KJCCM
Korean J Crit Care Med
2015 November 30(4):241-248 / http://dx.doi.org/10.4266/kjccm.2015.30.4.241
ISSN 2383-4870 (Print) · ISSN 2383-4889 (Online)

■ Original Article ■

Experience with *Elizabethkingia meningoseptica* Infection in Adult Patients at a Tertiary Hospital

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Background: Few reports have documented the clinical characteristics and treatment outcomes of adult patients with *Elizabethkingia meningoseptica* infection.
Methods: Medical records of patients over 18 years of age and suspected of having an *E. meningoseptica* infection from March 1, 2006 to February 28, 2013 were reviewed retrospectively. Their clinical characteristics, antimicrobial susceptibility results, and treatment outcomes were analyzed.
Results: *E. meningoseptica* was isolated from 30 patients. Median age was 68.5 years, and infections were more frequent in males (17, 56.7%). The most common isolation source was sputum (23, 76.7%), and pneumonia was the most common condition (21, 70%) after excluding two cases of colonization. This bacterium was most susceptible to minocycline (27, 90%) and fluoroquinolones, including levofloxacin (20, 66.7%) and ciprofloxacin (18, 60%). The mortality rate due directly to *E. meningoseptica* infection was 20% (6/30), and uncontrolled pneumonia was the only cause of death. After isolating *E. meningoseptica,* the numbers of patients with pneumonia (9/9, 100% vs. 12/21, 57.1%), history of hemodialysis (5/9, 55.6% vs. 3/21, 14.3%), tracheostomy (8/9, 88.9 vs. 10/21, 47.6%), and median Charlson comorbidity index score (6 [range, 3–9] vs. 4 [range, 0–9]) were significantly higher in non-survivors than those in survivors ($p < 0.05$, for each). However, only 12 (40%) patients received appropriate antibiotics.
Conclusions: *E. meningoseptica* infection most commonly presented as pneumonia in adults with severe underlying diseases. Despite the high mortality rate, the rate of appropriate antibiotic use was notably low.

Key Words: *Chryseobacterium meningosepticum*; *Elizabethkingia meningoseptica*; *Flavobacterium meningosepticum*; nosocomial infection; pneumonia.

Introduction

The increasing emergence of antibiotic-resistant nosocomial infections is a worldwide concern. *Elizabethkingia meningoseptica* (previously known as *Flavobacterium meningosepticum or Cryseobacterium meningosepticum*, Center for Disease Control and Prevention group II-a) is a non-fastidious oxidase-positive, non-glucose fermenting, Gram-negative aerobic rod bacterium that is widely distributed in soil, plants, and water but is not normally found in human microflora.[1] It is the most pathogenic *Cryseobacterium* sp. capable of infecting humans and infects the blood, cerebrospinal fluid, skin, soft tissues, respiratory system, and other sites.[2,3] In addition, it reportedly exhibits inherent resistance to several classes of important antibiotics, such as beta-lactams, aminoglycosides, carbapenems, clindamycin, tetracyclines, chloramphenicol,

Received on February 23, 2015 Revised on May 26, 2015
Accepted on June 7, 2015
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*No potential conflict of interest relevant to this article was reported.

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erythromycin, and teicoplanin, which are the most common antibiotics used to treat Gram-negative nosocomial infections.[3] However, choosing an effective antibiotic against *E. meningoseptica* is clinically quite difficult because no interpretive minimum inhibitory concentration (MIC) breakpoints of antibiotics against this organism have been reported and reports of antimicrobial responses and treatment outcomes are rare.[3]

Although most reports of *E. meningoseptica* infection in humans have been presented as meningitis outbreaks in premature newborns and infants,[4-6] several reports have emphasized its importance as a nosocomial infection in adult patients with severe underlying disease.[7-11] However, studies evaluating the clinical significance and treatment outcomes in adult patients with *E. meningoseptica* infection are rare.

In this study, we evaluated the clinical characteristics and results of antimicrobial susceptibility testing in adult patients with *E. meningoseptica* infection and analyzed their treatment outcomes.

