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Impact of angiotensin-converting enzyme inhibitors and statins on viral pneumonia

Christopher Henry, MD[a], Manaf Zaizafoun, MD[b], Eileen Stock, PhD[c], Shekhar Ghamande, MD[a], Alejandro C. Arroliga, MD[a], and Heath D. White, DO, MS[a]

[a]Division of Pulmonary, Critical Care, and Sleep Medicine, Baylor Scott & White Health, Temple, Texas; [b]Division of Pulmonary and Critical Care Medicine, University Hospitals, Ahuja Medical Center, Bedford, Ohio; [c]Perry Point/Baltimore Coordinating Center, Cooperative Studies Program, Office of Research and Development, US Department of Veterans Affairs, Perry Point, Maryland

ABSTRACT

Angiotensin-converting enzyme (ACE) inhibitors and statins may potentially benefit patients with viral infections and pneumonia. Our study aimed to evaluate the impact of ACE inhibitors and statins on the rates of intubation and death in viral pneumonia. We retrospectively studied 1055 adult patients admitted to a tertiary care center in central Texas with a positive respiratory viral polymerase chain reaction test. Of these, 539 had clinical presentation and imaging consistent with pneumonia. We collected information on demographic characteristics, microbiology, comorbid conditions, medication use, and outcomes. ACE inhibitors given prior to admission were associated with an increased risk of death or intubation (odds ratio [OR] = 3.02; 95% confidence interval [CI], 1.30–7.01), whereas statin use prior to admission did not change rates of death or intubation. Lower rates of death and intubation were noted with continued use of ACE inhibitors (OR =0.25; 95% CI, 0.09–0.64) and statins (OR =0.26; 95% CI, 0.08–0.81) throughout the hospital stay. We added further evidence of the beneficial effect of continued use of ACE inhibitors and statins in viral pneumonia.

KEYWORDS ACE inhibitors; statins; viral pneumonia

Respiratory viruses have been increasingly recognized as important pathogens causing community-acquired pneumonia, with an estimated prevalence in adults of 100 million cases worldwide per year.[1] Viral pneumonia represents up to 20% to 40% of all cases of community-acquired pneumonia that require hospitalization[2–5] and has been found to be a cause of nosocomial infection.[6,7] Despite being so common, viral pneumonia remains poorly characterized and underrecognized in clinical practice. HMG-CoA reductase inhibitors (statins), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) are medications commonly prescribed for chronic medical issues and have been associated with decreased mortality in patients with pneumonia. These are postulated to attenuate pulmonary and systemic inflammatory response by reducing cytokines.[8–10] Statins have the ability to inhibit influenza A virus replication in vitro,[11] decrease neutrophil influx, and alter the nitric oxide balance to promote hemodynamic stability.[12] ACE inhibitors and ARBs also have significant immunomodulatory effects[13] and protect against acute lung injury by blocking the classical ACE pathway.[14] This study evaluated the impact of statin, ACE inhibitor, and ARB use prior to and during hospitalization on outcomes in viral pneumonia.

METHODS

We performed a retrospective review of consecutive hospitalized patients with an acute respiratory illness and a positive respiratory viral polymerase chain reaction (PCR) test admitted at a tertiary care center in central Texas between January 2011 and February 2014. Inclusion criteria

Corresponding author: Christopher Henry, MD, Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, Scott & White Medical Center/Texas A&M University, 2401 S. 31st Street, Temple, TX 76508 (e-mail: chenryutmb@gmail.com)
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were a positive respiratory viral PCR, admission to hospital for >24 hours, and age >18 years.

A manual review of the electronic medical record was performed to obtain patient demographic characteristics, comorbidities, laboratory and culture results, initial triage location, intensive care unit (ICU) admission, use of mechanical or noninvasive positive pressure ventilation, hospital and ICU length of stay, 90-day hospital readmission, and hospital mortality. Data on the use of statins, ACE inhibitors, and ARBs prior to admission and during admission were collected. The medications were considered to be continued if they were given more than 50% of the days the patient was in the hospital.

Pneumonia was defined by the presence of a pulmonary infiltrate on chest radiograph as interpreted by a board-certified radiologist. Additionally, the diagnosis required a clinical history consistent with pneumonia, with two of the following features: fever, cough, purulent sputum production, dyspnea, and altered mental status.[15] Community-acquired pneumonia, hospital-acquired pneumonia, and health care–associated pneumonia were defined based on published guidelines at the time of data collection.[16] Patients who had clearly documented aspiration pneumonia and those who did not meet the above definition were excluded.

