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Impact of bacterial and viral coinfection in community-acquired pneumonia in adults

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ABSTRACT

Bacterial and viral coinfected community-acquired pneumonia (CAP) is poorly characterized in adults. The aim of this study was to investigate the influence of bacterial and viral coinfection in patients with CAP. A total of 235 adults who requested molecular tests of pneumonia and were diagnosed with CAP were enrolled in this study. Microbiological tests included blood and sputum cultures, PCR for bacterial and viral pathogens, antigen test for *Streptococcus pneumoniae* and the influenza virus, and antibody detection of *Mycoplasma pneumonia*. Of the 235 patients, 32 (13.6%) patients were coinfected with bacteria and virus. Among 64 severe CAP patients, the concurrent infections were confirmed in 14 patients (21.9%). The proportion of severe pneumonia was significantly higher in patients with coinfection, and they showed a significantly higher mortality rate. In conclusion, bacterial and viral coinfection in CAP is not a rare occurrence in adults. Viral and bacterial coinfections have an adverse impact on the severity of the pneumonia, and increase morbidity and mortality in patients with CAP.

1. Introduction

Pneumonia is an acute infectious disease, which is still one of the most common causes of death in the world. In 2015, the World Health Organization (WHO) reported that lower respiratory infection caused 3.2 million deaths worldwide (World Health Organization (WHO), 2017). In particular, pneumonia mortality rates are substantially higher in children under five and adults over 75 years of age. Community-acquired pneumonia (CAP) is a type of pneumonia that develops in people with limited or no contact with the healthcare system. The incidence of CAP varies by age, country, and gender; however, the clinical impact of CAP is clear that patients with CAP often require hospitalization and CAP increases mortality (Welte et al., 2012; Wunderink and Waterer, 2014).

CAP can be caused by various pathogens, such as bacteria, viruses, fungus, or parasites, and most cases of CAP are caused by a single pathogen (Welte et al., 2012). Through development of diagnostic techniques, various pathogens can be effectively detected in clinical samples (Huijskens et al., 2013; Jennings et al., 2008), and the clinical characteristics of mixed infection in CAP have been described in several reports (Chiu et al., 2015; Cilloniz et al., 2011; Jennings et al., 2008). A possible correlation between mixed infection and the severity of diseases was reported. However, data on the clinical features of bacterial and viral coinfection, especially in adult patients with CAP are still limited. Therefore, we retrospectively investigated adult, hospitalized patients with CAP and analyzed the incidence, etiology, clinical features, and outcomes of bacterial and viral coinfection in these patients.

2. Materials and methods

2.1. Subjects

This study was a retrospective analysis of hospitalized patients with CAP who had been referred for molecular diagnosis of pneumonia using blood, sputum, or urine specimens in the Chung-Ang University Hospital from January 2015 to December 2015. This study was approved by the Institutional Review Board of the Chung-Ang University Hospital (C2016204 (1947)).

Samples were collected from 3304 patients for molecular diagnosis of pneumonia. These subjects were classified according to age, and the medical records of 633 patients (18 years or older) were reviewed. Patients suspected as healthcare-associated pneumonia (HCAP) or hospital-acquired pneumonia (HAP) were excluded from this study. The HCAP and HAP patients were classified according to the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines (ATS and IDSA, 2005).

We confirmed 235 patients as diagnosed with CAP. CAP was defined as pneumonia based on the British Thoracic Society (BTS) guidelines,

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including clinical symptoms and signs were consistent with an acute lower respiratory tract infection associated with new radiographic shadowing for which there was no other cause (Lim et al., 2009). In the patients included in this study, CAP was the primary reason for hospitalization, and it was managed as pneumonia. Subsequently, CURB-65 (Lim et al., 2003) and pneumonia severity index (PSI) (Fine et al., 1997) were calculated and recorded at the time of admission for all subjects. Additionally, severe pneumonia patients were classified according to the IDSA/ATS guidelines (Mandell et al., 2007).

