
Other *Streptococcus* species	2 (7)		
Haemophilus influenzae	2 (7)		
Stomatococcus species	2 (7)		
Enterococcus species	1 (4)		
Klebsiella oxytoca	1 (4)		
Moraxella catarrhalis	1 (4)		
Proteus mirabilis	1 (4)		
Serratia marcescens	1 (4)‖		
Stenotrophomonas maltophilia	1 (4)‖		

Definition of abbreviations: NLR = neutrophil to lymphocyte ratio; RBC = red blood cell; WBC = white blood cell.
All data are presented as median and interquartile range unless designated separately.
*Data were unavailable for four patients with no superinfection.
†Data were unavailable for two patients with superinfection and one patient with no superinfection.
‡Data were unavailable for two patients with no superinfection.
§Data were unavailable for three patients with superinfection.
‖Positive cultures from five patients who were on antibiotics before BAL.
¶Data were unavailable for two patients with superinfection and 18 patients with no superinfection.
**Data were unavailable for one patient with superinfection and seven patients with no superinfection.
††Data were unavailable for one patient with superinfection and six patients with no superinfection.
‡‡Plasma cells, eosinophils, any other.
§§Data were unavailable for 16 patients with superinfection and 58 patients with no superinfection.
‖‖Pathogens detected by multiplex PCR only.
¶¶Two patients with methicillin-susceptible *Staphylococcus aureus*.

common for the first VAP episode (56/72; 77.8%) than for subsequent episodes (8/18; 44.4%; $P = 0.005$). Pathogens sensitive to narrow-spectrum antibiotics were often detected as causes of early VAP, with more resistant pathogens emerging only after a longer duration of mechanical ventilation (Figure 3A). Only 15 of the 72 (20.8%) initial VAP etiologies were difficult-to-treat pathogens, including nine caused by gram-negative pathogens resistant to piperacillin/tazobactam and cefepime and six MRSA VAPs. A substantial number of VAP episodes caused by gram-negative pathogens (48.6%) could be treated with cefazolin or ceftriaxone monotherapy. Only 33% of the 18 subsequent VAP episodes were caused by difficult-to-treat organisms (two MRSA and four gram-negative pathogens). Comparison of the NAT scores between patients with positive and negative BAL results for

