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Original Article

Clinical manifestations, risk factors and prognosis of patients with *Morganella morganii* sepsis

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Abstract *Background:* There are few studies of *Morganella* bacteremia. We evaluated risk factors and outcome of patients with *Morganella* bacteremia.
Methods: Medical records of patients with *Morganella* bacteremia were reviewed (1997–2014). Control group patients with *Escherichia coli* sepsis were matched by year of diagnosis and infection acquisition site.
Results: The study group included 136 adult patients. Mean age and gender of study and control groups were similar. Complicated soft tissue infection was more prevalent in the study group (30% versus 3.2%, $p < 0.05$). The Charlson Comorbidity Index (CCI) was higher in the study group (4.3 ± 2.5 versus 3.4 ± 2.8, $p < 0.05$). Only 78 (62%) of the study patients versus 101 (83%) of the control group ($p < 0.05$), received appropriate empirical antibiotic treatment. A significantly higher in-hospital mortality rate (42% versus 25%, $p < 0.05$) as well as longer length of stay (25 ± 22 versus 14 ± 16 days, $p < 0.05$) was observed in the study group. Multivariate analysis revealed that a debilitative state, a CCI > 4, septic shock and a clinical syndrome *other* than UTI were all significant risk factors for mortality ($p < 0.05$).

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Conclusions: Patients with *Morganella morganii* sepsis had more co-morbidities and a worse degree of sepsis. There is an increased risk of inappropriate empirical treatment, longer hospitalization and higher death rate.

Introduction

Morganella morganii (previously known as *Proteus morganii*), a Gram-negative bacillus of the Enterobacteriaceae family is part of the normal gastrointestinal flora of humans and other mammals.[1,2] Infections associated with this pathogen are less frequently acquired in non-hospital settings and in healthy individuals. *M. morganii* may be involved in soft tissue infections, e.g. pressure sores, and urinary tract infections[3–6] and bacteremia has been linked to hepatobiliary disease.[6–8] Other reported infections include meningitis,[9] chorioamnionitis,[10] endophthalmitis[11,12] and joint infections.[13,14] Nosocomial outbreaks with this pathogen have been reported.[3,4] Resistance to β-lactam antibiotics in *Morganella* is mediated by (typically inducible) *AmpC*-β-lactamases.[15] A review of the literature revealed only very few series of *Morganella* bacteremias, despite the significant morbidity associated with this pathogen. Most reports published in recent years are from Taiwan, with significant variability in the study cohorts' age, community versus hospital acquisition of bacteremia, site of infection and mortality rate. The aim of the present study was to characterize patients suffering from *M. morganii* bacteremia as compared to a control group of patients with *Escherichia coli* bacteremia, in terms of infection site, risk factors, appropriateness of empirical treatment and clinical outcome.

Methods

The study was conducted in Shaare Zedek Medical Center, a 1000-bed general, university-affiliated hospital. The hospital includes all major departments and services, except neurosurgery and solid organ transplantations.

Study and control patients

We performed a retrospective case–control study of patients, aged 18 years or older, diagnosed with *Morganella* bacteremia between 1997 and 2014. We defined community-onset sepsis as positive blood cultures, which had been obtained within 72 h of admission, and hospital acquired sepsis as positive blood cultures which had been taken after 72 h.

The control group consisted of patients with *E. coli* bacteremia, who were matched to the study group patients by two criteria: year of diagnosis and acquisition site of infection i.e. community or hospital/health care facility. Since the incidence of bacteremia due to *E. coli* is much higher than that of *Morganella*, control patients with *E. coli* bacteremia were chosen as close as possible in time with the study patients with *Morganella* sepsis.

Retrieved demographic and clinical data included age, gender, residence, debilitative state, admission diagnosis, probable source of bacteremia (as determined by isolation of the pathogen from additional sites and final clinical diagnosis), Charlson Comorbidity Index (CCI),[16] systemic inflammatory response syndrome (SIRS) criteria,[17] and acquisition site of infection. The main outcome measures included in-hospital mortality rate and length of stay (LOS). A secondary measure was appropriateness of empirical therapy, as defined by the organisms' antimicrobial susceptibilities.

