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The Case Fatality Rate of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infection among the Elderly in a Geriatric Hospital and Their Risk Factors

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WASHIO, M., KIYOHARA, C., HAMADA, T., MIYAKE, Y., ARAI, Y. and OKAYAMA, M. *The Case Fatality Rate of Methicillin-Resistant Staphylococcus aureus (MRSA) Infection among the Elderly in a Geriatric Hospital and Their Risk Factors.* Tohoku J. Exp. Med., 1997, **183** (1), 75-82 —— From April 1991 to March 1993, there were 49 elderly patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infection in a geriatric hospital in Fukuoka, Japan. The retrospective study was carried out in order to evaluate the various factors which may influence the case fatality rate of MRSA infection among the elderly. Among them, 33 patients (67.3%) died while only 16 patients became culture-negative for MRSA and discharged after recovering from MRSA infection. A univariate analysis revealed that male sex (odds ratio [OR] = 12.25, 95% confidence interval [CI] = 2.80-53.55), hypoalbuminemia (OR = 3.83, 95% CI = 1.11-13.21) and an excessive usage of antibiotics (OR = 6.67, 95% CI = 1.70-26.09) were risk factors for death among the patients with MRSA infection. In a multivariate analysis, male sex and an excessive usage of antibiotics were still risk factors while hypoalbuminemia was not. However, hypoalbuminemina was more common in male patients than female patients (78.3% vs. 42.3%, $p < 0.05$). These findings suggest that the case fatality rate of MRSA infection may be high and also suggest that the elderly with MRSA infection who had hypoalbuminemia and/or received many antibiotics may have a poor prognosis. ———— MRSA; case fatality rate; antibiotics; hypoalbuminemia; elderly

The first strain of methicillin-resistant *Staphylococcus aureus* (MRSA) was reported in the United Kingdom in 1961, only two years after the introduction of

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methicillin (Jevons 1961). Since then similar strains have been isolated in other part of the world (Barret et al. 1967). Because MRSA represents a high level of resistance for all antibiotics except for a few such as vancomycin and arbekacin in Japan (Yamaguchi and Ohno 1992), the development of MRSA strains has become a serious clinical and social problem as a causative pathogen of nosocomial infections. The elderly patients have been reported to be one of the high risk groups for MRSA infection (Inamatsu et al. 1992). It is, therefore, an urgent problem to reduce the incidence of MRSA infection in geriatric hospitals.

Our previous studies (Kajioka et al. 1993; Yoshimitsu et al. 1994; Washio et al. 1995, 1996, 1997) showed that inability or difficulty in performing activities of daily livings (ADL), poor nutritional status such as hypoalbuminemia and the use of antibiotics are the important risk factors for MRSA infection in the elderly. The purpose of the present study is to investigate the case fatality rate of the patients with MRSA infection in a geriatric hospital and their risk factors for death.

Subjects and Methods

In a geriatric hospital, 157 elderly patients underwent bacterial cultures on the basis of clinical evidence of infection during the two fiscal years from April 1991 to March 1993. The hospital chosen in the present study consisted of an internal medicine ward with rehabilitation units (120 beds) and a psychiatric ward for evaluating and treating dementia (60 beds). The average durations of hospitalization were 101 days for internal medicine ward patients and 125 days for psychiatric ward patients. About 35 patients were transferred to acute hospital units from our hospital every fiscal year. However, most patients, who could not return their own homes, were transferred to geriatric or psychiatric hospitals with long stay units or elderly care nursing homes after their treatments in our hospital.

MRSA was isolated from the materials of 49 patients, whose materials included sputum (35), urine (8), stool (1) and pus from decubital ulcer (5). Among them, 33 patients (67.3%) died while 16 patients (32.7%) became culture-negative for MRSA at least twice and were discharged after recovering from MRSA infection. The died patients were used as cases and the recovered patients as controls. A case-control study was carried out in order to evaluate the various factors which may influence the prognosis of the elderly with MRSA infection. The factors investigated were the number of antibiotics administered prior to the bacterial culture, the use of new cephems including third generation cephalosporin and monobactam and carbapenem, the coinfection with *Pseudomonas aeruginosa*, the age and sex of the patients, an evaluation of the ADL at the time of bacterial culture and the nutritional state as expressed by the serum albumin. The number of antibiotics administered and the ADL score were determined in the same manners as that described in the previous studies (Kajioka et al. 1993; Yoshimitsu et al. 1994; Washio et al. 1995, 1996, 1997). Any antibiotics administered more

than three days and within two weeks prior to the bacterial culture were counted as one antibiotics administered. When materials were examined for a bacterial culture more than twice, the number of antibiotics administered was the number of antibiotics prior to the first isolation of MRSA. The ADL score was calculated as the sum of the abilities to successfully perform ADL. Those who could take meals by themselves received one point for meals, those who could walk by themselves got one point for movement and those who could urinate and have bowel movements by themselves were given one point for toilet function.

