disturbance, low blood pressure), which is used in the CAP guidelines of the Japanese Respiratory Society [13]. Condition is mild if none of the items is present, moderate with one or two items present, severe with three items present, and very severe if there are four or five items present. If there is only one item present but it is shock (5), the condition is deemed very severe. In a multicenter prospective study ($n = 1{,}875$), ADROP score was correlated well with the mortality rate; mortality rates were 0 % for mild cases, 3.1 % for moderate, 9.9 % for severe, and 19.6 % for very severe cases [14]. For this study, patients were divided into three groups: mild-to-moderate, severe, and very severe groups.

NHCAP guidelines for empirical antimicrobial selection

The NHCAP guidelines divided patients into four groups, designated as Groups A to D, and recommended the choice of antimicrobials based on the category. Group A can be properly treated with outpatient care with oral medication. For Group D, at the greatest risk, multidisciplinary treatment, such as mechanical ventilation or ICU care, is needed with one or more anti-pseudomonal antimicrobials. For patients other than those in Groups A and D, (1) antibiotics administration within the past 90 days and (2) tube feeding are considered as risk factors for drug-resistant bacteria. Group B has no risk factors of drug-resistant bacteria; therefore, narrow-spectrum antibiotics are recommended. Group C has at least one risk factor. Because there is risk of drug-resistant bacteria, broad-spectrum antibiotics are recommended.

Statistical analysis

Data analysis software (IBM SPSS for Windows, version 19.0J; IBM SPSS, Chicago, IL, USA) was used for all statistical analyses. To compare categories between two groups, the chi-square test or Fisher's exact test was used. Continuous variables were shown as an interquartile range (IQR) or mean ± SD. The two-sample t test for a normal distribution and the Mann–Whitney test for a nonnormal distribution were used. Multiple logistic analysis was performed for the risk factors involved in mortality within 30 days and detection of drug-resistant bacteria in NHCAP. An α error of less than 5 % was considered significant.

Results

Criteria of NHCAP (Table 1)

Of the 718 patients who were evaluated, 477 (66.4 %) had NHCAP and 241 (33.4 %) had CAP. Elderly and physically handicapped patients who required nursing care accounted for the majority of NHCAP (418/477 patients, 87.6 %) and met two or more inclusion criteria for NHCAP.

Table 1 Criteria of nursing home- and healthcare-associated pneumonia (NHCAP)

NHCAP ($n = 477$)	n (%)
Number of criteria met for NHCAP[a] (IQR)	2 (1–2)
Admitted to long-term convalescent wards or nursing home	186 (39.0 %)
Discharged from the hospital within 90 days	142 (29.8 %)
Elderly and physically handicapped who require nursing care	418 (87.6 %)
Receiving intravascular treatment continuously on outpatient basis	24 (5.0 %)

IQR interquartile range

[a] Indicates inclusion of duplicated cases

Patient background and severity classification on admission (Table 2)

Significantly more patients with old age, poor PS, dementia, involvement of aspiration, gastrostoma, low serum albumin level, greater number of complications, chronic kidney disease, and central nervous system disease were found in the NHCAP group than in the CAP group. Significantly more patients had a history of previous administration of antibiotics or broad-spectrum antibiotics within 90 days and detection of MRSA in the NHCAP compared to the CAP group. Severity on admission was significantly higher in the NHCAP than in the CAP group.

Detected bacteria (Table 3)

Detected bacteria in NHCAP were more frequent, of the order of *S. pneumoniae*, MRSA, *Klebsiella* spp., and *Pseudomonas aeruginosa*; in CAP the frequency was of the order of *S. pneumoniae*, *Haemophilus influenzae*, and *Klebsiella* spp. Drug-resistant bacteria were detected in 60 cases (12.6 %) in the NHCAP group, which was significantly higher than the 5 cases (2.1 %) in the CAP group ($p < 0.001$). Although *S. pneumoniae* was detected most frequently in both NHCAP and CAP, the frequency was significantly higher in the CAP than in the NHCAP group ($p < 0.001$). *H. influenzae* was also detected with higher frequency in CAP than in NHCAP ($p = 0.025$).

Risk factors involved in the detection of drug-resistant bacteria in patients with NHCAP (Table 4)

Multiple logistic analysis was performed for risk factors involved in drug-resistant bacteria in the 195 NHCAP

Table 2 Background and severity classification on admission

	NHCAP ($n = 477$)	CAP ($n = 241$)	p value
Age (IQR)	84 (77–90)	74 (66–82)	<0.001
Male	274 (57.4 %)	153 (63.5 %)	0.119
PS (IQR)	4 (3–4)	0 (0–1)	<0.001
PS 0	29 (6.1 %)	163 (67.6 %)	
PS 1	13 (2.7 %)	45 (18.7 %)	
PS 2	19 (4.0 %)	33 (13.7 %)	
PS 3	93 (19.5 %)	0 (0 %)	
PS 4	323 (67.7 %)	0 (0 %)	
Complications (IQR)	2 (1–3)	1 (1–2)	<0.001
Malignant tumor	54 (11.3 %)	20 (8.3 %)	0.209
Chronic lung disease	141 (29.6 %)	101 (41.9 %)	0.001
Chronic heart disease	282 (59.1 %)	127 (52.7 %)	0.101
Chronic kidney disease	45 (9.4 %)	5 (2.1 %)	<0.001
Chronic liver disease	27 (5.7 %)	22 (9.1 %)	0.082
Central nervous system disease	253 (53.0 %)	38 (15.8 %)	<0.001
Diabetes	70 (14.7 %)	50 (20.7 %)	0.039
Immunodeficiency	32 (6.7 %)	9 (3.7 %)	0.105
Two or more underlying diseases	299 (62.7 %)	115 (47.7 %)	<0.001
Dementia[a]	342 (71.7 %)	23 (9.5 %)	<0.001
Involvement of aspiration[b]	358 (75.1 %)	24 (10.0 %)	<0.001
Gastrostoma	55 (11.5 %)	1 (0.4 %)	<0.001
History of previous administration of antibiotics within 90 days	231 (48.4 %)	87 (36.1 %)	0.002
History of previous administration of broad-spectrum antibiotics within 90 days[c]	125 (26.2 %)	39 (16.2 %)	0.003
History of MRSA detection	50 (10.5 %)	5 (2.1 %)	<0.001
Serum albumin level (g/dl) (IQR*)	3.1 (2.7–3.5)	3.4 (3.0–3.8)[d]	<0.001
A-DROP Score (IQR*)	3 (0–2–4–5)	0–2 (0–2–3)	<0.001
Mild to moderate (Score 0–2)[e]	160 (33.5 %)	167 (69.3 %)	
Severe (Score 3)	158 (33.1 %)	59 (24.5 %)	
Very severe (Score 4–5)	159 (33.3 %)	15 (6.2 %)	

