Pneumonia

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Can clinical findings at admission allow withholding of antibiotics in patients hospitalized for community acquired pneumonia when a test for a respiratory virus is positive?

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Abstract

Background Current guidelines recommend empiric antibiotic therapy for patients who require hospitalization for community-acquired pneumonia (CAP). We sought to determine whether clinical, imaging or laboratory features in patients hospitalized for CAP in whom PCR is positive for a respiratory virus enable exclusion of bacterial coinfection so that antibiotics can be withheld.

Methods For this prospective study, we selected patients in whom an etiologic diagnosis was likely to be reached, namely those who provided a high-quality sputum sample at or shortly after admission, and in whom PCR was done to test for a respiratory virus. We performed quantitative bacteriologic studies on sputum to determine the presence of bacterial infection or coinfection and reviewed all clinical, imaging and laboratory studies.

Results Of 122 CAP patients studied, 77 (63.1%) had bacterial infection, 16 (13.1%) viral infection, and 29 (23.8%) bacterial/viral coinfection. Underlying pulmonary disease and a history of smoking were more common in bacterial pneumonia. Upper respiratory symptoms were more common, and mean white blood cell (WBC) counts were lower viral pneumonia. Nevertheless, no clinical, laboratory or imaging findings allowed exclusion of bacterial coinfection in patients who tested positive for a respiratory virus. In fact, patients with bacterial/viral coinfection were sicker than those with bacterial or viral pneumonia; 30% were admitted required transfer to the ICU during their hospital course, compared to 17% and 19% of patients with bacterial or viral infection, respectively ($p < .05$). In this study, 64.4% of patients who tested positive for a respiratory virus had a bacterial coinfection.

Conclusions If a test for a respiratory virus test is positive in a patient hospitalized for CAP, no sufficiently differentiating features exclude bacterial coinfection, thereby supporting the recommendation that empiric antibiotics be administered to all patients who are sufficiently ill to require hospitalization for CAP.

Keywords Community acquired pneumonia, Viral pneumonia, Bacterial pneumonia, Bacterial-viral coinfection

Background

Community-acquired pneumonia (CAP) may result from infection by recognized bacterial pathogens, respiratory viruses, bacteria traditionally regarded as commensal bacteria but recently shown to cause pneumonia, or bacterial/viral coinfection [1–5]. Empiric

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antibacterial therapy is recommended for most patients hospitalized for CAP [6], as it is difficult to identify the underlying cause of infection; even the most exhaustive prospective studies utilizing available microbiologic techniques generally fail to identify an etiologic agent in > 50% of cases [1, 2]. The principal reason for this failure is that, except in the small proportion of patients who have positive blood cultures, diagnosis of bacterial infection requires a valid sputum sample for Gram stain, culture and/or molecular analysis [7–10]. At the time of hospitalization for CAP, a substantial proportion of patients are unable to provide a valid sputum sample, and timely administration of empiric antibiotics rapidly eradicates infecting bacteria from sputum [11].

Polymerase chain reaction (PCR) is increasingly available to identify the presence of a respiratory virus, and results may be positive within a few hours of presentation to hospital. This availability, together with increasing concern about potential harm by antibiotics [12], raises the question of whether antibiotic therapy should be withheld in patients who are hospitalized for pneumonia and who test positive for a respiratory virus. The problems of withholding antibiotics in patients with CAP with a PCR that identifies a respiratory virus are that: (1) bacterial coinfection is common in viral pneumonia; and (2) exclusion of a bacterial etiology requires a high-quality sputum specimen. Numerous reports show that about one-third of patients hospitalized with viral pneumonia have bacterial coinfection [4, 13–16]. Now that commensal flora have been found to cause CAP [3], the proportion with bacterial coinfection is probably even greater. And a substantial proportion of patients who are hospitalized for pneumonia are unable to provide a high-quality sputum specimen at admission.

Prior studies have varied in their ability to distinguish bacterial infection alone or bacterial/viral coinfection from viral infection alone [1, 5, 17, 18]. Such a diagnostic distinction could inform the decision to initiate antibiotic therapy in patients with CAP whose PCR is positive for a respiratory virus at the time of diagnosis. While elevated white blood cell (WBC) counts and serum procalcitonin are associated with bacterial infection, the absence of leukocytosis or a high procalcitonin does not preclude a bacterial etiology [19–21]. Similarly, while chest imaging showing multifocal or patchy pneumonia is conventionally associated with viral infection and consolidation with bacterial pneumonia, significant overlap with bacterial pneumonia has been reported [22, 23].

