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Clinical and Microbiological Analysis of Bloodstream Infections Caused by *Chryseobacterium meningosepticum* in Nonneonatal Patients

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***Chryseobacterium meningosepticum* bloodstream infections in 11 nonneonatal patients were reported. More than half of the infections were community acquired. PCR assays indicated that the organisms produced extended-spectrum β-lactamases as well as metallo-β-lactamases. Genotyping showed diverse fingerprints among the isolates. Six patients survived without appropriate antibiotic treatment. Host factors are the major determinant of the outcomes of *C. meningosepticum* infections.**

Chryseobacterium meningosepticum (formerly known as *Flavobacterium meningosepticum* or CDCII-a) is a gram-negative rod widely distributed in nature. It is known to cause meningitis in premature and newborn infants (6, 8, 9, 16). In adults, cases of pneumonia, endocarditis, postoperative bacteremia, and meningitis have been reported, usually associated with a severe underlying illness (2, 11, 15, 18). The organism is usually multiresistant to antibiotics typically prescribed for treating gram-negative bacterial infections, including extended-spectrum β-lactam agents and aminoglycosides, and thus constitutes a clinical concern. An earlier study reported infections caused by atypical *C. meningosepticum* infections in a medical center in Taiwan (4). During the following years, new cases of *C. meningosepticum* infections were continuously identified in our hospital. The aim of this study was to report clinical features of such infections and the antimicrobial susceptibility and genotypes of the isolates.

From 2001 to 2002, *C. meningosepticum* was identified from the blood cultures of 11 patients admitted and treated in Chang Gung Memorial Hospital and Chang Gung Children's Hospital. The primary cultures from the patients invariably showed pure growth of nonfastidious, glucose-nonfermenting bacilli that were oxidase positive and nonmotile. Final identification was made by using an ID 32 GN automatic identification system (bioMerieux Vitek, Hazelwood, Mo.). Susceptibilities of the isolates to antimicrobial agents, including piperacillin, ceftazidime, cefepime, imipenem, gentamicin, chloramphenicol, vancomycin, ciprofloxacin, minocycline, trimethoprim-sulfamethoxazole, erythromycin, azithromycin, and rifampin, were determined by E-test strips (AB Biodisk, Solona, Sweden). Demographic data, treatment, and patient outcomes were reviewed. Infections were deemed community acquired if the patient admitted with an acute illness and initial cultures at the time of presentation yielded a positive result. Infections were considered nosocomial if cultures were negative at the time of admission or symptomatic infections developed after the first 72 h of hospitalization.

Clinical isolates from the 11 patients and eight control strains (5) kindly provided by Brita Bruun, University of Copenhagen, Denmark, were subjected to further molecular analysis. PCR methods with primer sets blaB and blaB3 were used to detect metallo-β-lactamase genes *blaB1*, *blaB2*, and *blaB3* (19), while blaCME and blaCME-2 primers were used to specifically detect the extended-spectrum β-lactamase genes bla_{CME} and $bla_{CME\text{-}2}$, respectively (1, 12, 19). Two genotyping methods, pulsed-field gel electrophoresis (PFGE) and infrequent-restriction-site PCR (IRS-PCR), were performed using procedures described previously (10, 13). The DNA fingerprints generated by PFGE were analyzed according to the criteria proposed by Tenover et al. (14). As for IRS-PCR, isolates with identical banding patterns or that varied in less than four bands were arbitrarily designated as the same genotypes or subtypes of an existing genotype.

Clinical characteristics of the 11 patients are summarized in Table 1. Six patients acquired the infection from the community, while the other five acquired it from the hospital. All of these five patients had a prolonged hospital stay (mean, 32 days; range, 13 to 99 days) before the onset of the nosocomial infection. All the adult patients had major underlying diseases. Sepsis was the final diagnosis in all adult patients, with some focal infections. The two pediatric patients (cases 1 and 8) who were previously healthy presented with fever and leukocytosis. Blood cultures in the two patients unexpectedly yielded *C. meningosepticum*; however, fever subsided spontaneously without antibiotic therapy. In addition, four adult patients (cases 2, 5, 9, and 11) also recovered without appropriate antibiotic treatment (see Table 1 for those antibiotics used). Among the five patients who were offered appropriate antibiotic treatment based on the susceptibility testing, two died of sepsis.

The MIC ranges and the MICs at which 50 and 90% of the isolates were inhibited are listed in Table 2. The majority of antimicrobial agents tested displayed poor activities against *C. meningosepticum* isolates, except minocycline, ciprofloxacin, trimethoprim-sulfamethoxazole, and rifampin. The isolates

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TABLE 1. Clinical characteristics of the 11 patients with *C. meningoseptium* bloodstream infections[a]

Case no.	Sex	Age (yr)	Underlying disease(s)	Diagnosis	Mode of infection	Antibiotic treatment	Outcome
1	M	0.5	None	Occult bacteremia	C	None	Recovered
2	M	48	Liver cirrhosis, valvular heart disease	Wound infection, sepsis	H	Imipenem + amikacin	Recovered
3	M	74	Lung cancer	Sepsis, catheter associated	H	Ciprofloxacin	Died
4	M	42	Liver cirrhosis	Pneumonia, sepsis, DIC	C	Ciprofloxacin	Died
5	M	82	Lymphoma	Sepsis	H	Vancomycin	Recovered
6	F	74	Stroke	Sepsis	H	Ciprofloxacin	Recovered
7	M	68	Diabetes mellitus	Wound infection, sepsis	C	Ciprofloxacin	Recovered
8	F	1.5	None	Occult bacteremia	C	None	Recovered
9	F	47	Common bile duct stone	Sepsis	C	None	Recovered
10	M	62	Nasopharyngeal cancer, stroke	Cellulitis, sepsis	C	Ciprofloxacin	Recovered
11	M	40	Acute pancreatitis	Peritonitis, sepsis	H	Piperacillin + gentamicin	Recovered

