

論 文 概 要

Thesis Abstract

○ 論 文 題 目

Risk factors and treatment strategies on pneumonia

(肺炎の発症・重症化要因と抗菌薬治療戦略の検討)

○ 指 導 教 員

檜澤 伸之

人間総合科学研究科 疾患制御医学専攻 呼吸器内科学分野 主任教授

(所属) 筑波大学大学院人間総合科学研究科 疾患制御医学専攻

(氏名) 間辺 利江 (Toshie Manabe)

I. Purpose

Pneumonia is a major cause of hospitalization and mortality, especially in older adults. Along with the rapid growth of aging population, the importance of clinical practice for pneumonia and public health concerns have been increasing.

Pneumonia is classified as community-acquired pneumonia (CAP), or hospital-acquired pneumonia (HAP), depending on whether the infection developed while the patient is in an outpatient setting or in an inpatient setting. The distinction between CAP and HAP and understanding the etiologies on each pneumonia are critical for the clinical management on patients with pneumonia and the selection of appropriate antibiotic agents. In patients with HAP, the combination of resistant, difficult-to-treat organisms, along with the underlying disease conditions that accompany HAP, lead to a worse prognosis. The mortality rate associated with HAP was significantly higher than that for CAP. Ventilator-associated pneumonia (VAP) is defined as pneumonia developing in patients who have been on mechanical ventilation for > 48 hours, and is a leading cause of mortality in critically ill patients.

Aspiration pneumonia (AsP) is classified by the cause of pneumonia and involves CAP, HAP, and VAP. A multicenter study in Japan indicated that approximately 87% of HAP can be diagnosed as AsP. AsP increases with age and related to the high mortality and morbidity. However, the lack of the universal definition of AsP leads to the complication of clinical researches for elucidating the pathophysiology of AsP. Thus, HAP, VAP and AsP are important hospitalized infections that relate to severity and mortality.

The purposes of the present study were; to elucidate the risk factors for AsP; to evaluate the influence of pneumonia on patients with dementia; and to evaluate the effective antibiotics treatment strategies for patients with HAP, VAP and AsP. Findings from this study would be important implications for present and future clinical managements on patients with hospitalized pneumonia for reducing disease severity and mortality.

II. Materials and methods

In order to achieve the goal of present study, six sub-studies in three main themes were conducted. The materials and methods were as follow.

【Theme 1】 Risk factors on incidence of AsP

Study 1: Definition, diagnosis and risk factors on AsP – A systematic review

The studies published from 1949 to June 2015 were systematically reviewed. Among the eligible studies, the diagnostic or definition of AsP, common references that cited

as the definition of AsP, and risk disease and factors of AsP were assessed.

Study 2: Risk factors for AsP in older adults in nursing and geriatric facilities in Japan

The study subjects were 9930 patients in nursing and geriatric healthcare facilities in Japan (median age, 86 years; 76% female). The subjects were divided into two groups if they had an episode of AsP in the previous 3 months. Data on demographics, clinical status, activities of daily living, and major illness were compared between subjects with- and without-AsP. Factors relating to incidence of AsP were estimated using logistic regression model.

【Theme 2】 Effects of pneumonia on patients with dementia

Study 3: Factors relating to pneumonia-caused death in older adults with autopsy confirmed dementia.

The study subjects were 204 patients who were admitted, were underwent a post-mortem examination, and were neuropathologically diagnosed with dementia between 2005 and 2015 in a hospital, Toyohashi, Japan. The risk factors for pneumonia-caused death were examined both as underlying and immediate causes of death using logistic regression models.

Study 4: Pneumonia-caused hospital admission in patients with dementia in terminal stage

The study subjects were selected from the study 3 and 158 patients who became hospitalized and then died, and who underwent post-mortem autopsy and diagnosed Alzheimer's disease, dementia with Lewy bodies, and vascular dementia were included. The patients were divided into three groups based on the cause of hospital admission: CAP (pneumonia group; n=31), deterioration of dementia (dementia group; n=71), and other clinical causes (other-cause group; n=56). The survival-time after hospital admission was assessed according to the causes of hospital admission.

【Theme 3】 The antibiotics treatment strategies for patients with HAP, VAP and AsP.

Study 5: Chronological change on bacteriology of AsP – A systematic review

The data was selected from the systematic review in study 1. Of the 467 references screened, 17 studies reported bacteriology of AsP and were included the analysis. The bacteriology of AsP was chronologically evaluated by the stratified terms of years; 1970-1989; 1990-2009; and 2010-2014.

Study 6: Effect of de-escalation antibiotic therapy on HAP and VAP – A systematic review and meta-analysis

A systematic review and meta-analysis was performed on studies examining de-escalation therapy in patients with HAP or VAP. A meta-analysis was conducted

using a random-effects model. The primary outcome was mortality, and the secondary outcomes were lengths of hospital stay, intensive care unit (ICU) stay, and antibiotic therapy. Stratified subgroup analyses were conducted among group of studies of VAP and those of HAP.

III. Results

【Theme 1】 Risk factors on incidence of AsP

Study 1: Definition, diagnosis and risk factors on AsP – A systematic review

Of the 467 references screened, 86 studies included in the final analysis. Among them, six studies examined on subjects with head and neck cancer and five studies examined on subjects with stroke. Although the criteria of subjects varied, age, dysphagia, suctioning, dehydration were major factors to the incidence of AsP as well as risk diseases including dementia and stroke. The incidence of AsP also varied from 5% to 60% in the eligible studies.

