J Infect Chemother (2011) 17:640–645
DOI 10.1007/s10156-011-0228-z

ORIGINAL ARTICLE

Clinical and microbiological evaluation of hemodialysis-associated pneumonia (HDAP): should HDAP be included in healthcare-associated pneumonia?

Satoshi Kawasaki · Nobuki Aoki · Hiroshi Kikuchi · Hitoshi Nakayama · Noriko Saito · Hisaki Shimada · Shigeru Miyazaki · Shinji Sakai · Masashi Suzuki · Ichiei Narita

Received: 31 May 2010 / Accepted: 7 February 2011 / Published online: 3 March 2011

Abstract Although hemodialysis-associated pneumonia (HDAP) was included among the healthcare-associated pneumonias (HCAP) in the 2005 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guideline, little information relevant to clinical epidemiology, especially microbiological characteristics, is available. This study aimed to reveal microbiological characteristics and clinical outcomes of HDAP and to assess whether HDAP should be included in the HCAP category. We retrospectively analyzed 69 HDAP patients [42 with moderate and 27 with severe disease based on A-DROP (age, dehydration, respiratory failure, orientation disturbance, and low blood pressure)] in whom sputum cultures were performed at our hospital between 2007 and 2009. The most common pathogens were *Staphylococcus aureus* (37.7%), which were composed of methicillin-resistant *S. aureus* (MRSA) (27.5%) and methicillin-sensitive *S. aureus* (MSSA) (10.1%), followed by *Streptococcus pneumoniae* (10.1%), *Klebsiella pneumoniae* (8.7%), *Haemophilus influenzae* (7.2%), and *Moraxella catarrhalis* (5.8%). This distribution mostly resembled the microbiological characteristics of HCAP reported previously, except that the frequency of multi-drug-resistant (MDR) gram negatives such as *Pseudomonas aeruginosa* (2.9%) was clearly lower and that of MRSA was higher. There were no significant differences in microbiological findings, including the incidence of MDR pathogens, between the two severity groups. Despite most cases (82.6%) receiving only monotherapy, the prognosis (30-day survival and in-hospital mortality rates were 88.4% and, 17.4%, respectively) was similar to the past HCAP reports, but there were no significant correlations between prognosis and presence of MDR pathogens (30-day mortality rates 18.2% in MDR positive vs. 8.5% in MDR negative; $p = 0.242$). Assessment for not only MDR pathogens, but also severity of illness by the A-DROP system made it possible to conduct stratification based on prognosis. Our results suggest that HDAP should be included in the HCAP category, while understanding that there are some differences.

Keywords HCAP · HDAP · MDR pathogen · A-DROP · Monotherapy

Introduction

Infection is a major complication affecting both prognosis and survival and is ranked as the second leading cause of death in Japanese hemodialysis patients, following cardiovascular disease [1]. Hemodialysis-associated pneumonia (HDAP) is among the most common infection [2], and mortality rates from HDAP are 14–16 times higher than those from pneumonia in the general population [3]. For this reason, effective management is essential. On the other hand, guidelines for appropriate management of adult patients with community-acquired pneumonia (CAP) have been successively released in Japan [4], the USA [5], and

S. Kawasaki (✉) · N. Aoki
Department of Respirology, Shinrakuen Hospital,
3-3-11 Shindori-minami, Nishi-ku, Niigata 950-2087, Japan
e-mail: satoshi3231kawasaki@yahoo.co.jp

H. Kikuchi · H. Nakayama · N. Saito · H. Shimada · S. Miyazaki · S. Sakai · M. Suzuki
Department of Kidney Center, Shinrakuen Hospital, Niigata, Japan

I. Narita
Second Department of Internal Medicine, Niigata University School of Medicine, Niigata, Japan

Britain [6, 7]. To date, as a patient's life is based outside of the hospital, HDAP has been included in the CAP category. However, because hemodialysis patients, who manifest various degrees of immunodeficiency, regularly visit the hospital, usually several times a week, and receive ongoing healthcare, the question as to whether HDAP should be considered a CAP remains open.