IQR interquartile range, *CAP* community-acquired pneumonia, *MRSA* methicillin-resistant *Staphylococcus aureus*, *PS* performance status

PS 0, can be active without any problems or limitations, daily life the same as before the onset; PS 1, intense activity limited, but can walk and perform light work or work while sitting; PS 2, can walk and perform all personal care, but cannot work; more than 50 % of daytime hours out of bed; PS 3, can only do limited personal care; more than 50 % of daytime hours spent in bed or chair; PS 4, cannot move at all or perform personal care, all day spent in bed or chair

[a] Dementia: diagnosed by revised Hasegawa's Dementia Scale (HDS-R)

[b] Involvement of aspiration: dysphagia or aspiration confirmed or strongly suspected

[c] History of previous administration of broad-spectrum antibiotics: history of administration of anti-pseudomonal penicillin, third- and fourth-generation cephalosporin injection, new quinolone or carbapenem was present

[d] Score 0, 2 NHCAP cases, 34 CAP cases; Score 1–2, 158 NHCAP cases, 133 CAP cases

[e] Serum albumin level was measured in 238 cases

Mann–Whitney test

patients from whom 231 bacteria (more than 195 because of multiple isolation) were isolated, and their drug sensitivity was determined.

PS, central nervous system disease, gastrostoma, history of previous administration of antibiotics within 90 days, and being discharged from the hospital within 90 days were independent variables for the increased detection rate of drug-resistant bacteria.

Initial antibiotics (Table 5)

Monotherapy accounted for the majority of antibiotic therapies in both groups. The rate of monotherapy was significantly higher in NHCAP than in CAP ($p = 0.001$). The most frequent choice of drug was sulbactam/ampicillin (SBC/ABPC) in both groups, and the frequency of SBC/ABPC usage was significantly higher in NHCAP than in

Table 3 Detected bacteria

Detected bacteria	NHCAP ($n = 477$)	CAP ($n = 241$)
Gram-positive cocci	133 (27.9 %)	78 (32.4 %)
Streptococcus pneumoniae	76 (15.9 %)	71 (29.5 %)
MSSA	23 (4.8 %)	8 (3.3 %)
MRSA	38 (8.0 %)	2 (0.8 %)
Streptococci other than *Streptococcus pneumoniae*	10 (2.1 %)	0 (0 %)
Gram-negative bacilli	101 (21.2 %)	38 (15.8 %)
Pseudomonas aeruginosa	27 (5.7 %)	4 (1.7 %)
Klebsiella sp.	34 (7.1 %)	9 (3.7 %)
Klebsiella sp. ESBLs	1 (0.2 %)	0 (0 %)
Haemophilus influenzae	16 (3.4 %)	17 (7.1 %)
BLNAR	1 (0.2 %)	3 (1.2 %)
Enterobacter sp.	9 (1.9 %)	8 (3.3 %)
Esherichia coli	16 (3.4 %)	1 (0.4 %)
Esherichia coli ESBLs	0 (0 %)	0 (0 %)
Serratia sp.	3 (0.6 %)	1 (0.4 %)
Stenotrophomas maltophilia	0 (0 %)	0 (0 %)
Acinetobacter sp.	1 (0.2 %)	0 (0 %)
Citrobacter sp.	2 (0.4 %)	0 (0 %)
Moraxella catarrhalis	6 (1.3 %)	2 (0.8 %)
Proteus sp.	3 (0.6 %)	0 (0 %)
Anaerobic organisms	0 (0 %)	0 (0 %)
Other organisms	5 (1.0 %)	5 (2.1 %)
Atypical pathogens	0 (0 %)	4 (1.7 %)
Mycoplasma pneumoniae	0 (0 %)	2 (0.8 %)
Chlamydophila pneumoniae	0 (0 %)	0 (0 %)
Legionella pneumoniae	0 (0 %)	2 (0.8 %)
Unknown	280 (58.7 %)	132 (54.8 %)
Drug-resistant bacteria[a]	60 (12.6 %)	5 (2.1 %)

MSSA methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ESBLs* extended-spectrum β-lactamases, *BLNAR* β-lactamase-negative ampicillin-resistant *Haemophilus influenzae*

[a] Drug-resistant bacteria: *Pseudomonas aeruginosa*, MRSA, *Acinetobacter*, ESBL-producing *Enterobacteriaceae* were defined. When more than one organism was detected in the same patient, it was counted as one

Table 4 Risk factors involved in the detection of drug-resistant bacteria in NHCAP patients by multiple logistic analysis

	Adjusted odds ratio (95 % CI)	p value
Performance status	1.592 (1.111–2.282)	0.011
Central nervous system disease	2.756 (1.249–6.084)	0.012
Gastrostoma	5.459 (1.921–15.510)	0.001
History of previous administration of antibiotics within 90 days	4.108 (1.852–9.112)	0.001
Discharged from hospital within 90 days	3.448 (1.537–7.736)	0.003