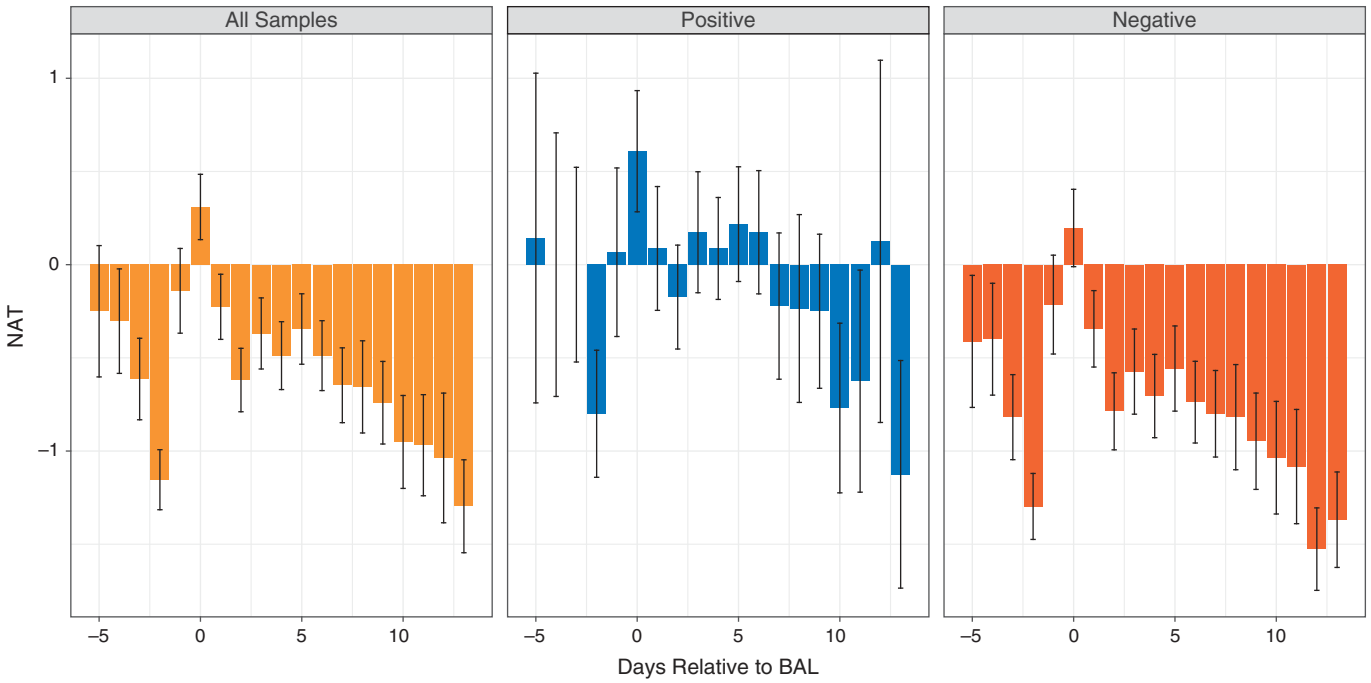

Figure 1. Median NAT score in response to BAL results overall and in response to positive and negative BAL results for patients undergoing bronchoscopy within 48 hours of intubation. A score of −2 indicates no antibiotic therapy, and a score of 0 corresponds to guideline-recommended treatment for patients with severe community-acquired pneumonia. NAT = narrow antibiotic therapy.

suspected VAP was complicated by other documented or suspected sources of nosocomial infection in these patients, including acalculous cholecystitis, suspected peritonitis, urinary tract infections, and central line–associated bacteremia. Nevertheless, Figure E4 demonstrates that antibiotics were still deescalated in a majority of patients on the basis of BAL results.

The overall VAP incidence rate in this cohort was 45.2 episodes/1000 days of mechanical ventilation. The VAP incidence rate was linear over cumulative days on mechanical ventilation until the number of patients still on mechanical ventilation became very low (Figure 3B). The distribution of ventilator day at VAP diagnosis is shown in Figure E3.

Clinical Outcomes

The overall hospital mortality rate was 19%. The mortality rate of patients transferred for quaternary care was higher than of patients admitted through the emergency department (34.3% vs. 15.3%; odds ratio, 2.87 [95% CI, 1.13–7.11]; $P = 0.01$). The mortality rate of patients with documented bacterial superinfection at the time of intubation was not higher than in those with only SARS-CoV-2 detected (Table 1). However, early bacterial superinfection was associated with a trend toward more prolonged ventilation and corresponding tracheostomy and the need for chronic respiratory support.

Discussion

Current guidelines recommend empirical administration of antibiotics to all patients with severe SARS-CoV-2 pneumonia (6–8). Using sensitive, gold-standard analysis of BAL fluid with multiplex PCR and quantitative culture to identify bacterial superinfections in patients with severe SARS-CoV-2 pneumonia requiring mechanical ventilation, we show that early antibiotics can be avoided in >75% of cases. For patients in our cohort with bacterial superinfection in the first 10 days after intubation, standard antibiotics to treat CAP (6) adequately covered the spectrum of pathogens detected in >75% of cases.

Our study complements a recent study of 568 patients with SARS-CoV-2 infection from multiple centers in Europe, each of which contributed fewer than 20 patients to the overall cohort (19). In our single-center study of consecutive patients managed using a standardized care plan that included the routine use of bronchoscopic sampling to manage antibiotics for pneumonia, we found the rate of bacterial superinfection at the time of intubation is higher (21%) than the 9.7% they reported. Several factors may explain the lower rate in their study. Most importantly, we required lower respiratory sampling to diagnose pneumonia, whereas respiratory samples were obtained in only 73% of the patients in that study. Furthermore, most respiratory samples in that study were endotracheal aspirates. BAL was used to diagnose pneumonia in only 16/55 cases, and the rate of negative BAL results was not reported. In addition, 89% of their patients were receiving antibiotics at the time of respiratory sampling compared with 32% in our series. Finally, multiplex PCR was not used in their series. Although we detected only two additional cases with this method, a positive PCR result allowed us to assign clinical significance to the detection of *S. viridans* and other bacteria. Because they colonize the oropharynx, the pathogenicity of these microorganisms is uncertain when detected in endotracheal aspirates. Nevertheless, viridans Streptococci include many clear-cut CAP pathogens, including *S.*

