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Original Study

Role of Atypical Pathogens in Nursing Home—Acquired Pneumonia

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A B S T R A C T

Objectives: No international consensus has been reached on the empirical use of antibiotics with atypical coverage in nursing home—acquired pneumonia (NHAP). Aspiration is an important cause of NHAP, but it may not require antimicrobial treatment. This study aimed to investigate the prevalence and clinical characteristics of AP infections and review the need for empirical antibiotics with atypical coverage in NHAP.

Design: A prospective cohort study.

Setting: Four nursing homes with a total number of 772 residents.

Participants: Patients were aged ≥ 65 years, hospitalized for NHAP, which was defined as the presence of respiratory symptoms and abnormal chest radiographs, from April 2006 to March 2007.

Measurements: Demographics, clinical parameters, and investigation results were recorded. Microbial investigations comprised sputum routine and mycobacterial cultures, blood and urine cultures, serology, and nasopharyngeal aspirate viral culture and polymerase chain reaction tests. Suspected aspiration pneumonitis was arbitrarily defined as NHAP without pathogens identified.

Results: After excluding lone bacteriuria, 108 episodes of NHAP in 94 patients were included. Twelve APs were detected in 11 patients. There was no clinical feature to distinguish between infections caused by APs and other pathogens. The commonest APs were Mycoplasma pneumoniae (6) and Chlamydophila pneumoniae (3). No Legionella pneumophila was detected by urinary antigen test. None of the patients with AP infection received antibiotics indicated for AP infections. However, AP infections did not result in mortality. No pathogen was isolated in 31.5% of cases. Patients without pathogens isolated were less likely to have purulent sputum and crepitations on chest auscultation, compared with those with pneumonia caused by identified pathogens.

Conclusions: Atypical pathogens (APs) were not associated with mortality even in cases where the prescribed antibiotics did not cover APs. NHAP may not necessarily be treated with empirical antibiotics covering APs.

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Pneumonia is a common cause of death among nursing home residents. Streptococcus pneumoniae and Haemophilus influenzae are the commonest bacterial pathogens in patients who are able to expectorate. 1 Aspiration is an important contributing factor. Aspiration pneumonitis, which is caused by chemical injury to the lung parenchyma without bacterial infection, does not necessitate antibiotic treatment. 2 In contrast, aspiration pneumonia is caused by bacterial pathogens of oropharynx, including gram-negative bacilli, Staphylococcus aureus, and anaerobic bacteria, which are commonly isolated in intubated patients. 3 Aspiration pneumonitis is difficult to differentiate from pneumonia clinically.

The empirical use of antibiotic regimens covering atypical pathogens (APs) in the management of community-acquired pneumonia (CAP) in adults is controversial. According to the Cochrane Systematic Review, the empirical use of antibiotics with atypical coverage, compared with those without atypical coverage, did not provide survival benefit or clinical efficacy in patients hospitalized for low-severity pneumonia. 4 The British Thoracic Society guidelines, however, recommend the empirical use of combination regimens of penicillin and macrolide antibiotics in patients hospitalized for moderate- to high-severity pneumonia. 5 The Infectious Diseases Society of America/American Thoracic Society guidelines have no
recommendation on the empirical use of antibiotics with atypical coverage in nursing home—acquired pneumonia (NHAP). The importance of APs (Mycoplasma pneumoniae, Chlamyphilia spp., and Coxieilla burnetii) and Legionella pneumonia in older patients with pneumonia is unclear. APs were more likely to infect older people with multiple comorbidities than younger ones, and were more common in CAP than in NHAP. There is little information regarding the prevalence and mortality of AP infections in NHAP and CAP, which are the major determining factors on the empirical use of antibiotic regimens with atypical coverage. Such information is needed to establish the role of APs and L. pneumonia in NHAP.

We performed a subgroup analysis of NHAP in a study on influenza-like illness (ILI) in old people living in nursing homes. This study aimed to investigate the prevalence and clinical characteristics of AP infections in NHAP and review the need for empirical antibiotic therapy with atypical coverage in NHAP.

Methods

Patient Recruitment

The methodology of this study was described elsewhere. Four nursing homes, which were located in the Shatin district of Hong Kong and had a total number of 772 residents, participated in this study from April 2006 to March 2007. Research staff liaised with the nurse or doctor of the Community Geriatric Outreach Team of the study from April 2006 to March 2007. Research staff liaised with the nurse or doctor of the Community Geriatric Outreach Team of the Hong Kong Hospital Authority to identify residents with ILI every day. An ILI episode was defined as fever \( \geq 37.8 \)\(^{\circ} \)C or 100 F (oral temperature) or an acute deterioration in physical or mental condition, plus either new onset of one or more respiratory symptoms or acute worsening of a chronic condition involving respiratory symptoms. A chest radiograph was taken in those with a chronic cough lasting \( \geq 2 \) weeks or taken when pneumonia was suspected. Respiratory and urinary specimens were collected within the first 2 days of illness and serology 2 weeks later, no matter whether the patients were in the hospital or in the nursing homes.