Materials and Methods

1) Data collection

This study was conducted retrospectively in patients admitted to Dankook University Hospital, a tertiary care and teaching hospital in South Korea, from March 1, 2006 to February 28, 2013. The study subjects were selected based on bacterial culture reports after excluding patients < 18 years of age, and the demographic and clinical features were obtained from their medical records, including age, sex, main cause for admission, comorbidities, isolation sources, infection types, clinical conditions predisposing the patient to hospital infection, antimicrobial susceptibility test results, and treatment outcome. Intermediate strains were classified into resistant strains to collect the antimicrobial susceptibility results.

2) Microbiology

The Clinical and Laboratory Standards Institute did not establish definite interpretative MIC breakpoints for *E. meningoseptica* until 2013; thus, most previous reports presented susceptibility test results using MIC breakpoint results for *Pseudomonas aeruginosa* or non-*Enterobacteriaceae* sp.[12] In this study, The VITEK2 system (bioMerieux Vitek; bioMerieux, Marcy I'Etoile, France) with the VITEK2 GN and antimicrobial susceptibility test cards were used to identify bacteria and confirm antimicrobial susceptibility. Antimicrobial susceptibilities were defined for amikacin, aztreonam, cefepime, cefotaxime, ceftazidime, ciprofloxacin, colistin, gentamicin, imipenem, levofloxacin, meropenem, minocycline, piperacillin, piperacillin/tazobactam, and trimethoprim/sulfamethoxazole using MIC standards (μg/mL) for other non-Enterobacteriaceae, including *Pseudomonas* sp. (except *P. aeruginosa*) and other nonfastidious, glucose-nonfermenting, Gram-negative bacilli, *Acinetobacter* sp., *Burkhoderia cepacia*, *B. mallei*, *B. pseudomallei*, and *Stenotrophomonas maltophilia*.

3) Definitions

"*E. meningoseptica* infection" was defined when the attending clinician decided to perform a bacterial culture and to started or changed the current antibiotic in patients with either a newly developed fever ≥ 38.3°C or leukocytosis > 10,000 /mm^3. "Colonization" was defined when patients did not meet the definition of "*E. meningoseptica* infection" described above and were stable without any symptoms or signs of infection after 1 week. "Pneumonia" was defined when patients met the definition of "*E. meningoseptica* infection" and showed both new infiltration on chest radiographs and documented changes in sputum color or quantity on medical records. "Prolonged hospitalization" was defined as hospitalization > 28 days prior to isolating *E. meningoseptica*. "Prior intensive care unit (ICU) stay" and "mechanical ventilation" were defined when patients stayed in the ICU or were mechanically ventilated for > 48 hours prior to isolating *E. meningoseptica*. "Recent surgery" was defined when a surgical procedure excluding tracheostomy was performed during the current hospitalization prior to isolating *E. meningoseptica*. "Appropriate antibiotic use" was defined when at least one susceptible intravenous antimicrobial agent was used within 48 hours after obtaining the culture report. "*E. meningoseptica*-related mortality" was defined when patients died within 2 weeks after *E. meningoseptica* was isolated, and no other explainable cause of death was found.

4) Statistical analysis

The statistical analysis was performed using Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. SPSS ver. 13.0 software (SPSS Inc., Chicago, IL, USA) was used for all analyses. A $p < 0.05$ indicated statistical significance.

Results

Thirty patients were included in this study, and their demographic and clinical characteristics are summarized in Table 1. Median age was 68.5 years (range, 19–90 years), and males made up the majority of patients (17, 56.7%). The most common cause of the current admission was pneumonia (7, 23.3%), followed by intracranial hemorrhage (5, 16.7%), and malignancy (5, 16.7%). Twenty-one (70%) patients had underlying comorbidities, including cardiovascular disease (14/21, 66.7%), malignancy (6/21, 28.6%), diabetes (6/21, 28.6%), chronic renal disease (4/21, 19.0%), steroid use (4/21, 19.0%), and chronic lung disease (3/21, 14.3%). Their median Charlson comorbidity index score was 5 (range, 0–9). The most common isolation source was sputum (23, 76.7%), and pneumonia was the most common infection type (21, 70%) after excluding two cases of colonization.