The purpose of the present study was to determine whether differences in the clinical presentation of pneumonia due to bacterial infection, viral infection or bacterial/viral coinfection are sufficiently consistent to justify withholding empiric antibiotics in patients admitted for CAP who test positive for a respiratory virus.

Methods

Patient selection

We studied a convenience sample of patients admitted to the Michael E. DeBakey VA Medical Center with a diagnosis of CAP between September 1, 2017, and December 31, 2019 (pre-COVID). Detailed methods were previously described [3]. Briefly, on select days, the principal investigator (DMM) examined all Gram-stained sputum samples submitted to the Clinical Microbiology Laboratory in the preceding 24 h. For all high-quality specimens (defined as showing > 25WBC/epithelial cell), the electronic medical record was reviewed to identify patients who: (1) were freshly admitted from the community; (2) had a newly recognized pulmonary infiltrate and (3) had ≥ 2 of the following findings: fever, increased cough, sputum production or shortness of breath, rales, confusion or hypoxia. Patients who met the above criteria were included in the present study if they also underwent PCR testing for respiratory viruses on a nasopharyngeal specimen at or soon after admission as seen in Table 1. The purpose of this selection process was to obtain a series of patients in whom an etiologic diagnosis had the best chance of being made, although inclusion only of patients who provided purulent sputum may cause an inherent selection bias (see "Discussion" below). Some of these patients were also included in a prior report on the etiology of CAP [3]. This research was approved by the Institutional Review Boards of Baylor College of Medicine and the Michael E. DeBakey VA Medical Center.

Diagnostic studies

Quantitative bacteriologic analysis was carried out in every case. An aliquot of sputum from patients who met inclusion criteria was drawn into 1 ml micropipetters using pipet tips with the ends cut to enlarge the aperture; detailed methods have been published previously [3]. Sputum was liquefied with 2% N-acetyl cysteine, and bacteria were quantified by making serial tenfold dilutions and streaking 10 µL aliquots on blood and chocolate agar. Recognized bacterial pathogens, if present at $\geq 10^5$ per ml, and commensal bacteria if present at $\geq 10^6$ per ml were identified by standard microbiologic techniques with verification by MALDI-TOF. All patients had nasopharyngeal swabs for PCR to identify respiratory viruses, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. Blood cultures, urine studies for pneumococcus and *Legionella* antigens, plasma procalcitonin, and B-natriuretic peptide were collected in > 95% of cases.