Drug-resistant bacteria: *Pseudomonas aeruginosa*, MRSA, *Acinetobacter*, ESBLs. Multiple logistic analysis was performed for factors involved in drug-resistant bacteria in 195 cases of NHCAP in which microorganisms were detected (*CI* confidence interval). Model chi-square test, $p < 0.001$; Hosmer–Lemeshow test, $p = 0.983$; discriminant accuracy rate, 76.8 %

Table 5 Initial antibiotics

	NHCAP ($n = 467$)[a]	CAP ($n = 241$)
Monotherapy	433 (90.8 %)	198 (82.2 %)
Sulbactam/ampicillin	308 (64.6 %)	95 (39.4 %)
Cephalosporin	68 (14.3 %)	47 (19.5 %)
Carbapenem	34 (7.1 %)	27 (11.2 %)
Quinolone	10 (2.1 %)	13 (5.4 %)
Macrolide	1 (0.2 %)	10 (4.1 %)
Others	12 (2.5 %)	6 (2.5 %)
Combination therapy	34 (7.1 %)	43 (17.8 %)
β-Lactam + quinolone	14 (2.9 %)	18 (7.5 %)
β-Lactam + macrolide	8 (1.7 %)	17 (7.1 %)
β-Lactam + clindamycin	5 (1.0 %)	0 (0 %)
β-Lactam + vancomycin	1 (0.2 %)	0 (0 %)
Others	6 (1.3 %)	8 (3.3 %)
Anti-pseudomonal agents[b]	82 (17.2 %)	68 (28.2 %)
Anti-MRSA agents[c]	1 (0.2 %)	0 (0 %)

[a] Ten cases in NHCAP were excluded because antibiotics used were unknown

[b] Anti-pseudomonal agents: antibiotics with a spectrum against *Pseudomonas aeruginosa*

[c] Anti-MRSA agents: antibiotics with a spectrum against MRSA

CAP ($p < 0.001$). Frequency of choice for combination therapy and an anti-pseudomonal agent were significantly lower in NHCAP than in CAP ($p < 0.001$ and $p = 0.001$, respectively). An anti-MRSA agent was used in only one case of NHCAP.

Success or failure of initial treatment (Table 6)

Rates of improper treatment and of failure despite proper initial treatment were significantly higher in NHCAP compared to CAP. However, the failure rate of improper initial treatment did not differ significantly between groups. Mortality within 30 days and total hospital mortality among patients who received proper initial treatment were significantly higher in NHCAP than in CAP, but there was no significant difference between the two groups regarding patients who received improper initial treatment. Within the NHCAP group, success rates for patients who did and did not receive proper initial treatment were 76.9 and 78.5 %, respectively; mortality rates within 30 days were 13.1 and 13.8 %, respectively; and total hospital mortality was 24.6 and 21.5 %, respectively; there were no

Table 6 Success or failure of initial treatment in patients with NHCAP and CAP in which microorganisms were identified

	NHCAP	CAP	*p* value
Proper initial treatment	130/195 (66.7 %)	100/108 (92.6 %)	
Success	100/130 (76.9 %)	91/100 (91.0 %)	
Failure	30/130 (23.1 %)	9/100 (9.0 %)	0.005
Mortality within 30 days	17/130 (13.1 %)	3/100 (3.0 %)	0.007
Total hospital mortality	32/130 (24.6 %)	3/100 (3.0 %)	<0.001
Improper initial treatment	65/195 (33.3 %)	8/108 (7.4 %)	<0.001
Success	51/65 (78.5 %)	6/8 (75.0 %)	
Failure	14/65 (21.5 %)	2/8 (25.0 %)	0.562[a]
Mortality within 30 days	9/65 (13.8 %)	0/8 (0 %)	0.329[a]
Total hospital mortality	14/65 (21.5 %)	1/8 (12.5 %)	0.478[a]

[a] Fisher's exact test

significant differences between the two groups. Among NHCAP patients who received proper initial treatment, serum albumin levels were 3.1 ± 0.5 and 2.7 ± 0.7 g/dl in successful and failed cases, respectively, with levels significantly lower in failed cases ($p = 0.001$; data not shown). No significant difference in serum albumin levels in NHCAP patients who received improper initial treatment was found between successful cases and failed cases.

Success rate of initial treatment in NHCAP with regard to initial treatment and detected bacteria (Table 7)

The success rate against typical nondrug-resistant bacteria in NHCAP was approximately 70 % in patients who received proper initial treatment. On the other hand, the success rate against drug-resistant bacteria in NHCAP was approximately 80 % in patients who received inappropriate initial treatment.

Clinical outcome (Table 8)

Mortality within 30 days and total hospital mortality were significantly higher in NHCAP than in CAP. Length of stay was significantly longer in NHCAP than in CAP. Mortality within 30 days in NHCAP with regard to severity was nearly identical in the mild-to-moderate and severe groups but was increased approximately twofold in the very severe group. Total hospital mortality in NHCAP with regard to severity tended to rise with increasing severity. The difference between mortality within 30 days and total hospital mortality was greater in NHCAP compared to CAP.

Table 7 Success rate of initial treatment in patients with NHCAP with regard to initial treatment and detected bacteria

Nondrug-resistant bacteria in NHCAP	Success rate of proper initial treatment group
Streptococcus pneumoniae	50/66 (75.8 %)
MSSA	14/19 (73.7 %)
Klebsiella sp.	22/26 (84.6 %)
Haemophilus influenzae	8/12 (66.7 %)
Escherichia coli	10/13 (76.9 %)
"Drug-resistant bacteria" in NHCAP	Success rate of improper initial treatment group
MRSA	29/37 (78.4 %)
Pseudomonas aeruginosa	16/20 (80.0 %)

There were 130 cases in the proper initial treatment group and 65 cases in the improper initial treatment group. Success rates of initial treatment for the detected bacteria in each treatment group are shown

