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Review

Role of vancomycin in the treatment of bacteraemia and meningitis caused by *Elizabethkingia meningoseptica*

Shio-Shin Jean [a,b], Tai-Chin Hsieh [c,d], Yong-Zhong Ning [e], Po-Ren Hsueh [f,*]

[a] *Department of Emergency Medicine, Department of Emergency and Critical Care Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan*
[b] *Department of Emergency, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[c] *Division of Infectious Diseases, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan*
[d] *Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[e] *Department of Microbiology, Peking University Third Hospital, Beijing, China*
[f] *Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*

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ABSTRACT

Elizabethkingia meningoseptica, a Gram-negative pathogen once deemed clinically insignificant, tends to cause infections among low-birth-weight infants and immunocompromised patients. Previously, vancomycin was reported to cure several patients with bacteraemia caused by *E. meningoseptica*. Nevertheless, some laboratory investigations also showed considerable discordance between in vitro vancomycin susceptibility results obtained by the disk diffusion and broth microdilution methods against clinical *E. meningoseptica* isolates as determined using the criteria for staphylococci recommended by the Clinical and Laboratory Standards Institute (CLSI). In this review, the PubMed database (1960–2017) was searched for studies that reported mainly cases with *E. meningoseptica* bacteraemia or meningitis treated with vancomycin alone or with regimens that included vancomycin. In addition, the in vitro synergy between vancomycin and other agents against isolates of *E. meningoseptica* was reviewed. *Elizabethkingia meningoseptica* bacteraemia appears not to universally respond to intravenous (i.v.) vancomycin-only therapy, especially in patients who require haemodialysis. If i.v. vancomycin is the favoured therapy against *E. meningoseptica* meningitis, the addition of ciprofloxacin, linezolid or rifampicin might be an option to effectively treat this difficult-to-treat infection. Further clinical studies are needed to determine the clinical efficacy of these combination regimens for the treatment of *E. meningoseptica* meningitis.

1. Introduction

Isolates of the genus *Chryseobacterium*, formerly *Flavobacterium*, named for its yellow pigment, are non-motile, non-fastidious, catalase- and oxidase-positive, glucose-non-fermentative Gram-negative bacilli [1]. In the natural environment, these organisms are microbial inhabitants of soil, plants, foodstuffs and water sources [2]. More than 90 species in the *Chryseobacterium* genus are recognised. *Chryseobacterium indologenes*, most frequently cultured from clinical samples, likely causes diverse infections (bacteraemia, pneumonia, artificial shunt, meningitis, intra-abdominal, as well as deep soft-tissue and wound infections), with protean clinical symptoms and signs [3–5]. The genus *Elizabethkingia*, which has been formally revised to comprise three species (*Elizabethkingia anophelis*, *Elizabethkingia meningoseptica* and *Elizabethkingia miricola*) using recently published data from whole-genome sequencing analysis [6], was proposed in 2005 based upon 16S rRNA sequence similarity between species initially categorised as the *Chryseobacterium* genus [7]. Similar to *C. indologenes*, *E. meningoseptica* (formerly also named *Flavobacterium meningosepticum*, *Chryseobacterium meningosepticum* or CDC II-a) has been known as an important healthcare-associated pathogen for more than five decades [1]. Akin to some *E. miricola* strains [8], *E. meningoseptica* usually displays resistance to the majority of β-lactam agents [2,9] since it harbours many heterogeneous types of high-number, chromosomally-mediated *blaB* metallo-β-lactamase, bla_{GOB} alleles that encode ample metallo-β-lactamases, as well as some resistance determinants encoding class A extended-spectrum β-lactamases [10–13]. Moreover, isolates of *E. meningoseptica* also have the potential to produce a biofilm, embedding intravascular *E. meningoseptica* organisms within [14], thereby protecting them from phagocytosis. The unique antimicrobial susceptibility profile of *E. meningoseptica* renders the commonly prescribed β-lactam drugs ineffective against community- or nosocomially-acquired infections and frequently causes delays in initiating appropriate antibiotic

* Corresponding author. Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan.
E-mail address: hsporen@ntu.edu.tw (P.-R. Hsueh).