Patients with ILI were managed by the physician of the Community Geriatric Outreach Team in the nursing homes. Residents were hospitalized if they were in critically ill condition or could no longer be managed in nursing homes. A follow-up visit was arranged by the research nurse after recovery of the illness.

This study was approved by the Research Ethics Committee of the Chinese University of Hong Kong. Appropriate informed written consent was obtained from the patients or their proxy.

Microbial Investigations

All patients with ILI symptoms had the following specimens collected for microbial investigations: sputum, blood and urine samples, nasopharyngeal aspirate (NPA), and serology.

Sputum samples were used for routine bacterial culture that covered S. pneumoniae, H. influenzae, Moraxella catarrhalis, Pseudomonas spp., and other pathogens. Sputum mycobacterial culture for tuberculosis was limited to those with prolonged respiratory symptoms, weight loss, or hospital admission.

NPA samples were sent for routine viral culture, including influenza A and B, parainfluenza virus types 1, 2, and 3, respiratory syncytial virus, and adenovirus. A rapid multiplex nested polymerase chain reaction (PCR) was undertaken to detect atypical organisms (M. pneumoniae, C. pneumoniae, and L. pneumonia) and viruses (influenza A and B, parainfluenza virus types 1, 2, 3, and 4, respiratory syncytial virus, rhinovirus, adenovirus, enterovirus, coronavirus, and metapneumovirus).

Paired serum samples were taken to identify APs (M. pneumoniae, Chlamyphilia spp., and C. burnetii), L. pneumoniae, and respiratory viruses (influenza A and B, parainfluenza 1, 2, 3, and 4, and adenovirus) by complement fixation tests. Blood and urine samples were collected for routine culture. Urinary antigen tests for L. pneumoniae serogroup 1 and S. pneumoniae were performed in hospitalized patients.

NHAP

NHAP was defined as the presence of respiratory symptoms supported by abnormal findings on chest radiographs, that is, ill-defined shadow, consolidation, or pleural effusion. Our study recruited residents hospitalized for NHAP.

Diagnostic Criteria

The cause of NHAP was definitive if one of the following criteria was met: (1) positive blood culture; (2) positive sputum culture for S. pneumoniae, H. influenzae, and M. catarrhalis; (3) positive NPA viral culture or PCR identification; (4) a seroconversion or 4-fold increase in antibody titer; (5) IgM positive; or (6) positive urinary antigen test for L. pneumoniae. The cause was probable if one of the following criteria was met: (1) positive sputum culture for other bacteria; (2) a single titer \( \geq 80 \) when paired serum samples were not available; or (3) positive urinary antigen test for S. pneumoniae.

Documentation of Clinical Course

The following characteristics of the study patients were recorded: demographic characteristics, comorbidities, vaccination status, prior hospitalization, premorbid functional status, Mini-Mental State Examination, body mass index, symptoms and signs of the illness, investigation results, antibiotics, hospitalization, length of stay, and mortality.

Premorbid functional status was assessed by the Barthel index. This score covers a wide range of activities of daily living with a total score of 20. A score of 20 indicates independence, 15–19 indicates mild to moderate functional limitation, and \( \leq 14 \) indicates severe limitation.

The burden of medical illnesses was represented by the Charlson comorbidity index and the severity of pneumonia measured by the CURB score (confusion, blood urea level, respiratory rate, and low blood pressure).

Statistical Analysis

Categorical variables were expressed as counts (percentages) and continuous variables as mean (± SD) or median (interquartile range). Two groups were compared by \( \chi^2 \) (or Fisher exact) test for categorical variables and by t test (or Mann–Whitney U test) for continuous variables. Two-tailed tests with a significance level of 5% (\( \alpha = 0.05 \)) were used for all analyses. The Statistical Package for Social Sciences 13.0 (SPSS Inc, Chicago, Illinois) was used for statistical analyses.

Results

A total of 259 episodes of ILI occurred in 194 patients. Abnormal chest radiographs were present in 128 episodes. All except one required hospitalization. Two episodes were excluded because of missing data. Of the remaining 125 episodes, bacteria were isolated only in the urine samples of 17 episodes, which were further excluded. Finally, 108 episodes of NHAP in 90 patients were included.
Sputum routine and mycobacterial cultures were performed in 61 (56.5%) and 41 (38.0%) patients, respectively. NPA samples were collected in all patients for PCR tests and 101 (93.5%) patients for viral cultures. The acute inflammatory condition of the lower respiratory tract was more likely caused by aspiration pneumonitis than aspiration pneumonia. A similar percentage of patients with and without nasogastric tube feeding was represented (30.0% vs 31.8%, P = 0.874).

