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Original Article

The clinical characteristics of *Acinetobacter* bacteremia differ among genomospecies: A hospital-based retrospective comparative analysis of genotypically identified strains

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Abstract *Background/purpose: Acinetobacter* is an aerobic, gram-negative coccobacillus, which causes nosocomial infections including bacteremia. Recent development of molecular techniques has made classification of the *Acinetobacter* genomospecies possible, but there are still only a few studies comparing clinical features of the subspecies. We investigated bacteremia caused by *Acinetobacter*, isolated subspecies, and compared clinical features for each group.
Methods: A retrospective analysis of *Acinetobacter* bacteremia cases was made in a 900-bed hospital in Japan. In addition to conventional procedures, subspecies identification based on *rpo*B sequence was made, and comparison of clinical characteristics between each subspecies were analyzed.
Results: We collected 35 cases (*Acinetobacter baumannii* 14, *A. nosocomialis* 12, *Acinetobacter ursingii* 6, and *A. seifertii* 3). All of the *A. seifertii* bacteremia cases were blood stream infection occurring in cerebrovascular disease patients, showing particularly higher incidence of shock (100%) and high Pitt bacteremia score (PBS) (6.33 ± 2.52) in comparison to *A. baumannii* (43% and 2.86 ± 2.25, respectively). Sequential Organ Failure Assessment (SOFA) score and

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the PBS were slightly higher in *A. nosocomialis* in comparison to *A. baumannii*, and the 7 day mortality rate was higher in *A. nosocomialis* (25%) than in *A. baumannii* (7%), though this difference was not found to be significant.
Conclusions: A.seifertii, the recently defined novel species, showed distinctive clinical features of bacteremia. And, in contrast to previous studies, the severity of *A. nosocomialis* infection was not lower than that of *A. baumannii*, which might suggest the influence of local epidemiology. Further characterization of these subspecies should be continued.

Introduction

Acinetobacter is an aerobic, gram-negative coccobacillus. Species of this bacteria, are ubiquitous in soil, water, and as a commensal part of the flora within the skin or throat. Incidence and occurrence rates of different species of this bacteria are increasing globally in hospital environments. Bacteria from this genus, include multidrug-resistant strains which are becoming a major source of nosocomial infections worldwide. Pathogenic species of *Acinetobacter* are common in hospitals and associated with a wide variety of nosocomial infections including: bacteremia, meningitis, pneumonia, skin and soft tissue infections, and urinary tract infections.[1] While multidrug-resistant strains are prevailing in many parts of the world,[2–4] incidence of multidrug related *Acinetobacter* infections are still low in Japan.[5] Currently, more than 50 named *Acinetobacter* spp. have been described,[6,7] many of which being reported as non-pathogenic to human. Traditionally, distinguishing between different genomospecies by routine biochemical methods has been difficult; for example, in the case of the *Acinetobacter calcoaceticus-A. baumannii* (ACB) complex, which comprises the following germospecies: *Acinetobacter baumannii* (former genomospecies 2), *A. nosocomialis* (former genomospecies 13TU), *A. calcoaceticus* (former genomospecies 1), and *Acinetobacter pittii* (former genomospecies 3).[8]

Development of new molecular techniques such as *rpo*B sequencing, has allowed researchers to achieve a more detailed level of species identification in recent years.[9–11] However, there are still only a few studies comparing clinical features of the subspecies. This study investigated bacteremia caused by *Acinetobacter,* isolated subspecies, and compared clinical features for each group.

Methods

Patient selection and bacterial isolates

This study was retrospectively conducted at Aichi Medical University Hospital, a 900-bed tertiary care center in Japan. Patients diagnosed at this hospital with *Acinetobacter* spp. associated bacteremia (via two sets of positive blood cultures) during the trial period January 2009 to December 2017 were included in this study. Clinical features and patient information including patient background, laboratory data, treatment, complications, and outcomes were compared among patients with bacteremia caused by different genomospecies of *Acinetobacter*. This study was approved by the Institutional Review Board of Aichi Medical University Hospital.

