J Infect Chemother 25 (2019) 639–642

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Note

Clinical manifestations and risk factors of community-onset *Acinetobacter* species pneumonia in Japan; case control study in a single institute in Japan☆

Nobuhiro Asai [a, b], Daisuke Sakanashi [b], Hiroyuki Suematsu [b], Hideo Kato [b], Hiroki Watanabe [a, b], Arufumi Shiota [b], Mao Hagihara [b], Yusuke Koizumi [a, b], Yuka Yamagishi [a, b], Hiroshige Mikamo [a, b, *]

[a] Department of Clinical Infectious Disease, Aichi Medical University Hospital, Aichi, Japan
[b] Department of Infection Control and Prevention, Aichi Medical University Hospital, Japan

ARTICLE INFO

Article history:
Received 7 November 2018
Received in revised form
12 March 2019
Accepted 18 March 2019
Available online 30 April 2019

Keywords:
Acinetobacter
Pneumonia
Community-acquired pneumonia
Healthcare-associated pneumonia

ABSTRACT

To clarify the etiology, patients' characteristics and risk factors for community-onset AP (*Acinetobacter* species pneumonia), we conducted this case-control study. We reviewed all patients with community-onset AP at our institute from 2010 until 2018. We defined non-AP group as a control. The patients with non-*Acinetobacter* spp. pneumonia (non-AP) were randomly selected during the study period without clinical information based on medical records' list among patients with community-onset pneumonia. The age (±2 years) and sex were matched to the patients with community-onset AP, and the ratio was AP:non-AP group = 1:3. Patients' characteristics, clinical outcomes, pathogens isolated and drug susceptibility were evaluated by comparing AP and non-AP group.

The mean age of community-onset AP group was 79 years. They were 8 males and 5 females. The 30-day and in-hospital mortality rates of community-onset AP were 23% (v.s. 3%, $p = 0.049$) and 31% (v.s. 5%, $p = 0.029$) respectively, which are higher than the control group. Heavy alcohol consumption (23% v.v. 0%, $p = 0.023$), higher Charlson Comorbidity index (3.2 v.s. 2.0, $p = 0.046$) and lobar pneumonia by chest radiology (50% v.s. 23%, $p = 0.071$) were seen more frequently in community-onset AP than in the control group.

In conclusion, community-onset AP shows poor outcomes despite the appropriate antibiotic therapy. Heavy alcohol history might be a risk factor of AP. Patients with community-onset AP could have more comorbidity and poor general conditions than the control group.

Acinetobacter spp. is a Gram-negative coccobacillus that is ubiquitous in fresh water and soil, and is also found frequently on the skin or in the throat commensal in humans [1,2]. While *Acinetobacter* spp. could cause community-onset pneumonia with a high mortality, the etiology, clinical manifestations and risk factors remain unknown [1,2].

For the purpose of identifying the etiology, patients' characteristics and the risk factors for community-onset AP, we conducted this case-control study. We retrospectively reviewed all patients with community-onset AP at Aichi Medical University hospital from 2010 until 2018. We defined non-AP group as a control. The patients with non-*Acinetobacter* spp. pneumonia (non-AP) were randomly selected during the study period without clinical information based on medical records' list among the patients with community-onset pneumonia. The age (±2 years) and sex were matched to the patients with community-onset AP, and the ratio was AP:non-AP group = 1:3. Patients' characteristics, clinical outcomes, radiological findings, pathogens isolated and drug susceptibility were evaluated by comparing AP and non-AP group. Pneumonia was diagnosed according to the previously published

☆ All authors meet the ICMJE authorship criteria.

* Corresponding author. Department of Clinical Infectious Diseases, Aichi Medical University School of Medicine, 〒480-1195 1-1 Yazakokarimata, Nagakute, Aichi, Japan. Tel.: +81 561 62 3311, Fax +81 561 62 4683.
E-mail address: mikamo@aichi-med-u.ac.jp (H. Mikamo).