In 2005, healthcare-associated pneumonia (HCAP) was documented in the American Thoracic Society (ATS)/ Infectious Diseases Society of America (IDSA) guideline as a new concept of pneumonia classification [8]. In this guideline, pneumonia developing in patients receiving chronic dialysis within 30 days was also included as one of the definitions of HCAP due to the epidemiological pattern of HDAP being more similar to that of HCAP than to that of CAP. The most important epidemiological characteristics noted were that the risks for multi-drug-resistant (MDR) pathogens, such as *Pseudomonas aeruginosa*, and mortality were increased in the HCAP compared with the CAP group. For these reasons, combination therapy with broad-spectrum antibiotics was recommended in this guideline as the initial empirical treatment for all HCAP cases. We can empirically understand the concept of HDAP being included in HCAP, but there is surprisingly little evidence for the clinical epidemiology of HDAP, especially microbiological findings. In this study, to determine whether HDAP should be included in the HCAP category, we examined microbiological findings, initial antibiotic selection, and clinical outcomes of HDAP cases.

Patients and methods

Patients and study design

We conducted a retrospective observational study of hemodialysis patients with pneumonia hospitalized at Shinrakuen Hospital (a 337-bed community general hospital with a kidney center, serving 423 patients receiving regular intermittent hemodialysis as of December 2009) between 1 January 2007 and 31 December 2009. During the observational periods, 2,564 sputum cultures were performed and 212 samples obtained from hemodialysis patients. Among these, all cases with sputum culture at the time of pneumonia diagnosis were considered to be participants in this study. Pneumonia was defined when all of the following conditions were met: (1) new infiltrates on chest radiographic examination, (2) elevation of inflammatory reaction white blood cell (WBC) count $\geq$10,000 or C-reactive protein (CRP) $\geq$0.4 mg/dl), and (3) beginning of antibiotic treatment. The severity of pneumonia was evaluated using the A-DROP (age, dehydration, respiratory failure, orientation disturbance, and low blood pressure) scoring system of the Japanese Respiratory Society [4], which is based on clinical prediction rules and assesses the following five parameters: (1) female $\geq$70 years or male $\geq$75 years, (2) blood urea nitrogen (BUN) of $\geq$21 mg/dl or presence of dehydration, (3) pulse oximeter oxygen saturation (SpO_2) $\leq$90% partial arterial pressure of oxygen (PaO_2) $\leq$60 Torr, (4) disturbance of consciousness, (5) blood pressure (systolic) $\leq$90 mmHg. If none of these five items are met, the severity classification is mild; 1 or 2, moderate; 3–5, severe. Because all patients in this study were positive for parameter (2), we divided the entire group into two severity classes (moderate or severe) and compared baseline characteristics, causative organisms, initial antibiotic choice, and clinical outcomes (30-day survival and in-hospital mortality) between these two groups. Initial treatment failure was defined as death during initial treatment or any change in therapeutic agents from the initial medications to others due to clinical instability (e.g., lack of response or worsening fever pattern, respiratory condition, and/or radiographic status).

Microbiological studies

On admission, if sputum was available, a Gram stain and quantitative culture were obtained using standard microbiological procedures. Positive bacterial cultures, except for normal flora, are described in the microbial identification table. In accordance with the 2005 ATS/IDSA guideline [8], methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa*, extended-spectrum β-lactamase (ESBL)-producing *Klebsiella* species, and *Escherichia coli*, *Acinetobacter* species, and *Stenotrophomonas maltophilia* were considered to be MDR pathogens.

Statistical analysis

All continuous variables were reported as means $\pm$ standard deviation (SD) and were compared using a two-tailed Student's t test. Categorical variables were reported as the number and percentage of patients. Differences in categorical variables were examined using the χ^2 test. A p value <0.05 was considered statistically significant.