Species identification

All isolates were identified via a series of tests including colony morphology, Gram staining, growth at 37 °C, negative oxidase test, and via oxidation of glucose. Further confirmation was made by the RAISUS bacterial identification system® (Nissui Pharmaceutical, Tokyo, Japan) and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) system (Bruker Biotyper®, Bruker Daltonics).[12] Further, in order to achieve a more detailed identification, *rpo*B Zone 1 and rpIL-*rpo*B spacer sequencing tests were performed using BLAST (http://www.ncbi.nlm.nih.gov/BLAST) Sequences which were aligned and compared to published *rpo*B sequences of different *Acinetobacter* type strains.[9] Patients with bacteremia caused by mixed genomospecies and unidentified species were excluded. OXA-51-like positivity was confirmed by methods previously reported.[13]

Antimicrobial susceptibility testing

Minimal inhibitory concentrations (MICs) of 13 agents (amikacin, ampicillin/sulbactam, aztreonam, cefepime, cefoperazone, ceftazidime, ciprofloxacin, imipenem, meropenem, minocycline, piperacillin, piperacillin/tazobactam, and sulfamethoxazole/trimethoprim) were determined utilizing the agar dilution method according to CLSI recommendations.[14]

Data collection

Medical records of all of the patients in the study group were utilized to obtain demographic and clinical data. Patient background included age, sex, comorbidities, days from admission to bacteremia onset, previous antimicrobial therapy, and risk factors for *Acinetobacter* infection. Charlson comorbidity index was calculated.[15] Microbiological data included time to culture positivity, antimicrobial susceptibilities, and OXA-51-like positivity as described above. Clinical data included the source of bacteremia (site

of infection), presence of septic shock, disseminated intravascular coagulation (DIC), as well as 7-day, 14-day, 30-day and in-hospital mortality. Pitt bacteremia score and Sequential Organ Failure Assessment (SOFA) score was also calculated on the day of admission.

Statistical analyses

Statistical analyses were performed using JMP®10 (SAS Institute Inc., Cary, NC, USA). Continuous variables were reported as the mean ± S.D. or median [Interquartile range (IQR)] and were compared with Student *t*-test or Mann–Whitney *U*-test depending on the distribution of the data. Categorical variables were expressed as percentages of the total number of patients analyzed and then were compared to the chi-square test or Fisher's exact test, as appropriate.

Results

Overall characteristics of *Acinetobacter* bacteremia cases (Table 1)

During the study period, 35 cases (22 males, 13 females) of *Acinetobacter* spp. bacteremia were identified. The presumed primary bacteremia sources/fomites were as follows: catheter-related 20 (57%), intra-abdominal 6 (17%), pneumonia 3 (9%), urinary tract 1 (3%), unknown 5 (14%). The median (IQR) for days from admission to bacteremia onset were 20 (6–41) days, and vast majority of the cases had vein catheter and prior antibiotics exposure within 30 days. Almost half of the cases presented septic shock or DIC. The 7 day, 14 day, and 28 day mortality rate was 11%,11%, and 17%, respectively.

Genomospecies distribution and comparison of patient background (Table 1)

The following genomospecies were identified: *A. baumannii* (Ab), 14 (40%), *A. nosocomialis* (An), 12 (34%), *Acinetobacter ursingii* (Au), 6 (17%), and *A. seifertii* (As), 3 (9%). The average age of patients at the onset of bacteremia was 66.4 years old with some differences between the genomospecies groups noted. A few species-specific results were noted among the patients in relation to symptoms as all cases of *A. seifertii* bacteremia involved bloodstream infection while pneumonia was only found to be present in *A. baumannii* cases. Comorbidities such as cerebrovascular diseases were present in all patients in the As group, this incidence was significantly higher than in the An group (8%) and also the Ab group (36%) ($p = 0.009$ and $p = 0.08$, Fisher's exact test). The frequency of malignant neoplasms was very high in the Au group (83%), which was higher than all of the other groups (Ab 36%, An 33%, As 33%) which showed no significant difference between them ($p = 0.14$, 0.13, 0.23, respectively, Fisher's exact test). Charlson comorbidity index (Median, IQR)in *A. baumannii*, *A. nosocomialis*, *A. seifertii*, and *A. ursingii* were 4 (1–6), 2.5 (1–3), 3 (2–9), and 2 (1.75–6.5) respectively. However, no significant differences were found between the groups.