https://doi.org/10.1016/j.jiac.2019.03.016
1341-321X/

international guidelines [3]. Patients with community-onset AP who met the following criteria were recruited to the case group: (1) patients who were consistent who met the criteria of community-acquired pneumonia (CAP) or of healthcare-associated pneumonia (HCAP), (2) displayed growth of *Acinetobacter* spp. in sputum culture collected predominantly or alone. Also, those who displayed predominant or sole growth of *Acinetobacter* spp. in sputum culture. Sputum culture by the Geckler classification 3–5 was available. (3) hospital-acquired pneumonia (HAP) patients were excluded from this study. CAP and HCAP were based on the criteria published by ATS/IDSA in 2006 [4,5]. Severity of pneumonia was evaluated by A-DROP [6], CURB-65 [7], Pneumonia Severity Index (PSI) [8] and I-ROAD [9]. The chest X-ray and computed tomography (CT) were reviewed by two pulmonologists (N.A and H.W). Patients' conditions were evaluated by Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) [10] and Karnofsky Performance Status (KPS) [11]. Comorbidity was assessed by the Charlson Comorbidity index (CCI) [12].

The antimicrobial susceptibility of isolated bacterial pathogens was assessed on the basis of the minimum inhibitory concentration by Clinical and Laboratory Standard Institute [13].

Heavy use of alcohol was defined as taking 60 g of alcohol daily for more than 5 years based on the criteria by the Ministry of health, Labor and Welfare in Japan [14]. Antibiotic treatment was classified as appropriate and as inappropriate when the identified pathogens were sensitive and resistant respectively to the initial prescribed antibiotics. Disseminated intravascular coagulation (DIC) is diagnosed according to the disseminated intravascular coagulation diagnostic criteria established by the Japanese Association for Acute Medicine (JAAM DIC diagnostic criteria) [15]. ARDS was defined as PaO2/FiO2 ratio<300 based on the Berlin Definition [16]. This study was approved by the Institutional Review Board of Aichi Medical University Hospital (IRB number 17-H106).

To identify the risk factors for community-onset AP, the following factors were evaluated by comparing AP and non-AP groups. The factors are patients' characteristics, conditions, and radiological findings. Continuous variables with a normal distribution were compared using paired *t*-test for non-normally distributed variables. The $\chi 2$ statistic or Fisher's exact test were used to compare categorical variables. Differences were assumed to be significant if $p < 0.05$. All the analyses were performed using SPSS version 23 for Windows (SPSS Inc., Chicago, IL, USA).

Patients' characteristics were shown in Table 1. A total of 13 patients with AP were enrolled in this study. Heavy alcohol consumption was seen more frequently in AP than non-AP group (23% v.v. 0%, $p = 0.023$). AP group had higher CCI scores than non-AP group (3.2 v.s. 2.0, $p = 0.046$). As for the radiological patterns, lobar infiltration was seen more frequently in AP than non-AP group (50% v.s. 23%, $p = 0.071$). On the other hand, bronchopneumonic infiltrations were seen less frequently in AP than non-AP group (17% v.s. 62%, $p = 0.007$). In terms of outcomes, AP group showed both higher 30-day (23% v.s. 3%, $p = 0.049$) and in-hospital mortality (31% v.s. 5%, $p = 0.029$) rates than non-AP group. There is no difference of frequency of both ARDS and DIC among the two groups.

As for pathogens isolated by sputum cultures, *A.baumannii* was cultured most frequently in 5 of the 13 (39%). *A. nosocomialis* was seen in one patient. *A. ursingii* was seen in another (different) patient. The rest (46%) were not confirmed as to the genus. Antibiotic susceptibility testing for *Acinetobacter* spp. isolated were performed (Table 1). The bacteria detected were susceptible to sulbactam/ampicillin (100%, 13/13), tazobactam/piperacillin (100%, 13/13), cefepime (100%, 13/13), meropenem (100%, 13/13), amikacin (100%, 13/13), levofloxacin (100%, 13/13), ciprofloxacin (100%, 13/13), sulfamethoxazole-trimethoprim (100%, 13/13), minocycline

Table 1
Comparison with the two groups; patients' characteristics, treatments and outcomes.