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therapy. Nevertheless, the clinical significance of *E. meningoseptica* isolates has always been questioned because it has been considered a bacterium of low pathogenic potential [15,16]. *Elizabethkingia meningoseptica* is sometimes co-cultured with methicillin-resistant *Staphylococcus aureus* (MRSA) and other multidrug-resistant Gram-negative bacilli such as *Acinetobacter baumannii* as well as *Enterobacter* spp. from a diversity of clinical samples following administration of broad-spectrum antibiotics (especially cephalosporins or carbapenem agents) [1,2]. However, numerous studies have reported that *E. meningoseptica* infections tend to occur in hospitalised patients, including immunocompromised hosts. Patients with this co-morbidity would be predisposed to prolonged hospital stays, subsequent necessity for intravascular indwelling catheters, and/or becoming recipients of broad-spectrum antibiotics [1,2,14,17,18]. In addition, *E. meningoseptica* is also likely to be cultured from infants or neonates of low birth weight (<2500 g), with overall mortality rates being particularly high (33–53%) [1,2,14,17]. As estimated in two medical centres in Taiwan, the yearly incidence of *E. meningoseptica* bacteraemia appears to have been increasing in the last decade [1,2,18]. Therefore, clinicians are becoming increasingly aware of its clinical importance.

Previous literature has frequently reported in vitro susceptible results for vancomycin against isolates of *E. meningoseptica* by disk diffusion testing. In addition, in 1984, Ratner strongly advocated that intravenous (i.v.) or intrathecal vancomycin could be chosen as the mainstay treatment agent against invasive infections due to *E. meningoseptica* [19]. Some patients with *E. meningoseptica* septicaemia indeed improved clinically after receiving vancomycin alone or as a vancomycin-inclusive regimen therapy, whilst others did not. To delineate the clinical feasibility of vancomycin therapy against *E. meningoseptica* isolates, in this review the PubMed database was searched for literature from 1960–2017 specifically for clinical cases with invasive infections due to monomicrobial *E. meningoseptica*. The search terms '*Flavobacterium* species', '*Flavobacterium meningosepticum*', '*Chryseobacterium meningosepticum*', '*Elizabethkingia meningoseptica*', 'bacteraemia', 'sepsis', 'septicaemia', 'bloodstream infection', 'invasive infection', 'meningitis', 'vancomycin', 'Clinical and Laboratory Standards Institute (CLSI)', 'National Committee for Clinical Laboratory Standards (NCCLS)', 'susceptibility' and 'resistance' were used to search extensively for English-written literature stored in the PubMed database. In addition, to ascertain the true in vitro susceptibility results for vancomycin against clinical *E. meningoseptica* isolates, literature reporting minimum inhibitory concentrations (MICs) to vancomycin determined by the agar dilution or broth microdilution (BMD) method were also reviewed.

2. In vitro susceptibility testing for vancomycin against *Elizabethkingia meningoseptica*

The effectiveness of vancomycin therapy against clinical infections caused by isolates of *E. meningoseptica* remains an arguable issue. In the past, to determine the susceptibility results for vancomycin against isolates of *E. meningoseptica*, the interpretive criteria for *Staphylococcus* spp. were adopted by the CLSI (formerly NCCLS). The reference defined a vancomycin MIC of >4 mg/L against *S. aureus* as the non-susceptible category, the interpretive MIC breakpoints recommended by the CLSI before 2006 [20]. By means of the diffusion method using a vancomycin disk (30 μg), a high degree of susceptibility (i.e. an inhibition zone diameter ≥12 mm [21,22]) to vancomycin was noted against clinical *E. meningoseptica* isolates collected from cerebrospinal fluid (CSF), peritoneal fluid effluent, blood and other body fluids [2,23–29]. However, when the results of the vancomycin BMD method against staphylococci were utilised as the reference, enormous discrepancies in vancomycin susceptibility results between the reference and disk diffusion method were recognised for most clinical isolates of *Chryseobacterium* spp., including *E. meningoseptica* [25,27,29–33].

3. In vitro and in vivo synergy between vancomycin and other agents against *Elizabethkingia meningoseptica*

In an outbreak investigation pertaining to three clusters of nosocomially-acquired bacteraemia and/or meningitis relevant to *E. meningoseptica* isolates, Ceyhan et al observed that 8 of 13 paediatric patients involved received therapeutic regimens that contained at least 10 days of i.v. vancomycin (doses were unavailable). Seven of these eight paediatric patients eventually survived (Table 1) [34]. In another cluster of *E. meningoseptica* bacteraemia that involved four neonates, three survived after they were prescribed a therapeutic regimen consisting of i.v. vancomycin plus oral rifampicin suspension [39]. All three of the above *E. meningoseptica* isolates exhibited inhibition zones of 19 mm diameter in vancomycin disk diffusion testing [39]. In another outbreak in a neonatal intensive care unit, three surviving neonates with *E. meningoseptica* bacteraemia significantly responded well to a regimen comprising i.v. vancomycin and ciprofloxacin plus rifampicin (doses were all unavailable) [40]. By the disk diffusion test, the three aetiological *E. meningoseptica* strains showed susceptibility to ciprofloxacin, whilst susceptibility data regarding vancomycin and rifampicin were not mentioned [40].

Of note, Di Pentima et al reported important in vitro synergy data using the fractional inhibitory concentration index (FICI) for vancomycin and other antimicrobial agents against four clinical *E. meningoseptica* isolates. They reported that i.v. vancomycin in combination with rifampicin exhibited good therapeutic efficacy clinically on three neonates with *E. meningoseptica* meningitis (vancomycin MIC range 16–64 mg/L by BMD) [32]. Corresponding well with the clinical efficacy in the above three neonates, vancomycin plus rifampicin exhibited excellent in vitro FICI data (0.39–0.625, i.e. synergistic or additive category) against four causative *E. meningoseptica* strains [32]. It is also noteworthy that in the investigation by Di Pentima et al, the other ideal combination regimens against *E. meningoseptica* isolates (i.e. in vitro FICI ≤ 1.0) include rifampicin plus trimethoprim/sulfamethoxazole, vancomycin plus ciprofloxacin, and vancomycin plus linezolid [32]. Apart from two cases mentioned in the case series of Ceyhan et al [34], similar success was also noted in one full-term neonate with neonatal *E. meningoseptica* meningitis with associated bacteraemia (Table 1) [35]. However, as stated by Nau et al, the in vivo penetration percentages across the blood–brain barrier for ciprofloxacin (43–92%) and linezolid (80–100%) are much better than those of trimethoprim (18–51%)/sulfamethoxazole (12–30%), rifampicin (22%) and vancomycin (14–30%) [41]. Therefore, combination regimens that contain i.v. vancomycin are likely to be beneficial for patients with *E. meningoseptica* meningitis.

4. Non-neonatal *Elizabethkingia meningoseptica* infections

In the PubMed literature documenting cases with *E. meningoseptica* bloodstream infections (BSIs), there were six non-neonatal patients without end-stage renal disease (ESRD) [33,42–44], five of whom had immunocompromised factors (seen in Table 2) [33,42–44,46]. Four of the aforementioned six patients were treated successfully solely with i.v. vancomycin for *E. meningoseptica* bacteraemia. The vancomycin MICs for six *E. meningoseptica* isolates ranged from 4 mg/L to ≥16 mg/L obtained using the Etest (AB BIODISK, Solna, Sweden) [33,42–44] (Table 2). By contrast, three of the other six non-neonatal ESRD patients (undergoing haemodialysis) with *E. meningoseptica* bacteraemia were successfully treated by combination regimens that included i.v. vancomycin infusion. All aetiological isolates showed susceptibility to vancomycin by disk diffusion testing,