Bacteriological features (Table 2)

The amount of time required to detect a positive blood culture was 24.5 ± 13.7 (mean ± S.D.) hours overall with no intergroup difference. OXA-51 like positivity in Ab, An, As, and Au groups were 75%, 8%, 33%, and 0%, respectively.

While all strains were susceptible to carbapenem, the overall susceptibility rates to aztreonam, cefoperazone, and cefepime were poor.

A. seifertii group showed lower susceptibility rate to cefoperazone (0%), aztreonam (0%), and piperacillin (33%). The susceptibility rate to piperacillin was slightly lower in As group than in other groups ($p = 0.083$ and 0.15 in comparison to Au group and An group, respectively). The susceptibility rate to cefoperazone was significantly lower in As group than in Ab group ($p = 0.044$). *A. ursingii* group showed lower susceptibility rate to cefoperazone (33%), aztreonam (33%), and ceftazidime (50%).

In *A. ursingii* group, Ceftazidime susceptibility rate was significantly lower than in the *A. nosocomialis* group (50%, vs. 100%, $p = 0.024$, Fisher's exact test).

Complications and outcomes (Table 1)

Pitt bacteremia score (Mean ± S.D.) was 6.33 ± 2.52 in *A. seiferti*, which was significantly higher than in *A. baumannii* (2.86 ± 2.25, $p = 0.041$, Student *t*-test) and *A. ursingii* (4.17 ± 3.01, $p = 0.028$, Student *t*-test). There was no significant difference between *A. baumannii* and *A. nosocomialis* (8.33 ± 5.12, $p = 0.20$, Student *t*-test). The rate of shock was very high in the *A. seiferti* group (100%) and was higher than that of other groups (Ab 43%, An 58%, Au 33%) which showed no significant difference from each other. The mean SOFA scores in Ab, An, As, and Au group were 5.14, 8.33, 9.67, and 4.50 respectively. These scores were slightly higher for the An and As group, however, the difference was not large enough to be significant. The overall 7-day and 28-day mortality rate was 11% and 17%, respectively. Of note, the 28-day mortality rate was 0% in As and Au groups, and the 7-day mortality rate was higher in An group (25%) than in Ab group (7%) though this difference also was not found to be significant.

Discussion

The results of RNA polymerase β-subunit (*rpo*B) gene and DNA gyrase B (*gyr*B) gene sequencing and/or by multi-locus sequence analysis (MLSA) most likely constitute the current reference standard for molecular identification.[9–11] In recent years, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF/MS) has evolved into a viable method of identifying *Acinetobacter* strains including novel species.[12] Despite this new Identification tool, there are still only a few reports describing infections caused by these distinct pathogens, even fewer report clinical features.[16–18]

In the current study, we aimed to identify subspecies by 16S rRNA sequencing and made a comparison of clinical features between the subspecies. This study only analyzed genotypically identified *Acinetobacter* strains and, as a result, two distinct features were noted.

Table 1 Patient background and clinical characteristics.

