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

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ABSTRACT

Bacterial and viral coinfection 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 pneumoniae. 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.

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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,
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 hos-
pitalization, 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 mor-
tality rate), (2) past medical history with comorbid disease (any mali-
gnancy, congestive heart failure, cerebrovascular disease, renal disease,
liver disease, chronic obstructive pulmonary disease (COPD), bronchiec-
tasis, 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
specimen, bacterial and viral antigen test, molecular test results of bac-
terial and viral pathogens, antibody test for M. pneumoniae, HIV screen-
ing 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, immuno-
compromised status, and intensive care unit (ICU) admission). In addi-
tion, chest computed tomography and bronchoscopy findings were also
collected when available.

2.2. Microbiological examination

At the time of hospitalization, blood, urine, sputum, and nasopha-
yngeal swab specimens were collected for the microbiological exami-
nation. 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 bac-
terial 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 bronchoalve-
lolar lavage fluid, cerebrospinal fluid, pleural puncture, and tracheobron-
chial aspirates were collected and cultured when available. For PCR
detection of bacterial and viral pathogens, nasopharyngeal swab speci-
mens were examined using the Seeplex PneumoBacter ACE Detection
(PneumoBacter; Seegene, Seoul, South Korea) and Anyplex II RV16 De-
tection (RV16; Seegene) systems. A qualitative PCR assay, PneumoBacter,
could detect six common lower respiratory tract infection pathogen:
Streptococcus pneumoniae, Haemophilus influenzae, Chlamydia pneumoniae, Legionella pneumophila, Bordetella pertussis,
and Mycoplasma pneumoniae. With real-time PCR-based RV16, 16 com-
mon pathogens causing respiratory infection could be detected, includ-
ing 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 En-
terovirus. Antibody test for M. pneumoniae (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 patho-
gen. 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 phys-
ical 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 as-
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 patho-
gens is summarized in Tables 1 and 2. The most commonly identified
bacterial pathogens were Streptococcus pneumoniae (28.9%), Haemophi-
lus influenza (25.6%), and Chlamydia pneumoniae (17.4%). In addi-
tion, two or more bacterial pathogens were isolated from 21 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 multi-
ple viruses was found in four patients, and all of them were coinfeated
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 bac-
terial 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 co-
infecion, 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%) |
| Chlamydia 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 | 6 (10.0%) |
| Virus A/B | | | |
| 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 | 2 (1.7%) | Influenza B | 4 (5.7%) |
| Staphylococcus | | | |
| Others† | 5 (4.1%) | Coronaviruses | 1 (1.4%) |
| Total | 121 (100%) | Total | 70 (100%) |

† Enterobacter aerogenes, Enterobacter cloacae, Morganella morgani, Providencia rettgeri, Streptococcus oralis.
3.3. Significant associations with coinfection of bacterial and viral pathogens, and mortality rate.

Table 2 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 (Huiskens 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.