Results

Patient characteristics

During the study period, 400 patients per year required chronic hemodialysis at our hospital. As shown Table 1, of these, 69 pneumonia patients, 42 in the moderate group (60.9%) and 27 in the severe group (39.1%), were evaluated. Forty-one cases had CAP, and 28 had HAP; 68.1%

Table 1 Baseline characteristics of 69 pneumonia cases in hemodialysis patients

Variables	Total (69 cases)	A-DROP moderate (42 cases)	A-DROP severe (27 cases)	*p* value
Male gender	47 (68.1)	28 (66.7)	19 (70.4)	NS
Age (years)	73.8 ± 10.2	72.1 ± 10.1	76.5 ± 10.0	NS
<59	6 (8.7)	4 (9.5)	2 (7.4)	NS
60–69	18 (26.1)	15 (35.7)	3 (11.1)	NS
70–79	23 (33.3)	14 (33.3)	9 (33.3)	NS
>80	22 (31.9)	9 (21.4)	13 (48.1)	NS
Duration of dialysis (years)	9.8 ± 8.4	10.8 ± 9.4	8.4 ± 6.5	NS
Primary renal disease				
Nephritis	33 (47.8)	24 (57.1)	9 (33.3)	NS
Diabetes	19 (27.5)	7 (16.7)	12 (44.4)	<0.05
Nephrosclerosis	10 (14.5)	6 (14.3)	4 (14.8)	NS
Others or unknown	7 (10.1)	5 (11.9)	2 (7.4)	NS
Underlying disease				
Chronic lung disease	5 (7.2)	3 (7.1)	2 (7.4)	NS
Neoplastic disease	1 (1.4)	0 (0.0)	1 (3.7)	NS
Central nervous system disorder	22 (31.9)	14 (33.3)	8 (29.6)	NS
Tube feeding	9 (13.0)	6 (14.3)	3 (11.1)	NS

A-DROP age, dehydration, respiratory failure, orientation disturbance, and low blood pressure, *NS* not significant

were men, and mean age (±SD) was 73.8 ± 10.2 (range 49–99) years. The mean duration (±SD) of dialysis was 9.8 ± 8.4 years (range 87 days to 34 years). The most common primary renal diseases were nephritis (47.8%), diabetes mellitus (27.5%), and nephrosclerosis (14.5%). Twenty-two patients (31.9%) had central nervous system disorders as their chronic underlying disease, and nine obtained nutrition via a feeding tube. The only statistically significant difference between the severity groups was that there were more diabetics with primary renal disease in the severe than in the moderate group.

Pathogen distribution

Of the 69 patients, 39 (56.5%) had pneumonia due to a single pathogen, 12 (17.4%) to two or more pathogens (two, 11; four, 1). No pathogens were identified in 18 patients (26.1%). Table 2 shows microbes identified in the total study population and each severity group. The most common pathogens were *S. aureus*, found in 26 cases (37.7%), which were composed of 19 MRSA (27.5%) and seven methicillin-sensitive *S. aureus* (MSSA) (10.1%), followed by *Streptococcus pneumoniae* in seven (10.1%), *K. pneumoniae* in six (8.7%), *Haemophilus influenzae* in five (7.2%), *Moraxella catarrhalis* in four (5.8%), and other streptococci in four (5.8%). All strains of *E. coli* and *K. pneumoniae* were ESBL nonproducing. There were 22 cases caused by MDR pathogens, and of these, the most common pathogens were MRSA, found in 19 cases, followed by *P. aeruginosa* in two, and *Acinetobacter* species in one. None had *S. maltophilia*. There were no significant differences between the severity groups.

Antibiotic therapy and clinical outcomes

Table 3 shows the initial antibiotic treatments and clinical outcomes of patients in each severity group. In both severity groups, most cases received antibiotic monotherapy as the initial treatment (85.7% in the moderate group vs. 77.8% in severe group). Among the monotherapies, carbapenems (58.0%) were most frequently chosen, followed by cephalosporins (14.5%). Among combination therapies, carbapenems plus glycopeptides (7.2%) were most frequently chosen, followed by carbapenems plus fluoroquinolones (5.8%).

Sixty-one patients (88.4%) were still alive 30 days after diagnosis of pneumonia, and 12 patients (17.4%) died in the hospital. Four patients died after the 30th day: two due to the pneumonia itself, and two because of other diseases. The 30-day survival rate was significantly lower and in-hospital mortality was significantly higher in the severe group, although there was no significant difference in the incidence of MDR pathogens between the two groups (33.3% in the moderate group vs. 29.8% in the severe group). In addition, there was no strong correlation between the presence of MDR pathogens and the 30 day mortality rates (18.2% in MDR positive vs. 8.5% in MDR negative; $p = 0.242$).

Therefore, we analyzed this new classification assessing not only the presence of MDR pathogens but also the

Table 2 Causative organisrns of 69 pneumonia cases in hemodialysis patients

Microbes	Total (69 cases)	A-DROP moderate (42 cases)	A-DROP severe (27 cases)	*p* value
Gram positives	39 (56.5)	24 (57.1)	15 (55.6)	NS
Streptococcus pneumoniae	7 (10.1)	5 (11.9)	2 (7.4)	NS
Other streptococci	4 (5.8)	1 (2.4)	3 (11.1)	NS
Staphylococcus aureus	26 (37.7)	16 (38.1)	10 (37.0)	NS
MSSA	7 (10.1)	5 (11.9)	2 (7.4)	NS
MRSA	19 (27.5)	11 (26.2)	8 (29.6)	NS
Other gram positives	2 (2.9)	2 (4.8)	0 (0.0)	NS
Gram negatives	26 (37.7)	19 (45.2)	7 (25.9)	NS
Haemophilus influenzae	5 (7.2)	4 (9.5)	1 (3.7)	NS
Moraxella catarrhalis	4 (5.8)	4 (9.5)	0 (0.0)	NS
Pseudomonas aeruginosa	2 (2.9)	2 (4.8)	0 (0.0)	NS
Escherichia coli	3 (4.3)	1 (2.4)	2 (7.4)	NS
Klebsiella pneumoniae	6 (8.7)	3 (7.1)	3 (11.1)	NS
Serratia marcescens	3 (4.3)	3 (7.1)	0 (0.0)	NS
Acinetobacter spp.	1 (1.4)	1 (2.4)	0 (0.0)	NS
Other gram negatives	1 (1.4)	1 (2.4)	0 (0.0)	NS
No pathogens identified	18 (26.1)	7 (16.7)	11 (40.7)	<0.05

A-DROP age, dehydration, respiratory failure, orientation disturbance, and low blood pressure, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*

Table 3 Occurrence of multi-drug-resistant (MDR) pathogens, antibiotic treatment, and clinical outcomes in each severity group assessed by age, dehydration, respiratory failure, orientation disturbance, and low blood pressure (A-DROP)

Parameter	Total (69 cases)	A-DROP moderate (42 cases)	A-DROP severe (27 cases)	*p* value
Initial antibiotics				
Monotherapy	57 (82.6)	36 (85.7)	21 (77.8)	NS
Carbapenems	40 (58.0)	23 (63.8)	17 (63.0)	NS
Cephalosporins	10 (14.5)	8 (19.0)	2 (7.4)	NS
Penicillins	1 (1.4)	0 (0.0)	1 (3.7)	NS
Fluoroquinolones	4 (5.8)	3 (7.1)	1 (3.7)	NS
Others	2 (2.9)	2 (4.8)	0 (0.0)	NS
Combination therapy	12 (17.4)	6 (14.3)	6 (22.2)	NS
Carbapenems + fluoroquinolones	4 (5.8)	2 (4.8)	2 (7.4)	NS
Carbapenems + clindamycin	1 (1.4)	1 (2.4)	0 (0.0)	NS
Carbapenems + glycopeptides	5 (7.2)	1 (2.4)	4 (14.8)	NS
Cephalosporins + macrolides	1 (1.4)	1 (2.4)	0 (0.0)	NS
Others	1 (1.4)	1 (2.4)	0 (0.0)	NS
Initial treatment failure	15 (21.7)	7 (16.7)	8 (29.6)	NS
Occurrence MDR Pathogens	22 (31.9)	14 (33.3)	8 (29.6)	NS
30-day survival	61 (88.4)	40 (95.2)	21 (77.8)	<0.05
In-hospital mortality	12 (17.4)	4 (9.5)	8 (29.6)	<0.05