	Overall	*A.baumannii (Ab)*	*A.nosocomialis (An)*	*A.seifertii (As)*	*A.ursingii (Au)*
	(n = 35)	(n = 14)	(n = 12)	(n-3)	(n = 6)
Male (%)	22 (64)	9 (64)	8 (67)	2 (67)	3 (50)
Age, mean ± S.D	66.4 ± 19.3	66.6 ± 17.8	76.0 ± 11.0	59.3 ± 13.7	50.3 ± 28.6
Days from admission to bacteremia onset median (IQR)[a]	20 (6–41)	25 (7.5–44.25)	9.5 (6.25–38.5)	20 (7–30)	23 (1.5–67.25)
Sites of infection (%)					
Bloodstream[b]	20 (57)	7 (50)	7 (58)	3 (100)	3 (50)
Intra-abdominal[c]	6 (17)	1 (17)	4 (33)	0 (0)	1 (17)
Pneumonia	3 (9)	3 (21)	0 (0)	0 (0)	0 (0)
Urinary tract	1 (3)	0 (0)	0 (0)	0 (0)	1 (17)
Unknown	5 (14)	3 (21)	1 (8)	0 (0)	1 (17)
Risk factors (%)					
Mechanical ventilation	13 (37)	5 (36)	6 (50)	1 (33)	1 (17)
Central vein catheter	11 (31)	4 (29)	4 (33)	1 (33)	2 (33)
Peripheral vein catheter	30 (86)	13 (93)	12 (100)	3 (100)	2 (33)
History of nursing home admission	2 (6)	1 (7)	1 (8)	0 (0)	0 (0)
Hospital admission for >30 days	18 (51)	8 (57)	5 (42)	1 (33)	4 (67)
ICU stay	12 (34)	5 (36)	5 (42)	1 (33)	1 (17)
Prior antibiotic exposure within 30 days	30 (86)	12 (86)	1 (92)	2 (67)	5 (83)
Charlson Comorbidity Index median, (IQR)	3 (1–6)	4 (1–6)	2.5 (1–3)	3 (2–9)	2 (1.75–6.5)
Comorbidity (%)					
Malignant neoplasms	15 (43)	5 (36)	4 (33)	1 (33)	5 (83)
Hemodialysis	2 (6)	1 (7)	1 (8)	0 (0)	0 (0)
Chronic kidney diseases	4 (11)	3 (21)	0 (0)	1 (33)	0 (0)
Cerebrovascular diseases	11 (31)	5 (36)	1 (8)	3 (100)	2 (33)
Peripheral arterial diseases	3 (9)	0 (0)	1 (8)	1 (33)	1 (17)
Heart diseases	8 (23)	3 (21)	3 (25)	1 (33)	117)
Hypertension[d]	10 (29)	5 (36)	1 (8)	2 (67)	2 (33)
Immunosuppression	7 (20)	2 (14)	4 (33)	1 (33)	0 (0)
Diabetes, Obesity[e]	6 (17)	2 (14)	2 (17)	2 (67)	0 (0)
Urinary tract obstruction	1 (3)	0 (0)	0 (0)	0 (0)	1 (17)
Biliary tract obstruction	7 (20)	3 (21)	3 (25)	1 (33)	0 (0)
Chemotherapy	6 (17)	4 (29)	0 (0)	0 (0)	2 (33)
Radiation	1 (3)	1 (7)	0 (0)	0 (0)	0 (0)
Dermatological diseases	3 (9)	1 (7)	2 (17)	0 (0)	0 (0)
Trauma	3 (9)	3 (21)	0 (0)	0 (0)	0 (0)
Gastrointestinal diseases	6 (17)	2 (14)	2 (17)	1 (33)	1 (17)
Shock	18 (51)	6 (43)	7 (58)	3 (100)	2 (33)
DIC	17 (49)	6 (43)	8 (67)	2 (67)	1 (17)
Pitt bacteremia score,mean±S.D.[f]	3.49 ± 2.70	2.86 ± 2.25	4.17 ± 3.01	6.33 ± 2.25	2.17 ± 2.23
SOFA score, mean[g]	6.57 ± 5.04	5.14 ± 4.41	8.33 ± 5.12	9.67 ± 7.23	4.50 ± 4.59
Mortality					
at day-7	4 (11)	1 (7)	3 (25)	0 (0)	0 (0)
at day-14	4 (11)	1 (7)	3 (25)	0 (0)	0 (0)
at day-28	6 (17)	3 (21)	3 (25)	0 (0)	0 (0)

The caption only shows the lines including p values of <0.2 as a result of appropriate statistical analyses between two groups.

[a] p = 0.013 (An vs. Au), 0.071 (Ab vs. Au), t-test.

[b] p = 0.23 (As vs.Ab), 0.51 (As vs.An), 0.46 (As vs. Au), Fisher's exact test.

[c] p = 0.15 (As vs.Ab), 0.51 (As vs.As), 0.61 (As vs. Au), Fisher's exact test.

[d] p = 0.08 (As vs. Ab), 0.009 (As vs.An), Fisher's exact test.

[e] p = 0.12 (As vs. Ab), 0.08 (As vs.Au), Fisher's exact test.

[f] p = 0.028 (As vs. Au), 0.041 (As vs. Ab), t-test.

