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Original Article

Retrospective analysis of Stenotrophomonas maltophilia bacteremia: clinical features, risk factors and therapeutic choices

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Abstract: Background: Stenotrophomonas maltophilia is an important nosocomial pathogen, which is of increasing frequency in blood stream infection, especially in immunocompromised patients. Objectives: Our study aims to investigate the demographics, clinical characteristics, risk factors, drug resistance and treatment choice of Stenotrophomonas maltophilia bacteremia, trying to find out the independent risk factors associated with attributable mortality and investigate appropriate therapeutic choices for Stenotrophomonas maltophilia bacteremia. Method: In this retrospective study of case series, the clinical records and laboratory tests of 95 patients with S. maltophilia bacteremia in the first hospital affiliated to Zhejiang University from January 2009 to May 2015 were reviewed. Data was analyzed using Chi-square test and multiple logistic regressions. P<0.05 was considered statistically significant. Results: A total of 95 patients (60 male, 35 female) were eligible for the study. Median age of the 95 patients was 61 years (range 15-95 years). Forty-three (45.26%) patients had an underlying malignant disease, of which 18 (18.95%) patients had underlying hematologic malignancies. Crude mortality and attributable mortality was 37.89% and 35.79%, respectively. Through multivariate analysis, neutropenia (Odds Ratio [OR] 0.132, 95% Confidence Interval [CI] 0.043-0.405, P<0.001) and mechanical ventilation (OR 0.254, 95% CI 0.089-0.719, P=0.010) were independent factors related to mortality. *In vitro* susceptibility data revealed that isolates were most sensitive to TMP/SMZ (95.45%) and most resistant to imipenem (97.8%). The most commonly used agent as monotherapy in definite treatment was levofloxacin and cefoperazone. No significant difference (P=0.967) in mortality was seen between monotherapy and combination therapy. Conclusion: Stenotrophomonas maltophilia bacteremia is a critical situation for patients with high attributable mortality. Our results suggest that neutropenia and mechanical ventilation were independent risk factors associated with mortality. We also believe that levofloxacin and tigecycline can be considered promising alternative agents except for TMP/SMZ.

Keywords: Stenotrophomonas maltophilia, bacteremia, risk factors, mortality, therapeutics

Introduction

Stenotrophomonas maltophilia (S. maltophilia) is a non-fermenting, Gram-negative opportunistic pathogen, which exists widely in nature and hospital equipment [1]. S. maltophilia has been recognized as a new multiple-drug-resistant organism (MDRO), responsible for various severe infections in humans, particularly in immunosuppressive and poor-conditioned patients [2]. Data from China CHINET Antimicrobial Resistance Surveillance Program (2005-2011) showed that isolating rate of S. Maltophilia accounted for 11.61% of non-fermenting maltophilia isolates provided by several hospitals ranges from 7.1 to 37.7 cases per 10,000 discharges [4]. Meanwhile, S. maltophilia has natural resistance to many antimicrobial drugs, including carbapenems, treatment of S. maltophilia infections is a real challenge [5].

Clinical characteristics and drug resistance of a certain bacteria varies in different geographic areas. Few reports were found about the current conditions of S. maltophilia bacteremia in

east-coast China, which are quite different from those in other areas, especially in the U.S. To get a more comprehensive view of the present situation of S. maltophilia bacteremia in Zhejiang, we retrospectively analyzed clinical characteristics and drug resistance of S. maltophilia bacteremia in one of the largest hospitals in Zhejiang province. We expect that our results would offer experiences in effectively preventing and treating S. maltophilia infections.

Patients and methods

Ethics statement

This study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (reference number: 235). We had access to information that could identify individual patients during data collection. When data collection was done, individual patients were represented by consecutive numbers.

Study population

The first hospital affiliated to Zhejiang University is a 3000-bed tertiary hospital as well as the largest medical, teaching and research center in Zhejiang province. We identified all discharges in our hospital with S. maltophilia bloodstream infection (BSI) from January 1, 2009 to May 31, 2015. Patients who had at least one positive blood culture with relevant clinical manifestation (symptoms, signs, lab results) were enrolled. We excluded patients without adequate medical records or any clinical manifestation.