Study 2: Risk factors for AsP in older adults

Two hundred and fifty-nine (2.6% of total) subjects were in a group of AsP. Risk factors for AsP by multiple logistic regression analysis of propensity-adjusted subjects (258 subjects each) were sputum suctioning (Odds ratio [OR], 3.276), deterioration of swallowing function in 3 months (OR, 3.584), dehydration (OR, 8.019), and dementia (OR, 1.618).

【Theme 2】 Effects of pneumonia on patients with dementia

Study 3: Factors relating to pneumonia-caused death in older adults with dementia.

The factors related to pneumonia-caused death (underlying) were subtypes of dementia; Alzheimer's disease (odds ratio [OR], 2.891); argyrophilic grain disease (OR, 3.148); and progressive supranuclear palsy (OR, 34.921), dysphagia (OR, 2.045), diabetes mellitus (OR, 3.084) and conversely related with heart failure (OR, 0.149). Factors relating to pneumonia-caused death (immediate) were incidence of pneumonia during hospitalizations (OR, 32.579), gender-male (OR, 2.060), and conversely related with malignant neoplasm (OR, 0.220).

Study 4: Pneumonia-caused hospital admission in patients with dementia in terminal stage

The mean duration of hospitalization was 20 months in the pneumonia group, 25.1 months in other-cause groups, and 56.6 months in the dementia group. 54.8% of patients in pneumonia group survived over one year after admission.

【Theme 3】 Antibiotics treatment strategies for patients with HAP, VAP and AsP.

Study 5: Chronological change on bacteriology of AsP – A systematic review

Total 1437 bacteriology in 17 studies was included the analysis of the present study. Of all eligible, 42% were gram-negative aerobic, 35% were gram positive aerobic, 11% of anaerobic and 8% were fungi. Although major bacteriology of AsP were anaerobic in the study in 1970 - 1989, those in recent years (2010-2014) were *Candida* sp (19.1%), *Staphylococcus aureus* (18.2%), and *Klebsiella pneumoniae* (12.7%).

Study 6: Effect of de-escalation antibiotic therapy on HAP and VAP – A systematic review and meta-analysis

Nineteen studies (4420 patients) were eligible. Among them, nine were observational studies that examined de-escalation vs. non-de-escalation therapies and others were studies examining guideline-oriented de-escalation therapy. In all eligible studies, de-escalation antibiotic therapy reduced hospital mortality (risk ratio [RR], 0.81; 95% confidence interval [95% CI], 0.65–0.99). Among observational studies, de-escalation therapy has also reduced the risk of hospital mortality (RR, 0.58; 95% CI, 0.39–0.86). As the stratified analysis in observational studies, de-escalation therapy on studies on HAP showed a significant reduced mortality (RR, 0.24; 95%CI, 0.07-0.85), while those on VAP tended to reduce mortality (RR, 0.69; 95%CI, 0.47-1.01).

IV. Discussion

The present study intended to elucidate the risk factor on incidence of AsP and the effect of antibiotics treatment strategy on HAP, VAP and AsP. The study revealed that factors relating to the incidence of AsP were sputum suctioning, deterioration of swallowing function in 3 months, dehydration, and dementia. HAP was the major factor for pneumonia-caused death on patients with dementia along with dysphagia, subtypes of dementia, gender-male and diabetes mellitus. Although anaerobic bacteria were the major pathogen for AsP in the 1970s, the bacteriology of AsP changed chronologically. In recent years, major bacteriology was fungi and drug-resistant bacteria, which might be influenced by the increasing number of aging patients. De-escalation antibiotics therapy was effective treatment strategies for reducing mortality, especially for severe HAP and VAP including AsP.

AsP does not have a universal definition. However, in Japan, AsP is defined according to the Japanese Study Group on Aspiration pulmonary Disease definition as pneumonia in a patient with a predisposition to aspiration because of dysphagia or swallowing disorders. Patients with dysphagia are likely to have pneumonia at a rate of 1.6 to 11.9 times greater than patients without dysphagia. Thus, dysphagia is the major risk factor of the AsP. The risk diseases relating to dysphagia such as dementia, stroke,

head and neck cancer were also the risks to AsP. The other risks were age-related condition in frail older adults, which partly explains why aging increases the risk of AsP. These factors can be included into the definition and diagnostic criteria of AsP.

Anaerobic has not been common in the recent years; however, fungi and multi-drug resistant pathogen appear to be common. Aging population as well as increased number of patients with bedridden may influenced those results. Although the reported bacteriology may not be the pathogen that caused AsP, the present study indicated that the selection of antibiotic therapy needs to consider the clinical and living conditions of patients. The use of broad-spectrum antimicrobials with subsequent de-escalation in patients with HAP, VAP, and HCAP was associated with a reduction in mortality, especially less severe pneumonia. Thus, the pneumonia severity and bacteriology may influence the effect of de-escalation antibiotic therapy on mortality. The underlying conditions of patients in the ICU may also impact the risk of mortality.

V. Conclusion

Risk factors to AsP were dysphagia and age-related disorders and frail condition. Clinical management on patients with AsP requires the comprehensive consideration both of clinical and general backgrounds of patients. De-escalation antibiotic therapy may contribute to reduce mortality on patients with HAP, VAP and HCAP.