Table 8 Outcome

	NHCAP	CAP	*p* value
Mortality within 30 days	67/477 (14.0 %)	10/241 (4.1 %)	<0.001
Total hospital mortality	118/477 (24.7 %)	13/241 (5.4 %)	<0.001
Length of stay (IQR)	17 (10–34)	9 (7–13)	<0.001*
A-DROP mild to moderate, mortality within 30 days	16/160 (10.0 %)	2/167 (1.2 %)	
A-DROP severe, mortality within 30 days	16/158 (10.1 %)	8/59 (13.6 %)	
A-DROP very severe, mortality within 30 days	35/159 (22.0 %)	0/15 (0 %)	
A-DROP mild to moderate, total hospital mortality	26/160 (16.3 %)	3/167 (1.8 %)	
A-DROP severe, total hospital mortality	37/158 (23.4 %)	8/59 (13.6 %)	
A-DROP very severe, total hospital mortality	55/159 (34.6 %)	2/15 (13.3 %)	

IQR interquartile range

* Mann–Whitney test

Risk factors involved in mortality within 30 days in patients with NHCAP (Table 9)

Multiple logistic analysis to identify factors involved in mortality within 30 days in 477 cases of NHCAP showed

Table 9 Risk factors involved in mortality within 30 days in patients with NHCAP by multiple logistic analysis

	Adjusted odds ratio (95 % CI)	*p* value
Diabetes	2.394 (1.241–4.622)	0.009
Albumin <2.5 g/dl	2.766 (1.431–5.348)	0.002
A-DROP very severe	1.930 (1.102–3.382)	0.021
Image of extensive pneumonia[a]	2.541 (1.419–4.551)	0.002

Multiple logistic analysis was performed for factors involved in mortality within 30 days in 477 cases of NHCAP

[a] Image of extensive pneumonia: shadow of more than two-thirds of the unilateral lung in a plain chest X-ray: model chi-square test $p < 0.001$; Hosmer–Lemeshow test $p = 0.686$; discriminant accuracy rate 86.8 %

that diabetes, albumin <2.5 g/dl, A-DROP very severe, and images indicating extensive pneumonia were independent variables involved in increased mortality within 30 days.

Discussion

A new concept of NHCAP was announced by the Japanese Respiratory Society in 2011 [12]. NHCAP guidelines were formulated to properly treat pneumonia patients who are in need of home-based or long-term medical treatment or care for their everyday conditions. In comparison to CAP, NHCAP patients were older and more likely to require nursing care. The rate of poor nutrition, dementia, aspiration, and severe cases were higher in NHCAP than in CAP patients (Tables 1, 2), suggesting that patients in the NHCAP group should have received extensive medical care for their pneumonia.

The detection rate of drug-resistant bacteria was significantly higher in NHCAP compared to CAP (Table 3). It was revealed that PS, central nervous system disease, gastrostoma, a history of prior treatment with antibiotics within 90 days, and being discharged within 90 days were independent variables involved in the increased detection rate of drug-resistant bacteria in NHCAP (Table 4). Patients with NHCAP often had difficulty in expectorating sputum and in undergoing invasive tests, making it difficult to obtain good specimens. Because isolates from these patients contained indigenous bacteria from the oral cavity and colonizers of the airways, interpretation of pathogenic bacteria and their drug susceptibility was difficult. Because there was the potential for excessive antimicrobial therapy, sufficient consideration was necessary in choosing antibiotics to avoid excessive use of broad-spectrum drugs.

Bacteriological examination in this study might have three limitations: half of cases did not reveal any pathogenic bacteria, atypical pathogens were not examined elaborately, and more than one pathogenic bacteria was detected in 57 of 195 patients. In HCAP, including many aspiration pneumonia cases, anaerobe infection may be more frequent, leading to less detection of the causative bacteria [15, 16]. Even if aspiration pneumonia would have been caused by anaerobic bacteria, the drug-resistant bacteria might be that which was isolated. This possibility may have affected the result that improper antimicrobial selection did not change the survival. As for atypical pathogens, it had been reported that *Legionella* infections and atypical pathogens were uncommon [17, 18]. Therefore, meticulous effort to detect atypical pathogens might not change the results. The last limitation was the multiple isolation of pathogenic bacteria. Because we could not determine which of these caused the pneumonia, the case with at least one bacteria resistant to the antibiotics was categorized as improper initial treatment.

Previous reports of HCAP showed a significantly poorer prognosis in patients who received improper treatment compared to patients who received proper treatment [3, 4, 7, 8, 19–21]. However, we found no differences in the success rate, mortality within 30 days, and total hospital mortality between NHCAP patients who did or did not receive proper initial treatment (Table 6). The success rate was approximately 70 % with initial proper antibiotic use and approximately 80 % with initial improper treatment (Table 7). Therefore, we suspect that the drug-resistant bacteria detected in NHCAP, such as *Pseudomonas aeruginosa* and MRSA, might be colonizers, not the pathogens. Thus, in many cases SBT/ABPC was effective even when MRSA was detected in sputum. Brito et al. [22] and Ewig et al. [23] also raised similar issues. In our hospital, a medium-sized community hospital, the variety and frequency of detected bacteria might be different from those in large-scale or university hospitals, which could be the reason for high efficiency of SBT/ABPC and low importance of resistant bacteria in this study.

Mortality within 30 days and total hospital mortality were significantly higher and length of stay was significantly longer in NHCAP than in CAP (Table 8). Risk factors involved in mortality within 30 days were diabetes, albumin <2.5 g/dl, an image of extensive pneumonia, and A-DROP score indicating a "very severe" state (Table 9). This result demonstrated that the patients' nutritional conditions at baseline, diabetes, and albumin, as well as severity of the pneumonia, were important for their survival, rather than the drug susceptibility of the bacteria detected in their sputum. Yende et al. [24] also reported a high rate of mortality from pneumonia in diabetic patients.

There are several issues regarding NHCAP in this study to be resolved in the future. First, the treatment success rate was approximately 70 % even when appropriate antibiotics were used against nondrug-resistant bacteria in NHCAP,

such as *S. pneumoniae*. The prospective clinical trial of a pneumococcal vaccine demonstrated that both incidence of all pneumonia and mortality from pneumococcal pneumonia were reduced [25]. The rate of pneumococcal vaccination in Japan was about 10 %. It is hoped that vaccination will be actively promoted.