Table 1 Clinical presentations of patients with pneumonia

Characteristic	All patients (*n* = 122)	Bacterial infection (*n* = 77, 63%)	Bacterial/viral co-infection (*n* = 29, 24%)	Viral infection (*n* = 16, 13%)	*P* value
Mean age, years (SD)	69.3 (9.9)	69.9 (9.67)	68.4 (10.48)	67.4 (9.51)	0.56
Sex, *n* (%)					
Male	117 (95.9)	75 (97.4)	26 (90)	16 (100)	0.21
History of smoking, *n* (%)					
Smokers	76 (62.3)	54 (70.1)	15 (51.7)	8 (50)	0.12
Comorbidity, *n* (%)					
Alcohol use disorder	21 (17.2)	14 (18.2)	5 (17.2)	2 (12.5)	0.94
Lung disease	62 (50.8)	45 (58.4)	14 (48.3)	4 (25)	**0.05**
Immunosuppression	30 (24.6)	18 (23.4)	7 (24.1)	5 (31.3)	0.78
Heart disease	46 (37.7)	33 (42.9)	9 (31)	3 (18.8)	0.15
Mean Hgb A1C (SD)	6.29 (1.26)	6.43 (1.39)	6.09 (1.02)	6.01 (0.84)	0.3
Outcomes					
Respiratory failure, *n* (%)	9 (7.4)	6 (7.8)	4 (13.8)	3 (18.8)	0.29
ICU admission, *n* (%)	23 (18.9)	13 (16.9)	7 (24.1)	3 (18.8)	0.7
14-day mortality, *n* (%)	7 (5.7)	5 (6.5)	0 (0)	2 (12.5)	0.16
90-day mortality, *n* (%)	22 (18.0)	17 (22.1)	2 (6.9)	3 (18.8)	0.19
Subjective History					
Fever, *n* (%)	44 (36.1)	23 (29.9)	14 (48.3)	7 (43.8)	0.17
Cough, *n* (%)	79 (64.8)	45 (58.4)	22 (75.9)	12 (75)	0.18
Shortness of breath, *n* (%)	82 (67.2)	58 (75.3)	22 (75.9)	12 (75)	1
Sputum production, *n* (%)	42 (34.4)	23 (33.8)	12 (41.4)	7 (43.8)	0.38
URI symptoms, *n* (%)	17 (13.9)	5 (6.5)	7 (24.1)	5 (31.3)	**0.004**
Objective Findings					
Vital signs					
Mean temperature, °F (SD)	99.13 (1.35)	99.06 (1.24)	99.46 (1.67)	99.01 (1.15)	0.51
Mean respiratory rate, breaths/min (SD)	21.72 (12.3)	22.42 (14.97)	20.5 (3.84)	21.06 (4.12)	0.64
Mean heart rate, beats/min (SD)	98.63 (20.8)	99.04 (21.3)	98.5 (18.7)	97.13 (21.7)	0.99
Mean O2 saturation, % (SD)	92.2 (5.48)	92.01 (5.97)	90.41 (2.93)	90.8 (6.01)	0.32
Mean SBP, mmHg (SD)	126.4 (24.5)	121.73 (22.75)	134.17 (21.9)	134.06 (31.6)	**0.047**
Mean DBP, mmHg (SD)	74.6 (15)	72.18 (14.48)	79.66 (13.8)	76.75 (17)	0.09
Imaging findings					
Lobar consolidation, *n* (%)	71 (58.2)	47 (61)	16 (55.2)	8 (50)	0.64
Multifocal consolidation, *n* (%)	25 (20.5)	15 (19.5)	8 (27.6)	2 (12.5)	0.48
Pleural effusion, *n* (%)	20 (16.4)	12 (15.6)	2 (10.3)	5 (31.3)	0.11
Atelectasis, *n* (%)	28 (23)	14 (18.1)	8 (27.6)	7 (43.8)	0.07
Laboratory values					
Mean BNP, pg/mL (SD)	347.4 (546)	56.18 (379.3)	342 (830)	348 (523)	0.11
Mean lactate, mmol/L (SD)	2.01 (1.1)	0.28 (0.52)	1.08 (0.78)	2.2 (1.32)	0.95
Median WBC, cells/μL (SD)	12,420 (5,800)	11,470 (5,2450)	11,730 (6,100)	8,560 (3,540)	**0.005**
Mean procalcitonin, ng/mL (SD)	3.76 (14.9)	6.12 (22.3)	1.03 (1.52)	0.78 (0.94)	0.85
Mean PSI score (SD)	99.3 (34.7)	101.6 (30.2)	90.48 (27.55)	89.93 (34)	0.18
Troponin > 0.03 ng/ml, *n* (%)	41.(33.6)	25 (32.5)	11 (37.9)	5 (31.3)	0.85

P values refer to the null hypothesis that the distribution of each variable does not differ between etiological groups. For continuous variables (age, A1C, vital signs, and laboratory values) a Kruskal–Wallis test was used. For dichotomous variables, a Fisher's Exact test was used. Parentheses included represent the standard deviations of mean values. For values presented as whole numbers, parentheses represent the proportion of each respective group

Abbreviations: *BNP* B-type natriuretic peptide, *DBP* Diastolic blood pressure, *Hgb A1c* Hemoglobin A1C, *PSI* Pneumonia Severity Index, *SBP* Systolic blood pressure, *SD* Standard deviation, *WBC* White blood cell

Chart review

Thorough review of each patient's admitting electronic medical record including all notes by nurses, emergency room doctors, medical students, residents and attendings was performed, and data were recorded for age, sex, race, ethnicity, smoking and alcohol use, other comorbidities such as chronic obstructive pulmonary disease (COPD), heart disease, immunodeficiency (induced by immunosuppressive drugs, hematologic malignancy, or chronic immunodeficiency such as AIDS), and date of death. Clinical symptoms reported at the time of admission, vital signs, and radiographic findings were also recorded. Symptoms such as sore throat, rhinorrhea, sneezing, or sinus pressure were collectively listed as upper respiratory infection (URI) symptoms. The pneumonia severity index (PSI) [24] was calculated for each patient.