Data and statistical analysis

Demographic, clinical and laboratory variables were entered in an Excel spreadsheet. Quantitative variables were compared using the t-test, for two independent groups, and the Mann–Whitney test when the distribution of the tested variable was abnormal. For qualitative variables a χ^2 test or Fisher's Exact Test was used. Variables found statistically significant ($p < 0.05$) were further examined using a multivariate logistic regression model. All statistical analyses were carried out using SPSS software (version 21). p values < 0.05 were considered statistically significant. The study was approved by the Institutional Review Board of Shaare Zedek Medical Center.

Results

One hundred and fifty one patients with *M. morganii* bacteremia were identified in the clinical microbiology laboratory database between 1997 and 2014. Six cases were younger than 18 and critical data was missing in nine other patients; therefore, the final study cohort consisted of 136 patients. In the control group 136 patients were matched to the study group patients. Of these, ten were excluded due to missing data.

Demographic and clinical data of patients in the study group and in the control group are presented in Table 1. Sixty two percent of the study group patients were debilitated patients (compared to 41% in the control group, $p = 0.002$), many of whom resided in nursing homes or chronic health care facilities. CCI was higher in the study group ($p = 0.01$). A high incidence of soft tissue infections was noted in patients with *Morganella* sepsis, while the most common source of bacteremia in the control group was UTI ($p = 0.001$). The incidence of severe sepsis and septic shock was higher in the study group than in the

control group (54% versus 38%, respectively; $p = 0.01$). The incidence of polymicrobial infection was higher in the study group compared to the control group (44.1% Vs 13.5%, respectively; $p < 0.0001$). In most cases concurrent pathogens included other enterobacteriaceae and enterococci. Extended Spectrum β-Lactamase (ESBL) was detected in 10.5% of *Morganella* isolates and in 19.7% of *E. coli* isolates. In both groups, ESBL was more prevalent in health-care associated isolates. No *Morganella* isolates were susceptible to 1st generation cephalosporins and only 11% were susceptible to 2nd generation cephalosporins. More than a third of *Morganella* isolates were ciprofloxacin resistant. Eighty percent and 93% of *Morganella* isolates were susceptible to 3rd and 4th generation cephalosporins, respectively. Only 64% were susceptible to gentamicin, but more than 97% were susceptible to amikacin. All isolates were susceptible to piperacillin-tazobactam or carbapenems.

Table 2 presents clinical outcomes of the two groups. Length of hospitalization was significantly longer in the study group; the difference was even more pronounced after exclusion of patients who died ($p < 0.001$). In-hospital mortality rate in the *Morganella* group was significantly higher than in the control group (42% versus 25%; $p = 0.004$). Notably, the incidence of appropriate empirical therapy in the study group (either community onset or hospital acquired) was significantly lower compared to the control group (62% versus 83%; $p < 0.001$). Table 3 presents univariate and multivariate analyses of factors associated with in-hospital mortality. *Morganella* bacteremia was found to be associated with increased mortality using univariate analysis, but not multivariate analysis. After multiple adjustments, debilitative state, multiple comorbidities (CCI > 4), septic shock, and associated clinical syndrome *other* than UTI, were all found to be associated with mortality.

Discussion

The present series included 136 adult patients with *Morganella* sepsis. To our knowledge, this is the largest cohort of patients with *Morganella* bacteremia described in the literature. In our study, the source of *Morganella* bacteremia was soft tissue infection in 30% of patients, mostly secondary to decubitus ulcers and diabetic wounds, in contrast to only 3% of patients with *E. coli* bacteremia ($p < 0.001$). In this context it is important to note that 44% of patients with *M. morganii* sepsis had polymicrobial infection, as compared to only 13% in the control group ($p < 0.0001$). Polymicrobial bacteremia has been well described in patients with deep wound infections and decubitus ulcers.[18]

The fact that more than a third of the patients in the study group (versus 24% in the control group) reside in nursing homes, and 62% (versus 41%) was debilitated, is compatible with the high rate of decubitus ulcers. In studies from the Far East (Taiwan), the rate of soft tissue infections ranged from 5%[6] to 21% (8) (Table 4). An additional important source of *M. morganii* bacteremia in our series, was hepatobiliary tract infection (20%), in accordance with findings reported in series from Taiwan where the predominant source of bacteremia was intra-abdominal infection, mainly involving the biliary tract (cholangitis, cholecystitis).[6–8] This may reflect the high prevalence of liver and bile duct diseases in Taiwan[19] (Table 4).