	AP group (n = 13)	Non-AP (n = 39)	*p*-value
Mean age (±SD)	79.4 ± 10.9	79.5 ± 9.6	0.968
Male gender (%)	8 (62)	24 (62)	1.000
Category of pneumonia (%)			
Community-acquired pneumonia	3 (23)	6 (15)	0.674
Healthcare associated pneumonia	10 (77)	33 (85)	
Severity of pneumonia (%)			
A-DROP			
0-2	7 (54)	23 (59)	0-3 v.s. 4-5
3	3 (23)	9 (23)	0.697
4-5	3 (23)	7 (18)	
CURB-65			
0-1	4 (31)	9 (23)	0-2 v.s. 3-5
2	4 (31)	15 (39)	1.000
3-5	5 (38)	15 (39)	
PSI			
I-II	1 (8)	4 (10)	I-III v.s. IV-V
III	1 (8)	7 (18)	0.475
IV-V	11 (85)	28 (72)	
I-ROAD			
A	3 (23)	13 (33)	A,B v.s. C
B	4 (31)	2 (5)	0.353
C	6 (46)	24 (62)	
Smoking history (%)			
Ever smoker	10 (77)	22 (56)	
Never smoker	2 (15)	11 (28)	0.266
Unknown	1 (8)	6 (15)	
Heavy use of alcohol (%)	3 (23)	0	0.013
Comorbidity (%)			
Cardiac disease	6 (46)	14 (36)	0.529
Cerebrovascular disease	1 (8)	11 (28)	0.253
Chronic pulmonary disease	5 (38)	20 (51)	0.528
COPD	2 (15)	11 (28)	0.475
Diabetes mellitus	1 (8)	6 (15)	0.664
Kidney disease	0	5 (13)	0.314
Hemodialysis	0	4 (10)	0.561
Hepatic disease	0	4 (10)	0.561
Collargen disease	1 (8)	5 (13)	1.000
Malignancy	4 (31)	10 (26)	0.729
Dementia	5 (38)	10 (26)	0.483
GERD	0	3 (8)	0.564
Charlson comorbidity index (mean ± SD)	3.2 ± 2.8	2.0 ± 1.5	0.046
Conditions			
ECOG-PS (mean ± SD)	2.9 ± 1.1	2.4 ± 1.1	0.138
KPS (mean ± SD)	51.5 ± 11.5	60.5 ± 18.1	0.134
ARDS (%)	5 (38)	14 (36)	1.000
DIC (%)	0	0	1.000
Bacteremia (%)	1 (14)	0	0.25
Radiological pattern (%)[a]			
Lobar	6 (50)	9 (23)	0.071
Bronchopneumonic	2 (17)	24 (62)	0.007
Ground grass opacity	1 (8)	3 (8)	1.000
Cavity	0	1 (3)	1.000
Mixed	3 (25)	4 (10)	0.337
Effusion	6 (50)	10 (26)	0.163
Portion of pneumonia			
Right	5 (42)	14 (36)	
Left	0	10 (26)	0.28
Bilateral	7 (58)	15 (38)	
Treatment and outcome (%)			
Antibiotics initially used			
SBT/ABPC	6 (46)	10 (26)	0.184
TAZ/PIPC	5 (38)	11 (28)	0.506
Cephalosporins	0	6 (15)	0.317
Carbapenems	0	8 (21)	0.177
β-lactams + NQ	2 (16)	0	0.059
Others	0	4 (10)	0.561
Outcome			
30-days mortality	3 (23)	1 (3)	0.049
In-hospital mortality	4 (31)	2 (5)	0.029
Pathogens isolated by sputum cultures[b]			
Acinetobacter baumannii	5		

Table 1 (*continued*)

	AP group (n = 13)	Non-AP (n = 39)	*p*-value
Acinetobacter nosocomialis	1		
Acinetobacter ursingii	1		
Acinetobacter spp.	6		
Streptococcus pneumoniae	1	2	
Streptococcus agalactiae		2	
Klebsiella pneumoniae		1	
Staphylococcus aureus	1	5	
MRSA	1	2	
MRCNS		1	
Escherichia coli		4	
Moraxella catarrahlis		2	
Hemophilis influenzae		2	
Enterobacter spp.		1	
Serratia marcescens		1	
Achromobacter spp.	1		
Raoultella ornithinolytica	1		
Normal flora		14[c]	

*AP, *Acinetobacter* spp. pneumonia; SD, standard deviation; SBT/ABPC, sulbactam/ampicillin; TAZ/PIPC, tazobactam/piperacillin; NQ, new quinolone; COPD, chronic pulmonary disease; GERD, ECOG-PS, Eastern Cooperative Oncology Group-performance status; KPS, Karnofsky Performance Status; ARDS, acute respiratory distress syndrome; DIC, Disseminated intravascular coagulation.

[a] One patient had no CT findings.