Second, a new classification of NHCAP patients based on severity of pneumonia was needed. The A-DROP system may be potentially useful in considering total hospital mortality with regard to the severity of NHCAP. However, mortality within 30 days was almost the same in the mild-to-moderate and the severe groups. Therefore, a new index of severity must include the absence or presence of diabetes, serum albumin concentration, and the range of consolidation on chest X-ray. The use of serum albumin level was also recommended by Hedlund et al. [26].

Third, caution is urged with regard to gastrostomy. The risk of aspiration pneumonia in patients with NHCAP was high, and when oral intake becomes difficult, gastrostomy may be performed. However, we suggest that gastrostomy is not recommended as a precaution against pneumonia [27]. In this study, the presence of a gastrostoma was found to increase the risk of resistant bacteria.

NHCAP, primarily occurring in the elderly requiring nursing and home-based medical care, needed special consideration for treatment. We conclude that the severity of pneumonia, rather than the risk of resistant bacteria, should be considered as well as physicians' ethical judgment and end-of-life decisions of the patients and their families in the initial treatment strategy to avoid excessive use of broad-spectrum antimicrobials.

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Conflict of interest None.

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●症 例

重症インフルエンザA（H1N1）2009 pdm肺炎の3例

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要旨：2011年1～2月にインフルエンザA（H1N1）2009 pdm重症肺炎の3例を経験した．内訳は40～45歳の男性2例と女性1例で，2例に肥満あり，2例は精神疾患治療中で1例は糖尿病であった．ワクチン接種済みは1例であった．発症から呼吸不全発現までは5～7日の経過で，鼻腔拭い迅速検査陽性は1例のみ．CT上はいずれも汎小葉性すりガラス影主体の重症肺炎で，1例は挿管管理を要した．診断は，2例で施行した咽頭拭いインフルエンザRNAの陽性，ほか1例でのペア血清AH1の有意上昇で行ったが，いずれの症例も初期の診断・治療に難渋した．

キーワード：インフルエンザA（H1N1）2009 pdm，重症肺炎，集学的治療
Influenza A (H1N1) 2009 pdm, Severe pneumonia, Combined modality therapy

緒 言

新型インフルエンザA/H1N1感染症は，我が国では2009年5月に最初の患者が確認されて以来，2009年度は累計2,061万人が外来受診をした．国立病院機構東京病院でも若年者を中心にインフルエンザ患者が増加し，インフルエンザを契機に呼吸器疾患を合併した症例を経験した[1]．2010年度は冬にインフルエンザ患者数のピークを迎え，例年の季節型インフルエンザと同時期の流行・患者数であり，また複数のウイルス型が混在していたことから，ポストパンデミック（pdm）の状態への移行が示唆された．これを受け，2010年度をもって新型インフルエンザA/H1N1は感染症法に基づく「新型インフルエンザ等感染症」とせず，インフルエンザA(H1N1) 2009 pdmと名称変更された[2]．

その一方で，インフルエンザA（H1N1）2009 pdmの重症患者が認められた．2011年初頭に国立病院機構東京病院において中年層の患者3名のインフルエンザA（H1N1）2009 pdm重症肺炎を経験したので，若干の文献的考察を加えて報告する．

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症 例

【症例1】

患者：40歳，女性．無職．喫煙 なし．

主訴：咳嗽，呼吸困難．

既往歴：糖尿病．脂肪肝．統合失調症のため抗精神病薬を多数内服．

現病歴：2011年1月，入院9日前に感冒症状が出現した．2日前に38℃の発熱を認め近医を受診し，鼻腔迅速インフルエンザ検査を受けたが陰性のため，解熱薬が処方された．その頃から咳嗽・呼吸困難が出現した．入院前日夜間に症状悪化し，翌日近医にて室内気でSpO_2 65%と著明な低酸素血症が認められ，国立病院機構東京病院へ救急搬送された．当院での鼻腔迅速インフルエンザ検査も再度陰性であった．

入院時身体所見：身長157 cm，体重92 kg（BMI 37.3 kg/m^2），血圧154/77 mmHg，脈拍111回/min，呼吸数24回/min，体温37.4℃，SpO_2 90%（O_2 10 L/min吸入下）．両側下肺野でfine cracklesを聴取．皮疹・関節痛・筋肉痛認めず．四肢に浮腫軽度触知する．

検査所見：WBC 5,600/μl（Seg 79%，Band 6%，Mono 3%，Lym 12%），Hb 13.0 g/dl，Plt 10.9×10^4/μl，TP 6.6 g/dl，Alb 3.2 g/dl，T-Bil 0.43 mg/dl，AST 93 U/L，ALT 79 U/L，LDH 587 U/L，CPK 590 IU/L，BUN 8.1 mg/dl，CRE 0.56 mg/dl，CRP 19.3 mg/dl，Na 138 mEq/L，K 4.3 mEq/L，HbA1c（JDS）8.9%，KL-6 216 U/ml，SP-D 252 ng/ml，マイコプラズマPA 20倍未満，抗核

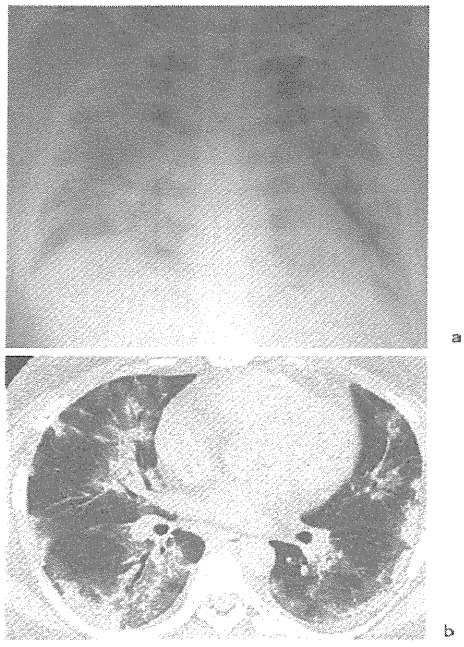

Fig. 1 (a) Chest X-ray on admission showed bilateral diffuse infiltration. (b) Chest CT showed diffuse panlobular ground glass opacity (GGO) and consolidation, along with the bronchovascular bundles.