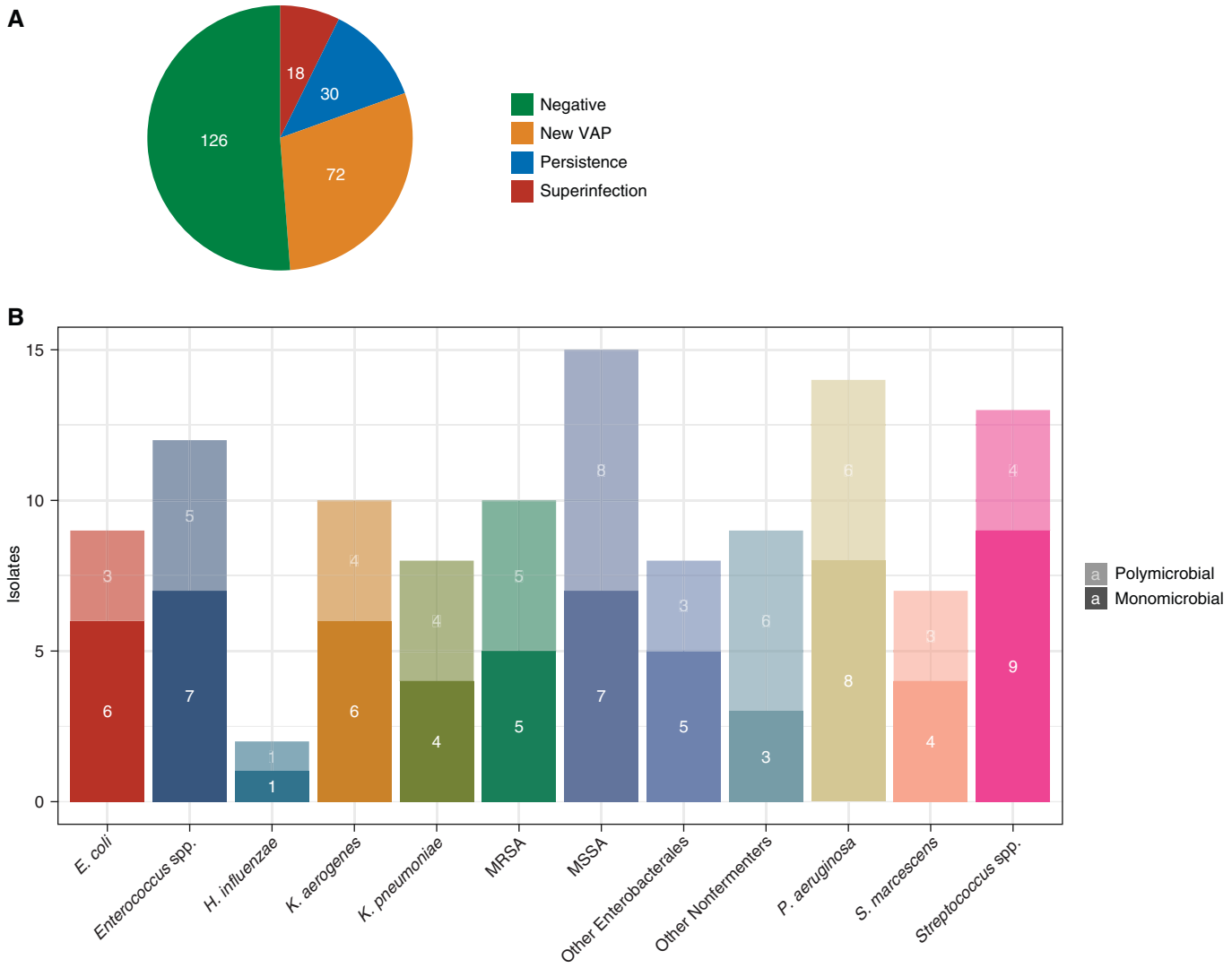

Figure 2. (*A* and *B*) BAL results for suspected VAP (*A*) and pathogens detected in positive BAL results (*B*). Dark bars are pathogens detected in monomicrobial episodes, whereas lighter bars are presence in polymicrobial pneumonias. *E. coli* = *Escherichia coli*; *H. influenzae* = *Haemophilus influenzae*; *K. aerogenes* = *Klebsiella aerogenes*; *K. pneumoniae* = *Klebsiella pneumoniae*; MRSA = methicillin-resistant *S. aureus*; *MSSA* = methicillin-susceptible *S. aureus*; *P. aeruginosa* = *Pseudomonas aeruginosa*; *S. aureus* = *Staphylococcus aureus*; *S. marcescens* = *Serratia marcescens*; VAP = ventilator-associated pneumonia.

anginosis, S, milleri, S. mitis, and *S. sanguis*, and have been commonly found in other studies of severe viral pneumonia (30).