Means and frequencies were calculated for patient characteristics and clinical measures, collectively and by pneumonia group status (pneumonia-positive vs. pneumonia-negative/other). Bivariate analyses assessed underlying differences by group status. Chi-square analyses compared categorical characteristics across groups (with Fisher's exact test used for small expected cell counts). The nonparametric Wilcoxon rank-sum test assessed differences for continuous measures between patient groups. Multivariable logistic regression analysis was used to further assess the association between patient characteristics and pneumonia clinical outcomes. A type I error of $\alpha = 0.05$ was used for all tests. All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC). Research was approved by the local institutional review board and the need for consent was waived due to the retrospective nature of the study.

The primary outcome was a combined in-hospital mortality and intubation for the patients with viral pneumonia on ACE inhibitors, ARBs, or statins. Secondary outcomes that were assessed included hospital length of stay, intubation, ICU admission, hospital readmission, and use of noninvasive positive pressure ventilation.

RESULTS

There were 1055 patients with a positive respiratory viral PCR. Five hundred thirty-nine patients (51%) had radiographic and clinical signs of pneumonia. Demographic information and comorbid conditions for the pneumonia-positive and pneumonia-negative groups are listed in *Table 1*. Use of a statin, ACE inhibitor, or ARB prior to hospitalization or continued use during hospitalization did not affect the risk of being diagnosed with pneumonia.

Table 1. Cohort characteristics

Variable	Pneumonia positive ($N = 539$)	Pneumonia negative ($N = 516$)	*P* value
Age (years)	63.8 (±19.1)	60.5 (±18.0)	<0.01
Women	286 (53.1%)	319 (61.8%)	<0.01
Body mass index	29.3 (±9.9)	31.0 (±9.3)	<0.01
Smoker (ever)	289 (53.6%)	291 (56.4%)	0.36
Acute exacerbation of COPD	89 (16.5%)	113 (21.9%)	0.03
Acute decompensation of CHF	46 (8.5%)	51 (9.9%)	0.45
Diabetes mellitus	126 (23.4%)	151 (29.3%)	0.03
Chronic kidney disease	98 (18.2%)	77 (14.9%)	0.15
HIV infection	12 (2.2%)	6 (1.2%)	0.18
Cirrhosis	6 (1.1%)	6 (1.2%)	0.94
Hepatitis	14 (2.6%)	10 (1.9%)	0.47
Immunocompromised	59 (11.0%)	47 (9.1%)	0.32
Heart disease	201 (37.3%)	204 (39.5%)	0.45
COPD	138 (25.6%)	150 (29.1%)	0.21
Asthma	37 (6.9%)	94 (18.2%)	<0.01
Interstitial lung disease	13 (2.4%)	7 (1.4%)	0.21
Drug abuse	14 (2.6%)	19 (3.7%)	0.31
Alcoholic	17 (3.2%)	18 (3.5%)	0.76
Coinfection	103 (19.1%)	28 (5.4%)	<0.01
ACE prior to hospitalization	145 (26.9%)	144 (27.9%)	0.71
ACE continued in hospital	108 (20.0%)	122 (23.6%)	0.16
ARB prior to hospital	52 (9.7%)	53 (10.3%)	0.74
ARB continued in hospital	35 (6.5%)	45 (8.7%)	0.17
Statin prior to hospital	197 (36.6%)	199 (38.6%)	0.50
Statin continued in hospital	175 (32.5%)	188 (36.4%)	0.18

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

The types of viruses for the total population, the pneumonia-positive group, and the pneumonia-negative group are shown in *Figure 1*. Of patients with pneumonia, the most common viral pathogens recovered were rhinovirus/enterovirus (37.5%), influenza A (33%), and respiratory syncytial virus (10%). The rate of bacterial coinfection was 19.1% in the pneumonia-positive group, with *Staphylococcus aureus* (combined methicillin-resistant and methicillin-sensitive) being the most common (6.2%), followed by *Pseudomonas aeruginosa* (5.4%) and *Streptococcus pneumoniae* (4.5%). Sputum bacterial cultures in the pneumonia-

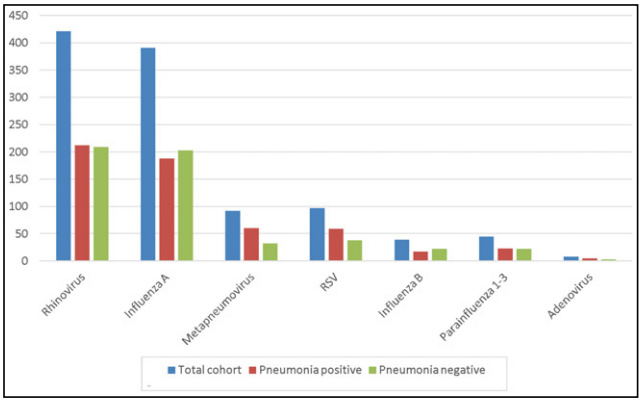

Figure 1. Distribution of viruses.