Determining etiology

Patients whose sputum contained $\geq 10^5$ colony-forming units (cfu)/mL of a recognized bacterial pathogen (such as *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Klebsiella pneumoninae*) or $\geq 10^6$ cfu/mL of commensal bacteria (such as *Streptococcus mitis* or *Corynebacteria* spp) were categorized as having bacterial infection. Note that criteria for inclusion was more stringent for commensal bacteria requiring microscopic examination of Gram-stained sputum, completed before culture results were available, which would confirm the presence of quantitative bacteriology [3, 25]. Cases in which PCR of a nasopharyngeal swab revealed a respiratory virus were diagnosed with viral infection. Patients who met criteria for bacterial infection and also had a positive viral PCR were regarded as having bacterial/viral coinfection. These criteria were used to stratify pneumonia into 5 etiologic groups: pneumonia due to (1) a recognized bacterial pathogen; (2) a respiratory virus; (3) coinfection by a recognized bacterial pathogen and a respiratory virus; (4) commensal bacteria; and (5) coinfection by commensal bacteria and a respiratory virus. In some analyses, data from Groups 1 and 4 are presented as bacterial infection, Group 2 as viral infection and Groups 3 and 5 as bacterial/viral coinfection. The etiologies agents discovered are summarized in Table 2.

Statistics

Fisher's Exact and Kruskal–Wallis tests were performed for categorical and continuous variables, respectively, and are displayed in Table 1. Median serum procalcitonin values for each etiologic group were compared using analysis of variance and Tukey tests of significance. Fisher's Exact and Kruskal–Wallis tests compared data in patients with recognized bacterial pathogens and commensal flora, and in some comparisons, results from these two groups were combined and are presented as 'bacterial pneumonia.'

Results

Patients

The mean age was 69, and 117 (95.9%) of the patients were male. Based on self-identification in the medical records, 73 (59.9%) patients were white, 41 (33.6%) were Black, and 8 (6.6%) patients did not have a race documented; 10 (8.2%) patients were of Hispanic ethnicity. Patients in this study had not received antibiotics before hospital admission. The median time to antibiotic administration before a high-quality sputum sample was provided was 0 h (range 0–12). Eighty (65.6%) patients had received no antibiotics, and an additional 9.0% had received antibiotics for < 2 h prior to sputum collection.

Diagnostic categories

Overall, 122 patients were studied. Seventy-seven (63.1%) had bacterial infection, of whom 56 were infected with recognized bacterial pathogens and 21 with commensal bacteria. Sixteen (13.1%) had viral infection, and 29 (23.8%) had bacterial and viral coinfection. There were no significant differences in age, race, or ethnicity among these etiologic groups.

Past medical history, exposures

Patients with bacterial infection tended to be more likely to have a smoking history than patients with viral infection or bacterial/viral coinfection (70.1% vs 50.0%, and 51.7%, respectively, $p = 0.12$). Patients with bacterial infection and bacterial/viral coinfection were significantly more likely to have underlying lung disease than patients with viral infection (58.4% and 48.3%, vs. 25.0%, respectively, ($p = 0.05$). No differences were observed among groups with regards to alcohol use disorder, immunosuppression, or mean hemoglobin A1c values. Although there appeared to be a trend toward a difference in the proportion of patients who self-reported recent exposure to sick contacts amongst the three groups (bacterial infection 8%, viral infection 19%, bacterial/viral coinfection 18%) the difference did not achieve statistical signifance ($p = 0.18$).