抗体 40 倍未満，尿中肺炎球菌抗原（−），尿中レジオネラ抗原（−），鼻腔迅速インフルエンザ検査（−）．

画像所見：胸部単純 X 線写真（Fig. 1a）では両側肺びまん性すりガラス影，浸潤影を認め，胸部単純 CT（Fig. 1b）では末梢側と気管支血管束に沿った汎小葉性のすりガラス影・浸潤影を多発性に認めた．

入院後経過：経過としてインフルエンザ感染症も疑われたが，鼻腔迅速インフルエンザ検査は前医 2 回，国立病院機構東京病院で 1 回の計 3 回陰性であった．非定型肺炎，急性間質性肺炎，薬剤性肺炎が当初考慮され，入院日よりステロイドパルス療法，およびセフトリアキソン（ceftriaxone）＋シプロフロキサシン（ciprofloxacin）の投与が行われた．しかし呼吸状態は悪化し，第 3 病日に挿管・人工呼吸管理となった．第 4〜5 病日に polymyxin-B direct hemoperfusion（PMX-DHP）療法を施行した．臨床的にはインフルエンザ肺炎も否定できなかったため，第 4 病日よりオセルタミビル（oseltamivir）も追加投与した．呼吸状態は PMX-DHP 療法 2 回目終了時点より徐々に改善に転じ，第 11 病日に抜管できた．その後再燃なく治癒した．ペア血清でインフルエンザ A H1 抗体価が 10 倍未満から 320 倍に上昇を認め，重症インフルエンザ肺炎と診断した．

【症例 2】

患者：41 歳，男性．職業　郵便局員．喫煙　なし．

主訴：発熱，咳嗽，呼吸困難．

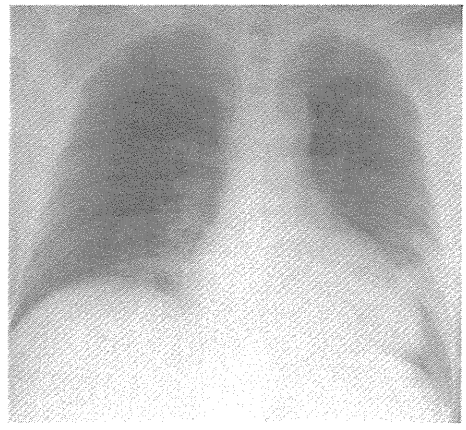

Fig. 2 Chest X-ray on admission showed dominant bilateral lower lung field GGO.

既往歴：慢性心不全（内服加療中）．

現病歴：2011 年 2 月，入院 6 日前より発熱・咳嗽が出現した．様子をみるも症状悪化し，5 日後近医を受診した．体温 40℃，SpO_2 90%（室内気），鼻腔インフルエンザ迅速検査（−）であった．肺炎の診断のもとに近医に入院したが，抗菌薬の効果は乏しく，翌日呼吸不全の急速な進行が認められ，同日国立病院機構東京病院に転院となった．

入院時身体所見：身長 178 cm，体重 83 kg（BMI 26.1 kg/m^2），血圧 140/80 mmHg，脈拍 110 回/min，呼吸数 21 回/min，体温 39.8℃，SpO_2 92%（O_2 10 L/min 吸入下）．両側下肺野で fine crackles 聴取．皮疹・関節痛・筋肉痛・末梢浮腫認めず．

検査所見：WBC 3,900/μl（Neu 88%，Mono 3%，Lym 9%），Hb 13.0 g/dl，Plt 12.8×10^4/μl，TP 6.8 g/dl，Alb 3.6 g/dl，T-Bil 0.43 mg/dl，AST 117 U/L，ALT 94 U/L，LDH 852 U/L，CPK 1,213 IU/L，BUN 22.7 mg/dl，CRE 1.13 mg/dl，CRP 15.3 mg/dl，Na 131 mEq/L，K 3.3 mEq/L，HbA1c（JDS）6.0%，KL-6 230 U/ml，SP-D 106 ng/ml，マイコプラズマ PA 40 倍，抗核抗体 40 倍未満，尿中肺炎球菌抗原（−），尿中レジオネラ抗原（−），鼻腔迅速インフルエンザ検査（−）．

画像所見：胸部単純 X 線写真（Fig. 2）では両側肺びまん性すりガラス影を認め，胸部単純 CT では両側下葉を中心に気管支血管束に沿った汎小葉性のすりガラス影・浸潤影を多発性に認めた．

入院後経過：本症例でも鼻腔迅速インフルエンザ検査は前医 1 回，当院で 1 回の計 2 回陰性であった．しかし経過からインフルエンザ肺炎が疑われ，ペラミビル（peramivir）/パズフロキサシン（pazufloxacin）/シベレスタット（sivelestat）使用に加えステロイドパルス療法を 3 日間施行し，当初 NPPV（non-invasive positive

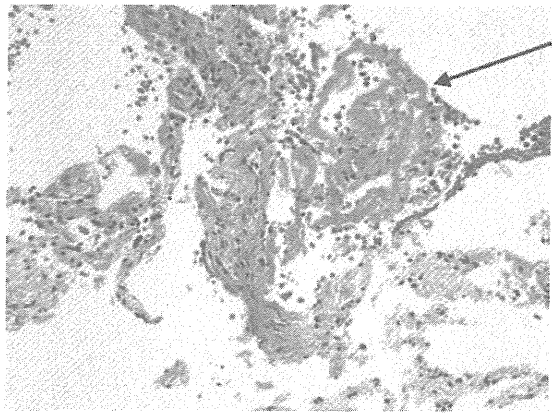

Fig. 3　The specimen of transbronchial lung biopsy (TBLB) showed diffuse thickening of the alveolar wall and hyaline membrane formation (arrow), namely, diffuse alveolar damage (DAD) (hematoxylin-eosin stain).