Data collection

Demographic (age, sex, dates of birth), clinical characteristics (dates of positive blood cultures and negative blood culture post bacteremia, body temperature at onset of bacteremia, department, underlying diseases, admission to the intensive care units, history of mechanical ventilation and surgery, use of antibiotics and immunosuppressors) and laboratory tests (blood routine test, liver function test, C-reaction protein (CRP), procalcitonin (PCT)) were collected from the Electronic Medical Record. Microbiological data (susceptibility results, coisolated organisms) were confirmed through the laboratory information system.

Definitions

We defined some of the following terms according to the literature [6-9].

Bacteremia was defined as the isolation of bacteria from at least one culture of peripheral venous blood collected from a patient who had relevant symptoms and signs [6]. A positive blood culture without evidence of infection was considered as contamination and excluded from the analysis. Polymicrobial bacteremia was defined as the identification of one or more bacterial species other than S. maltophilia in multiple blood samples within 24 h [7]. An absolute value of neutrophil $<500/mm^3$ at the onset of bacteremia was defined as neutropenia [9]. Intensive care unit (ICU) stay was defined as ≥24 h stay in ICU prior to bacteremia. Prior antibiotic therapy was defined as use of antibiotics (oral, intramuscular, or intravenous) within 2 weeks before the positive blood cultures [8]. Steroid therapy was defined as the use of corticosteroids at a dose of ≥10 mg daily of prednisolone-equivalent for over 2 weeks or as a regular therapy [9]. Immunosuppressive therapy was considered to be administration of immunosuppressive agents (cyclosporine, azathioprine, leflunomide, cyclophosphamide, antithymocyte globulin, and cytotoxic chemotherapy) in 30 days prior to bacteremia [8]. Surgical procedure was considered to be abdominal, pectoral, osteoarticular invasive procedure within 14 days prior to the bacteremia, including percutaneous endoscopy [8]. If the blood culture was found to be negative before death, the patient was excluded from infection-related death. The outcome was recorded as either death of bacteremia within 30 days or survival beyond 30 days. Empirical therapy was considered as the use of antibiotics at the onset of infection by experience. Definite treatment was defined as the targeted administration of sensitive antimicrobial according to S. maltophilia susceptibility test *in vitro*.

Statistical analysis

We calculated descriptive statistics, including frequency counts and percentages of categorical variables, to describe the demographics and clinical characteristics by EXCEL. Chi-square test by SPSS version 22.0 (IBM, USA) was performed to determine whether the risk

Table 1. Demographics and underlying conditions of patients with S. maltophilia BSI

Characteristics	Cases (N=95)
Sex	
Male	60 (63.16%)
Female	35 (36.84%)
Age (years)	
≥60	51 (53.68%)
<60	44 (46.32%)
Median age	61
Department	
ICU	25 (26.32%)
Department of infectious diseases	18 (18.95%)
Hematology department	14 (14.74%)
Internal medicine department	13 (13.68%)
Underlying diseases	
Solid tumor	25 (26.32%)
Hepatobiliary and pancreatic tumor	14
Gastrointestinal tumor	5
Lung cancer	3
Gynecolgical tumor	2
Hematological malignancies	18 (18.95%)
ALL[a]	9
AML[b]	7
NHL[c]	2
Mean duration of neutropenia	17.8 days (7-56 days)
Diabetes	18 (18.95%)
Hypertention	16 (16.84%)
COPD[d]	13 (13.68%)
Transplantation	12 (12.63%)
Chronic renal disease	6 (6.32%)
Mortality	
Overall mortality	37.89%
Attributable mortality	35.79%

[a]ALL: acute lymphoblastic leukemia; [b]AML: Acute myeloid leukemia; [c]NHL: non-Hodgkin's lymphoma; [d]COPD: chronic obstructive pulmonary disease.

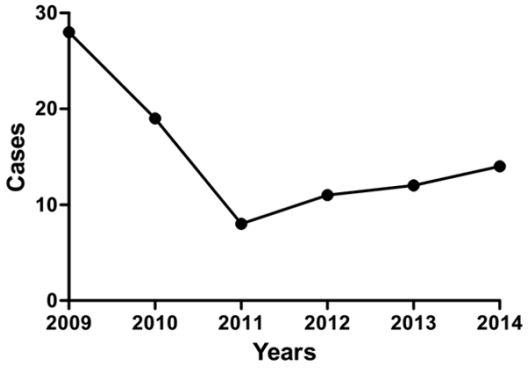

Figure 1. Number of S. maltophilia bacteremia cases.

factors have significant difference. Variables which showed a *P* value less than 0.05 in the univariate analysis were analyzed by multiple logistic regressions to determine which variables independently predicted mortality. P<0.05 was considered statistically significant.

Results

A total of 106 records were screened and 95 of them were analyzed. As for the patients who were excluded, the medical records of 7 patients were unavailable, and 4 were thought to be contamination rather than true infection.

Patient characteristics

Demographics and underlying conditions of the patients are presented in **Table 1**. Male patients accounted for a larger proportion (60 pts, 63.16%) than female patients (35 pts, 36.84%). The median age of patients was 61 years (range 15-94 ys), and 51 patients (53.68%) were over 60 years old. All patients were of Han ethnicity.

Figure 1 shows the trend of cases with S. maltophilia bacteremia per year, except for 2015. S. maltophilia bacteremia was detected in a total of 28 patients from August 2009 to January 2010. Moreover, 10 (35.71%) of them were from the department of infectious diseases and 9 (32.14%) from the department of internal medicine. There seems to be an outbreak of S. maltophilia throughout the 6-month period. In addition, the number of patients with S. maltophilia bacteremia has been growing since 2011.

In regard to the department distribution, 25 patients (26.32%) were from ICU. Other major sources were department of infectious diseases (18pts, 18.95%), hematology department (14pts, 14.74%), and internal medicine department (13pts, 13.68%). Malignancy was the most common underlying disease (43pts, 45.26%), among which 25 patients (26.32%) had solid tumor and 18 patients (18.95%) suffered from hematological malignancies.

In the 18 patients with hematological malignancies, 12 (66.67%) patients died from bacte-

Table 2. Clinical manifestations of patients with S. maltophilia BSI

Characteristics	Cases (N=95)
Fever (T≥38°C)	89 (93.68%)
Mean temperature (°C)	39.23
Previous antibiotics	89 (93.68%)
Carbapenems treatment	56 (58.95%)
Elevated CRP[a] (>10 mg/L)	84 (88.42%)
Presence of central venous catheter	39 (41.05%)
Elevated WBC[b] (>10×10^9/L)	28 (29.47%)
Mechanical ventilation	25 (26.32%)
ICU stay	25 (26.32%)
Previous surgical procedure	23 (24.21%)
Neutropenia	23 (24.21%)
Previous chemotherapy	22 (23.16%)
Previous steroids therapy	15 (15.79%)
Previous immunosuppressor therapy	12 (12.63%)

[a]CRP: C-reactive protein; [b]WBC: white blood cell.

remia itself. The infection occurred in six patients (33.33%) during initial treatment, ten (55.56%) in refractory/relapse condition, one in complete remission (CR)1, one in consolidation chemotherapy after CR2. All 18 patients were in neutropenia at the onset of bacteremia.

The majority of patients (86 of 95, 93.75%) had a febrile response (≥38°C). Only 25 patients (26.32%) had a history of ICU stay prior to the bacteremia, which was lower than the reported data (45%-52%) [10, 11]. Clinical characteristics are presented in **Table 2**.

Risk factors

In our study, 34 of 95 patients died of S. maltophilia infection itself, and 2 patients who recovered from bacteremia died in the following 2 months from liver transplant complications and respiratory failure, respectively. The results of univariate and multivariate analysis are presented in **Tables 3** and **4**. From **Table 3**, we can see that neutropenia, carbapenems treatment in past 30 days, hematological malignancy as an underlying disease, antibiotic treatment over 14 days, presence of central venous catheter, ICU stay, and mechanical ventilation are significantly associated with mortality. However, no significant difference in mortality was observed in polymicrobial bacteremia (P=0.650), positive cultures from other sources (P=0.277), steroids use within 30 days (P=0.829), surgical procedure in past 2 weeks (P=0.701), and immunosuppressor treatment in past 30 days (P=0.650). After the multivariate logistic regression analysis, we drew a conclusion that neutropenia and mechanical ventilation are independent risk factors for mortality.