Table 2. Outcomes

Variable	Pneumonia positive ($N = 539$)	Pneumonia negative ($N = 516$)	P value
Median hospital length of stay (days)	6.0 (4–9 IQR)	4.0 (3–6 IQR)	<0.01
In-hospital death	43 (8.0%)	17 (3.3%)	<0.01
Noninvasive ventilation	69 (12.8%)	53 (10.3%)	0.20
Intubation	96 (17.8%)	19 (3.7%)	<0.01
ICU admission	101 (18.7%)	29 (5.6%)	<0.01
Median ICU length of stay (days)	5.0 (3–12 IQR)	3.0 (1–5 IQR)	<0.01
Readmission rate	128 (23.8%)	114 (22.1%)	0.52
In-hospital death and/or intubation	112 (20.8%)	33 (6.4%)	<0.01

ICU indicates intensive care unit; IQR, interquartile range.

positive group were negative in 42.1% of the patients, and no culture was performed in 39.2%. Outcomes for patients with pneumonia versus those without pneumonia are listed in *Table 2*.

In the patients with viral pneumonia, the risk of death increased with use of ACE inhibitors prior to admission (odds ratio [OR] = 3.02; 95% confidence interval [CI], 1.30–7.01; $P = 0.01$), though continued use of ACE inhibitors or continued use of statins was associated with decreased mortality and/or intubation (ACE inhibitors: OR = 0.25; 95% CI, 0.09–0.64; $P < 0.01$; statins: OR = 0.26; 95% CI, 0.08–0.81; $P = 0.02$).

Hospital length of stay for patients with pneumonia increased with use of statins on admission (OR = 2.18; 95% CI, 1.61–2.95; $P < 0.01$). Length of stay in the hospital was lower for patients with continued use of ACE inhibitors during hospital stay (OR = 0.70; 95% CI, 0.53–0.91; $P < 0.01$). *Table 3* lists other results from the multivariate regression analysis, several of which were statistically significant but beyond the scope of this article.

DISCUSSION

In our cohort of patients hospitalized with acute respiratory illness who tested positive for respiratory virus by PCR, over half developed pneumonia; among those with pneumonia, continued use of statins and continued use of ACE inhibitors correlated with a decreased risk of mortality or intubation.

The major goal of our study was to assess the effect of ACE inhibitors, ARBs, and statins in patients with viral pneumonia. Mortensen et al found a significant decrease in mortality, length of stay, and mechanical ventilation in patients taking statins, ACE inhibitors, or ARBs who were hospitalized with pneumonia compared to a matched cohort.[17] A meta-analysis by Chopra et al noted a decrease in pneumonia-related mortality for those taking statins.[9] Similarly, we found a decrease in intubation or mortality in patients with continued use of ACE inhibitors or statins during their hospital admission for viral pneumonia, though not for continued ARB use. Furthermore, those who were on ACE inhibitors prior to admission and subsequently discontinued the medication had a higher mortality than those not on an ACE inhibitor prior to admission. We speculate that the ACE inhibitors were discontinued in patients with shock or acute renal failure, thus representing more severe viral pneumonia than those in whom it was continued throughout their hospital stay. Alternatively, this difference could be due to the attenuating effects of ACE inhibitors on the innate immune system through deactivation of the classical ACE pathway.[14] In the aforementioned study by Mortensen et al, patients were included only if the medication was started as an outpatient, with a sufficient supply to last through the hospitalization, and was subsequently administered within the first 48 hours of admission.[8] A similar effect was not seen for ARBs, though a trend was noted that did not reach statistical significance. This could be due to the relatively small sample of patients on an ARB in our study.