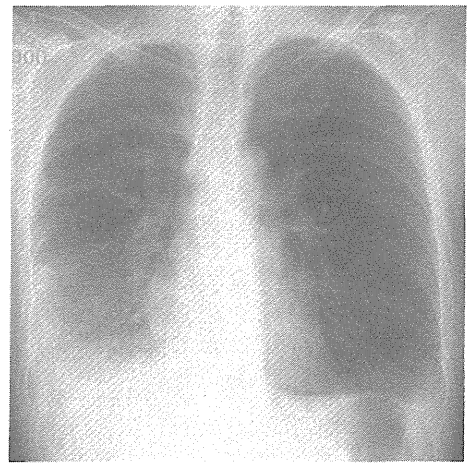

Fig. 4　Chest X-ray on admission showed bilateral GGO and consolidation.

pressure ventilation）も併用した．第3病日に入院初日に採取した咽頭拭い液におけるインフルエンザ（H1N1）2009 pdm RT-PCR 陽性と判明した．一方，入院後呼吸状態の改善は不十分であったため，第5～6病日にPMX-DHP 療法を施行，その後治癒した．本症例では第2病日に気管支鏡検査を施行し，右下葉の経気管支肺生検（Fig. 3）において胞隔のびまん性の肥厚・硝子膜形成を認めており，びまん性肺胞障害（diffuse alveolar damage: DAD）の所見であった．生検検体を用いたインフルエンザA（H1N1）2009 pdm PCR は陽性であった．

【症例3】

患者：45歳，男性．職業　元板金屋．喫煙　20本×20年．

主訴：発熱．

既往歴：うつ病・パニック障害（内服加療中）．

現病歴：2011年1月，入院6日前に38℃の発熱が出現し，様子をみるも改善せず4日後近医を受診した．鼻腔インフルエンザ迅速キットA型陽性であり，インフルエンザと診断された．発症後時間経過していたため，抗インフルエンザ薬は投与されなかった．発熱が持続し抗菌薬の効果が乏しく，入院当日，近医での胸部単純X線写真にて両側肺炎像を認め，国立病院機構東京病院に紹介となった．

入院時身体所見：身長・体重　不測（明らかな肥満・痩せなし），血圧91/60 mmHg，脈拍106回/min，呼吸数20回/min，体温40.0℃，SpO_2 82%（室内気）．右下肺野で fine crackles 聴取．両下肢膝関節痛・筋肉把握痛あり．皮疹・末梢浮腫認めず．

検査所見：WBC 8,800/μl（Neu 79%，Mono 8%，Lym 13%），Hb 12.7g/dl，Plt 21.9×10^4/μl，TP 5.5 g/dl，Alb 2.7 g/dl，T-Bil 0.3 mg/dl，AST 136 U/L，ALT 91 U/L，LDH 635 U/L，CPK 148 IU/L，BUN 9.3 mg/dl，CRE 0.98 mg/dl，CRP 31.0 mg/dl，Na 135 mEq/L，K 5.3 mEq/L，HbA1c（JDS）5.4%，マイコプラズマPA 20倍未満，尿中肺炎球菌抗原（－），尿中レジオネラ抗原（－），鼻腔迅速インフルエンザ検査（－）．

画像所見：胸部単純X線写真（Fig. 4）では下肺野優位（右肺＞左肺）にすりガラス影・浸潤影を認め，胸部単純CTでは両側下葉を中心に胸膜直下優位の浸潤影・すりガラス陰影と小葉間隔壁の肥厚を認めた．

入院後経過：鼻腔拭い液によるインフルエンザ迅速検査は前医で陽性であったが，当院で2回施行した検査は陰性であった．インフルエンザ肺炎と細菌性肺炎の合併が疑われ，oseltamivir/ceftriaxone/ciprofloxacin を使用した．第3病日に第2病日採取の咽頭拭い液におけるインフルエンザA（H1N1）2009 pdm RT-PCR 陽性と判明．上記治療にて改善不十分であったため，第5病日にperamivir を追加投与したところ，再燃なく治癒した．本症例では第6病日に気管支鏡検査を施行し，右下葉の経気管支肺生検において肺胞腔の滲出性・器質化病変を広範に認めた．なお，気管支肺胞洗浄液は血性で，インフルエンザ PCR は陰性であった．

今回我々が経験したインフルエンザA（H1N1）2009 pdm 重症肺炎3例の特徴を Table 1 に示す．

患者背景としては年齢40～45歳の男性2例と女性1例で，2例に肥満あり，基礎疾患として2例は精神疾患治療中で1例は糖尿病であった．ワクチン接種済みは1例，また発症から医療機関受診まで2～5日であった．

Table 1 Characteristics of the three patients

	Case 1	Case 2	Case 3
Age	40	41	45
Obesity	(+)	(+)	(−)
Psychiatric disorder	(+)	(−)	(+)
Vaccination	(−)	(−)	(+)
CT findings	diffused GGO and consolidation	lower lung dominant GGO	lower lung dominant GGO and consolidation
Diagnostic evidence	serological test	pharyngeal swabs RT-PCR TBLB specimen RT-PCR serological test	pharyngeal swabs RT-PCR serological test
Antiinfluenza drug (onset-administration days)	oseltamivir (12)	peramivir (6)	oseltamivir (7), peramivir (10)
PMX-DHP/ steroid	(+/+)	(+/+)	(−/−)
Mechanical ventilation	(+) IPPV	(+) NPPV	(−)
Outcome	cured	cured	cured