severity of illness. As shown in Fig. 1, all cases were classified into four groups (group I: A-DROP moderate and MDR-pathogen negative; group II: A-DROP moderate and MDR pathogen positive; group III: A-DROP severe and MDR pathogen negative; group IV: A-DROP severe and MDR pathogen positive). There was a clear linear relation between the 30-day mortality rates in each group (3.6% in group I; 7.1% in II; 15.8% in III; 37.5% in IV).

Discussion

HDAP has long been regarded as a form of CAP, because most hemodialysis patients live outside of hospitals. However, inherent in this concept is a major incongruity regarding the clinical situation, because hemodialysis patients regularly receive far more healthcare within the hospital setting than nondialysis patients and have various

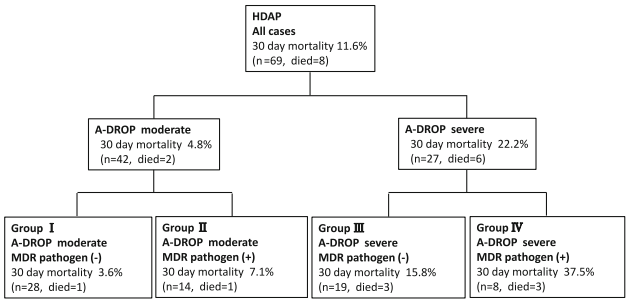

Fig. 1 Correlation of the 30-day mortality rate with classification by severity of illness and the presence of multi-drug-resistant (MDR) pathogens

degrees of immunodeficiency comparable with that of HAP patients. Furthermore, the ATS/IDSA guideline of 2005 readily facilitates understanding that HDAP fits one of the HCAP definitions.

The most important characteristic of HCAP is that the incidence of MDR pathogens as causative bacteria is higher than in CAP [9]. Past reports [10–12] have shown the incidence of *S. pneumoniae* and *H. influenzae*, two major causative pathogens [13, 14] of CAP, to be lower in HCAP than in CAP, whereas *P. aeruginosa* and MRSA were more common in HCAP than in CAP.

On the other hand, little information is available on microbiological findings of HDAP. Because most reports were based on large databases [15, 16] involving numerous cases without microbiological examination, direct comparison to our data was not possible. To our knowledge, only one report [2] presented data, obtained in a similar setting, that could be compared with ours. In their study, the most common pathogen was *S. aureus* (29.1%), followed by *E. faecalis* (16.6%), *Kl. pneumoniae* (10.3%), and *P. aeruginosa* (8.3%), with the incidences of *S. pneumoniae* (2.1%) and *H. influenzae* (4.2%) pneumonias not being particularly high. Our data showed similar tendencies except that incidences of *S. pneumoniae* (10.1%) and *H. influenzae* (7.2%) were slightly higher and that of *P. aeruginosa* (2.9%) was lower. However, because this report was published before the concept of MDR pathogens was established, we cannot know the incidence of MRSA and ESBL producing Enterobacteriaceae.

Another Japanese report [17] showed the microbiological spectrum of only HAP in hemodialysis patients. Because normal flora were not excluded, *Candida albicans* and *S. epidermidis* were the top two organisms. After the normal flora, MRSA were most frequently detected, followed by *P. aeruginosa* and *S. maltophilia*. The incidence of *P. aeruginosa* and *S. maltophilia* were different from our data, perhaps because there were the differences in that our objective was the study of only HAP patients treated in a university hospital.

