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Anti-anaerobic coverage is not necessary for *Klebsiella pneumoniae* liver abscess: a propensity score–matched cohort study

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ABSTRACT

Although most *Klebsiella pneumoniae* liver abscesses have been reported to be monomicrobial, clinical outcomes have not been compared between antimicrobial therapy with and without anti-anaerobic coverage. A propensity score–matched cohort study was conducted using the 731 cases of *K. pneumoniae* liver abscess. Clinical outcomes were compared between a group discontinuing anti-anaerobic agents after *K. pneumoniae* identification and a group continuing. A total of 170 cases were matched at a 1:1 ratio using their propensity to discontinue anti-anaerobic agents. The McNemar's test showed no difference in mortality rates (1.8% for discontinuation versus 2.3% for continuation; $P = 1.00$) or relapse (1.8% versus 2.9%; $P = 0.73$) between groups. Early discontinuation of anti-anaerobic agents had no association with treatment failure by means of the generalized estimating equation model (odds ratio 0.48; $P = 0.14$) and the Kaplan–Meier method ($P = 0.85$) in matched groups. Early discontinuation of anti-anaerobic agents does not affect the clinical outcomes of patients with *K. pneumoniae* liver abscess.

1. Introduction

Klebsiella pneumoniae has become the most common etiology of liver abscess in Taiwan and Korea (Chung et al., 2007; Wang et al., 1998), and recently, cases of *K. pneumoniae* liver abscess have also been increasingly reported in many Western countries (Anstey et al., 2010; Decre et al., 2011; Fierer et al., 2011; Frazee et al., 2009; Rahimian et al., 2004; Rodriguez-Lagos et al., 2013; Vila et al., 2011). *K. pneumoniae* liver abscesses are clinically characterized by high rates of metastatic infection and association with diabetes mellitus, and their probable modes of infection are cryptogenic rather than biliary origin (Kim et al., 2009). Such an increasing incidence of *K. pneumoniae* liver abscess is associated with a newly emerging, highly virulent serotype K1 strain (Chung et al., 2008; Fang et al., 2007; Siu et al., 2012).

Most cases of *K. pneumoniae* liver abscess were reported as monomicrobial infections (Chung et al., 2007; Wang et al., 1998), contrasted with the classical notion that pyogenic liver abscess is a mixed aerobic and anaerobic infection that requires broad-spectrum antimicrobial therapy (Baron and Kasper, 2012; Chu et al., 1996; Frey et al., 1989; Sifri and Madoff, 2010). Accordingly, antimicrobial therapy specific for *K. pneumoniae* without anti-anaerobic coverage has been suggested (Siu et al., 2012). In a study from Taiwan comparing the rates of severe complications from *K. pneumoniae* liver abscess between cefazolin and ceftriaxone, anti-anaerobic agent was not given during the

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whole treatment period (Cheng et al., 2003). However, there has been no controlled study to compare the clinical outcomes between treatment groups with and without combined use of anti-anaerobic agents. This lack of evidence has led many physicians to continue combining anti-anaerobic agents during the treatment of pyogenic liver abscess despite isolation of *K. pneumoniae*.

In this study, we determined whether we could discontinue anti-anaerobic agents early in the course of treatment of cryptogenic pyogenic liver abscess in which *K. pneumoniae* was isolated without affecting clinical outcomes.

2. Materials and methods

2.1. Study design, patient selection, and data collection

This is a retrospective propensity score–matched cohort study. We identified the cases diagnosed as *K. pneumoniae* liver abscess at 15 secondary- or tertiary-care hospitals in Korea from 2006 to 2011. Patients over 18 years of age with community-onset, cryptogenic, monomicrobial *K. pneumoniae* liver abscess were eligible. Patients with hepatobiliary malignancy, cholangitis, cholecystitis, or intrahepatic stone diseases were excluded. Patients with a history of intraabdominal infection at the portal-drained area within the previous 6 months were also excluded. Cases with polymicrobial infection and hospital-onset were excluded. Patients dying within 5 days after diagnosis and those who were transferred to other hospitals during this period were excluded. Treatment outcomes were compared between the group discontinuing anti-anaerobic agents after *K. pneumoniae* was identified and the group continuing anti-anaerobic agents.

We retrospectively reviewed medical and microbiological records to identify patients with *K. pneumoniae* liver abscess and to collect demographic and clinical information. The data for antibiotic administration were collected by reviewing the doctors' orders and the nursing charts. This study was approved by the Institute Review Board of Samsung Medical Center (IRB file no. 2011-08-082).