Similar to previous studies, rhinovirus/enterovirus and influenza A made up the majority of the infections, both with and without pneumonia.[2,4,18,19] Our viral findings are in concordance with the meta-analysis by Burk et al.[18] Our study also included the 2013–2014 H1N1 influenza virus, which may explain the severity of illness seen as well as the worse outcomes with younger patients. This particular influenza season was noted to have a high mortality rate in adults <65 years.[20,21] Bacterial coinfection was seen in one-fifth of the patients, much higher than the 3% reported by Jain et al.[4] Not surprisingly, those with bacterial coinfection had a threefold higher risk of death or intubation compared to those without a bacterial coinfection. Viral infection has a synergistic effect on bacterial infection, allowing for a more severe infection.[1,3,22,23] *Staphylococcus aureus* and *Streptococcus pneumoniae* were the most common bacterial pathogens, thought to be due to the high number of H1N1 influenza infections.[24]

Table 3. Multivariate analysis

	Risk of pneumonia		In-hospital death and/or intubation		Hospital length of stay	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (decade effect)	1.12 (1.04–1.22)	<0.01	0.82 (0.72–0.94)	<0.01	0.94 (0.91–0.97)	<0.01
Women	0.77 (0.59–1.00)	<0.05	0.98 (0.62–1.56)	0.94	1.06 (0.94–1.20)	0.31
ACE prior to hospital	1.34 (0.74–2.44)	0.33	3.02 (1.30–7.01)	0.01	1.22 (0.96–1.56)	0.10
ACE continued in hospital	0.64 (0.34–1.19)	0.16	0.25 (0.09–0.64)	<0.01	0.70 (0.53–0.91)	0.01
ARB prior to hospital	1.65 (0.63–4.29)	0.30	1.12 (0.30–4.10)	0.87	0.97 (0.68–1.39)	0.88
ARB continued in hospital	0.48 (0.17–1.37)	0.17	0.75 (0.16–3.44)	0.71	0.80 (0.53–1.21)	0.30
Statin prior to hospital	1.15 (0.5–2.67)	0.74	2.66 (0.90–7.81)	0.08	2.18 (1.61–2.95)	<0.01
Statin continued in hospital	0.78 (0.33–1.81)	0.56	0.26 (0.08–0.81)	0.02	0.39 (0.28–0.53)	<0.01
Smoker (ever)	1.04 (0.78–1.39)	0.81	0.83 (0.50–1.38)	0.47	0.84 (0.74–0.96)	0.01
Coinfection	4.25 (2.70–6.69)	<0.01	2.90 (1.75–4.82)	<0.01	1.29 (1.11–1.49)	<0.01
Chronic kidney disease	1.30 (0.90–1.89)	0.16	1.78 (0.96–3.31)	0.07	1.33 (1.13–1.56)	<0.01
Asthma	0.35 (0.23–0.54)	<0.01	0.56 (0.20–1.56)	0.27	0.78 (0.61–0.99)	0.04

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; OR, odds ratio.

Several studies have evaluated the risk of developing pneumonia when on ACE inhibitors or ARBs, with mixed results. ACE inhibitor use in stroke patients has been found to decrease the risk of pneumonia in several studies from Asia.[25] These results have not been consistently replicated in other populations.[26–28] A meta-analysis by Caldeira et al reported a significant decrease in the risk of developing pneumonia and decrease in mortality among those taking ACE inhibitors or ARBs.[29] We found no difference in rates of use of these medications prior to hospitalization between those with a viral infection who developed pneumonia and those who did not develop pneumonia.

Our study has several limitations. First, as with all retrospective observational studies, our study can only present associations and not causality pertaining to improved outcomes with continued use of ACE inhibitors and statins. Secondly, this study only represents the experience of a single center. Thirdly, nearly 20% of patients had a bacterial coinfection by sputum culture. It is possible that we could have underestimated the true bacterial burden because this depended on adequate and timely sputum sampling prior to antibiotic administration. Previous studies have revealed that cultures are negative in up to 68% of bacterial pneumonia[4] and that coinfection is present in up to 10% of patients with viral pneumonia.[18] Fourthly, being a pragmatic study, this study did not account for the code status of the patients, which could have affected the primary outcome. The number of viral PCRs obtained via bronchoalveolar lavage was not available. There is an increased rate of positive viral PCR results in studies where lower respiratory tract samples were obtained.[2,30]

Our study supports the continued use of statins and ACE inhibitors in patients admitted with viral pneumonia and encourages further prospective studies on the beneficial effects of ACE inhibitors and statins in pneumonia.

ORCID

Christopher Henry http://orcid.org/0000-0002-1130-4267
Shekhar Ghamande http://orcid.org/0000-0001-6924-9494
Alejandro C. Arroliga http://orcid.org/0000-0002-7245-2159
Heath D. White http://orcid.org/0000-0003-1065-3681

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