For subjects enrolled in this study, the following data were collected: (1) basic patient information (age, sex, hospitalization period, and mortality rate), (2) past medical history with comorbid disease (any malignancy, congestive heart failure, cerebrovascular disease, renal disease, liver disease, chronic obstructive pulmonary disease (COPD), bronchiectasis, asthma, previous Mycobacteria infection history, and HIV (human immunodeficiency virus) infection history), (3) physical findings (body temperature, heart rate, blood pressure, respiratory rate, and mental status), and (4) laboratory findings (bacterial culture results for any specimens, bacterial and viral antigen test, molecular test results of bacterial and viral pathogens, antibody test for *M. pneumoniae*, HIV screening assay, arterial blood gas analysis (ABGA), complete blood cell count (CBC), blood nitrogen urea (BUN), sodium, glucose, C-reactive protein (CRP), chest radiographic findings, mechanical ventilation, immunocompromised status, and intensive care unit (ICU) admission). In addition, chest computed tomography and bronchoscopy findings were also collected when available.

2.2. Microbiological examination

At the time of hospitalization, blood, urine, sputum, and nasopharyngeal swab specimens were collected for the microbiological examination. Blood cultures were performed aerobically and anaerobically using the BacT/Alert 3D blood culture system (bioMérieux Inc., Marcy-l'Etoile, France). The Vitek 2 system (bioMérieux Inc.) was used for bacterial identification. Sputum samples were Gram-stained and examined. Following, they were accepted as suitable for quantitative culture when more than 25 leukocytes per 100× microscopic field were visible with few epithelial cells. Suitable sputum specimens were cultured on blood agar plates and MacConkey agar. The specimens of bronchoalveolar lavage fluid, cerebrospinal fluid, pleural puncture, and tracheobronchial aspirates were collected and cultured when available. For PCR detection of bacterial and viral pathogens, nasopharyngeal swab specimens were examined using the Seeplex PneumoBacter ACE Detection (PneumoBacter; Seegene, Seoul, South Korea) and Anyplex II RV16 Detection (RV16; Seegene) systems. A qualitative PCR assay, PneumoBacter, could detect six common lower respiratory tract infection pathogens: *Streptococcus pneumoniae*, *Haemophilus influenza*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, *Bordetella pertussis*, and *Mycoplasma pneumoniae*. With real-time PCR-based RV16, 16 common pathogens causing respiratory infection could be detected, including Adenovirus, Influenza A and B, Parainfluenza virus 1, 2, 3 and 4, Rhinovirus A/B/C, Respiratory syncytial virus (RSV) A and B, Bocavirus 1/2/3/4, Metapneumovirus, Coronavirus 229E, NL63, and OC43, and Enterovirus. Antibody test for *M. pneumonia* (*M. pneumoniae* ELISA Kit, Zeus Scientific, NJ, USA) was tested in paired serum samples, and a four-fold increment of serum IgG was considered as a causative pathogen. Additionally, HIV screening assay (ARCHITECT HIV Ag/Ab Combo, Abbott Laboratories, Wiesbaden, Germany), urinary *Streptococcus pneumoniae* antigen test (SD BIOLINE Strep A strip, Alere, MA, USA) and rapid influenza antigen test (SD BIOLINE Influenza Ag, Alere) were performed.

2.3. Statistical analysis

Data were entered into Microsoft Excel (Microsoft, WA, USA) and analyzed using SPSS v.19.0 (IBM Corp., NY, USA). Values were presented as median with interquartile ranges for continuous variables and counts with percentages for categorical variables. To compare the continuous variables, the Mann–Whitney U-test was used. The Fisher's exact test was performed to compare differences between categorical variables. A *P*-value of less than 0.05 was considered as a significant difference. Multivariate logistic regression analysis was employed to identify risk factors for bacterial and viral coinfection. To select the final model, we used stepwise backward selection with an entry probability of 0.05 and a removal probability of 0.1. Baseline characteristics, such as physical findings, laboratory findings, or previous medical histories, were included to analyze risk factors for dependent variable. In addition, similar statistical analysis was performed to identify independent variables associated with mortality.