Prolonged hospitalization > 28 days prior to isolating *E. meningoseptica* (26, 86.7%), prior ICU stay (23, 76.7%), and mechanical ventilation (23, 76.7%) were observed frequently in the study population among the variables used to evaluate which clinical conditions predisposed patients to developing the infection while in the hospital. The median duration and number of antibiotics used before isolating *E. meningoseptica* was 33 days (range, 1–216 days) and four (range, 1–11), respectively.

The *in vitro* antimicrobial susceptibility test results are presented in Table 2. *E. meningoseptica* was most often susceptible to minocycline (27, 90%) and fluoroquinolones, including levofloxacin (20, 66.7%) and ciprofloxacin (18, 60%). However, most antibiotics that target Gram-negative bacteria were not very effective against *E. meningoseptica*.

Treatment outcomes are presented in Table 3. The all-cause mortality rate after isolating *E. meningoseptica* was 30% (9/30), and the mortality rate assumed to be directly

Table 1. Demographic characteristics of the study population

Characteristics	Number (%) (N = 30)
Median age, years (range)	68.5 (19-90)
Male	17 (56.7)
Main causes of current admission	
Pneumonia	7 (23.3)
Intracranial hemorrhage	5 (16.7)
Malignancy	5 (16.7)
Bone and joint infection	3 (10.0)
Cardiac diseases	2 (6.7)
Renal diseases	2 (6.7)
Others*	6 (20.0)
Comorbidities (may be multiple) (N = 21)	
Cardiovascular disease	14 (66.7)
Diabetes	6 (28.6)
Malignancy	6 (28.6)
Chronic renal disease	4 (19.0)
Steroid use	4 (19.0)
Chronic lung disease	3 (14.3)
Adrenal insufficiency	2 (9.5)
Cerebrovascular disease	1 (4.8)
Charlson comorbidity index, median (range)	5 (0-9)
Sources of isolation	
Sputum	23 (76.7)
Catheter	5 (16.7)
Blood	1 (3.3)
Urine	1 (3.3)
Types of infection	
Pneumonia	21 (70.0)
Catheter related infection	5 (16.7)
Urinary tract infection	1 (3.3)
Bacteremia of undefined source	1 (3.3)
Colonization	2 (6.7)
Clinical conditions predisposing hospital infection	
Prolonged hospitalization (> 28 days)	26 (86.7)
Total duration (days) of previous antibiotic use, median (range)	33 (1-216)
Number of previous antibiotics, median (range)	4 (1-11)
Prior intensive care unit stay	23 (76.7)
Mechanical ventilation	23 (76.7)
Hemodialysis	8 (26.7)
Tracheostomy	18 (60.0)
Recent surgery	14 (46.7)

Data are presented as the median (range) or number (%).
*Others include tuberculous pleurisy, peritonitis, soft tissue infection, encephalitis, spinal cord injury, and multiple fractures.

Table 2. *In vitro* activities of the tested antimicrobial agents against *Elizabethkingia meningoseptica* isolates

Antimicrobial agent	MIC interpretive criteria (μg/mL)			No. (%) of isolates susceptible (N = 30)
	S	I	R	
Amikacin	≤ 16	32	≥ 64	1 (3.3)
Aztreonam	≤ 8	16	≥ 32	0 (0.0)
Cefepime	≤ 8	16	≥ 32	1 (3.3)
Cefotaxime	≤ 8	16-32	≥ 32	0 (0.0)
Ceftazidime	≤ 8	16	≥ 32	1 (3.3)
Ciprofloxacin	≤ 1	2	≥ 4	18 (60.0)
Colistin	≤ 2	4	≥ 8	0 (0.0)
Gentamicin	≤ 4	8	≥ 16	3 (10.0)
Imipenem	≤ 4	8	≥ 16	0 (0.0)
Levofloxacin	≤ 2	4	≥ 8	20 (66.7)
Meropenem	≤ 4	8	≥ 16	1 (3.3)
Minocycline	≤ 4	8	≥ 16	27 (90.0)
Piperacillin	≤ 16	32-64	≥ 128	1 (3.3)
Piperacillin/tazobactam	≤ 16/4	32/4-64/4	≥ 32	6 (20.0)
Trimethoprim/sulfamethoxazole	≤ 2/38	-	≥ 4/76	9 (30.0)

Data are presented as number (%).
MIC: minimal inhibitory concentration; S: susceptible; I: intermediate; R: resistant.