Symptoms and subjective findings

Patients with bacterial infection were less likely to report URI symptoms than patients with viral or bacterial/viral coinfection (6.5%, 31.3% and 24.1%, respectively, $p = 0.004$). Patients with bacterial infection tended to be less likely than those with viral or bacterial/viral coinfection to report subjective fever (29.9% vs 43.8.% or 48.3%) and cough (58.4% vs 75.0% or 75.9%, respectively

Table 2 Etiologic agents of pneumonia in 122 patients[ab]

Bacteria	
Recognized bacterial pathogens	
Streptococcus pneumoniae	24
Haemophilus influenzae	31
Staphylococcus aureus	11
Moraxella catarrhalis	8
Klebsiella sp.	1
Pseudomonas aeruginosa	5
Other	2
Commensal bacteria	
Streptococcus mitis/oralis, or mixed	
viridans including *S. mitis*	30
Corynebacteria	8
Other	20
Viruses	
Rhinovirus	13
Influenza	15
Parainfluenza	2
Human metapneumovirus	5
Respiratory syncytial	5
Adenovirus	1
Bacterial/viral coinfection	
Influenza + recognized bacteria	6
Influenza + commensals	4
Other viruses + recognized bacteria	8
Other viruses + commensals	9
Chlamydophila	0
Mycoplasma	0
Fungi	0

[a] Total number of identified organisms exceeds total number of cases because > 1 organism was identified in many cases

[b] When commensal organisms were identified together bacterial pathogens, we followed convention by not mentioning them, even though their presence in large numbers by Gram stain and quantitative bacteriology suggests that they contributed to the pneumonia

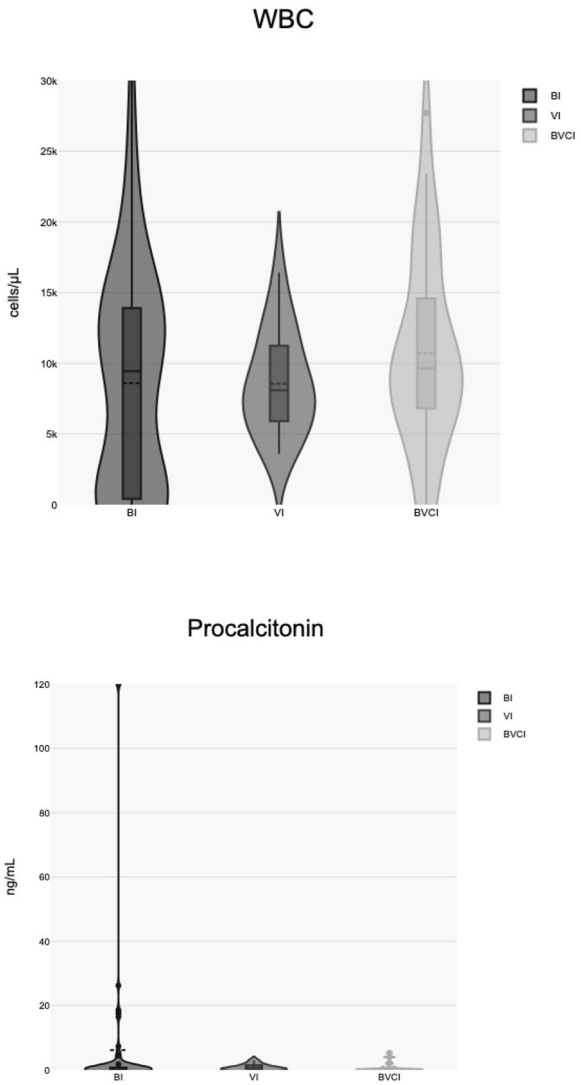

Fig. 1 **A** Forrest plot showing white blood cell counts for each group. **B** Forrest plot showing procalcitonin for each group

(differences not significant, p > 0.05). Lung disease was significantly less frequent and heart disease tended to be less frequent in patients with viral pneumonia. No differences were observed in the proportions of patients reporting shortness of breath (75.3%, 75%, 75.9%, $p = 1.0$) or sputum production (33.8%, 43.8%, 41.4, $p = 0.38$) for the three groups, respectively.