3. Results

3.1. Study populations and distributions of pathogens

Of the 3304 patients referred for pneumonia molecular testing, the majority of them (80.8%, 2671/3304) were pediatric patients, and 633 adult patients (19.2%, 633/3304) were enrolled in our study. With reviewing medical records, CAP diagnosis could be established in 235 adult subjects (37.1%, 235/633). Among them, a total of 191 pathogens (121 bacterial pathogens and 70 viral pathogens) were confirmed and identified in 130 patients (55.3%, 130/235). The distribution of pathogens is summarized in Tables 1 and 2. The most commonly identified bacterial pathogens were *Streptococcus pneumoniae* (28.9%), *Haemophilus influenza* (25.6%), and *Chlamydophila pneumoniae* (17.4%). In addition, two or more bacterial pathogens were isolated from 23 patients, of which 11 were found to be coinfected with viral pathogens. In the virus, the most frequently confirmed viruses were rhinovirus (18.6%), influenza A virus (17.1%), and adenovirus (12.9%). Infection with multiple viruses was found in four patients, and all of them were coinfected with bacterial pathogens. The most frequently identified virus to cause bacterial and viral coinfection was RSV, resulting in concurrent infection in a total of six patients.

3.2. Clinical characteristics according to bacterial and viral coinfection

Table 3 shows the characteristics of patients with CAP. Of the 235 patients with CAP, 32 patients (13.6%) were diagnosed with viral and bacterial coinfection. When the basic patient information, past medical history with comorbid disease, and physical and laboratory findings were compared between those with and without bacterial and viral coinfection, significant differences were found for bronchiectasis ($P = 0.013$), previous nontuberculous Mycobacteria (NTM) infection ($P = 0.019$), body temperature ($P = 0.038$), percentage of neutrophils

Table 1
Pathogens identified in adults with community-acquired pneumonia.

Bacterial pathogens	Subjects		Viral pathogens	Subjects	
Streptococcus pneumoniae	35	(28.9%)	Rhinovirus A/B/C	13	(18.6%)
Haemophilus influenzae	31	(25.6%)	Influenza A	12	(17.1%)
Chlamydophila pneumoniae	21	(17.4%)	Adenovirus	9	(12.9%)
Staphylococcus aureus	11	(9.1%)	Enterovirus	8	(11.4%)
Mycoplasma pneumoniae	5	(4.1%)	Metapneumovirus	7	(10.0%)
Escherichia coli	4	(3.3%)	Respiratory Syncytial Virus A/B	6	(10.0%)
Klebsiella pneumoniae	4	(3.3%)	Parainfluenza 1/2/3/4	5	(7.1%)
Pseudomonas aeruginosa	3	(2.5%)	Bocavirus 1/2/3/4	4	(5.7%)
Coagulase negative *Staphylococcus*	2	(1.7%)	Influenza B	4	(5.7%)
Others[†]	5	(4.1%)	Coronavirus	1	(1.4%)
Total	121	(100%)	Total	70	(100%)

[†] *Enterobacter aerogenes, Enterobacter cloacae, Morganella morganii, Providencia rettgeri, Streptococcus oralis.*

Table 2
Mixed bacterial and viral coinfections (32 patients) in 235 adults with community-acquired pneumonia.

Pathogens	Subjects	Pathogens	Subjects
Respiratory syncytial virus A/B Plus:		Metapneumovirus Plus:	
Haemophilus influenzae	2	*Streptococcus pneumoniae*	1
Streptococcus pneumoniae	1	*Haemophilus influenzae*	1
Staphylococcus aureus	1	Multiple bacteria	1
Multiple bacteria	2	Influenza B Plus:	
Enterovirus Plus:		*Streptococcus pneumoniae*	1
Pseudomonas aeruginosa	2	Multiple bacteria	1
Chlamydophila pneumoniae	1	Parainfluenza 1/2/3/4 Plus:	
Multiple bacteria	2	*Chlamydophila pneumoniae*	1
Influenza A Plus:		*Streptococcus pneumoniae*	1
Klebsiella pneumoniae	1	Adenovirus Plus:	
Chlamydophila pneumoniae	1	Multiple bacteria	1
Streptococcus pneumoniae	1	Bocavirus Plus:	
Multiple bacteria	1	Multiple bacteria	1
Rhinovirus A/B/C Plus:		Multiple viruses Plus:	
Haemophilus influenzae	2	*Haemophilus influenzae*	2
Escherichia coli	1	Multiple bacteria	2
Streptococcus pneumoniae	1		

($P = 0.013$), absolute neutrophil count ($P = 0.034$), and CRP ($P = 0.030$). There were no differences in CURB-65 score and pneumonia severity index between subjects with or without coinfection. The proportion of patients who met the IDSA/ATS severe pneumonia criteria was significantly higher in patients with coinfection ($P = 0.032$). In addition, coinfected patients showed longer hospital stays and higher mortality rates; however, a significant difference was found only in mortality rate ($P = 0.038$).