Urinary tract infection was identified as a source of bacteremia in 27 (20%) patients in our cohort, similar to findings reported from Greece by Falagas et al.[5] No clear source of bacteremia (i.e., primary bacteremia) was detected in 35 (26%) patients in our series.

Patients with *M. morganii* bacteremia were more severely ill than those in the control group. This was reflected in a higher CCI ($p = 0.01$) and worse SIRS score ($p = 0.01$) as compared with the control group patients.

Notably, appropriate empirical therapy was given to only 62% of patients with *M. morganii* bacteremia, as compared

Table 1 Demographic and clinical characteristics of patients with *M. morganii* bacteremia and *E. coli* bacteremia (1997–2014), n (%).

Characteristic	*M. morganii* n = 136	*E. coli* n = 126	*p* value
Age, y, mean (±SD)	74.6 (±14.6)	74 (±15.7)	0.7
Male gender	65 (47.8)	63 (50)	0.4
Residence[a]			
Home	86 (64.7)	95 (76)	
HCF	47 (35.3)	30 (24)	0.06
Debilitative state[b]	69 (61.6)	45 (40.9)	0.002
Admission ward			
Medical	94 (69.1)	85 (67.5)	0.6
Surgical	32 (23.5)	27 (21.4)	0.8
ICU	10 (7.4)	14 (11.1)	0.4
Clinical syndrome-associated bacteremia			
CLABSI	4 (2.9)	4 (3.2)	1.0
GI/Hepatobiliary infection	27 (19.9)	38 (30.4)	0.06
Primary bacteremia	35 (25.7)	29 (23.2)	0.7
Respiratory infection	2 (1.5)	0	0.5
Soft tissue infection	41 (30.1)	4 (3.2)	<0.001
UTI/urosepsis	27 (19.9)	50 (40)	0.001
Charlson score (±SD)	7.3 (±3.2)	6.4 (±3.3)	0.04
Charlson Index (±SD)	4.3 (±2.5)	3.4 (±2.8)	0.01
SIRS severity[c]			
Sepsis	61 (46.2)	76 (62.3)	0.01
Severe sepsis	47 (35.6)	27 (22.1)	0.02
Septic shock	24 (18.2)	19 (15.6)	0.6
Severe sepsis and septic shock	71 (53.8)	46 (37.7)	0.01
Acquisition site of infection			
Community	42 (31.6)	49 (39.2)	0.3
HCF/Hospital acquired	91 (68.4)	76 (60.8)	0.3

[a] Available data – *M. morganii* n = 133; *E. coli* n = 125.
[b] Available data – *M. morganii* n = 112; *E. coli* n = 117.
[c] Available data – *M. morganii* n = 132; *E. coli* n = 122.
Abbreviations: SD, standard deviation; HCF, health care facility; ICU, intensive care unit; GI, gastrointestinal; UTI, urinary tract infection; CLABSI, central line-associated blood stream infections.

Table 2 Clinical outcomes of patients with *M. morganii* bacteremia and *E. coli* bacteremia (1997–2014), n (%).

Characteristic	*Morganella morganii* n = 136	*Escherichia coli* n = 126	*p* value
LOS (days, mean ± SD)	20 ± 22.3	14.9 ± 21	0.06
LOS excluding patients who died[a]	25 ± 22.1	13.6 ± 16	<0.001
Appropriate empirical treatment[b]	78 (62)	101 (82.7)	0.0001
Community	28/42 (66.7)	44/49 (89.8)	0.009
HCF/Hospital Acquired[c]	50/86 (58.1)	56/73 (76.7)	0.018
Treatment duration (days, ±SD)	13.5 (±14.6)	10 (±9.3)	0.02
In-hospital mortality	57 (41.9)	31 (24.6)	0.004
30-day mortality[d]	60 (51.7)	35 (36.8)	0.01

[a] Length of stay (LOS) excluding patients who died – *M. morganii* n = 79; *E. coli* n = 95.
[b] Available data – *M. morganii* n = 128; *E. coli* n = 122. Accurate antibiotic regimen was unavailable in eight isolates (five *M. morganii* cases and three *E. coli* cases).
[c] Data regarding residence was unavailable in 3 *Morganella* cases and in one *E. Coli* case.
[d] Available data – *M. morganii* n = 116; *E. coli* n = 98.
Abbreviations: SD, standard deviation; HCF, health care facility.