A major strength of our study is that our clinicians managed antibiotics on the basis of BAL results. All other studies report rates but do not demonstrate that antibiotic therapy can be safely stopped, withheld, or narrowed on the basis of the results of diagnostic tests (19, 31–35). Bronchoscopic sampling to direct antimicrobial therapy for pneumonia can only affect clinical outcomes if clinicians modify antibiotics in response to test results (36, 37). More than half of all our BAL results were negative for bacterial superinfection. The median daily NAT score—a measure of both the number and spectrum of antibiotics administered to a patient on a given day, with 0 designating CAP guideline-recommended combination therapy—after an early BAL was significantly less than 0, suggesting that clinical teams narrowed or stopped early antibiotic therapy in response to BAL fluid results.

We cannot determine from this observational study whether the use of BAL-guided antimicrobial therapy was beneficial. The low mortality in our cohort argues against harm associated with management of antibiotics based on the results of BAL fluid analysis, consistent with previous randomized trials of this approach (14, 24). Furthermore, our low observed mortality suggests that negative BAL fluid results were likely true negatives. Some findings of our study suggest that BAL-guided antibiotic management may be beneficial, as the administration of empirical antibiotic therapy increases the rates of subsequent VAP caused by difficult-to-treat pathogens (11). Despite the high incidence rate of VAP in our cohort, the majority of VAP pathogens in our cohort were not difficult-to-treat pathogens, possibly reflecting avoidance of

Table 3. Late BAL Clinical Characteristics at Time of BAL and Results

	With VAP (*n* = 120)	Without VAP (*n* = 126)	*P* Value
Lab/vitals at time of BAL			
Maximum temperature before BAL, °F	100.8 (2.7)	100.6 (1.9)	0.97
WBC count, ×1,000/μl	12.8 (8.4)	11.8 (6.6)	0.47
Absolute neutrophil count, ×1,000/μl	8.7 (8.5)	8.4 (8.2)	0.58
Absolute lymphocyte count, ×1,000/μl	1.0 (0.9)	1.0 (1.0)	0.82
NLR*	7.6 (12.6)	8.8 (7.4)	0.97
C-reactive protein, mg/L†	14.8 (16.7)	15.3 (21.5)	0.53
Procalcitonin, ng/ml	0.7 (3.2)	0.7 (2.0)	0.78
D-dimer, ng/ml‡	2,356 (2,699)	2,091 (2,276)	0.64
Ferritin, ng/ml	559 (1,013)	586 (1,127)	0.95
Antibiotics >24 h before BAL, *n* (%)§	32 (27)	29 (23)	0.82
Day of hospitalization before BAL	16 (11)	10 (11)	<0.0003
BAL characteristics			
RBC/mm^3‖	2,525 (8,390)	1,450 (4,475)	0.34
WBC/mm^3¶	488 (1,635)	242 (440)	0.002
Neutrophils, *n* (%)**	77 (41)	48 (48)	<0.0001
Neutrophil >50%, *n* (%)**	83 (69)	57 (45)	<0.0004
Lymphocytes, *n* (%)**	5 (15)	14 (24)	<0.0003
Lymphocyte % >10%, *n* (%)**	38 (32)	75 (59)	<0.0003
Macrophages, *n* (%)**	6 (13)	12 (23)	0.011
Monocytes, *n* (%)**	3 (5)	5 (8)	0.13
Others, *n* (%)**††	1 (4)	3 (6)	0.002
Amylase‡‡	31 (76)	20 (75)	0.47
Amylase >105 IU/L, *n* (%)‡‡	15 (13)	8 (6)	0.33

Definition of abbreviations: NLR = neutrophil to lymphocyte ratio; RBC = red blood cell; VAP = ventilator-associated pneumonia; WBC = white blood cell.

All data are presented as median and interquartile range unless designated separately.

*Data were unavailable at the time of BAL for 16 patients with superinfection and 19 patients with no superinfection.

†Data were unavailable at the time of BAL for four patients with superinfection and six patients with no superinfection.

‡Data were unavailable at the time of BAL for 32 patients with superinfection and 36 patients with no superinfection.

§Data were unavailable at the time of BAL for five patients with superinfection and two patients with no superinfection.

‖Data were unavailable at the time of BAL for 11 patients with superinfection and 13 patients with no superinfection.