3.3. Significant associations with coinfection of bacterial and viral pathogens, and mortality rate.

Table 4 shows the significant associations with concurrent infection in patients with CAP. Bronchiectasis and previous NTM infection were strong predisposing factors for coinfection, and any physical and laboratory findings were not associated with coinfection in this study. The likelihood of mortality increased with age, respiratory rate, WBC, CRP, IDSA/ATS severe pneumonia, and presence of bacterial and viral coinfection, and decreased with pulse rate and hemoglobin (Table 5).

4. Discussion

CAP plays a significant role as a cause of death in adults worldwide (World Health Organization (WHO), 2017). In Asia, CAP is estimated to cause approximately 1 million deaths per year (Peto et al., 2014). Many studies have been conducted to detect the etiology of adult CAP; however, most studies focused on pneumonia caused by bacterial or viral pathogens (Cilloniz et al., 2011; Peto et al., 2014), and concurrent infection of both pathogens has been poorly studied. Therefore, the clinical impact of bacterial and viral coinfection on adult CAP has not been fully investigated.

Our study is one of few studies to focus on the etiology of bacterial and viral concurrent infection and to confirm its clinical significance. Our findings indicated that more than half of adult patients with CAP (55.3%) had evidence of infection with one or more bacteria and/or viruses, and 32 patients with CAP (13.6%) could be classified with bacterial and viral coinfection. In another study of 304 adult patients with CAP, bacterial and viral coinfection was identified in 45 patients (14.8%) (Jennings et al., 2008). Among 64 severe CAP patients, the bacterial and viral coinfections were confirmed in 14 patients (21.9%) in our study, and this result was similar with previous reports that showed about 16.6–39% in severe CAP or critically ill patients (Karhu et al., 2014; Martin-Loeches et al., 2017; Voiriot et al., 2016). These findings suggested that at least one tenth of adult CAP patients and one fifth of severe CAP patients were suffering from bacterial and viral concurrent infection.

Similar to previous reports, rhinoviruses were the most frequently identified viral pathogens in adult patients with CAP (Huijskens et al., 2013; Lieberman et al., 2010; Templeton et al., 2005; Wiemken et al., 2013). In this study, the most commonly identified viral pathogen causing concurrent coinfection was RSV, which differs from a previous report (Jennings et al., 2008). We believe that this difference could be caused by many factors, such as different racial backgrounds and geographical factors. However, due to the limited number of coinfected patients available for analysis, we could not confirm how the patient's prognosis might change depending on the combination of causative viral and bacterial pathogens. This problem should be addressed through additional large cohort studies.

In the multivariate logistic regression analysis, we found that bronchiectasis and previous NTM infection were risk factors for bacterial and viral coinfection. We suspected that structural lung abnormalities would have an effect on the bacterial and viral coinfection; however, it remained unclear how these factors would affect the coinfection. In comparisons between the coinfected group and other groups, there were few differences in baseline characteristics. In physical findings, body temperature, neutrophil percentage and count, and CRP were higher in bacterial and viral coinfected patients with CAP. As for the clinical prognosis, there were no differences in distribution of CURB-65 and PSI. However, the proportion of IDSA/ATS severe pneumonia and mortality rate were higher in the bacterial and viral coinfected CAP group than in the group without coinfection. In addition, our data showed that the concurrent infection of bacterial and viral pathogens was identified as one of the significant risk factors independently associated with mortality. These findings were consistent with the results of previous reports (Cawcutt and Kalil, 2017; Martin-Loeches et al., 2017; Voiriot et al., 2016), and would suggest that the concurrent bacterial and viral infection would be directly associated with more severe symptoms and worse prognosis.