考 察

我が国の2010年9月～2011年3月上旬のインフルエンザの発生動向によると[2]，国民の12人に1人，累計1,030万人がインフルエンザで医療機関を受診し，受診者の2万人に1人が重症化したと推計された．重症者報告数は417例，平均年齢39.5歳，65歳未満の割合は76%であり，前年度より高年齢にシフトしたものの，依然比較的若年層に多かった．15歳以上に絞ると，何らかの基礎疾患をもつ患者が76%であった．また，海外では高度肥満を重症化因子とする報告が多い[3][4]．年齢層・基礎疾患や肥満の有無に関しては，当院症例においても重症例の特徴が少なからず認められた．

本症例におけるインフルエンザの診断はペア血清，咽頭拭い液インフルエンザRT-PCR，肺組織PCR検査によってなされた．当院における鼻腔拭い液迅速診断キット検査（ラピッドテスタ®FLUスティック使用）は3症例計4回すべて陰性であった．インフルエンザ迅速診断キットのインフルエンザA（H1N1）2009 pdm感染症における感度は報告によりばらつきがあるが，2009年のCDCの報告では40～69%[5]と低い．また，使用キット間による感度差の報告もあり，検出原理や抽出法の違いが指摘されている[6]．当院症例はいずれも発症から検体採取までの期間に開きがあること，検体採取部位がいずれも鼻腔であったことが，感度の低さにかかわっていた可能性がある．重症例においては，より感度が良いといわれる気管支洗浄液等の下気道検体を用いた診断も考慮される．また，インフルエンザA（H1N1）2009 pdmを従来のインフルエンザA型と分離して診断可能な迅速抗原キット（クリアライン®）や，迅速RT-PCRキット（新型インフルエンザA（H1N1）Real-Time Detection kit®）も今後使用が検討される．

Bautistaら[3]，Gomezら[7]は，本疾患の画像所見に関して，単純X線写真ではびまん性の間質性あるいは肺胞性陰影の混合，単葉性・多葉性の分布を示し，CTでは，多発性すりガラス陰影や肺胞浸潤影と気管支透亮像など多彩であると報告しており，細菌性肺炎の合併も相まって画像所見は複雑である．しかしながら，ウイルス性肺炎の画像所見としては，末梢の多発性すりガラス陰影，気管支血管周囲のすりガラス陰影が特徴的である[8][9]という指摘があり，当院の症例でも同様の所見が認められる．

当院症例における経気管支肺生検所見は症例2でDAD，症例3は器質化肺炎の所見を呈していた．本疾患の病理所見としては，DAD，胞隔肥厚，気管気管支炎，壊死性細気管支炎，肺胞出血が観察されるとされており[10]，症例2はこれに合致していた．症例3は非典型的であったが，治療にて改善してきた時点の生検であり，治癒過程にある所見と判断した．

治療では，今回の症例はいずれも発症日から抗インフルエンザ薬投与まで6～12日経過しており，oseltamivirやperamivirが使用されていた．抗インフルエンザ薬開始の遅れは重症化と死亡率上昇に関与するといわれている[11][12]．Kelvinらによれば[13]，インフルエンザA（H1N1）2009 pdm感染症で入院した74人の患者のなかで，ARDSを呈した重症者37人と軽症者37人で臨床的特徴を比較したところ，重症者においては症状発現から入院までの日数が長く，高サイトカイン血症を呈し，抗インフルエンザ薬使用によるウイルス量低下が遅れたことを報告している．本症例でも医療機関受診の遅れと診断困難により抗インフルエンザ薬の開始が遅れ，重症化したことが示唆された．また，インフルエンザA（H1N1）2009 pdmにおいてoseltamivir耐性は1%程度との報告がある[14]．今回症例2，3においてperamivirが使用されたが，peramivirは経静脈的に投与可能であり，内服

困難な症例やoseltamivir耐性が疑われる症例での投与が考慮される[15]．重症例ではステロイド投与・PMX-DHP療法が使用された．インフルエンザA（H1N1）2009 pdm重症肺炎におけるステロイド治療に関しては見解が割れており[16][17]，またPMX-DHP療法の有用性に関する報告も現時点では少ないが[18]，いずれも炎症性サイトカインの過剰発現による「サイトカインストーム」状態の制御による病態改善が期待される．今回自験例2例において上記使用後の病態改善が認められ，重症呼吸不全を呈する例において，早期に，集学的治療の一環として考慮される治療手段と思われた．

今回の3症例は発症から治療開始までに時間を要しており，インフルエンザ流行期では，インフルエンザの早期受診の啓蒙と，重症肺炎症例では鼻腔拭い液迅速診断キット検査が陰性の場合でも，臨床的にインフルエンザ肺炎が疑われる場合は早期に抗インフルエンザ薬による治療を開始し，集学的治療を行うことが肝要と考えられた．

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Abstract

Three cases of influenza A (H1N1) 2009 pdm severe pneumonia

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In January and February 2011, we experienced on 3 cases of severe pneumonia caused by influenza A (H1N1) 2009 pdm. The patients were 2 males and 1 female: 2 were obese, 2 with psychiatric disorders, 1 was diabetic, and 1 had been vaccinated for the influenza virus. The disease progressed in the 5 to 7 days from the onset of symptoms to admission with acute respiratory failure. Although nasal swab rapid-diagnostic tests were negative except for one patient, the final diagnosis of the other pneumonia was later made. A detection of the other RNA in two cases and with elevation of anti-H1 antibody titer by paired serum in the other. HRCT images demonstrated panlobular ground glass opacities in all cases. A transbronchial lung biopsy, performed in two cases, detected diffuse alveolar damage in one case and organizing pneumonia in the other. As for treatment, along with oseltamivir and/or peramivir applied as antiviral drugs, steroid pulse therapy and/or polymyxin-B direct hemoperfusion (PMX-DHP) therapy were applied in two cases. One patient was intubated and mechanically ventilated, and the other was noninvasively ventilated. All cases were fully recovered and discharged, although we experienced difficulty in initial diagnosis and treatment.

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