The diagnosis of MRSA was made by the Showa disk method (Showa Yakuhin Kako, Tokyo) (Yamane and Tosaka 1991). Serum albumin was measured by using autoanalyzer (Olympus, Tokyo).

A statistical analysis was performed using the Statistical Analysis System package (SAS Institute Inc., Cary, NC, USA). Significance was determined by the chi-square test and p value of less than 0.05 taken as significant. A logistic regression analysis was used to control for the possible confounding factors on the death from MRSA infection. The sizes of effects were reported as odds ratio (OR) and 95% confidence interval (95% CI).

TABLE 1. *Risk factors for death among the patients with MRSA infection in a geriatric hospital: A univariate analysis*

Risk factor	Died ($n=33$)	Recovered ($n=16$)	OR (95% CI)
Gender Male vs. Female	21/12	2/14	12.55 (12.80−53.55)
Age (years) 80+ vs. −79	17/16	10/6	0.64 (0.19−2.18)
Hypoalbuminemia +vs. −	23/10	6/10	3.83 (1.11−13.21)
Activities of daily livings			
Dining function + vs. −	6/27	5/11	0.49 (0.12−1.94)
Toilet function + vs. −	3/30	4/12	0.30 (0.06−1.48)
Walking function + vs. −	3/30	5/11	0.22 (0.05−1.01)
ADL score 2-3 vs. 0-1	3/30	5/11	0.22 (0.05−1.01)
No. of antibiotics 2+ vs. 0-1	20/13	3/13	6.67 (1.70−26.09)
3rd generation cephems + vs. −	19/14	5/11	2.99 (0.85−10.45)
P. aeruginosa + vs. −	22/11	7/9	2.57 (0.76−8.73)

OR, odds ratio; 95% CI, 95% confidence interval; Hypoalbuminemia, serum albumin <3.5 g/100 ml; ADL score, ADL score was calculated as the sum of the abilities to successfully perform ADL.

Those who could take meals by themselves received one point for meals, those who could walk by themselves got one point for movement and those who could urinate and have bowel movements by themselves were given one point for toilet function.

No. of antibiotics, the number of antibiotics prior to the first isolation of MRSA; 3rd generation cephems, third generation cepharosporin, monobactam and carbapenem; *P. aeruginosa*, co-infection with *Pseudomonas aeruginosa*.

Results

A univariate analysis revealed that male sex, hypoalbuminemia and the use of two and more antibiotics were risk factors for death from MRSA infection (Table 1). Higher ADL score tended to reduce the risk for death but failed to show the statistical significance ($p=0.051$). In a multivariate analysis, male sex and the use of two and more antibiotics were still significant risk factors for death while hypoalbuminemia was not so (Table 2). However, hypoalbuminemia was more common in male patients than female patients (Table 3). In contrast, the proportion of the patients who had received two and more antibiotics was similar between two sexes. In addition, the proportion of the elderly who had received two and more antibiotics before bacterial culture was similar between the patients with and without hypoalbuminemia (Table 4). Therefore the result of a

Table 2. *Risk factors for death among the patients with MRSA infection in a geriatric hospital: A multivariate analysis*

Risk factor	Died ($n=33$)	Recovered ($n=16$)	OR (95% CI)
Gender Male vs. Female	21/12	2/14	3.46 (1.37−8.73)
Hypoalbuminemia + vs. −	23/10	6/10	1.59 (0.71−3.56)
No. of antibiotics 2+ vs. 0-1	20/13	3/13	3.09 (1.32−7.25)

OR, odds ratio; 95% CI, 95% confidence interval; Hypoalbuminemia, serum albumin <3.5 g/100 ml; No. of antibiotics, the number of antibiotics prior to the first isolation of MRSA.

Table 3. *The hypoalbuminemia and a lot of usage of antibiotics in male patients and female patients*

Fcator	Male ($n=23$)	Female ($n=26$)	p-Value
Hypoalbuminemia + vs. −	18/5	11/15	$p<0.05$
No. of antibiotics 0-1 vs. 2+	11/12	15/11	n.s.

Hypoalbuminemia, serum albumin <3.5 g/100 ml; No. of antibiotics, the number of antibiotics prior to the first isolation of MRSA; n.s., not significant.

Table 4. *A lot of usage of antibiotics in patients with and without hypoalbuminemia*

Fcator	Hypoalbuminemia		p-Value
	with ($n=29$)	without ($n=20$)	
No. of antibiotics 0-1 vs. 2+	15/14	11/9	n.s.

Hypoalbuminemia, serum albumin <3.5 g/100 ml; No. of antibiotics, the number of antibiotics prior to the first isolation of MRSA; n.s., not significant.

multivariate analysis must have underestimated the effect of gender and hypoalbuminemia.

These results of the statistical analysis indicated that either male sex, hypoalbuminemia or the use of two and more antibiotics was a risk factor for death from MRSA infection. In addition, they also indicated that hypoalbuminemia and the use of two and more antibiotics as well as male sex and the use of two and more antibiotics were independent risk factors.