[b] Among AP group, other pathogens were detected in 6 of 13. *Acinetobacter* spp. were isolated in 7 of the 13 patients.

[c] As for identified pathogens, 14 showed normal flora. Six patients did not have sputum in non-AP group.

(100%, 13/13) and ceftazidime (83%, 10/13), except for aztreonam (8%, 1/13). This is the first case-control study of community-onset AP in Japan. Also, this is the second largest case-control study of community-onset AP in Southeast Asia. Previous studies reported that smoking history, alcohol consumption and existence of COPD were associated with community-onset AP [17–19]. These clinical features of community-onset AP were supported consistent with later theories. Alcohol has been shown to impair the phagocytic ability of neutrophils and lead to the dissemination of *A. baumannii*-infected mice [20]. Smoking decrease function in macrophages in lungs [21]. In our study, we noted features similar to most previous studies regarding patients' characteristics and clinical manifestations of community-onset AP. All patients were over 60 years. They showed unfavorable outcomes, had heavy alcohol consumption and poorer KPS compared with the control group as some previous reports had documented [17–19].

As for radiologic findings, lobar infiltrations were less frequently seen and bronchopneumonic infiltrations were more frequently seen among AP than in the non-AP group. As for laterality, 7 of the 12 (58%) showed the bilateral lung involvements and only right lung involvements were seen in 5 patients (42%), which may suggest transbronchial aspiration. In fact, 11 of the 13 patients (85%) had risk factors for aspiration pneumonia, such as cerebrovascular disorder, neurovascular disease or the use of a sleeping drug. It has previously been reported that community-onset AP is predominant in the rainy season due to bacterial character of *Acinetobacter* spp. In our study, 3 patients (17%) were diagnosed as AP in the rainy season, and 5 patients (28%) were seen in the winter season. There was no predominant seasonality which AP occurs more frequently in the rainy season. These features were quite different from those of the previous cohorts [17–19], and the difference may be attributable to the difference of weather condition among Japan, Thailand, Taiwan and Australia.

Outstandingly, susceptible testings for *Acinetobacter* spp. isolated in our study were sensitive for almost all the antibiotics except AZT. In contrast, previous studies in South Asia, *Acinetobacter* spp. were resistant to multiple-antibiotics [17–19]. The reason of this discrepancy remains unknown. Although all patients had received appropriate antibiotic therapy as initial treatment including doses used, mortality rates were as high as previous studies. These might be associated with poor general conditions of the patients, or unknown virulent factors might have existed.

Table 2
Severity by predictive values and prognosis of community-onset *Acinetobacter* spp. pneumonia (n = 13).

Predictive value	Category of pneumonia n (%)	30-day mortality rate[a] n (%)
A-DROP		
0-2	7 (54)	1 (14)
3	3 (23)	1 (33)
4-5	3 (23)	1 (33)
CURB-65		
0-1	4 (31)	1 (25)
2	4 (31)	1 (25)
3-5	5 (38)	1 (20)
PSI		
I-II	1 (8)	0
III	1 (8)	0
IV-V	11 (85)	3 (27)
I-ROAD		
A	3 (23)	0
B	4 (31)	1 (25)
C	6 (46)	2 (33)

[a] The denominator in frequency (%) for category of pneumonia is 3.

Some patients with community-onset AP who were categorized as mild to moderate by A-DROP and by CURB-65 died (Table 2). This might suggest that severity of community-onset AP might be underestimated, leading to the poor outcomes.

There are some limitations in our study. First, this is a retrospective study in a small population. Second, this study was a case-control design in which the level of the risk factors was not equal to the expected level in the population. Third, patients who were diagnosed as having AP based on Geckler 3 classification might be misclassified as having AP [22].

We concluded that patients with community-onset AP tended to have a history of heavy alcohol consumption and have more comorbidity showing a higher CCI score. More cases should be estimated and examined for clarifying the etiology and manifestations of AP.

COI statement

Mikamo H received Research funding from Sumitomo Dainippon Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Daiichi Sankyo Co., Ltd., Pfizer Co. Ltd., Astellas Pharma Inc., MSD K.K., Toyama Chemical Co. Ltd., MIYARISAN Pharmaceutical Co., Ltd., Shionogi & Co. Ltd.; Consulting fee/honorarium from Sumitomo Dainippon Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Daiichi Sankyo Co., Ltd., Pfizer Co. Ltd., MSD K.K., Astellas Pharma Inc., MIYARISAN Pharmaceutical Co., Ltd.