Antibiotic susceptibilities

All *in vitro* susceptibility data of 95 patients was acquired through our electronic medical records system. The resistance top 5 and susceptibility top 5 are shown in **Figure 2**. 97.8% (89 of 91) are resistant to imipenem, and 87.64% (78 of 89) to gentamicin, 85.56% (77 of 90) to amikacin, 83.15% (74 of 89) to aztreonam, and 78.79% (52 of 66) to cefotaxime. On the other side, the susceptibility to trimethoprim-sulfamethoxazole (TMP/SMZ) was 95.45% (84 of 88), followed by minocycline 90.20% (46 of 51), cefopcrazone 85.71% (66 of 77), levofloxacin 82.61% (57 of 69), and clavulanic acid 81.97% (50 of 61).

Therapeutic regimens

Apart from 12 patients who died or were transferred to local hospital before antibiotics treatment was adjusted, and 5 patients who were never given antibiotics during their stay in hospital, 78 patients had received appropriate antibiotics once the infection was confirmed.

38.46% (30 of 78) received definite treatment and 61.54% (48 of 78) were under empirical treatment. 10 patients (33.33%) died of infection in the definite treatment group, compared to 10 patients (20.83%) in the other group. No statistical difference in associated mortality was observed between two groups (P=0.219).

From another aspect, 65.38% (51 of 78) underwent monotherapy, compared to 34.62% (27 of 78) with combinations of at least two agents. Yet, the associated mortality in monotherapy group is 25.49% (13 of 51), compared to 25.93% (7 of 27) in combination therapy group. No significant difference (P=0.967) was seen between the two therapeutic choices. However, our research shows that the mean fever subsidence time in patients with combination therapy exhibits a slightly longer trend than monotherapy (5.6 d VS 5.4 d). Main therapeutic regimens in both monotherapy and combination therapy are shown in **Table 5**.

Table 3. Results of univariate analysis by Chi-square test

Factor	Death (n=34) %	Survival (n=61) %	*P*-value
Neutropenia	14 (41.18%)	7 (11.48%)	0.001
Carbapenems treatment	27 (79.41%)	29 (47.54%)	0.002
Hematological malignancy	12 (35.29%)	6 (9.84%)	0.002
Antibiotic treatment over 14 days	20 (58.82%)	18 (29.51%)	0.005
Central venous catheter	19 (55.88%)	20 (32.79%)	0.028
Mechanical ventilation	13 (38.24%)	12 (19.67%)	0.049
ICU stay	13 (38.24%)	12 (19.67%)	0.049

Table 4. Results of multivariate analysis by Logistic regression

Factor	OR[a] (95% CI[b])	*P*-value
Neutropenia	0.132 (0.043-0.405)	<0.001
Mechanical ventilation	0.254 (0.089-0.719)	0.010

[a]OR: odds ratio; [b]CI: confidence interval.

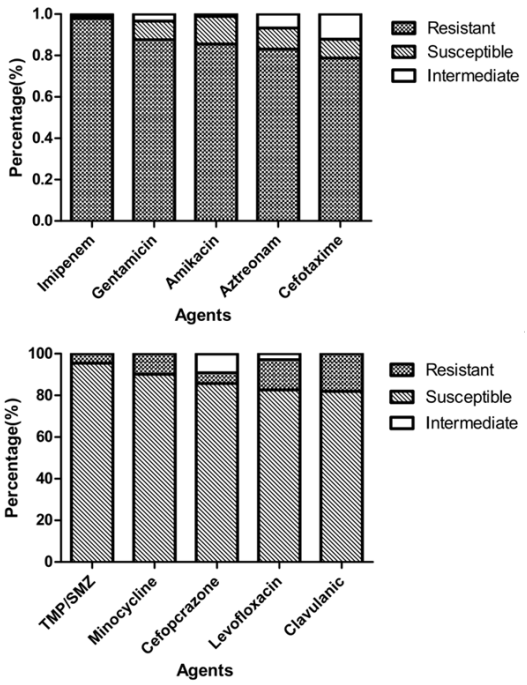

Figure 2. Antibiotic susceptibility results for 95 episodes of S. maltophilia bacteremia.

Discussion

Of all nosocomial bacteremias, approximately 1% are caused by S. maltophilia [12]. Some previous reports have elucidated that S. maltophilia infection has significantly increased over the past 2 decades [10, 11, 13]. Only few researchers around the world have investigated the cases with S. maltophilia bacteremia, mostly about select groups of patients (ICU, hematology or oncology) [14-17]. Our current study consisted of the largest series of episodes ever published in Asia and covered all departments in our hospital.