Discussion

In the present study, 33 out of 49 (67.3%) of patients with MRSA infection died while only 16 patients (32.7%) recovered from MRSA infection. The very high case fatality rate (67.3%) in the present study suggests that the elderly with MRSA infection may have a poor prognosis. Although intensive infectious control measures are less justified in nursing homes (Inamatsu and Fukayama 1993; Duckworth and Heathcock 1995), these MRSA carriers from long-term care facilities are the potential sources for hospital outbreak following admission (Fraise et al. 1997). Furthermore, our previous study showed that the MRSA isolation during the previous hospitalization is a risk factor for MRSA infection among the nursing home residents (Washio et al. 1996). The prevention of MRSA infection in geriatric hospitals seems to be very important.

We have already reported that an excessive usage of antibiotics is an important risk factor for MRSA infection in the elderly (Kajioka et al. 1993; Yoshimitsu et al. 1994; Washio et al. 1995, 1996, 1997; Washio 1997). In the present study, an excessive usage of antibiotics was suggested to be a risk factor for death due to MRSA infection as well.

Previous studies have shown that there are high levels of prescribing in geriatric hospitals as well as nursing homes (Primrose et al. 1987; Nolan and O'Malley 1989) and that such polypharmacy has resulted in iatrogenic complications (Hepple et al. 1989). British Geriatric Society has established a guideline for optimizing drug use (Royal College of Physicians of London 1992). In contrast, despite the frequent usage of antibiotics in Japan, such a guideline has not been established. The possible practical implication of our studies is that we should set a national guideline for optimizing drug use in order to reduce the incidence of MRSA infection as well as the death from MRSA infection.

Our previous studies (Yoshimitsu et al. 1994; Washio et al. 1995, 1996, 1997) showed that poor nutritional status such as hypoalbuminemia is an important risk factor for MRSA infection in the elderly. In the present study, hypoalbuminemia increased a risk for death in the patients with MRSA infection as well (Table 1). This result is consist with the previous reports (Salive et al. 1992; Washio et al. 1993), which have been suggested that the elderly with hypoalbuminemia have a high risk for death. These results of our studies may be partly explained by the following possibilities. The patients with poor nutritional state may lack the

ability to recover from MRSA infection. Another possibility is that hypoalbuminemia may be the result of the drug induced liver damage with use of many antibiotics. In the present study, however, the proportion of the elderly who had received two and more antibiotics before bacterial culture was similar between the patients with and without hypoalbuminemia (Table 4).

Hypoalbuminemia in the elderly population have been also reported to be associated with limitations in ADL (Salive et al. 1992; Washio et al. 1993). Furthermore, our previous studies showed that limited ADL is also a risk factor for MRSA infection (Kajioka et al. 1993; Yoshimitsu et al. 1994; Washio et al. 1996, 1997). In the present study, however, limitations in ADL tended to be a risk factor for death but failed to show the statistical significance. The result may be partly due to the fact that the patients with liver cirrhosis, nephrotic syndrome or malignancy usually have hypoalbuminemia regardless of their ADL abilities. Another explanation is the small number of subjects in the present study.

Our previous studies (Yoshimitsu et al. 1994; Washio et al. 1997) showed that old age (80 years and older) is not a risk factor for MRSA infection while hypoalbuminemia is so. In the present study, hypoalbumineima was a risk factor for death as well while old age was not either. These results of our studies suggest that the nutritional state such as serum albumin level may be more important than the actual age among the elderly.

Pseudomonas aeruginosa as well as MRSA is considered as an important causative pathogen of nosocomial infection. In the present study, the co-isolation of *Pseudomonas aeruginosa* did not increase a risk for death among the elderly with MRSA infection (Table 1). Inamatsu and Masuda (1993) described that most of MRSA infection in the elderly are mixed infection and MRSA causes infectious diseases only 10-20% of them. In this study, 29 out of 49 patients (59.2%) were the mixed infection of MRSA and *Pseudomonas aeruginosa*.

As shown in Table 1, only 2 out of 23 male patients (8.6%) recovered from MRSA infection while 14 out of 26 female patients (53.8%) did. The result suggest that male sex may be a risk factor for death from MRSA infection. The poor prognosis of male patients in this study may be partly explained by the fact that hypoalbuminemia was more common in male patients than female patients (Table 3). These results of the present study are consist with the fact that life expectancy always stands greater for females compared with males (Japan Public Health Association 1995).

In summary, the present study showed that male sex, hypoalbumemia and an excessive usage of antibiotics may be risk factors for death from MRSA infection among the elderly population. Since hypoalbuminemia and an excessive usage of antibiotics are also risk factors for MRSA infection among the elderly (Kajioka et al. 1993; Yoshimitsu et al. 1994; Washio et al. 1995, 1996, 1997; Washio 1977), the physicians should not unnecessarily administer antibiotics, especially in the

elderly with hypoalbuminemia.

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