BMC Infectious Diseases

RESEARCH Open Access

Clinical presentation and outcomes of bloodstream infection with intrinsically carbapenem-resistant non-fermenting gram-negative organisms: *Stenotrophomonas maltophilia*, *Elizabethkingia* spp. and *Chryseobacterium* spp. in Singapore, from 2012 to 2024

Matthew Chung Yi Koh[1], Jinghao Nicholas Ngiam[1*], Ka Lip Chew[2*], Nares Smitasin[1,3], