A rare agent; Growth of *Elizabethkingia Meningoseptica*, 11 years of evaluation

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Abstract
Aim: In this study, we aimed to present *E. meningoseptica* infections, which grew on the cultures of inpatients in our hospital’s various clinics.

Material and Methods: All patients with a positive culture of *E. meningoseptica* admitted to our hospital between April 2008 and July 2019 were retrospectively included in this study. Demographic data, clinical diagnosis, outcomes and antimicrobial susceptibility for all isolates were extracted from patient electronic medical records.

Results: Over an 11-year period, seventeen patients have been infected with *E. meningoseptica* in our hospital. Most of them (n:11) were from intensive care units (ICU). Eight of the samples from which growth detected, were blood, 6 were endotracheal aspirate, 2 were cerebrospinal fluid, and 1 was wound swab. Most of them were children (76%). Cefoperazone/sulbactam, ciprofloxacin and trimethoprim/sulfamethoxazole were found to be the most effective antibiotics.

Discussion: *E. meningoseptica* is usually isolated as hospital acquired infection. It can make outbreaks in ICUs and also can be isolated from individual cases. Variable mortality rates of the infection have been reported. *E. meningoseptica* is resistant to antibiotics frequently used in the treatment of gram-negative infections as carbapenems, beta-lactams and aminoglycosides. In contrast to previous studies, we found lower susceptibility rates (18.1%) against piperacillin/tazobactam. This infection should be kept in mind for patients at risk group who do not respond to treatment.

Keywords
Elizabethkingia Meningoseptica; Hospital infection; Antibiotic resistance

The abstract will be presented as an oral presentation at the Klimik Congress 2021 on May 26-30, 2021.
Introduction
Elizabethkingia meningoseptica (Chryseobacterium meningosepticum), formerly known as Flavobacterium meningosepticum, is a rod-shaped gram-negative bacterium that is widespread in nature (for example, in water, plants and soil). Many environmental studies have shown that E. meningoseptica can survive in chlorine-treated municipal water supplies, often colonizing sink basins and taps, and has become a potential reservoir of infections in the hospital environment. Organisms have been recovered from dialysis systems, pharmaceuticals, and medical devices (including intravascular catheters, respirators and intubation tubes) [1]. They do not normally exist in the human body, but have been reported to cause various invasive infections like meningitis, pneumonia, endocarditis, and bacteremia in adults and neonates in association with a severe underlying illness [2]. It usually has low virulence and is prone to infecting newborns and immunocompromised hosts. It can also cause nosocomial outbreaks, especially in critical care and neonatal units, and these are difficult to control. Risk factors associated with acquiring this infection include immunosuppression, underlying medical diseases, prolonged hospital stay, prior use of higher antibiotics, indwelling central venous catheter and other invasive devices [3]. This organism is resistant to many antibiotics like beta-lactam antibiotics, aminoglycosides, tetracyclines, and chloramphenicol [2]. Many possess two different types of beta-lactamases, namely class A extended-spectrum beta-lactamases and class B metallo-beta-lactamases (MBLs); the latter confer resistance to carbapenems, which are widely used to treat infections caused by multidrug-resistant gram-negative bacteria. Two types of MBL, BlaB and GOB, have been identified in isolates of E. meningoseptica. They are constitutively resistant to multiple antibiotic classes and has unusual resistance patterns and mechanisms [4]. The selection of appropriate antimicrobial agents for patients infected with E. meningoseptica is difficult due to the lack of data on the clinical response to different treatments, as well as due to multiple drug resistance [2].

In this study, it was aimed to present the infections of E. meningoseptica which have grown on the cultures of inpatients in our hospital’s various clinics.

Material and Methods
All patients with a positive culture of E. meningoseptica admitted to our hospital between April 2008 and July 2019 were retrospectively included in this study. Demographic data, clinical diagnosis, outcome and antimicrobial susceptibilities for all isolates were extracted from patients’ electronic medical records. Moist grey and white colonies on blood agar and, typically lactose-negative small colonies on EM agar are picked up. Identification of isolates was done using conventional methods, the VITEK 2 Compact (bioMerieux, France) automated system and MALDI-TOF MS (Bruker, Germany). Susceptibility testing was performed for all isolates using the Kirby-Bauer disc diffusion method and the VITEK 2 Compact (bioMerieux, France) automated system according to the CLSI and EUCAST standards. When repetitive growth was found, only the first strain of each patient was included in the study.

Results
Over an 11-year period, seventeen patients have been infected with E. meningoseptica in our hospital. Most of them (n:11) were from intensive care units (ICU). Eight of the samples from which growth detected were blood, 6 were endotracheal aspirate, 2 were cerebrospinal fluid and 1 was wound swab. Except for one patient (whose blood culture was positive for E. meningoseptica on the first day of admission to the hospital), the mean-time from admission to the isolation of E. meningoseptica was 50 days range (5-162 days). All the patients had long term hospitalization (mean: 71 days, from 19 to 187 days) and had various underlying diseases. Only one of thirteen pediatric patients and all four adult patients died. According to the antibiograms of the strains, the most effective antibiotics were cefoperazone/sulbactam, ciprofloxacin and trimethoprim/sulfamethoxazole.

The clinical characteristics of the patients (Table 1) and antibiotic susceptibility of the strains (Table 2) are presented in the tables.

Discussion
E. meningoseptica are isolated primarily as hospital acquired infection agents and can cause outbreaks, especially in ICUs. It has been observed that the number of patients with E. meningoseptica bacteremia is increasing; indeed, at a medical center in Taiwan, the incidence (per 100,000 admissions) of E. meningoseptica bacteremia increased from 7.5 in 1996 to 35.6 in 2006 [5]. The incidence of E. meningoseptica bacteremia in the present series was not associated with a hospital outbreak, and we did not observe any increase by years. This may be because of the successful implementation of infection control program in our hospital, isolation precautions, and a hand hygiene program. E. meningoseptica infection in humans is usually acquired in the hospital and is most likely associated with the presence of invasive equipment, treatment with long-term broad-spectrum antibiotics, or long periods of hospitalization [1,5]. Ratnamani et al. reported eight patients infected with E. meningoseptica in their hospital over a 6-month period. All were on mechanical ventilation and bedside hemodialysis in ICU [4]. Weaver et al. reported nineteen patients on mechanical ventilation and infected with E. meningoseptica in ICU and eight died [6]. In our study, patients with severely debilitating diseases who had ICU admission and received antibiotics during a long period of hospitalization were at high risk for E. meningoseptica infection. In previous studies, E. meningoseptica outbreaks have been reported, and pediatric patients, especially neonates and premature infants, are at greater risk for E. meningoseptica infection [7,8]. Lin et al. searched the relationship between 28 isolates of E. meningoseptica, which they collected over a 3-year period, by pulsed-field gel electrophoresis. They demonstrated that most of the isolates were epidemiologically unrelated [9]. In the present study, however, we had a neonates clinic in our hospital, all of our patients were older pediatric and adult individuals. Unfortunately, we could not have any molecular analysis of the isolates, to detect if any relationship existed between them, as it is one major limitation of our study.
Table 1. Clinical characteristics of the patients