With respect to S. maltophilia bacteremia, crude mortalities and attributable mortalities reported have ranged from 14% to 69% and from 12.5% to 41%, respectively [18]. The infection-associated mortality of 35.79% in our research is in the middle of the aforementioned rates. No information concerning department distribution was ever published as we could find. In regard to the clinical characteristics of the enrolled patients, up to 93.75% of 80 patients were found to be febrile on the bacteremia according to our data, considerably higher than that in other reports (48%-58.8%) [9, 10]. One possible reason for this phenomenon is that, in clinical practice, blood culture would most likely be performed when the patient's temperature increased instead of taken as a regular test. It reminds clinicians that blood culture should be performed immediately as long as there is any chance of infections in case of missed diagnosis.

Compared with previous studies (57%-84%), we had a lower percentage of presence of CVC (41.05%), which was perceived as a major source of infection [6, 10, 16, 19]. Our analysis manifests that presence of CVC is significantly associated with mortality. A previous study in Australia found a significant correlation between deaths and a failure to remove the CVC (P<0.01) [8]. Moreover, Jeon et al. believe that removing a CVC may considerably reduce mortality in patients with S. maltophilia bacteremia [20].

Neutropenia, carbapenems treatment, CVC, ICU stay, hematological malignancy and mechanical ventilation were identified to be significantly related to mortality by us and other authors [6, 8, 9, 13, 20]. We also observed that antibiotic treatment over 14 days may indicate significantly worse prognosis. Other risk factors have been reported including septic shock [9], combined bacteremia with enterococci [6],

Table 5. Main therapeutic regimens in monotherapy and combination therapy

Regimens	Patients (N=78) (%)
Monotherapy	51 (56.67%)
Cefoperazone	15 (19.23%)
Piperacillin/tazobactam	8 (10.26%)
Levofloxacin	7 (8.97%)
Ceftazidime	4 (5.13%)
Tigecycline	3 (3.85%)
Combination therapy	27 (34.62%)
Levofloxacin, cefoperazone	7 (8.97%)
Levofloxacin, tigecycline	5 (6.41%)
Levofloxacin, piperacillin/tazobactam	4 (5.13%)
Levofloxacin, efotiam	2 (2.56%)
Minocycline, piperacillin/tazobactam	2 (2.56%)

prior use of three or more antibiotics, Multiple Organ Dysfunction Syndrome (MODS), Acute Physiology and Chronic Health Evaluation II (APACHE II) score >20, Sepsis-Related Organ Failure Assessment (SOFA) index >6, and thrombocytopenia [11, 20]. Neutropenia and mechanical ventilation were independent risk factors associated with mortality in our research. The former one was confirmed in several studies [6, 9]. It is obvious that patients in neutropenia are more vulnerable to any kind of infections, including bacteremia. According to Ahn et al., procalcitonin (PCT) ≥0.5 ng/ml, respiration rate ≥24 and Eastern Cooperative Oncology Group PS ≥2 were predictive of bacteraemia in the low-risk patients with febrile neutropenia. Also, they believe that for patients with high possibility of bacteraemia, parenteral antibiotic treatment while awaiting the blood culture results may be beneficial [21]. A previous report from a general adult ICU in Sweden revealed that the mechanical ventilation time were the longest for S. maltophilia among all pathogens in the lower respiratory tract. They presumed that such patients had received prior antibiotic treatment and therefore were particularly at risk for acquiring infections with S. maltophilia which is resistant to many antibiotics [22]. Accordingly, it is inferred that mechanical ventilation facilitates the development of multidrug resistant S. maltophilia baceremia and thus predicts worse outcome. Besides, some literature also found combined bacteremia with enterococci (P=0.022) [6], hypotensive shock (P=0.0013), receipt of carbapenem antibiotic (P=0.0016), ICU stay (P=0.025) [9], SOFA score >6 (P=0.009) [23], CVC removal (P=0.049) [20], inappropriate antibiotic use (P<0.001) and presence of MODS (P=0.001) [24] to be independent risk factors.