¶Data were unavailable at the time of BAL for nine patients with superinfection and five patients with no superinfection.

**Data were unavailable at the time of BAL for five patients with superinfection and two patients with no superinfection.

††Plasma cells, eosinophils, any other.

‡‡Data were unavailable at the time of BAL for 60 patients with superinfection and 65 patients with no superinfection.

antibiotics in most patients early in their clinical course (13, 25).

We found a VAP prevalence of 44% and an incidence rate of 45.2/1,000 days of mechanical ventilation. Although often unreported, this rate of bacterial infection exceeds those reported in interventional trials of IL-6 receptor antagonists and corticosteroids in patients with SARS-CoV-2 pneumonia (0.1–25%) even though these agents might be predicted to increase the rates of VAP (4, 5, 38, 39). Because a key finding of our study is that clinical criteria do not distinguish patients with bacterial superinfection from those with persistent clinical features of SARS-CoV-2 pneumonia, we suspect these low VAP rates reflect underdiagnosis in these trials. Our observed rate of VAP is also higher than that reported in critically ill patients receiving mechanical ventilation for other reasons (34, 40, 41). By inclusion of all cases of VAP, rather than only first episodes, as used in other studies (35), we demonstrate a higher rate as well as a linear increase in VAP incidence rate. Our higher VAP rate therefore likely reflects the longer average duration of mechanical ventilation among patients with SARS-CoV-2 pneumonia and the low mortality in our cohort. Whether the incidence of VAP in severe SARS-CoV-2 pneumonia differs from other causes of prolonged mechanical ventilation, whether infectious or not, is unclear and requires further study. The multiplex PCR technology used in our study is unlikely to be the explanation for higher VAP rates, as a positive PCR alone was used to make the diagnosis in only seven cases in our cohort (34, 35). Instead, the main advantage of the PCR was the rapid availability of results (<3 h), including the absence of common antibiotic resistance genes, allowing clinicians to quickly narrow or discontinue antibiotics.

Our findings suggest that many cases of VAP in patients with SARS-CoV-2 pneumonia are unrecognized or may be empirically treated with unnecessarily broad-spectrum antibiotics (13, 25), highlighting the need for surveillance for secondary infections, particularly when immunosuppressive therapies are used for treatment (4, 5, 38, 39). Our findings also call into question the results of studies that do not rely on sensitive or specific microbiologic techniques for diagnosis of bacterial superinfection (42, 43). A recent meta-analysis, in which the diagnosis of pneumonia relied on cultures of endotracheal aspirates or sputum, reported that the prevalence of bacterial superinfection was only 14% in severe SARS-CoV-2 pneumonia (33).