Acknowledgment

We are grateful for the diligent and thorough critical reading of our manuscript by Dr. Yoshihiro Ohkuni, Chief Physician, Taiyo and Mr. John Wocher, Executive Vice President and Director, International Affairs/International Patient Services, Kameda Medical Center (Japan). This study was partially supported by Research Grants

from the Ministry of Health, Labour, and Welfare inJapan (H28-Shinkou-Ippan-003).

References

[1] Houang ET, Chu YW, Leung CM, Chu KY, Berlau J, Ng KC, et al. Epidemiology and infection control implications of Acinetobacter spp. in Hong Kong. J Clin Microbiol 2001;39:228–34.
[2] Leung WS, Chu CM, Tsang KY, Lo FH, Lo KF, Ho PL. Fulminant community-acquired Acinetobacter baumannii pneumonia as a distinct clinical syndrome. Chest 2006;129:102–9.
[3] Metlay JP, Schulz R, Li YH, Singer DE, Marrie TJ, Coley CM, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. Arch Intern Med 1997;157:1453–9.
[4] 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:S27–72.
[5] Shindo Y, Sato S, Maruyama E, Ohashi T, Ogawa M, Hashimoto N, et al. Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. Chest 2009;135:633–40.
[6] Miyashita N, Matsushima T, Oka M. Japanese Respiratory Society. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. Intern Med 2006;45:419–28.
[7] British Thoracic Society Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults. Thorax 2001;56(4):1–64.
[8] Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730–54.
[9] Seki M, Watanabe A, Mikasa K, Kadota J, Kohno S. Revision of the severity rating and classification of hospital-acquired pneumonia in the Japanese Respiratory Society guidelines. Respirology 2008;13:880–5.
[10] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the eastern cooperative Oncology group. Am J Clin Oncol 1982;5:649–55.
[11] de Kock I, Mirhosseini M, Lau F, Thai V, Downing M, Quan H, et al. Conversion of Karnofsky performance status (KPS) and eastern cooperative Oncology group performance status (ECOG) to palliative performance scale (PPS), and the interchangeability of PPS and KPS in prognostic tools. J Palliat Care 2013;29:163–9.
[12] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[13] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 21st informational supplement. Wayne, PA: CLSI; 2011. M 100-S21.
[14] The Ministry of health, Labour and Welfare. Homepage https://www.mhlw.go.jp/www1/topics/kenko21_11/b5.html last accessed on 15 Apr 2019.
[15] Respiratory Society Japanese. Establishment of new severity ratings based on analysis of hospital-acquired pneumonia. Respirology 2009;14(2):S4–9.
[16] ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. J Am Med Assoc 2012;307:2526–33.
[17] Chen MZ, Hsueh PR, Lee LN, Yu CJ, Yang PC, Luh KT. Severe community-acquired pneumonia due to Acinetobacter baumannii. Chest 2001;120:1072–7.
[18] Anstey NM, Currie BJ, Withnall KM. Community-acquired acinetobacter pneumonia in the northern territory of Australia. Clin Infect Dis 1992;14:83–91.
[19] Patamatamkul S, Klungboonkrong V, Praisarnti P, Jirakiat K. A case-control study of community-acquired Acinetobacter baumannii pneumonia and melioidosis pneumonia in northeast Thailand: an emerging fatal disease with unique clinical features. Diagn Microbiol Infect Dis 2017;87:79–86.
[20] Gandhi JA, Ekhar VV, Asplund MB, Abdulkareem AF, Ahmadi M, Coelho C, et al. Alcohol enhances Acinetobacter baumannii-associated pneumonia and systemic dissemination by impairing neutrophil antimicrobial activity in a murine model of infection. PLoS One 2014;9:e95707.
[21] Graff JW, Powers LS, Dickson AM, Kim J, Reisetter AC, Hassan IH, et al. Cigarette smoking decreases global microRNA expression in human alveolar macrophages. PLoS One 2012;7:e44066.
[22] Geckler RW, Gremillion DH, McAllister CK, Ellenbogen C. Microscopic and bacteriological comparison of paired sputa and transtracheal aspirates. J Clin Microbiol 1977;6:396–9.