The presence of purulent sputum and crepitations on chest auscultation were the features that distinguished patients with and without pathogens identified, as listed in Table 4.

**AP Infections and Antimicrobials**

The prevalence rate of AP infections in NHAP was 10.2% (11/108). The commonest APs were *M. pneumoniae* (6) and *C. pneumoniae* (3). Coinfections with viruses or other bacteria occurred in five of them. Urinary antigen tests did not detect any *L. pneumophila*. There was no difference in the clinical characteristics of pneumonia caused by APs and other pathogens (Table 5). The atypical isolates were not clustered in time or in a specific facility.

With one exception, none of the patients with AP infection was treated with antibiotic covering APs during hospitalization. This patient was treated with levofloxacin on admission because of allergy to penicillin. The other 10 patients received penicillin antibiotics. AP despite extensive microbial investigations for respiratory and urinary pathogens. The acute inflammatory condition of the lower respiratory tract was more likely caused by aspiration pneumonitis than aspiration pneumonia. A similar percentage of patients with and without nasogastric tube feeding was represented (30.0% vs 31.8%, P = 0.874).

The presence of purulent sputum and crepitations on chest auscultation were the features that distinguished patients with and without pathogens identified, as listed in Table 4.

**Table 1**

Clinical Characteristics and Investigation Results of the Study Population (N = 108)

| Variables                          | Values (Normal Range) |
|------------------------------------|-----------------------|
| Demographics                       |                       |
| Age, y, mean (±SD)                 | 85.6 (±9.2)           |
| Sex, n [%]                         | 50 (46.3)             |
| Mini-Mental State Examination score, mean (±SD) | 15.8 (±6.2) |
| Barthel index, median (IQR)        | 4 (2–10)              |
| Body mass index, kg/m², median (IQR) | 20.8 (18.1–24.6) |
| Nasogastric tube feeding, n [%]    | 20 (18.5)             |
| Charlson comorbidity index, median (IQR) | 3 (1–4)     |
| Hospitalization within past 4 weeks, n [%] | 29 (26.9) |
| Flu vaccination within past 6 months, n [%] | 57 (52.8) |
| Flu vaccination within past 6–12 months, n [%] | 41 (38.0) |
| Comorbidities, n [%]               |                       |
| Cerebrovascular accident           | 52 (48.1)             |
| Dementia                           | 59 (54.6)             |
| Diabetes                           | 26 (24.1)             |
| Ischemic heart disease             | 17 (15.7)             |
| Congestive heart failure           | 18 (16.7)             |
| Chronic obstructive pulmonary diseases | 21 (19.4) |
| Chronic kidney diseases            | 18 (16.7)             |
| Chronic liver diseases             | 3 (2.8)               |
| Active malignancy                  | 6 (5.6)               |
| Respiratory symptom, n [%]         |                       |
| Fever                              | 98 (90.7)             |
| Shortness of breath                | 81 (75.0)             |
| Cough*                             | 99 (91.7)             |
| Mucoid sputum                      | 45 (41.7)             |
| Purulent sputum                    | 47 (43.5)             |
| Hemoptysis                         | 3 (2.8)               |
| Respiratory signs, n [%]           |                       |
| Rhonchi                            | 21 (19.4)             |
| Bronchial breath sounds            | 8 (7.4)               |
| Crepitations                       | 84 (77.8)             |
| Chest radiographics, n [%]         |                       |
| Ill-defined shadows                | 69 (63.9)             |
| Consolidation                      | 39 (36.1)             |
| Pleural effusion                   | 11 (10.2)             |
| Blood tests                        |                       |
| Sodium, mmol/L                     | 134 (129–137)         |
| Urea, mmol/L                       | 7.5 (5.6–10.1)        |
| Creatinine, μmol/L                 | 97 (72–126)           |
| Albumin, g/L                       | 32.3 (±4.8)           |
| White cell counts, ×10⁹/L          | 12.1 (8.6–15.7)       |
| CURB score, n [%]                  |                       |
| 0–1                                | 40 (37.0)             |
| 2–4                                | 68 (63.0)             |

CURB, confusion, blood urea level, respiratory rate, and low blood pressure; IQR, interquartile range.

*Eighteen (16.7%) patients had cough longer than 2 weeks.

in this study. Clinical characteristics and investigation results of the study population are listed in Table 1.