Our findings support that patients coinfected with bacteria and virus might show a worse clinical course. As such, mixed infection could be a poor prognostic factor of adult CAP. There are several possible reasons for such results. First, interactions between bacteria and viruses would underlie the pathogenesis of CAP. As well-known synergism exists between influenza and *S. pneumoniae* (Klein et al., 2016; McCullers, 2006), bacterial-viral interaction would be fatal to pneumonia patients and increase mortality dramatically. Various viral mechanisms, such as disruption of the epithelial barrier, upregulation of adhesion proteins, or dysfunction of the immune system, could facilitate the bacterial infection (Bosch et al., 2013; Morris et al., 2017), and we assume that these synergisms could play a role in worsening pneumonia. Second, most patients with CAP were treated with appropriate antimicrobial therapy; however, antiviral agents were very limited and treatment of

Table 3
Characteristics of two groups with or without bacterial and viral coinfection in community-acquired pneumonia.

	Total (n = 235)		Group with bacterial and viral coinfection (n = 32)		Group without bacterial and viral coinfection (n = 203)		*P*-value†
Age	72	(57–80)	77	(63–81)	70	(56–80)	0.203
Sex (male)	121	(51.5%)	15	(46.9%)	106	(52.2%)	0.704
Any comorbidity							
Malignancy	42	(17.9%)	4	(12.5%)	38	(18.7%)	0.467
Congestive heart failure	24	(10.2%)	3	(9.4%)	21	(10.3%)	1.000
Cerebrovascular disease	34	(14.5%)	5	(15.6%)	29	(14.3%)	1.000
Renal disease	44	(18.7%)	7	(21.9%)	37	(18.2%)	0.628
Liver disease	12	(5.1%)	1	(3.1%)	11	(5.4%)	1.000
COPD	31	(13.2%)	3	(9.4%)	28	(13.8%)	0.778
Bronchiectasis	12	(5.1%)	5	(15.6%)	7	(3.4%)	0.013
Asthma	16	(6.8%)	2	(6.3%)	14	(6.9%)	1.000
Previous mycobacteria infection history							
Previous tuberculosis history	16	(6.8%)	2	(6.3%)	14	(6.9%)	1.000
Previous nontuberculous Mycobacteria infection	5	(2.1%)	3	(9.4%)	2	(1.0%)	0.019
Physical findings							
Body temperature (°C)	37.8	(37.3–38.5)	38.3	(37.5–39.0)	37.8	(37.3–38.5)	0.038
Pulse rate (beats/min)	96	(90–98)	98	(92–99)	96	(90–98)	0.144
Systolic blood pressure (mm Hg)	120	(99–140)	120	(100–140)	120	(98–140)	0.739
Diastolic blood pressure (mm Hg)	80	(80–90)	80	(80–90)	82	(80–90)	0.356
Respiratory rate (breaths/min)	24	(20–28)	25	(22–31)	24	(20–28)	0.084
Altered mental status	9	(3.8%)	3	(9.4%)	6	(3.0%)	0.109
Laboratory findings							
pO_2 (mm Hg)	68.6	(58.7–83.1)	64.0	(57.5–81.6)	69.2	(59.0–83.3)	0.241
O_2 saturation (%)	93.7	(89.9–96.2)	93.2	(90.2–95.7)	93.9	(89.8–96.4)	0.391
pH	7.43	(7.40–7.46)	7.44	(7.39–7.48)	7.43	(7.40–7.46)	0.292
WBC (10^9/L)	9.61	(6.42–14.58)	11.42	(8.92–15.26)	9.32	(6.35–14.47)	0.077
Neutrophil (%)	78.5	(70.6–87.3)	84.5	(76.8–90.3)	77.1	(68.9–86.2)	0.013
Absolute neutrophil count(10^6/L)	7300	(4600–12,000)	9800	(6500–13,700)	7100	(4400–11,700)	0.034
RBC (10^{12}/L)	3.9	(3.5–4.3)	4.0	(3.5–4.3)	3.9	(3.5–4.4)	0.726
Hemoglobin (g/dL)	11.8	(10.4–13.2)	12.2	(10.0–13.1)	11.7	(10.4–13.3)	0.983
Hematocrit (%)	35.8	(32.1–39.8)	37.4	(31.8–40.0)	35.7	(32.1–39.6)	0.646
Platelet (10^9/L)	206	(149–276)	204	(163–289)	208	(149–275)	0.673
BUN (mg/dL)	18	(12–25)	19	(13–33)	17	(11–25)	0.169
Sodium (mmol/L)	136	(133–139)	136	(134–139)	136	(133–139)	0.718
Glucose (mg/dL)	128	(106–162)	137	(111–199)	127	(105–160)	0.213
CPR (mg/L)	90.0	(37.7–176.1)	118.6	(72.8–201.2)	85.1	(31.8–167.5)	0.030
Intubation	26	(11.1%)	4	(12.5%)	22	(10.8%)	0.763
Immunocompromised status	9	(3.8%)	0	(0%)	9	(4.4%)	0.614
HIV infection	0	(0.0%)	0	(0.0%)	0	(0.0%)	1.000
ICU admission	60	(25.5%)	11	(34.4%)	49	(24.1%)	0.274
CURB-65 score							
0–3	223	(94.9%)	29	(90.6%)	194	(95.6%)	0.227
4	9	(3.8%)	2	(6.3%)	7	(3.4%)	
5	3	(1.3%)	1	(3.1%)	2	(1.0%)	
Pneumonia severity index							
1–3	110	(46.8%)	14	(43.8%)	96	(47.3%)	0.726
4	78	(33.2%)	10	(31.3%)	68	(33.5%)	
5	47	(20.0%)	8	(25.0%)	39	(19.2%)	
IDSA/ATS severe pneumonia	64	(27.2%)	14	(43.8%)	50	(24.6%)	0.032
Length of hospital stay (days)	10	(7–20)	14	(6–24)	10	(7–20)	0.279
Mortality rate	20	(8.5%)	6	(18.8%)	14	(6.9%)	0.038