| Variable                                | Group with bacterial and viral coinfection (n = 32) | Group without bacterial and viral coinfection (n = 203) | P-value† |
|-----------------------------------------|---------------------------------------------------|---------------------------------------------------------|----------|
| Age                                     | 77 (57–80)                                        | 70 (56–80)                                              | 0.203    |
| Sex (male)                              | 15 (46.9%)                                        | 106 (52.2%)                                             | 0.704    |
| Any comorbidity                         |                                                   |                                                         |          |
| Malignancy                              | 4 (12.5%)                                         | 38 (18.7%)                                              | 0.467    |
| Congestive heart failure                | 3 (9.4%)                                          | 21 (10.3%)                                              | 1.000    |
| Cerebrovascular disease                 | 5 (15.6%)                                         | 29 (14.3%)                                              | 1.000    |
| Renal disease                           | 7 (21.9%)                                         | 37 (18.2%)                                              | 0.628    |
| Liver disease                           | 1 (3.1%)                                          | 11 (5.4%)                                               | 1.000    |
| COPD                                    | 3 (9.4%)                                          | 26 (13.8%)                                              | 0.778    |
| Bronchiectasis                          | 5 (15.6%)                                         | 7 (3.4%)                                                | 0.013    |
| Asthma                                  | 2 (6.3%)                                          | 14 (6.9%)                                               | 1.000    |
| Previous mycobacteria infection history | 16 (6.8%)                                         | 14 (6.9%)                                               | 1.000    |
| Previous tuberculosis history           | 5 (2.1%)                                          | 2 (1.0%)                                                | 0.019    |
| Physical findings                       |                                                   |                                                         |          |
| Body temperature (˚C)                   | 37.8 (37.3–38.5)                                  | 37.8 (37.3–38.5)                                        | 0.038    |
| Pulse rate (beats/min)                  | 96 (90–98)                                        | 96 (90–98)                                              | 0.144    |
| Systolic blood pressure (mm Hg)         | 120 (99–140)                                      | 120 (98–140)                                            | 0.759    |
| Diastolic blood pressure (mm Hg)        | 80 (80–90)                                        | 82 (80–90)                                              | 0.356    |
| Respiratory rate (breaths/min)          | 24 (20–28)                                        | 24 (20–28)                                              | 0.084    |
| Altered mental status                   | 9 (3.8%)                                          | 6 (3.0%)                                                | 0.109    |
| Laboratory findings                     |                                                   |                                                         |          |
| pO2 (mm Hg)                             | 68.6 (58.7–83.1)                                  | 69.2 (59.0–83.3)                                        | 0.241    |
| O2 saturation (%)                       | 93.7 (89.9–96.2)                                  | 93.9 (89.6–94.4)                                        | 0.391    |
| pH                                      | 7.43 (7.40–7.46)                                  | 7.43 (7.40–7.46)                                        | 0.292    |
| WBC (10³/L)                             | 9.61 (6.42–14.58)                                 | 9.32 (6.35–14.47)                                       | 0.077    |
| Neutrophil (%)                          | 78.5 (70.6–87.3)                                  | 77.1 (68.9–86.2)                                        | 0.013    |
| Absolute neutrophil count (10³/L)       | 7300 (6000–12,000)                                | 7100 (4400–11,700)                                      | 0.034    |
| RBC (10¹²/L)                            | 3.9 (3.5–4.3)                                     | 4.0 (3.5–4.3)                                           | 0.726    |
| Hemoglobin (g/dL)                       | 11.8 (10.4–13.2)                                  | 11.7 (10.4–13.3)                                        | 0.983    |
| Hematocrit (%)                          | 35.8 (32.1–39.8)                                  | 35.7 (32.1–39.6)                                        | 0.646    |
| Platelet (10³/L)                        | 206 (149–276)                                     | 208 (149–275)                                           | 0.673    |
| BUN (mg/dL)                             | 18 (12–25)                                        | 17 (11–25)                                              | 0.169    |
| Sodium (mmol/L)                         | 136 (133–139)                                     | 136 (133–139)                                           | 0.718    |
| Glucose (mg/dL)                         | 128 (106–162)                                     | 127 (105–160)                                           | 0.213    |
| CPR (mg/L)                              | 90.0 (37.7–176.1)                                 | 85.1 (31.8–167.5)                                       | 0.030    |
| Intubation                              | 26 (11.1%)                                        | 22 (10.8%)                                              | 0.763    |
| Immunocompromised status                | 0 (3.8%)                                          | 9 (4.4%)                                                | 0.614    |
| HIV infection                           | 0 (0.0%)                                          | 0 (0.0%)                                                | 1.000    |
| ICU admission                           | 60 (25.5%)                                        | 49 (24.1%)                                              | 0.274    |
| CURB-65 score                           | 223 (94.9%)                                       | 194 (95.6%)                                             | 0.227    |
| 0–3                                     | 29 (90.6%)                                        |                                                         |          |
| 4                                       | 2 (6.3%)                                          | 7 (3.4%)                                                |          |
| 5                                       | 1 (3.1%)                                          | 2 (1.0%)                                                |          |
| Pneumonia severity index                |                                                   |                                                         |          |
| 1–3                                     | 110 (46.8%)                                       | 96 (47.3%)                                              | 0.726    |
| 4                                       | 73 (33.2%)                                        | 68 (33.5%)                                              | 0.077    |
| 5                                       | 47 (20.0%)                                        | 39 (19.2%)                                              | 0.032    |
| IDSA/ATS severe pneumonia               | 64 (27.2%)                                        | 50 (24.6%)                                              | 0.032    |
| Length of hospital stay (days)          | 10 (7–20)                                         | 10 (7–20)                                               | 0.279    |
| Mortality rate                          | 20 (8.5%)                                         | 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.

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| 1.62 (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 (1.07–1.13)         | 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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