| Case | Age | Gender | Date   | Sample | Location | Underlying Disease | Clinical Diagnosis | Outcome |
|------|-----|--------|--------|--------|----------|--------------------|-------------------|---------|
| 1    | 71  | M      | 2008   | Blood culture | ICU      | Cerebrovascular Disease, Lung Edema, Tracheostomy | Bacteremia Exitus |
| 2    | 3   | F      | 2009   | Blood culture | Pediatric ICU | Acute Lymphoblastic Leukemia | Febrile Neutropenia | Recovered |
| 3    | 69  | M      | 2012   | Blood culture | Anesthesia ICU | Chronic Obstructive Lung Disease, Chronic Renal Failure, Hemodialysis | Bacteremia Exitus |
| 4    | 6 months | F | 2012   | Endotracheal aspiration fluid culture | Pediatric ICU | Epilepsy | Bronchopneumonia | Recovered |
| 5    | 3   | M      | 2013   | Blood culture | 3. Pediatric Clinic | Acute Disseminated Encephalomyelitis | Septicemia Recovered |
| 6    | 2   | M      | 2013   | Endotracheal aspiration fluid culture | Pediatric ICU | Epilepsy, Joubert Syndrome | Septicemia Exitus |
| 7    | 3 months | F | 2013   | Blood culture | 4. Pediatric Clinic | Cystic Fibrosis, Aganglionic Bowel, Colostomy | Septicemia Recovered |
| 8    | 5 months | F | 2014   | Endotracheal aspiration fluid culture | Pediatric ICU | Arnold Chiari Syndrome, Hydrocephalus | Septicemia Recovered |
| 9    | 2   | M      | 2015   | Wound swap culture | Pediatric Gastroenterology Clinic | Ileus, Chronic Diarrhea | Septicemia Recovered |
| 10   | 5   | M      | 2015   | Blood culture | Pediatric ICU | Atrial Septal Defect | Septicemia Recovered |
| 11   | 40  | F      | 2016   | Blood culture | Anesthesia ICU | Operation because of Aortic Dissection, Acute Renal Failure | Septicemia Exitus |
| 12   | 4   | F      | 2016   | Blood culture | Pediatric ICU | Cerebral Palsy, Epilepsy | Aspiration pneumonia, Septicemia | Recovered |
| 13   | 5 months | F | 2017   | Cerebrospinal fluid | Nursing Clinic | Hydrocephalus, Acute Renal Failure | Meningitis, Ventriculoperitoneal Shunt Infection Recovered (Transferred to another hospital on family’s request) |
| 14   | 1   | M      | 2018   | Cerebrospinal fluid | Nursing Clinic | Hydrocephalus | Meningitis, Ventriculoperitoneal Shunt Infection | Recovered |
| 15   | 17  | F      | 2018   | Endotracheal aspiration fluid culture | Pediatric ICU | Cerebral Palsy, Acute Renal Failure, Tracheostomy | Septicemia Recovered |
| 16   | 1   | M      | 2019   | Blood culture | Nursing Clinic | Trizomy 21, Hirschsprung Disease, Colostomy | Septicemia Recovered |
| 17   | 65  | F      | 2019   | Endotracheal aspiration fluid culture | Nursing Clinic | Hydrocephalus, Acute Renal Failure | Cerebrovascular Disease | Exitus |