[a] M, male; F, female; C, community acquired; H, hospital acquired; DIC, disseminated intravascular coagulation.

showed relatively higher resistance to the β-lactam antibiotics tested, including imipenem. Nine of the 11 clinical isolates contained either *blaB1* or *blaB2* genes; in contrast, only three control strains from Denmark contained such genes. The two isolates that contained neither *blaB1* nor *blaB2* also did not harbor *blaB3*. MICs of imipenem for the two isolates were 0.33 and 24 μg/ml, respectively. Only two clinical isolates and one control strain were positive for the *blaB3* gene. All clinical isolates were positive in the PCR with primers targeted at $bla_{\text{CME-2}}$, but none was positive for bla_{CME}. In contrast, all of the eight control strains were positive for both bla_{CME} and $bla_{\text{CME-2}}$.

PFGE and IRS-PCR demonstrated a similar efficiency in the discrimination of *C. meningosepticum*. Both methods clearly identified 11 distinct genotypes among the 11 clinical isolates. Six different PFGE fingerprints were obtained from the eight control strains that were differentiated into six ribotypes in an earlier study (5). By IRS-PCR, six major types with two subtypes of a major type were identified in the control strains. These results indicated that the 11 clinical isolates and most of the eight control strains were genetically unrelated.

Although the role of *C. meningosepticum* in the infections of newborns and the immunocompromised has been recognized, clinical data detailing these infections remain limited (2, 4, 8, 9, 11, 15, 16, 18). The present study, in accordance with previous reports, showed that most of the infections occurred in the immunocompromised adults. Nevertheless, this study identified two important points. First, more than half of the infections were community acquired. Second, two young children, aged 0.5 and 1.5 years, respectively, presented with occult bacteremia. Given the fact that *C. meningosepticum* is widely distributed in the natural environment, its role in the pathogenicity of community-acquired infections in the immunocompromised and occult bacteremia in healthy young children deserves further studies. In the literature, infections with *C. meningosepticum* were generally associated with a poor outcome, with a cumulative mortality of 33% among postneonates (2). In contrast, patients of this series experienced a relatively lower mortality. It appears that the use of appropriate antibiotics did not necessarily correlate with a favorable outcome; host factors, on the other hand, are the critical determinant in predicting the outcomes of *C. meningosepticum* infections.

TABLE 2. In vitro activity of various antibiotics against 11 clinical isolates of *C. meningosepticum*

Antibiotic	MIC (μg/ml)[b]		
	Range	50%	90%
Piperacillin	0.016 ~ 24	8	16
Ceftazidime	0.064 ~ >128	64	128
Cefepime	0.03 ~ 256	24	128
Imipenem	0.033 ~ >32	32	>32
Gentamicin	3 ~ >256	64	>256
Chloramphenicol	0.5 ~ 48	8	32
Vancomycin	16 ~ >32	16	24
Ciprofloxacin	0.019 ~ 1	0.25	0.75
Minocycline	0.023 ~ 1	0.03	1
SXT[a]	0.094 ~ 1	0.75	1
Erythromycin	1 ~ 8	4	6
Azithromycin	4 ~ 64	6	12
Rifampin	0.25 ~ 0.75	0.5	0.75

[a] SXT, trimethoprim-sulfamethoxazole.
[b] 50% and 90%, the MICs at which 50 and 90% of the isolates were inhibited.

The overall β-lactam susceptibility patterns of the *C. meningosepticum* isolates studied generally corresponded to those previously described and characterized by the resistance to all β-lactams tested, including extended-spectrum cephalosporins and imipenem, and a moderate susceptibility to piperacillin (1, 3, 7). The resistance phenotypes could be explained by results of the PCR assay which indicated that a majority of the clinical isolates produced at least two β-lactamases, with one being an extended-spectrum β-lactamase and the other a metallo-β-lactamase. Because of the multiresistant nature of the organisms, clinical experience in choosing optimal therapeutic regimens for treating *C. meningosepticum* infections is extremely limited. Vancomycin has been previously recommended as the drug of choice for the treatment of neonatal meningitis due to *C. meningosepticum* (6). However, the high MICs (≥16 μg/ml) of vancomycin for the organisms, as demonstrated in our study as well as those of others (3), indicate that vancomycin should not be considered the drug of choice for treating *C. meningosepticum* infections, especially meningitis. On the other hand, this study confirms the superior activity of ciprofloxacin against *C. meningosepticum*, as has been heralded by previous reports (3, 4, 7). We also found minocycline, trimethoprim-sulfamethoxazole, and rifampin may be good alternatives; however, the use of these agents to treat invasive infections caused by *C. meningosepticum* needs further evaluation.

Few molecular methods have been evaluated to differentiate strains of *C. meningosepticum* (5, 17). The isolates of *C. meningosepticum* collected in this study showed different genotypes by both PFGE and IRS-PCR, suggesting that they were clonally unrelated. The effectiveness of the two methods in the discrimination of such isolates, as demonstrated in this study, is impressive. Compared to those previously used methods, including ribotyping, which are usually time-consuming and difficult to perform, the two methods appear to provide a much more efficient way for differentiating isolates of *C. meningosepticum*. Thus, the two methods would be more suitable for epidemiological investigations when an outbreak is suspected and a large number of isolates are waiting for examination.

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