Table 3. Treatment outcomes and appropriate antibiotic use

Treatment outcomes	Number (%) (N = 30)
The all-cause mortality after isolation of *E. meningoseptica*	9 (30.0)
E. meningoseptica -related mortality*	6 (20.0)
Hypoxic brain death	1 (3.3)
Arrhythmia (ventricular tachycardia)	1 (3.3)
Massive hemoptysis	1 (3.3)
Appropriate antibiotic use based on culture reports	12 (40.0)

Data are presented as number (%).
*All causes of death were defined as *Elizabethkingia meningoseptica* pneumonia.

affected by *E. meningoseptica* infection was 20% (6/30). Uncontrolled pneumonia was defined as the only cause of *E. meningoseptica*-related mortality but three patients died of hypoxic brain injury, arrhythmia, and massive hemoptysis. Despite the high mortality, the appropriate antibiotics based on culture results were only provided to 12 (40.0%) patients.

Differences in the clinical characteristics between survivors and non-survivors after isolating *E. meningoseptica* are shown in Table 4. The presence of *Elizabethkingia* pneumonia (9/9, 100% vs. 12/21, 57.1%), median Charlson comorbidity index score (6 [range, 3–9] vs. 4 [range, 0–9])), history of hemodialysis (5/9, 55.6% vs. 3/21, 14.3%), and tracheostomy (8/9, 88.9% vs. 10/21, 47.6%) were significantly higher in non-survivors than those in survivors ($p < 0.05$, for each) based on a univariate analysis. *E. meningoseptica* infection presented as pneumonia in all non-survivors, and appropriate antibiotics based on antimicrobial susceptibility test results were not provided for any of the six *E. meningoseptica*-related deaths. Despite a lack of statistical significance, prolonged hospitalization, prior ICU stay, and the use of mechanical ventilation were more frequently observed in non-survivors than those in survivors.

Discussion

The role of *E. meningoseptica* in nosocomial infections, particularly among immunocompromised patients with severe underlying disease, has been raised continuously in previous reports, even though these infections are considered uncommon in adults.[7-11,13] However, information on the clinical significance and treatment outcomes in adults with *E. meningoseptica* nosocomial infection has

Table 4. Comparison of survivors and non-survivors after isolating *Elizabethkingia meningoseptica*

Clinical characteristics	Survivors (N = 21)	Non-survivors (N = 9)	p-value
Median age, years (range)	67.0 (19-90)	70.0 (40-81)	0.892
Male	12 (57.1)	5 (55.6)	1.000
The most common site of isolation			
Sputum	14 (66.7)	9 (100.0)	0.071
Others	7 (33.3)	0 (0.0)	
The most common type of infection			
Pneumonia*	12 (57.1)	9 (100.0)	0.029
Others	9 (42.9)	0 (0.0)	
Appropriate antibiotic use based on culture results†	9 (42.9)	3 (33.3)	0.704
Clinical conditions predisposing hospital infection during current admission			
Median Charlson comorbidity index (range)	4 (0-9)	6 (3-9)	0.033
Prolonged hospitalization (> 28 days)	17 (81.0)	9 (100.0)	0.287
Total duration (days) of previous antibiotic use, median (range)	32 (2-216)	44 (1-107)	0.751
Number of previous antibiotics, median (range)	4 (2-11)	4 (1-11)	0.766
Prior intensive care unit stay	14 (66.7)	9 (100.0)	0.071
Mechanical ventilation	14 (66.7)	9 (100.0)	0.071
Hemodialysis	3 (14.3)	5 (55.6)	0.032
Tracheostomy	10 (47.6)	8 (88.9)	0.049
Recent surgery	11 (52.4)	3 (33.3)	0.440

Data are presented as the median (range) or number (%).
*Among nine patients with pneumonia, *E. meningoseptica* pneumonia was the direct cause of death in six, and the others died due to hypoxic brain injury, arrhythmia, and massive hemoptysis.
†Appropriate antibiotics were not provided for any of the six *E. meningoseptica*-related deaths.