M: Male, F: Female ICU: Intensive Care Unit

Table 2. Antibiotic susceptibility of the strains

| Case | Ceftazidime | Cefepime | Ceferozone-sulbactam | Piperacillin-tazobactam | Amikacin | Gentamicin | Trimethoprim-sulfamethoxazole | Ciprofloxacin | Imipenem | Meropenem |
|------|-------------|----------|----------------------|------------------------|----------|-----------|-------------------------------|--------------|----------|-----------|
| 1    | R           | R        | -                    | R                      | R        | R         | R                             | S            | -        | -         |
| 2    | R           | R        | -                    | R                      | R        | R         | R                             | R            | R        | I         |
| 3    | -           | -        | R                    | R                      | R        | R         | -                             | -            | -        | -         |
| 4    | R           | R        | S                    | -                      | -        | -         | -                             | S            | R        | R         |
| 5    | -           | S        | S                    | -                      | S        | R         | S                             | R            | R        | -         |
| 6    | R           | R        | -                    | -                      | -        | -         | R                             | S            | R        | R         |
| 7    | R           | R        | S                    | -                      | -        | -         | R                             | S            | R        | R         |
| 8    | R           | R        | S                    | R                      | S        | R         | R                             | R            | I        | R         |
| 9    | R           | R        | S                    | R                      | R        | R         | S                             | S            | S        | R         |
| 10   | R           | R        | -                    | S                      | I        | S         | -                             | S            | R        | R         |
| 11   | R           | -        | -                    | R                      | R        | R         | S                             | R            | R        | R         |
| 12   | R           | R        | R                    | R                      | R        | R         | -                             | S            | R        | R         |
| 13   | R           | R        | -                    | R                      | -        | R         | S                             | R            | R        | R         |
| 14   | R           | R        | -                    | R                      | R        | R         | -                             | R            | R        | R         |
| 15   | -           | -        | R                    | S                      | S        | S         | S                             | S            | R        | R         |
| 16   | R           | R        | R                    | R                      | R        | S         | R                             | R            | R        | R         |
| 17   | -           | -        | -                    | -                      | -        | -         | S                             | S            | -        | R         |

R: Resistant, S: Susceptible, I: Intermediate
Previous studies revealed a cumulative mortality rate of 52% in neonates and 33% in non-neonates with *E. meningoseptica* infections [10]. In the largest series of 118 patients with *E. meningoseptica* bacteremia at a medical center in Taiwan, the 14-day mortality rate was 23% [5]. The acquisition of the infection in an ICU was a significant predictor of mortality. These results all support previous findings by Lin et al. that host factors were the critical determinant in predicting outcomes [11]. Aldoghaim et al. reported that although most of the patients did not receive appropriate antibiotic treatment, the mortality rate in their study was low (16.5%), which was much lower than that reported in past studies [1,5,10]. In our study, the mortality rate was 29.4% and they were all from ICU. Only one of them was pediatric aged and died within 12 days after isolation of *E. meningoseptica* from endotracheal aspiration material because of septicemia. All of our adult patients have died; three of them had renal failure (all underwent hemodialysis), and one had cardiac arrest because of cerebrovascular disease. In addition, only one of the adult deaths in this study was related to *E. meningoseptica* septicemia (which underwent hemodialysis), while the other cultures were negative for *E. meningoseptica* when they died.

The choice of optimal antibiotic agents for the treatment of *E. meningoseptica* infection is difficult because of the unpredictability and breadth of antimicrobial resistance of this organism, which is often resistant to antibiotics prescribed for the treatment of serious gram-negative bacteria, such as β-lactam agents, aminoglycosides and carbapenems [1]. Lin et al. reported that 54.5% of patients infected with *E. meningoseptica* bacteremia recovered without receiving appropriate antibiotic treatment [11]. Aldoghaim et al. reported that in their study, among those receiving an inappropriate antibiotic for *E. meningoseptica* bacteremia, five of six patients recovered [1]. This may be attributable to the low virulence of *E. meningoseptica*. However, further studies are required to understand the virulence mechanisms of *E. meningoseptica*.

Chan et al. detected piperacillin/tazobactam as the most effective antibiotic (100% susceptibility) against *E. meningoseptica*, followed by, trimethoprim/sulfamethoxazole (78.6% susceptibility) and fluoroquinolones (87.5% susceptibility for levofloxacin and moxifloxacin and 33.3% susceptibility for ciprofloxacin) [5]. In a study, they treated all patients with injectible minocycline and co-trimoxazole (Narayan MD, Kumar AL, Kaushik M. Emerging nosocomial pathogens in bedside hemodialysis patients. Indian J Crit Care Med. 2013;17(S):304-7). However, some anecdotal reports have revealed the successful treatment of *E. meningoseptica* meningitis using a combination therapy of piperacillin/tazobactam and trimethoprim/sulfamethoxazole or fluoroquinolones. J Med Microbiol. 2019;68(8):1167-72.

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