to 83% of patients with *E. coli* bacteremia ($p < 0.001$). The mechanism of resistance to first-line therapy was probably not the presence of ESBL (extended spectrum beta-lactamases) among *Morganella* bacteria, as ESBL was detected in only 10% of the study group. Rates of appropriate empirical therapy, as low as 57%, 55%, and 66% have been previously reported by Falagas et al., Kim et al., and Lee et al. respectively[5,7,8] (Table 4). Sensitivity assays in previous reports identified resistance to 1st generation cephalosporins in all isolates, as well as very high rates of resistance to cefuroxime and amoxicillin-clavulanate.[5,6] Similarly, in the present series most isolates were resistant to 1st and 2nd generation cephalosporins and more than a third were ciprofloxacin-resistant. *Morganella* isolates were susceptible to 4th generation cephalosporins, amikacin, piperacillin-tazobactam and carbapenems (data not shown). Aside resistance patterns, the lower rate of appropriate empirical therapy in the *Morganella* study group may also be explained by the infection-associated clinical syndrome. The high rate of soft tissue infections in patients with *Morganella* bacteremia may account for initial treatment with cefazolin (or vancomycin) to cover streptococcal and staphylococcal infections, not considering the possibility of resistant Gram negative pathogens. Moreover, even if ciprofloxacin was added, it did not cover more than a third of *Morganella* isolates. In contrast, *E. coli* bacteremic patients, often presented with UTI and hepatobiliary or gastrointestinal disease (Table 1), and had a higher probability of being treated appropriately with cephalosporins of any generation and the "surgical triad" of ampicillin, *gentamicin (or ceftriaxone)*, and metronidazole, commonly prescribed for hepatobiliary/GI infections.

Although emergency department physicians are not expected to predict which infective agent is responsible for the infectious syndrome, patients should be stratified according to their risk of harboring a resistant pathogen. If risk factors for resistant bacteria (repeat hospitalizations, nursing home residence, permanent catheter, complex decubitus ulcers, etc.) are present, broad-spectrum antibiotic therapy, such as amikacin, piperacillin-tazobactam or a carbapenem should be administered empirically. In the absence of risk factors, first-line, narrower-spectrum antibiotics, such as gentamicin or ceftriaxone may suffice. Thus, a higher rate of appropriate empirical treatment would be achieved, while avoiding over-utilization of broad-spectrum anti-infective agents.[20]

The mean length of hospitalization of patients in the study group was 9 days longer than that of the control

Table 3 Factors associated with in-hospital mortality within the study cohort - univariate and adjusted multivariate analyses.[a]

		Univariate analysis			Multivariate analysis		
Characteristic	n (%)	OR	95% CI	*p*	OR	95% CI	*p*
M. morganii bacteremia	57/136 (41.9)	2.2	1.3–3.8	0.003	1.4	0.6–3.5	0.47
Appropriate empirical Rx	179/250 (71.6)	0.58	0.3–1.02	0.04	0.73	0.3–1.9	0.53
ESBL positive pathogens	20/38 (52.6)	2.5	1.3–5.1	0.008	1.6	0.3–2.9	0.46
Nursing home residence	37/77 (48.1)	2.6	1.5–4.5	0.001	0.65	0.2–1.9	0.43
Debilitative state	56/114 (49.1)	5.6	2.9–10.8	<0.001	8.1	2.5–26	<0.001
Charlson index > 4	61/133 (45.9)	3.2	1.9–5.5	<0.001	3.7	1.5–8.8	0.004
Septic shock	34/43 (79.1)	11.9	5.3–26.4	<0.001	22	7.3–66	<0.001
Primary bacteremia	29/64 (45.3)	1.9	1.1–3.5	0.024	0.71	0.5–5.1	0.54
Clinical syndrome *other* than UTI	75/184 (40.8)	3.4	1.7–6.6	<0.001	6	1.9–19.3	0.003
Soft tissue infection	22/45 (48.9)	2.2	1.1–4.2	0.018	0.89	0.2–2.1	0.85

[a] Overall in-hospital mortality - 88/262 (33.6%).
Abbreviations: OR – odds ratio; UTI – urinary tract infection; ESBL, extended spectrum beta-lactamase; CI, Confidence Interval, Rx, treatment.

Table 4 Comparison of the results with other published series of *M. morganii* bacteremia, n (%).