been scarce. Only a few case studies of *E. meningoseptica* infection have bee reported in Korea, including patients with keratitis, peritonitis, ventriculitis, and meningitis.[14-20] In this study, we evaluated the clinical characteristics, antimicrobial susceptibility, and treatment outcomes in adult patients suspected to have an *E. meningoseptica* infection at a tertiary hospital. Nosocomial infection by *E. meningoseptica* in adult patients was not as uncommon as we expected, particular in patients with severe underlying diseases, a history of prolonged hospitalization, an ICU stay, and who used mechanical ventilation. Pneumonia was the most common infection caused by *E. meningoseptica*, and the mortality rate was quite high. However, despite the high mortality rate, the rate of appropriate antibiotic use was notably low.

Increasing incidence of antibiotic resistance by nosocomial infections is a global concern due to the increased use of broad-spectrum antibiotics. *E. meningoseptica* is intrinsically resistant to most β-lactams commonly used to treat nosocomial infections. Chromosomally linked metallo-β-lactamases and multiple heterogeneous carbapenem-hydrolyzing enzymes have been identified as key antibiotic resistance factors in *E. meningoseptica,*[3,21,22] and one report suggested that carbapenem resistance by *E. meningoseptica* is mediated by metallo-β-lactamase BlaB.[23] Because of its resistance to carbapenem, increasing use of this antibiotic for severe nosocomial infections caused by extended-spectrum β-lactamase-producing Gram-negative bacteria, such as *Pseudomonas* and *Acinetobacter* spp., might contribute to the emergence of *E. meningoseptica* infection, particularly in the ICU. Research from Taiwan reported an increased incidence of bacteremia caused by *E. meningoseptica* that developed mostly in adult hospitalized patients between 1999 and 2006, with an incidence rate of 7.5–35.6 per 100,000 admissions.[7] Considering the difficulty isolating this bacterium from clinical specimens and the relatively low accuracy (74.8%) of culture,[3,24] healthcare providers

need to monitor the probability for an increased incidence of nosocomial infections caused by *E. meningoseptica* in patients at risk.

E. meningoseptica is a waterborne saprophytic bacterium that is widely distributed in nature and in hospitals. Although the mode of transmission is not well known, various reports have suggested a possible association between contaminated water, mechanical ventilation respiratory equipment, and indwelling devices and hospital outbreaks.[1,25] In support of these previous suggestions, *E. meningoseptica* was most frequently isolated from respiratory specimens (23/30, 76.7%) and usually manifested as pneumonia (21/30, 70%) in our study population. There was a possibility of overestimating the incidence of pneumonia in our study because of the limitations of a retrospective study design. A more accurate method, such as a clinical pulmonary infection score, to define the presence of pneumonia was not applied in most patients. However, *E. meningoseptica*-related mortality was evaluated completely after reviewing all nurse and doctor records as well as laboratory and radiological test results, and no other explainable causes of death were found, except *E. meningoseptica* pneumonia. The 20% (6/30) rate of *E. meningoseptica*-related mortality in our study population was similar to the 23% rate observed in the majority of adults in a previous report.[7] Based on these findings, pneumonia may be the most common type of *E. meningoseptica* infection in adults and isolating *E. meningoseptica* from a respiratory specimen in a patients suspected to have pneumonia should not be considered contamination or colonization until a more probable causative organism is found.

Prolonged hospitalization > 28 days (86.7%), history of ICU stay (76.7%), and mechanical ventilation (76.7%) were frequently observed when we evaluated the clinical characteristics of our study population. In addition, the median Charlson comorbidity index score, prolonged hospitalization, total duration of previous antibiotic use, prior ICU stay, mechanical ventilation, hemodialysis, and a tracheostomy were observed at higher rates in non-survivors than those of survivors, despite the lack of statistical significance in some variables. These findings suggest that severe underlying illnesses and comorbidities that predispose patients to prolonged hospitalization could be risk factors for *E. meningoseptica* infection. However, the possibility that the high rate of all-cause mortality might be more affected by a patient's condition rather than the *E. meningoseptica* infection itself, indicating that the infection is just a sign of overall poor health, cannot be excluded completely.