Objective findings

No significant differences among the three groups were observed in mean body temperature, heart rate, respiratory rate, O2 saturation, or diastolic blood pressure at the time of admission, although patients with bacterial pneumonia had a lower mean systolic blood pressure (122 mmHg) than those with viral infection (134 mmHg) or bacterial/viral coinfection (134 mmHg, $p = 0.047$). Somewhat surprisingly, patients in these three groups did not differ in their imaging findings, as rates of lobar consolidation, multifocal consolidation, new pleural effusion, and atelectasis were similar. Fifty percent of patients with viral pneumonia had lobar consolidation on chest radiography, and 19.5% of patients with bacterial infection alone had multifocal areas of consolidation. Patients with bacterial infection or bacterial/viral coinfection had significantly higher peripheral blood WBC counts on admission (12,990 WBC/mm^3, and 12,200 cells/mm^3) compared to patients with viral infection (8,560 cells/mm^3) ($p < 0.005$). Median WBC counts in all sputum samples were 1.2×10^7/ml (range 4.5×10^5 to 1.6×10^8), 1.8×10^7 in bacterial and 3.8×10^6 in viral pneumonia.

Median procalcitonin at admission was 0.25, 0.27, and 0.37 ng/mL for patients in these three groups, respectively ($p=0.85$) (Fig. 1). The proportions of patients whose serum troponin at admission exceeded 0.03 ng/mL were also similar, ranging from 31.3% to 37.9%, $p=0.85$). Pneumonia severity index scores were highest for patients with bacterial pneumonia (101.6, 89.9 and 90.5 for the three groups of patients, respectively), but the differences were not significant ($p=0.18$). No significant differences were noted between patients who had pneumonia due to recognized bacterial pathogens when compared to those with pneumonia due to commensal flora.

Combinations of factors

A previous study from our medical center [1] suggested that a bacterial etiology was likely in patients with pneumonia if ≥ 2 of the following findings were present: negative viral PCR panel, no sick contact, WBC > 11,000 cells/ mm^3, and procalcitonin > 0.25 ng/mL. Each patient was scored according to these criteria, and the test was found to be 88.8% sensitive (95% CI: 81.4–93.5) but only 45.5% specific (95% CI: 21.3–72.0) for correctly identifying patients with either bacerial infection or bacterial/viral coinfection, as opposed to patients with viral infection alone. Using the bacterial prevalence of 0.87 in our sample, the negative predictive value of this test was 0.38.

Outcomes

No significant differences in rates of respiratory failure requiring intubation were seen among groups, but a significantly greater proportion of patients with bacterial/viral coinfection (30%) were admitted or transferred to the ICU during their hospital course, compared to 17% and 19% of patients with bacterial or viral infection, respectively ($p<0.05$). There were no differences among the groups in mortality at 14 or 90 days after admission.

Discussion

In this study, we sought to determine whether clinical, laboratory and imaging features of patients who are hospitalized for CAP and test positive for a respiratory virus are sufficiently distinct to safely avoid empiric antibiotic therapy at admission. Our study differs from previous ones: (1) we only included patients who provided a high-quality purulent sputum, defined as showing ≥ 25WBC/epithelial cell on microscopic examination, at or shortly after admission; (2) quantitative bacteriologic testing was done on all sputum samples; and (3) patients with pneumonia due to recognized bacterial pathogens or due to commensal bacteria were included. Admittedly, reliance on a valid sputum sample introduces a selection bias, but there is no other way to establish the diagnosis in most cases, and, with this methodology, we were able to achieve an etiologic diagnosis in every case and could, with high likelihood, establish or exclude a bacterial infection.

Our results show that, in patients hospitalized for pneumonia, the clinical presentation, laboratory and radiologic findings do not differ sufficiently among those whose PCR is positive for a respiratory virus to determine whether a bacterial coinfection is present. An exception might be the absence of bacteria on microscopic examination of a high-quality sputum sample from a patient who has not received an antibiotic. Otherwise, there were no differences that would support a decision to withhold antibiotic treatment in patients admitted for CAP who have a positive viral PCR. These findings are consistent with current ATS/IDSA guidelines that recommend antibiotic therapy in all patients who are sick enough to be hospitalized for CAP even if they test positive for the presence of a respiratory virus [6]. Patients with bacterial pneumonia were more likely to have been smokers and to have chronic pulmonary disease. Upper respiratory symptoms were more common in patients with viral pneumonia, and peripheral blood WBC counts were higher in patients with bacterial pneumonia, but there was substantial overlap. Patients with viral pneumonia may have been more likely to be immunocompromised, as has been reported previously [15]. The similarity in radiologic findings, with the finding of consolidation in viral pneumonia, is especially worth noting, since it is at odds with earlier reports [26, 27] and general opinion that viral pneumonias are 'patchy' whereas bacterial pneumonias are consolidative.