Among results pertaining to microbiological findings of HDAP in our data, it seemed to be a common characteristic that the incidence of *S. aureus*, especially MRSA, was clearly higher than in CAP. It is known that hemodialysis patients have higher rates of nasal MRSA carriage than the healthy population [18, 19] and that this nasal carriage plays a key role in the development of infection. Although we could not strictly discern whether MRSA were colonizing or causative pathogens in this study, it is noteworthy that sputum culture from HDAP patients shows a high incidence of MRSA, because the ATS/IDSA guideline recommends using anti-MRSA drugs if MRSA risk factors are present or there is a high incidence locally. On the other hand, it is unclear why the incidences of MDR gram negatives were clearly lower in our study than the previous HCAP reports. Further multicenter study is needed in order to judge whether this result is due to local factors or the specificity of HDAP.

Except for these differences, our data revealed the microbiological characteristics of HDAP to include a distribution very similar to that of HCAP. This result is probably attributable to the lifestyles of hemodialysis patients who live both inside and outside the hospital setting and supports the concept that HCAP is in the spectrum between CAP and HAP [9]. Comparison between the moderate and severe groups using the A-DROP system revealed no differences in microbiological findings, and outcomes (in-hospital mortality and 30-day survival) were also worse in the severe group. Furthermore, there were no significant differences in 30-day mortality between HDAP patients with (18.2%) and without (8.5%) MDR pathogens ($p = 0.242$). These results may suggest that MDR pathogens may not be the only influence on disease severity and outcomes, at least in HDAP patients.

On the other hand, the 2005 ATS/IDSA guideline recommends combined use of broad-spectrum antibiotics with an antipseudomonal effect in all HCAP cases due to concern about MDR pathogens only. We were concerned with an increased risk of overtreatment. Indeed, even though most cases in the moderate group were given monotherapy (85.7%), 30-day survival rates (95.2%) were generally good compared with those of CAP patients [12]. Furthermore, the many studies of pneumonia [20, 21] have shown no significant differences in outcomes between monotherapy and combination therapy. These results suggest that we need the new strategy based on prognostication. Therefore, we additionally analyzed the new classification by both the severity of illness using A-DROP and the presence of MDR pathogens. By dividing our patients into four groups, we elucidated the differences in prognosis among groups. Although the question of how to predict the possibility of MDR pathogens and how to choose the different antibiotics in groups II and IV remains, we consider

this classification is available to the algorithm for choosing the initial empirical therapy. For example, if a patient is deemed to have nonsevere illness and a low risk for MDR pathogens, monotherapy corresponding to that of CAP is recommended. A similar concept was proposed by Brito et al. [22] and can be applied to the HCAP management strategy as well.

In conclusion, we found that the incidence of MDR pathogens in HDAP was more similar to that of HCAP than CAP reported previously. At the same time, we recognized the differences in microbiological distribution among MDR pathogens between HDAP and HCAP, of which MRSA was more common than MDR gram negatives. The prognosis of HDAP (30-day survival and in-hospital mortality) was also similar to the past HCAP reports. These results suggested that HDAP should be included in the HCAP category while understanding such differences. Moreover, we showed that there were no significant correlation in HDAP cases between prognosis and the presence of MDR pathogens only, which the 2005 ATS/IDSA guideline emphasized as being the most important factor in considering the strategy of HCAP treatments. The new classification by assessment for not only MDR pathogens but also severity of illness made it possible to predict the prognosis of HDAP cases.