Data are shown as number (percent) or median (interquartile range).
†*P*-values were calculated using the Mann–Whitney *U* test or Fisher's exact test.
COPD, chronic obstructive pulmonary disease; WBC, white blood cell; RBC, red blood cell; BUN, blood urea nitrogen; CRP, C-reactive protein; HIV, human immunodeficiency virus; ICU, intensive care unit; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society.

adult pneumonia patients with confirmed causative viral pathogens required supportive care. These treatments could not prevent viral replication, and we suspected that it would be associated with worsened outcomes in adult patients with CAP. With the exception of bacterial

Table 4
Significant risk factors for bacterial and viral coinfection.

Variable	Adjusted ORs with 95% CI		*P*-value
Bronchiectasis	5.51	(1.60–18.93)	0.007
Previous nontuberculous mycobacteria infection	14.62	(1.89–113.03)	0.010

OR, odds ratio; CI, confidence interval.

Table 5
Multivariate logistic regression analysis of the adjusted risk factors associated with mortality.

Variable	Adjusted ORs with 95% CI		*P*-value
Age	1.11	(1.03–1.21)	0.008
Pulse rate	0.90	(0.83–0.98)	0.016
Respiratory rate	1.10	(1.03–1.17)	0.004
WBC	4.73	(1.54–14.52)	0.007
Hemoglobin	0.13	(0.02–0.70)	0.018
CRP	1.01	(1.00–1.02)	0.013
IDSA/ATS severe pneumonia	8.42	(1.04–68.02)	0.046
Bacterial and viral coinfection	6.82	(1.06–43.91)	0.043

OR, odds ratio; CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society.

coinfection in influenza (Chertow and Memoli, 2013; Morris et al., 2017), however, the role of antiviral agents in bacterial and viral coinfected patients with CAP has not yet been elucidated.

Although we attempted to minimize errors, several limitations exist in the study as follows: first, because of the nature of the retrospective study, we had to rely on chart review for the patients' information. We were limited in obtaining detailed patient information, such as socioeconomic factors, lifestyle, physical and psychiatric status, or previous hospitalization history. Second, although various tests were performed to identify pathogens causing CAP, there were limitations in discovering all causative pathogens. Additionally, there was a possibility that methodological issues could have made it difficult to detect every bacterial and viral coinfection. Third, medical records only tracked the disease histories of patients with CAP during hospital stays. We admit that some clinical outcomes could be misjudged in this study due to voluntary discharge, transfer to other hospitals, or euthanasia. Further large prospective research is needed to resolve the present limitations and confirm the results of this study.