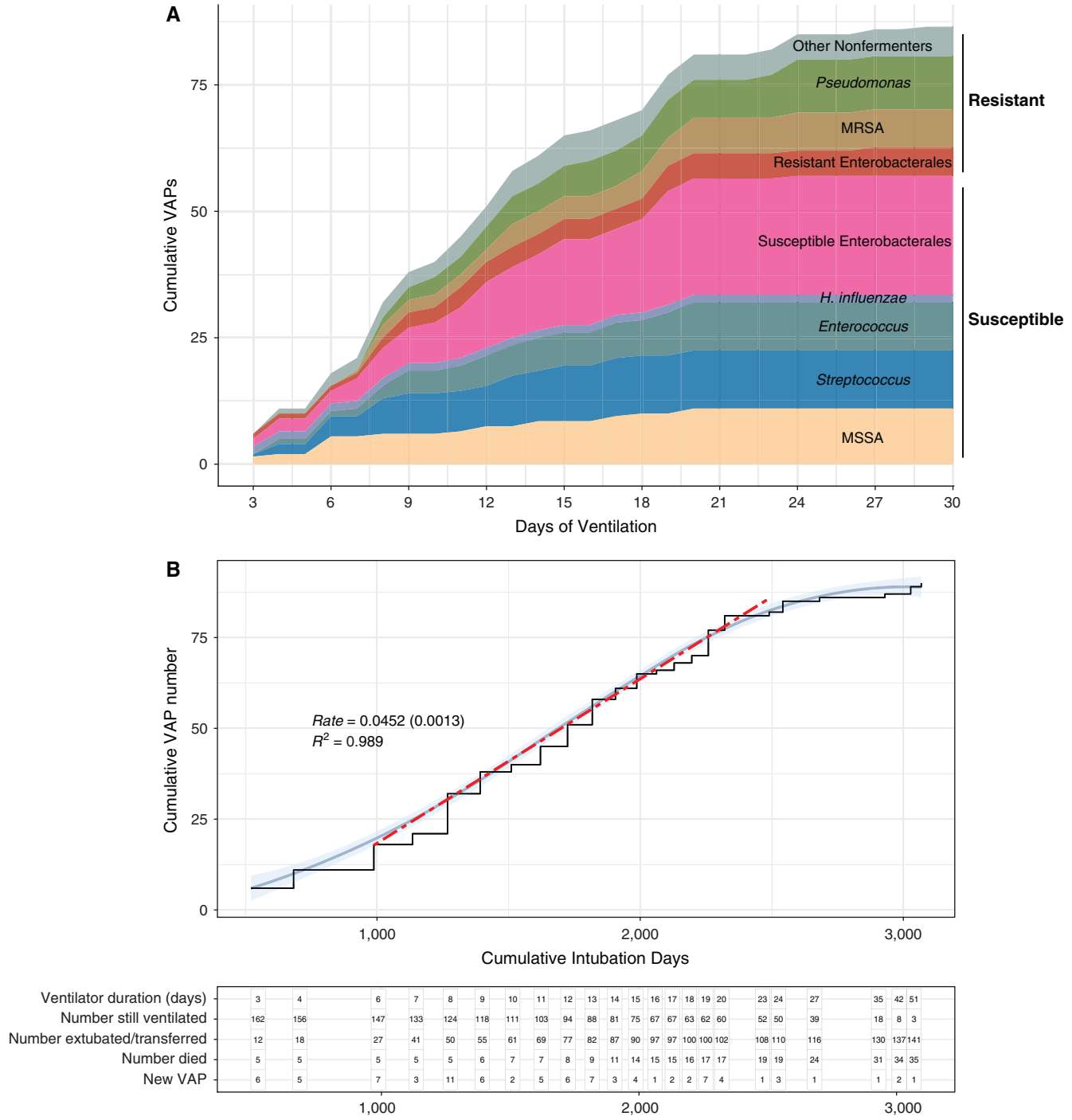

Figure 3. (*A*) Cumulative ventilator-associated pneumonias (VAPs) by etiology and resistance pattern. For Enterobacterales, resistant isolates were defined as requiring carbapenem or broader spectrum β-lactam treatment. (*B*) Incidence of VAP. Cumulative new VAP diagnoses per cumulative ventilator days. Individual patients can have more than one VAP episode. *H. influenzae* = *Haemophilus influenzae*; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

Although BAL cultures are more specific than endotracheal aspirates (14, 15), sensitivity may be adversely affected by prior antibiotic therapy. Given that guidelines recommend empirical antibiotics for all patients with severe SARS-CoV-2 pneumonia, we emphasized sensitive techniques and criteria to diagnose superinfection, including multiplex PCR and the use of a lower quantitative culture threshold for early BALs; however, our data may still underestimate the true frequency of early superinfection. Although results of multiplex PCR testing were unavailable in 13% of samples, all of these samples were

analyzed with quantitative culture, widely considered the gold standard for the diagnosis of VAP, and an *S. aureus*/MRSA PCR assay (24). Like all single-center studies, the generalizability of our findings to other centers is unclear. Other aspects of COVID-19 pneumonia management, such as timing of intubation, use of noninvasive ventilation, ventilator strategy, adjunctive therapies, and availability of ECMO, may affect the duration of ventilation and may therefore affect pneumonia incidence. The routine continuous availability of the multiplex PCR assay results and clinicians empowered to change antibiotics allowed more rapid antibiotic adjustment within hours of acquisition of a BAL sample. These logistical issues may limit reproducibility of our results in other centers. However, although the specific multiplex PCR pneumonia panel may not be currently available in all centers, PCR-based technologies are widely used in most clinical laboratories, are relatively inexpensive, and do not require specialized technician skills.

Our study is also from the early surge of SARS-CoV-2 infections, and bacterial superinfection may be affected by different viral variants and the widespread use of corticosteroids and other immunosuppressive therapies. Our relatively low mortality with an associated longer duration of ventilation compared with that reported from other centers will tend to increase the observed prevalence of VAP. The higher mortality in patients who did not undergo early BAL reflects a disproportionate number of patients in this group who were either deemed too acutely ill to undergo bronchoscopy, undergoing active discussions of shift to comfort-focused care, or transferred for consideration of advanced interventions such as ECMO (44) and lung transplant (45), with their higher attendant mortality.