[g] p = 0.13 (An vs. Au) (An vs.Ab), 0.15 (As vs. Au), t-test.

Table 2 Microbiological data.

	Overall	*A.baumannii (Ab)*	*A.nosocomialis (An)*	*A. seifertii (As)*	*A. ursingii (Au)*
	(n = 35)	(n = 14)	(n = 12)	(n-3)	(n = 6)
Time to blood culture positivity (h) mean ± S.D	24.5 ± 14	28.2 ± 16	21.6 ± 9.9	19.7 ± 4.0	24.3 ± 17.2
OXA-51 like positivity[a]	33%	75%	8%	33%	0%
Susceptibility					
Sulbactam. Ampicillin	94%	86%	100%	100%	100%
Piperacillin[b]	80%	79%	83%	33%	100%
Piperacillin/Tazobactam	83%	83%	92%	100%	83%
Cefoperazone[c]	55%	75%	60%	0%	33%
Ceftazidime[d]	83%	79%	100%	100%	50%
Cefepime	57%	83%	91%	100%	100%
Aztreonam	32%	50%	20%	0%	33%
Imipenem	100%	100%	100%	100%	100%
Meropenem	100%	100%	100%	100%	100%
Ciprofloxacin	86%	86%	83%	100%	83%
Sulfamethoxazole/Trimethoprim	89%	86%	83%	100%	100%
Minocycline	97%	93%	100%	100%	100%
Amikacin	97%	93%	100%	100%	100%

The caption only shows the lines including p values of <0.2 as a result of appropriate statistical analyses between two groups.
[a] p = 0.003 (Ab vs. An), p = 0.009 (Ab vs. Au). Fisher's exact.
[b] p = 0.083 (As vs. Au), p = 0.15 (As vs. An). Fisher's exact.
[c] p = 0.044 (Ab vs. As), p = 0.067 (Ab vs. Au). Fisher's exact.
[d] p = 0.024 (Au vs. An), p = 0.13(Au vs. Ab). Fisher's exact.

Firstly, clinical features of *A. seifertii*, which is a novel strain, previously known as *Acinetobacter* genomic species "close to 13TU" was evaluated.[19] Since the taxonomic definition in 2015, there have been few reports describing the clinical features of *A. seifertii* bacteremia.[20,21] This strain has some unique features such as genetic profile or temperature preference. The *rpo*B gene analysis showed intraspecies similarity for *A. seifertii* is in the range of 98.4—100%, while similarities for *A. seifertii* strains and other members of the ACB complex ranged from 92.0% (*A. calcoaceticus*) to 94.7% (*A. nosocomialis*).[19] This species grows fastidiously at 41 °C but is inhibited at 44 °C which is unusual as other strains such as *A. baumannii*, *A. nosocomialis*, and *A. calcoaceticus* strains grow effectively at 44 °C. *A. seifertii* strains are unable to utilize L-arabinose. In this study, the *A. seifertii* strains were resistant to cefoperazone, piperacillin, and aztreonam, suggesting its uniqueness in comparison to other species belonging to ACB complex. Moreover, all of the *A. seifertii* bacteremia cases had cerebrovascular diseases as underlying disease and presented as catheter related infections, which is consistent with the results of another study.[20] In detail, all the three patients in the As group had complicated history with recent or ongoing cerebrovascular diseases such as multiple infarction or multiple aneurysms, with frequent catheterization and antibiotic use. The number of the As bacteremia cases are too few to draw conclusions, but at least we could say cerebrovascular diseases might be a risk factor of *A. seifertii* bacteremia.

The higher Pitt bacteremia scores at presentation or the absence of pneumonia might be explained by unique biological features of this bacteria. Unfortunately, there are only a few reports outlining this novel species and the pathogenicity of *A. seifertii* is still to be elucidated. However, one *in vitro* study has reported that *A. seifertii* demonstrated a higher degree of biofilm formation, cell adherence, and resistance to serum in comparison to other species. With the exception of ST (sequence type)110, which is a highly biofilm forming strain, *A. baumannii* strains showed lower virulence than non-baumannii *Acinetobacter* strains including *A. nosocomialis* or *A. seifertii* strains.[22] These results indicated that *A. seifertii* bacteremia showed severe bacteremia score than *A. baumannii* might be associated with, due to this species intrinsic virulence, but further investigation is warranted.