In conclusion, we demonstrated that 13.6% of adult patients with CAP were coinfected with bacteria and virus. It was clear that concurrent coinfection was not uncommon. In fact, coinfection may adversely impact the severity of pneumonia and increase the effects of morbidity in adult patients with CAP. However, additional clinical studies should be conducted to gain better insight into the etiology and clinical role of bacterial and viral coinfections.

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References

ATS, IDSA. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171(4):388–416.

Bosch AA, Biesbroek G, Trzcinski K, Sanders EA, Bogaert D. Viral and bacterial interactions in the upper respiratory tract. PLoS Pathog 2013;9(1), e1003057.

Cawcutt K, Kalil AC. Pneumonia with bacterial and viral coinfection. Curr Opin Crit Care 2017;23(5):385–90.

Chertow DS, Memoli MJ. Bacterial coinfection in influenza: a grand rounds review. JAMA 2013;309(3):275–82.

Chiu CY, Chen CJ, Wong KS, Tsai MH, Chiu CH, Huang YC. Impact of bacterial and viral co-infection on mycoplasmal pneumonia in childhood community-acquired pneumonia. J Microbiol Immunol Infect 2015;48(1):51–6.

Cilloniz C, Ewig S, Polverino E, Marcos MA, Esquinas C, Gabarrus A, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. Thorax 2011;66(4):340–6.

Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336(4):243–50.

Huijskens EG, van Erkel AJ, Palmen FM, Buiting AG, Kluytmans JA, Rossen JW. Viral and bacterial aetiology of community-acquired pneumonia in adults. Influenza Other Respir Viruses 2013;7(4):567–73.

Jennings LC, Anderson TP, Beynon KA, Chua A, Laing RT, Werno AM, et al. Incidence and characteristics of viral community-acquired pneumonia in adults. Thorax 2008;63(1):42–8.

Karhu J, Ala-Kokko TI, Vuorinen T, Ohtonen P, Syrjala H. Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. Clin Infect Dis 2014;59(1):62–70.

Klein EY, Monteforte B, Gupta A, Jiang W, May L, Hsieh YH, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza Other Respir Viruses 2016;10(5):394–403.

Lieberman D, Shimoni A, Shemer-Avni Y, Keren-Naos A, Shtainberg R, Lieberman D. Respiratory viruses in adults with community-acquired pneumonia. Chest 2010;138(4):811–6.

Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009;64(Suppl. 3):iii1–55.

Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58(5):377–82.

Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(Suppl. 2):S27–72.

Martin-Loeches I, M JS, Vincent JL, Alvarez-Lerma F, Bos LD, Sole-Violan J, et al. Increased incidence of co-infection in critically ill patients with influenza. Intensive Care Med 2017;43(1):48–58.

McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev 2006;19(3):571–82.

Morris DE, Cleary DW, Clarke SC. Secondary bacterial infections associated with influenza pandemics. Front Microbiol 2017;8:1041.

Peto L, Nadjm B, Horby P, Ngan TT, van Doorn R, Van Kinh N, et al. The bacterial aetiology of adult community-acquired pneumonia in Asia: a systematic review. Trans R Soc Trop Med Hyg 2014;108(6):326–37.

Templeton KE, Scheltinga SA, van den Eeden WC, Graffelman AW, van den Broek PJ, Claas EC. Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. Clin Infect Dis 2005;41(3):345–51.

Voiriot G, Visseaux B, Cohen J, Nguyen LB, Neuville M, Morbieu C, et al. Viral-bacterial coinfection affects the presentation and alters the prognosis of severe community-acquired pneumonia. Crit Care 2016;20(1):375.

Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax 2012;67(1):71–9.

Wiemken T, Peyrani P, Bryant K, Kelley RR, Summersgill J, Arnold F, et al. Incidence of respiratory viruses in patients with community-acquired pneumonia admitted to the intensive care unit: results from the severe influenza pneumonia surveillance (SIPS) project. Eur J Clin Microbiol Infect Dis 2013;32(5):705–10.

World Health Organization (WHO). World Health Organization, The top 10 causes of death. [Available from: http://www.who.int/mediacentre/factsheets/fs310/en/, 2017.

Wunderink RG, Waterer GW. Community-acquired pneumonia. N Engl J Med 2014;370(19):1863.