No consensus has been reached about the drug of choice for treating patients with an *E. meningoseptica* infection because of the lack of interpretive MIC breakpoints and the rarity of studies that have evaluated the clinical response of antibiotics against the organism. Minocycline, ciprofloxacin, trimethoprim/sulfamethoxazole, rifampin, and new respiratory fluoroquinolones, such as levofloxacin, gatifloxacin, and piperacillin/tazobactam, have been suggested for treating *E. meningoseptica* based on *in vitro* susceptibility results.[1,3,8,10,18] Markedly discrepant results between the disc diffusion and broth microdilution methods for vancomycin using staphylococcal breakpoints has also been reported even though *E. meningoseptica* has been reported to be susceptible to antibiotics effective against Gram-positive cocci.[26] These finding suggest unreliability of the disc diffusion method for determining *E. meningoseptica* antimicrobial susceptibility. As a consequence, vancomycin and other antibiotics against Gram positive cocci, including teicoplanin, linezolid, and quinupristin-dalfopristin are not recommended to treat this organism, except rifampin.[3,26] A few reports have presented cases of *E. meningoseptica* infection that only responded to a combined antibiotic treatment, including piperacillin/tazobactam plus rifampin, vancomycin plus rifampin, or fluoroquinolone combined with vancomycin plus rifampin.[5,27-30] Thus, the role of vancomycin as a combination agent with other antibiotics has not been fully determined.

According to the SENTRY Antimicrobial Surveillance Program (1997–2001), which was a world-wide study about the susceptibility and resistance patterns of bacterial and fungal pathogens, the susceptibility rates of gatifloxacin and levofloxacin are 95–100% and the rates of trimethoprim/sulfamethoxazole and piperacillin/tazobactam are 79% and 71%, respectively.[3] However, our antimicrobial susceptibility test results only showed a 67% susceptibility rate for levofloxacin, 30% for trimethoprim/sulfamethoxazole, and 20% for piperacillin/tazobactam. This difference is assumed to be the result of widespread empirical use of anti-pseudomonal antibiotics for nosocomial infections and subsequent selection of a resistant strain in our hospital environment.

However, the possibility of different antimicrobial susceptibility patterns for this organism in Korea should also be considered.

Even if effective antibiotic use after culture results were available was an independent predictor of 14-day mortality in a Taiwanese study (odds ratio, 0.31; p = 0.049),[7] effective antibiotics were only provided for 12 (40%) patients in this study. Because *E. meningoseptica* is a strange organism to clinicians, most might think its presence in culture specimens is due to contamination or colonization. They would rather use carbapenems and vancomycin to treat bacterial pneumonia rather than use an antibiotic effective against *E. meningoseptica* based on culture results. However, appropriate antibiotics trended to be more commonly used in survivors, despite a lack of statistical significance (42.9% vs. 33.3%, p = 0.704) in our study. Considering the high rate of *E. meningoseptica*-related mortality, if this organism was isolated from specimens of patients with an increased risk of infection, clinicians should pay attention to the disease progression and evaluate the response to current antibiotics, and if possible, consider using effective antibiotics based on culture reports.

This study had several limitations inherent to its retrospective nature. First, the bacterial culture and antimicrobial susceptibility results were obtained by using only MIC standards (μg/mL) of Gram-negative bacilli with an automatic system, and thus, antimicrobial susceptibility results for vancomycin and rifampin were not evaluated in this study. Because all specimens had been discarded, no further evaluations were performed. Second, our definitions to define *E. meningoseptica* infection were a little arbitrary, such as pneumonia. Third, because our sample size was too small to evaluate treatment outcomes and predictors of poor outcomes, whether *E. meningoseptica* infection truly affected the mortality rate or not was not clearly defined. Fourth, the data were obtained retrospectively from patients admitted to a single tertiary hospital; thus, the result should not be generalized.

Despite these limitations, considering the increasing number of reports on the clinical importance and high mortality rate caused by *E. meningoseptic*a infection in adult patients with nosocomial infections, further studies are needed to establish its clinical impact and determine the most effective therapeutic strategy on a large scale in Korea.

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http://dx.doi.org/10.4266/kjccm.2015.30.4.241