References

1. Nakai S, Masakane I, Shigematsu T, Hamano T, Yamagata K, Watanabe Y, et al. An overview of regular dialysis treatment in Japan (As of 31 December 2007). Ther Apher Dial. 2009;13:457–504.
2. Muraya Y, Oozono Y, Kadota J, Miyazaki M, Hashimoto A, Iida K, et al. Clinical and immunological evaluation of infection in patients on Hemodialysis. J Infect Chemother. 1996;2:247–53.
3. Sarnak MJ, Jaber BL. Pulmonary infectious mortality among patients with end-stage renal disease. Chest. 2001;120:1883–7.
4. Committee for the Japanese Respiratory Society Guidelines for the Management of Respiratory Infections. The Japanese Respiratory Society guidelines for the management of community-acquired pneumonia in adults. Respirology. 2006;11:S79–133.
5. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Disease Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44:S27–72.
6. British Thoracic Society Research Committee. Community-acquired pneumonia in adults in British hospitals in 1982–1983: a survey of aetiology, mortality, prognostic factors, and outcome. Q J Med. 1987;62:195–220.
7. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377–82.
8. American Thoracic Society, Infectious Disease Society of America. Guidelines for the management of adults with hospital-acquired, ventilator- associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388–416.
9. Kollef MH, Marrow LE, Baughman RP, Craven DE, McGowan JE, Micek ST, et al. Health care-associated pneumonia (HCAP): a critical appraisal to improve identification, management, and outcomes-proceedings of the HCAP summit. Clin Infect Dis. 2008;46:296S–334S.
10. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcome of health-care-associated pneumonia; results from a large US database of culture-positive pneumonia. Chest. 2005;128:3854–62.
11. Micek ST, Kollef KE, Reichley RM, Roubinian N, Kollef MH. Health care-associated pneumonia and community-acquired pneumonia: a single-center experience. Antimicrob Agents Chemother. 2007;51:3568–73.
12. Shindo Y, Sato S, Maruyama E, Ohashi T, Ogawa M, Hashimoto N, et al. Health-care-associated pneumonia among hospitalized patients in Japanese community hospital. Chest. 2009;135:633–40.
13. Ishida T, Hashimoto T, Arita M, Ito I, Osawa M. Etiology of community-acquired pneumonia in hospitalized patients. 1998;114:1588–1593.
14. Woodhead M. Community-acquired pneumonia guideline-an international comparison: a view from Europe. Chest. 1998;113:183S–7S.
15. Slinin Y, Foley RN, Collins AJ. Clinical epidemiology of pneumonia in hemodialysis patients: the USRDS waves 1, 3, and 4 study. Kidney Int. 2006;70:1135–41.
16. Guo H, Liu J, Collins AJ, Foley RN. Pneumonia in incident dialysis patients—the United States Renal Data System. Nephrol Dial Transplant. 2008;23:680–6.
17. Wakino S, Imai E, Yoshioka K, Kamayachi T, Minakuchi H, Hayashi K, et al. Clinical importance of *Stenotrophomonas maltophilia* nosocomial pneumonia due to its high mortality in hemodialysis patients. Ther Apher Dial. 2009;13:193–8.
18. Duran N, Ocak S, Eskiocak AF. *Staphylococcus aureus* nasal carriage among the diabetic and non-diabetic haemodialysis patients. Int J Clin Pract. 2006;60:1204–9.
19. Lederer SR, Riedelsdorf G, Schiffl H. Nasal carriage of meticillin resistant *Staphylococcus aureus*: the prevalence, patients at risk and the effect of elimination on outcomes among outclinic haemodialysis patients. Eur J Med Res. 2007;12:284–8.
20. Aarts MA, Hancock JN, Heyland D, McLeod RS, Marshall JC. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. Crit Care Med. 2008;36:108–17.
21. Heyland DK, Dodek P, Mscedere J, Day A, Cook D. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med. 2008;36:737–44.
22. Brito V, Niederman MS. Healthcare-associated pneumonia is a heterogeneous disease, and all patients do not need the same broad-spectrum antibiotic therapy as complex nosocomial pneumonia. Curr Opin Infect Dis. 2009;22:316–25.