Treatment of S. maltophilia infections has always been challenging because of its intrinsic resistance to most antimicrobial agents, especially carbapenem. TMP/SMZ remains the most effective antimicrobial agent against S. maltophilia and the recommended first-line agent [25, 26]. In a worldwide study which comprised 1586 S. maltophilia strains, the highest resistance rate to TMP/SMZ was 9.2% in Asian-Pacific region, compared with the lowest (1.1%) in Europe [27]. Resistance rate of 4.55% to TMP/SMZ was observed in our study. Still, treatment for S. maltophilia infection with TMP/SMZ may not be possible due to resistance, allergies, toxicities, or drug shortages [28]. Therefore, newer agents like ticarcillin/clavulanic, new fluoroquinolones (such as moxifloxacin and levofloxacin), tetracyclines (such as minocycline and tigecycline) have been proposed as promising alternative agents [19]. A recent survey evaluated the efficacy of levofloxacin in the treatment of S. maltophilia bacteremia. Results showed that patients receiving levofloxacin showed clinical outcomes similar to those receiving TMP-SMZ but suffered less adverse events [29]. Similar conclusion was drawn in another research by Wang et al. [28]. According to our study, levofloxacin was most common agent used in combination therapy, while TMP/SMZ was used as combination therapy in only 2 patients.

A novel agent tigecycline is gradually being administrated against S. maltophilia infections for its good in vitro activity (94.5%-96.5%) [27]. However, tigecycline has great bio-distribution after intravenous injection, leading to lower serum drug levels [26]. Is this obstructive of using tigecycline agaist bacteremia? Wu and Shao administrated tigecycline at the dose of 100 mg every 12 hours to treat a female patient who was diagnosed with AML and confirmed S. maltophilia bacteremia under bone marrow suppression. Finally, the patient recovered from persistent fever and the CT scan of the chest turned normal [30]. We may conclude that the approved dosage of tigecycline might not be

sufficient for bacteremia due to its low blood concentration and increasing the dosage could help. While Falagas et al. concerned that safety of high-dose tigecycline was still uncertain for its dose-dependent adverse effects [31]. And it needs to be noted that, in a recent study, no significant differences was found in mortality and clinical response rates between TMP/SMZ and tigecycline treatment in S. maltophilia infections [32]. In conclusion, tigecycline might be considered an alternative for patients who are unable to tolerate TMP/SMZ and the dose should be individualized. It is regrettable that tigecycline treatment was not elaborated in our analysis, for only five patients had used this drug to full course after identified with S. maltophilia bacteremia. Tigecycline was first approved for clinical use in 2012 in China and has not yet been widely used.

Still, the choice of monotherapy or combination therapy remains controversial. An *in vitro* study demonstrated that all combinations which consisted of TMP/SMZ were more active than TMP/SMZ alone [33]. As to TMP/SMZ-resistant S. maltophilia infection, combinations with inactive or intermediately susceptible agents was still effective [34]. It was reported that administration of ciprofloxacin combined with ticarcillin/clavulanate or ceftazidime may be effective [35], which were of similar effect to combination of levofloxacin and cefoperazone in our study. It can be considered as one of the alternatives in clinical practice. In clinical situations, combination therapy was usually chosen to treat critically-ill patients with difficult-to-treat infection. This may be a reason why no significant advantage in patients' outcome was observed in combination therapy.

Our review has several limitations that should be considered. First, some medical information of a few patients was unavailable owing to the Electronic Medical Records System update, leading to the reduction in the case number. Second, some patients were transferred to local hospital or went home directly at their last stage, and we failed to follow up. So the final outcome had to be inferred in these cases. Third, this research is merely a retrospective single-center analysis with limited sample capacity, providing certain reference significance. Clinical guidance of high reliability requires prospective multi-center trial, which can be directional of our forthcoming work.

Conclusion

Bacteremia due to Stenotrophomonas maltophilia is a critical situation for patients with high attributable mortality. Our results suggest that neutropenia and mechanical ventilation were independently associated with mortality. Physicians should give enough attention to patients under such conditions and take precautions in necessity. TMP/SMZ is the most susceptible agent according to *in vitro* susceptibility results. We also believe that levofloxacin and tigecycline could be considered as promising alternative agents. The comparison between monotherapy and combination therapy remains to be further investigated. *In vitro* susceptibility test and individual characteristics need to be taken into consideration when choosing appropriate treatment.

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Disclosure of conflict of interest

None.

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