A unique feature of this study is the inclusion of patients who were infected with commensal bacteria, a finding that was made possible by selection only of patients who provided high-quality sputum, the use of quantitative bacteriology and MALDI-TOF idenfication of all organisms. This is also the first study to compare clinical features of pneumonia due to recognized bacterial pathogens and commensal bacteria; interestingly, no differences were observed.

Interestingly, although this study was confined to patients whose sputum contained large numbers of WBCs and was, in many instances, frankly purulent, 13% of our patients had only viral infection, emphasizing that patients with purely viral pneumonia clearly may produce purulent sputum. Because previous studies did not have adequate sputum samples on all their patients and certainly did not include quantitative bacteriology to identify commensal bacteria, they may have diagnosed

viral pneumonia when bacterial coinfection was actually present.

Existing literature regarding the utility of peripheral WBC counts in differentiating bacterial from viral pneumonia presents inconsistent results. Some studies, including our own [1], found higher median peripheral WBC counts in bacterial than in viral infection as was shown again in the present study, while others have found no significant difference [28]. A very high serum procalcitonin level was observed in 3 patients with bacterial infection but there was great variability in results, and procalcitonin was normal in 29.3% patients with bacterial infection, indicating that a decision to treat with, or to withhold antibiotics can not be based on this test [19, 21].

The primary objective of the present study was to determine, in patients with CAP and a documented respiratory virus by PCR, the possibility of excluding a bacterial etiology in order to avoid prescribing empiric antibiotic therapy. Current guidelines recommend empiric antibiotics for patients who are hospitalized with CAP. However, debate persists regarding the appropriateness of antibiotics in patients with a positive viral PCR test and negative or inconclusive bacterial microbiological testing. A receiver-operator curve suggested that a patient with a positive viral PCR, known sick contact, normal WBC, and normal procalcitonin might not have bacterial infection and, therefore, might not require immediate antibiotics. However, the negative predictive value of this tool was only 0.38 and therefore could not be used to justify withholding antibiotics. Thus, our study further supports consensus guidelines for initiating empiric antibiotic therapy in all patients who are deemed sufficiently ill to require hospitalization for CAP even if a respiratory virus is shown to be present.

This study has several limitations. The total number of patients is small and it was done at a single center, but this kind of intense study is unlikely to be done in large groups of patients, and a single center assures uniform quality of laboratory work. The population consisted largely of older men, many of whom had comorbidities, and all of whom were hospitalized. Patients were only included if they provided high-quality purulent sputum. Although this requirement introduces an important inclusion bias, it was felt to be necessary because, without a high-quality sputum specimen, the diagnosis of bacterial pneumonia can not be established or excluded in about one-half of cases. The standard teaching that viral infection does not cause purulent sputum was not supported by our results. Finally, the number of patients with a pure viral pneumonia was too small to allow for meaningful comparisons in some categories, potentially limiting the generalizability of our results, although this degree of overlap in small numbers of cases probably means that a physician caring for an individual patient can not make therapeutic decisions based on any of the criteria studied.

In conclusion, the present study shows modest differences in clinical presentation of patients with bacterial and viral pneumonia or bacterial/viral coinfection, with substantial overlap in symptoms, laboratory, and imaging findings, precluding the ability to identify patients who may not require antibiotic therapy. If empiric antibiotics are to be withheld in patients hospitalized for CAP, further studies are needed to identify potential biomarkers or other clinical signs that can more clearly exclude a bacterial etiology.

Acknowledgements
None.

Authors' contributions
All laboratory work was done by DMM. All four authors participated in obtaining data from medical records, analyzing data, and writing and editing the manuscript, and all approved the final version that is being submitted.

Funding
None.

Data availability
Excel file spread sheets with anonymized data are available upon request to Daniel.musher@va.gov.

Declarations

Ethics approval and consent to participate
This protocol was approved by the Institutional Review Board, Baylor College of Medicine, protocol H-29468.

Consent for publication
None required.

Competing interests
The authors declare no competing interests.

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Received: 21 June 2024 Accepted: 16 October 2024
Published online: 05 January 2025

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