Conclusions

Superinfection bacterial pneumonia was present at the time of intubation in 21% of patients with severe SARS-CoV-2 pneumonia. Empirical treatment of severe SARS-CoV-2 pneumonia based on current guideline-based recommendations would have resulted in substantial antibiotic overuse in our cohort. The prevalence of subsequent VAP was 44% with an incidence rate of 45.2/1,000 ventilator days. Superinfection bacterial pneumonias at time of intubation and early VAPs were predominantly caused by pathogens usually associated with CAP and susceptible to narrow-spectrum antibiotic therapy. These findings suggest that, in the absence of BAL sampling, VAP may be underrecognized yet overtreated with unnecessarily broad antibiotics. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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References

1. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J Infect Dis* 2008;198:962–970.
2. Gill JR, Sheng ZM, Ely SF, Guinee DG, Beasley MB, Suh J, *et al.* Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. *Arch Pathol Lab Med* 2010;134:235–243.
3. Clancy CJ, Schwartz IS, Kula B, Nguyen MH. Bacterial superinfections among persons with coronavirus disease 2019: a comprehensive review of data from postmortem studies. *Open Forum Infect Dis* 2021; 8: ofab065.
4. REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021;384:1491–1502.
5. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, *et al.* Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. *N Engl J Med* 2021;384:1503–1516.
6. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, *et al.* Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019;200:e45–e67.
7. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, *et al.* Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med* 2020;48:e440–e469.
8. World Health Organization. Clinical management of COVID-19. 2020 [accessed 2021 Jun 3]. Available from: https://www.who.int/publications/i/item/10665-332299.
9. Grant RA, Morales-Nebreda L, Markov NS, Swaminathan S, Querrey M, Guzman ER, *et al.*; NU SCRIPT Study Investigators. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. *Nature* 2021;590:635–641.
10. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, *et al.*; COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020;323:1574–1581.
11. Gamberini L, Tonetti T, Spadaro S, Zani G, Mazzoli CA, Capozzi C, *et al.*; ICU-RER COVID-19 Collaboration. Factors influencing liberation from mechanical ventilation in coronavirus disease 2019: multicenter observational study in fifteen Italian ICUs. *J Intensive Care* 2020;8:80.
12. Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: potentially lethal and unexplored in COVID-19. *Lancet Microbe* 2020;1:e11.
13. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, *et al.* International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). *Eur Respir J* 2017;50:1700582.
14. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stéphan F, *et al.* Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med* 2000;132:621–630.
15. Fujitani S, Cohen-Melamed MH, Tuttle RP, Delgado E, Taira Y, Darby JM. Comparison of semi-quantitative endotracheal aspirates to quantitative non-bronchoscopic bronchoalveolar lavage in diagnosing ventilator-associated pneumonia. *Respir Care* 2009;54:1453–1461.
16. Gao CA, Cuttica MJ, Malsin ES, Argento AC, Wunderink RG, Smith SB; NU COVID Investigators. Comparing nasopharyngeal and BAL SARS-CoV-2 assays in respiratory failure. *Am J Respir Crit Care Med* 2021; 203:127–129.
17. Wahidi MM, Shojaee S, Lamb CR, Ost D, Maldonado F, Eapen G, *et al.* The use of bronchoscopy during the coronavirus disease 2019 pandemic: CHEST/AABIP guideline and expert panel report. *Chest* 2020;158:1268–1281.
18. Bassetti M, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. *Intensive Care Med* 2020;46:2071–2074.
19. Rouze A, Martin-Loeches I, Povoa P, Metzelard M, Du Cheyron D, Lambiotte F, *et al.*; coVAPid Study Group. Early bacterial identification among intubated patients with COVID-19 or influenza pneumonia: a European multicenter comparative cohort study. *Am J Respir Crit Care*