2.2. Definitions

K. pneumoniae liver abscess was defined as an abscess diagnosed by imaging studies (ultrasonography or computed tomography) with *K. pneumoniae* isolated from culture of the blood or abscess aspirate. The severity of the underlying medical condition was determined by McCabe classification, which was categorized into non-fatal, ultimately fatal, and rapidly fatal (McCabe and Jackson, 1962). Septic shock and severe sepsis were defined on the basis of Society of Critical Care Medicine/American College of Chest Physicians criteria (Bone et al., 1992). Discontinuation group was defined as the cases in which anti-anaerobic agents were discontinued within 7 days, and continuation group was defined as those continuing anti-anaerobic coverage. Improvement was defined as disappearance of the abscess in imaging studies and improvement of the relevant symptoms. All-cause mortality and infection-related mortality were assessed at the end of the hospital stay. Relapse was defined as a relapsed abscess within one year. Treatment failure was defined as either all-cause mortality or relapse. Length of hospital stay was calculated from the day of admission to day of discharge. Possible neurotoxicity associated with metronidazole was defined as peripheral neuropathy or encephalopathy diagnosed by a neurologist without any other explainable cause.

2.3. Statistical analysis

All statistical analyses were performed with Stata version 11.2 (StataCorp, College Station, TX, USA). All tests of significance were 2-tailed, and a P value of 0.05 was considered significant. Categorical variables were compared between the discontinuation and continuation groups by chi-square test or Fisher's exact test, and continuous variables were compared by Mann–Whitney U test. The dependent variable for the risk factor analysis was treatment failure. Independent variables for this analysis included age, gender, underlying diseases or conditions, severity of underlying diseases, severe sepsis or septic shock, bacteremia, gas formation, local complication or metastatic infections, total duration of antibiotics, total duration of anti-anaerobic agents, and drainage of abscess.

To reduce the effect of selection bias and potential confounders in this retrospective study, we adjusted for differences in baseline characteristics between treatment groups by propensity score analysis. The propensity for discontinuing anti-anaerobic agents was determined without regard to outcome, using multivariate logistic regression. The propensity score model included 15 covariates, which were gender, age, diabetes mellitus, malignancy, liver cirrhosis, chronic kidney disease, chronic obstructive pulmonary diseases, congestive heart failure, previous abdominal surgery, recent use of antibiotics, bacteremia, severity of underlying diseases, septic shock, metastatic infection, and drainage of abscess. Propensity score was generated using the pscore (logit) command in Stata 11.2. Patients in the discontinuation group were matched with those in the continuation group at a 1:1 ratio according to propensity score, as described previously (Gum et al., 2001; Kim et al., 2011). Each case in the discontinuation group was matched with a case in the continuation group that had a propensity score identical to 5 digits. Alternatively, the next highest digit match (4, 3, 2, or 1 digit) on propensity score was determined. Cases that could not be matched on the first digit of the propensity score were excluded. For propensity score–matched analyses, we used McNemar's test to compare categorical variables and the Wilcoxon paired signed rank test for continuous variables. The risks of treatment failure were compared using a generalized estimating equation (GEE) model. Time-to-event curves during the follow-up period were calculated by the Kaplan–Meier method and compared between matched cohorts using a frailty model.

We also determined the risk factors for treatment failure in 731 unmatched cases using the multivariate logistic regression analysis. Independent variables including treatment group, age, gender, liver cirrhosis, use of corticosteroid or immunosuppressant, previous abdominal surgery, and metastatic infection were selected for backward stepwise regression. The covariates showing $P \geq 0.2$ were removed from the final model.

3. Results

3.1. Characteristics of the study population

During the study period, 1150 cases of *K. pneumoniae* liver abscess were screened. Among them, 331 cases associated with hepatobiliary disease or a previous history of intraabdominal infection was excluded. Cases with polymicrobial etiology (n = 40) or hospital onset (n = 21) were excluded. Out of 758 cases of community-onset, cryptogenic *K. pneumoniae* liver abscess, 12 patients who died and 15 who were transferred to other hospitals within 5 days of diagnosis were excluded. All these 27 cases were empirically treated with antimicrobial agents including anti-anaerobic coverage until their death or transfer. Finally, 731 cases were analyzed (Fig. 1).

Anti-anaerobic agents were discontinued after *K. pneumoniae* was identified in 170 cases (23.3%), whereas anti-anaerobic agents were continued for longer than 7 days in 561 cases (76.7%) (Table 1). In all cases discontinuing anti-anaerobic agents within 7 days, the reasons were that cultures of blood or aspirated pus grew only *K. pneumoniae*. Severity of the underlying diseases determined by McCabe classification did not differ between the discontinuation and continuation groups. There was no difference in the proportion of septic shock between the 2 groups. The rate of local complications and metastatic infections, including peritonitis, pleural empyema, lung abscess, septic pneumonia, endophthalmitis, meningitis, and prostatic abscess, did not differ between groups. The percentage of *K. pneumoniae* isolates susceptible to ciprofloxacin was 95.3% and 97.3% in the discontinuation and continuation groups, respectively (P = 0.44). The rate of susceptibility to the third-generation cephalosporins did not differ between the 2 groups (100% versus 98.8%, P = 0.54).

The third-generation cephalosporins and metronidazole were the most frequent initial empiric antimicrobial agents selected in both groups (78.2% and 83.2%). Median duration of antibiotic use was shorter in the discontinuation group compared to the continuation group (39 versus 43 days, P = 0.005). Median duration of anti-anaerobic therapy was 5 days in the discontinuation group and 20 days in the continuation group (interquartile range 14–36) (P < 0.0001). Percutaneous drainage, single aspiration, or