Author	Falagas (5)	Lin (6)	Kim (7)	Lee and Liu (8)	Present
Year of publication	2006	2014	2003	2006	–
Number of patients	24	109	61	73	136
Male n (%)	11 (46)	62 (57)	39 (63.9)	39 (53.4)	65 (47.8)
Age, mean (SD)	57.5	72.8	52.2	64.4 ± 16.58	74.6 ± 14.6
Polymicrobial BSI (%)	14 (58.3)	33 (31.1)	21 (34.4)	33 (45.2)	60 (44.1)
Source of bacteremia (%)					
UTI	5 (20.1)	45 (41.3)	1 (1.6)	27 (37)	27 (19.9)
Skin and soft tissue	13 (54.2)	23 (21.1)	3 (4.9)	11 (15)	41 (30.1)
Primary bacteremia	0	11 (10)	15 (24.6)	13 (17.8)	35 (25.7)
Intra-abdominal infection	1 (4.2)	30 (27.5)	39 (63.9)	16 (22)	27 (19.9)
Other	5 (20.1)	0 (0)	3 (4.9)	6 (8.2)	6 (4.4)
Community-acquired infection	NA	82 (75.2)	18 (29.5)	51 (69.9)	42 (31.6)
Appropriate empirical Rx	16 (66)	109 (100)	33 (55)[a]	42 (57.5)	78 (62)
Length of stay, days (±SD)	19.4 (±8.5)	12.12	NA	NA	20 (±22.3)
Mortality	2 (8.3)	16 (14.7)[b]	9 (15)	28 (38.3)[b]	57 (41.9)[c]

[a] n = 60.
[b] Mortality was defined as death within 14 days after the onset of *M. morganii* bacteremia.
[c] Mortality rate within 14 days of bacteremia was 30.9%.
Abbreviations: BSI, blood stream infection, UTI, urinary tract infection, Rx, treatment.

group; 25 ± 22 days versus 16 ± 14 days ($p < 0.001$). In addition, a higher rate of death was observed in the *Morganella* group (42% versus 25% in the *E. coli* group, $p = 0.004$). Mortality rates were similar to those described by Lee et al.[8] but significantly higher than shown in other series (8–15%).[5–7] This discrepancy may be explained by several factors: first, in the study by Lin et al.,[6] attributable mortality was defined as death within 14 days after the index blood culture. Of note, in the present study, mortality rate during the first 14 days since the index culture was 31%, and only subsequently increased to 42% (in-hospital mortality). Second, in the present series, a predominant source of infection was soft tissue infections (primarily decubitus ulcers) accompanied by polymicrobial bacteremia in many cases. This reflects a rather ill population. Third, in the studies above, the patients were younger with a mean age range of 52–73, as compared with a mean age of 75 (±14.6) in the present cohort.

Morganella bacteremia by itself did not predict mortality after adjustment for other risk factors. However, debilitative state, CCI>4, septic shock and infection other than UTI were independent predictors of mortality (Table 3). Of these factors, debilitative state was most significant, with an odds ratio of 8.1 (2.5–26, 95% CI; $p < 0.001$).

The current study has several limitations. First, as a retrospective study, data were not complete in some cases, and it is difficult to accurately determine cause of death. Second, for some patients, it was not possible to identify the source of bacteremia (35 patients had primary bacteremia). It should be noted that the rates of primary bacteremia in other published series were similar, ranging between 10 and 25%.[6–8] A third limitation is that appropriate empirical therapy was provided in only 60% of the cases, similar to findings in other studies.[5,7,8] Interestingly, and in contrast to Lin's report,[6] this parameter was not significantly associated with mortality. Other important covariates which were not assessed in this study, such as time-to-first dose of appropriate antibiotics or antibiotics' doses, may have affected mortality. Nevertheless, a similar finding was noted in a previous study by Reisfeld et al., where even in proven Gram-negative sepsis, inappropriate empirical antibiotic therapy had no mortality effect on the sickest group of patients, and those with decubitus ulcers.[21]

In conclusion, in this retrospective series of 136 patients with *M. morganii* bacteremia soft tissue infection was the most common source of bacteremia and was accompanied, in many cases, by polymicrobial sepsis. Appropriate empirical treatment was provided in only 60% of the cases. Clinicians should suspect infection due to *M. morganii* in debilitative, septic patients with soft tissue infections and treatment with broad-spectrum antibiotics should be considered.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2017.08.010.