Secondly, the clinical background and prognoses of *A. baumannii* and *A. nosocomialis were compared*, finding that the latter group did not demonstrate lower severity or mortality rate. The SOFA score and 7-day mortality were found to be higher in the *A. nosocomialis* group than in the *A. baumannii* group, although not significantly. This result was not expected as it is inconsistent with previous studies. In 2014, Chusri et al. reported clinical outcomes from hospital acquired *Acinetobacter* infection in a university hospital in Thailand. Their research focused on a comparison between non-*baumannii* ACB complex group (*A. nosocomialis* and *A. pittii*) and *A. baumannii* group, discovering that 30-day mortality was significantly lower in non-*baumannii* ACB complex group than in the *A. baumannii* group, regardless of carbapenem sensitivity of *A. baumannii*.[16] Likewise, Chuang et al., in Taiwan, reported a higher mortality rate of *A. baumannii* bacteremia cases in comparison to non-*baumannii Acinetobacter* bacteremia in the ICU setting.[23] The inconsistency between the present study and results of past studies, might be explained simply by the fact that the focus of the patient population in each study was different. For example, Chusri et al., only chose a few patients with bacteremia while the new study solely

utilized data from bacteremia patients. Further, the bacterial strains treated would be different endemic strains. It is already known that virulence characteristics of *A. baumannii* are different for each strain.[24] Further, growing evidence suggests that members of even a single sequence type can differ due to mobile elements, presence or absence of resistance genes, and resistance islands. Although, we did not perform multi-locus sequence typing or other molecular typing, our results may accurately reflect the epidemiology of this bacteria in Japan, where resistance rates of sulbactam/ampicillin, meropenem, amikacin, levofloxacin, and multidrug are as low as (5.4%, 1.9%, 2.3%, 8.2%, and 2.4%, respectively).[25] In contrast to vast drug resistance occurring in other countries, many strains in Japan clearly belong to unique domestic sequence types which are still susceptible to beta-lactams and other antibiotics.[5] Thus, our result, that the severity or prognosis of *A. baumannii* is better than in the reports elsewhere, might be explained by local epidemiological factors. Additionally, these factors may play a role in the fact that *A. ursingii* strains are genetically and phenotypically different from ACB complex strains. As expected, *A. ursingii* strains showed low sensitivity to ceftazidime and bacteremia patients and expressed more malignant neoplasms as comorbidity to this infection. This group showed distinct features in comparison to ACB species, suggesting further uniqueness of this subspecies. Known as an emerging pathogen, *A. ursingii* warrants further investigation such as patient background, susceptibility tests, or clinical features.

The limitation of our study is its nature as a retrospective single center study reflecting the local epidemiology. Also, the small size of the study hinders some data from statistical significance. Nevertheless, our data provide important information with carbapenem sensitive *Acinetobacter* bacteremia, highlighting the clinical features of distinct genomospecies.

In conclusion, this was a comparative study based upon clinical features of *Acinetobacter* species with corresponding genomospecies identification. In contrast to previous studies, results from this study clearly suggest that the severity of *A. nosocomialis* infection was not lower than that of *A. baumannii*. Moreover, this study described the unique clinical characteristics of *A. seifertii* bacteremia. These results might reflect epidemiological background of our country. Although this is a descriptive single center study, results suggest that the pathogenicity or prognosis of *Acinetobacter* bacteremia might be different, when influenced by local epidemiology.

Ethics approval and consent to participate

Permission for this study was provided by the Institutional Ethics Committee at Aichi Medical University. All the procedures have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declaration of Competing Interest

None of the authors have financial and non-financial competing interests.

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None of the authors have financial relationships with any commercial entity with an interest in the subject of this manuscript.

Authors' contributions

YK, DS and MH and HS concepted and designed the study. TO, AY, HW, and NA made contribution in data acquisition. AS, HK, MW, and MK contributed in data analysis and/or interpretation.

YK, YY and HM drafted the manuscript. HM contributed in giving advice from the point of Microbiology. All authors reviewed and approved the final version of this manuscript.

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