Med [online ahead of print] 26 May 2021; DOI: 10.1164/rccm.202101-0030OC.
20. Gao CA, Bailey JI, Walter JM, Coleman JM, Malsin ES, Argento AC, *et al.* Bronchoscopy on intubated patients with COVID-19 is associated with low infectious risk to operators. *Ann Am Thorac Soc* 2021;18: 1243–1246.
21. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, *et al.*; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015;373:415–427.
22. Wolff BJ, Bramley AM, Thurman KA, Whitney CG, Whitaker B, Self WH, *et al.* Improved detection of respiratory pathogens by use of high-quality sputum with TaqMan array card technology. *J Clin Microbiol* 2016;55:110–121.
23. Gadsby NJ, Russell CD, McHugh MP, Mark H, Conway Morris A, Laurenson IF, *et al.* Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. *Clin Infect Dis* 2016;62: 817–823.
24. Paonessa JR, Shah RD, Pickens CI, Lizza BD, Donnelly HK, Malczynski M, *et al.* Rapid detection of methicillin-resistant *Staphylococcus aureus* in BAL: a pilot randomized controlled trial. *Chest* 2019;155:999–1007.
25. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, *et al.* Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016;63:e61–e111.
26. Wang AA, Pickens CO, He H, Scholtens DM, Pawlowski AE, Singer BD, *et al.* The narrow-spectrum antibiotic treatment score: a novel quantitative tool for assessing broad- and narrow-spectrum antibiotic use in severe community-acquired pneumonia [abstract]. *Am J Respir Crit Care Med* 2020;201:A2929.
27. Kadri SS, Adjemian J, Lai YL, Spaulding AB, Ricotta E, Prevots DR, *et al.*; National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH–ARORI). Difficult-to-treat resistance in gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. *Clin Infect Dis* 2018;67:1803–1814.
28. Walter JM, Ren Z, Yacoub T, Reyfman PA, Shah RD, Abdala-Valencia H, *et al.* Multidimensional assessment of the host response in mechanically ventilated patients with suspected pneumonia. *Am J Respir Crit Care Med* 2019;199:1225–1237.
29. Gelarden I, Nguyen J, Gao J, Chen Q, Morales-Nebreda L, Wunderink R, *et al.* Comprehensive evaluation of bronchoalveolar lavage from patients with severe COVID-19 and correlation with clinical outcomes. *Hum Pathol* 2021;113:92–103.
30. Centers for Disease Control and Prevention (CDC). Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) - United States, May-August 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:1071–1074.
31. Contou D, Claudinon A, Pajot O, Micaëlo M, Longuet Flandre P, Dubert M, *et al.* Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. *Ann Intensive Care* 2020; 10:119.
32. Kreitmann L, Monard C, Dauwalder O, Simon M, Argaud L. Early bacterial co-infection in ARDS related to COVID-19. *Intensive Care Med* 2020;46:1787–1789.
33. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect* 2020;81: 266–275.
34. Maes M, Higginson E, Pereira-Dias J, Curran MD, Parmar S, Khokhar F, *et al.* Ventilator-associated pneumonia in critically ill patients with COVID-19. *Crit Care* 2021;25:25.
35. Rouzé A, Martin-Loeches I, Povoa P, Makris D, Artigas A, Bouchereau M, *et al.*; coVAPid Study Group. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. *Intensive Care Med* 2021;47:188–198.
36. Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med* 2006; 355:2619–2630.
37. Hellyer TP, McAuley DF, Walsh TS, Anderson N, Conway Morris A, Singh S, *et al.* Biomarker-guided antibiotic stewardship in suspected ventilator-associated pneumonia (VAPrapid2): a randomised controlled trial and process evaluation. *Lancet Respir Med* 2020;8:182–191.
38. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:1637–1645.
39. Recovery Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:693–704.
40. Skrupky LP, McConnell K, Dallas J, Kollef MH. A comparison of ventilator-associated pneumonia rates as identified according to the National Healthcare Safety Network and American College of Chest Physicians criteria. *Crit Care Med* 2012;40:281–284.
41. Rosenthal VD, Bijie H, Maki DG, Mehta Y, Apisarnthanarak A, Medeiros EA, *et al.*; INICC Members. International Nosocomial Infection Control Consortium (INICC) report, data summary of 36 countries, for 2004-2009. *Am J Infect Control* 2012;40:396–407.
42. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, *et al.* Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020;323:1612–1614.
43. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, *et al.* Covid-19 in critically ill patients in the Seattle region - case series. *N Engl J Med* 2020;382:2012–2022.
44. Shaefi S, Brenner SK, Gupta S, O'Gara BP, Krajewski ML, Charytan DM, *et al.*; STOP-COVID Investigators. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. *Intensive Care Med* 2021;47:208–221.
45. Bharat A, Machuca TN, Querrey M, Kurihara C, Garza-Castillon R Jr, Kim S, *et al.* Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries. *Lancet Respir Med* 2021;9:487–497.