**Microbial Findings**

Sputum routine and mycobacterial cultures were performed in 61 (56.5%) and 41 (38.0%) patients, respectively. NPA samples were collected in all patients for PCR tests and 101 (93.5%) patients for viral culture. A paired serology was available in 92 (85.2%) patients. Urinary antigen tests for *L. pneumophila* and *S. pneumoniae* were carried out in 94 (87.0%) patients. Blood and urine samples were collected for routine culture in 92 (85.2%) patients.

Causative factors were established in 74 (68.5%) patients. The microbial findings are summarized in Tables 2 and 3. Comonitant bacteriuria was found in 16 patients.

**Pneumonia of Unknown Cause**

More than 30% of the study patients belonged to a category of "pneumonia of unknown etiology." They had no pathogen identified...
infection did not result in any death. The overall in-hospital mortality rate of the study population was 14.8%.

Discussion

Our study demonstrated that APs are not an important cause of NHAP, as reflected by the low prevalence and the lack of antibiotic treatment with atypical coverage not resulting in mortality. Despite some advances in technology with availability of multiplex PCR for detection of common pathogens in the NPA specimen, the cause of NHAP could not be identified in 31.5% of cases. Aspiration pneumonia is presumably accounted for some of these cases. The prevalence rate of AP infections in this study was 10.2% (11/108), which was greater than the findings (<5%) of previous studies. There was no reliable clinical characteristic to differentiate between NAHP caused by APs and other pathogens. The combined use of NPA PCR tests and traditional serology likely had contributed to a greater prevalence of AP infections in our study. M. pneumoniae and C. pneumoniae infections were diagnosed exclusively by NPA PCR tests, but not serology. Meanwhile, Chlamydia phila and C. burnetii can be detected only by serology. All the patients with AP infection survived, whereas only one of them had received antibiotic covering APs. Another study also showed that AP infection resulted in a lower 30-day mortality than other pathogens, although the difference was not statistically significant (2.2% vs 6.0%, P = .09). It is hypothesized that APs cause pneumonia of milder severity, and its clinical course is usually self-limiting without antibiotic therapy, even in older people of lower immunity. Thus, we recommend that antibiotics with atypical coverage should not be biotic therapy, even in older people of lower immunity. Thus, we

Bi, Barthel index; CCI, Charlson comorbidity index; CHF, congestive heart failure; CVA, cerebrovascular accident; IHD, ischemic heart disease; MMSE, Mini-Mental State Examination. Numerical ranges indicate interquartile range.
(<5%) pathogen in NHAP.\textsuperscript{8,9,13,14} Our study has confirmed the rarity of \textit{Legionella} infection in NHAP, based on the result of urinary antigen tests that were performed in nearly 90% of the study patients. This finding further supports our recommendation that empirical antibiotic with atypical coverage is not indicated routinely for NHAP. On the basis of our local data, urinary antigen test for \textit{L. pneumophila} would not be a part of routine workup for NHAP because of low cost-effectiveness.

Aspiration pneumonitis, which is a clinical diagnosis by exclusion, is a significant cause of NHAP. Our study suggested that those nursing home residents with pneumonia who had no pathogens identified did not have purulent sputum and chest crepitations on examination. Some of these cases could be caused by aspiration pneumonitis. Because it is difficult to clinically distinguish between aspiration pneumonitis and aspiration pneumonia, especially on initial assessment,\textsuperscript{16} it is advisable to adopt a “de-escalation” approach and refrain from prescribing prolonged empirical antibiotics in patients with bulbar dysfunction and aspiration pneumonitis. This would help to reduce antibiotic resistance and the cost of unnecessary antibiotics.

This study had some limitations. First, the 4 nursing homes were chosen because they were close to the Prince of Wales Hospital for easy and quick transportation of specimens. Second, the incidence of atypical infections may vary in time and place. Our experience may not be applicable in other settings. Legionnaires’ disease may be endemic in some facilities where the water supply is colonized. \textit{Chlamydia phila} infection may cause local outbreaks. Third, we did not examine the relationship between patients’ swallowing ability and aspiration pneumonitis. Fourth, the definition of aspiration pneumonitis was arbitrary in this study. Our patients without pathogens identified did not necessarily meet the classical definition of aspiration pneumonitis, that is, sudden onset of choking after vomiting.\textsuperscript{2,16} Fifth, although NPA and blood serology were collected from the majority of patients, only 57% and 38% of the patients could cough up sputum suitable for routine culture and mycobacterial culture, respectively.

Conclusions

This study has shown that the overall in-hospital mortality rate of the study population with NHAP was 14.8%, whereas APs were neither a common cause of NHAP nor a significant cause of mortality. Most of the patients with APs isolated had not received antibiotics that covered the APs. Thus, patients with NHAP should not require empirical antibiotic treatment with atypical coverage.

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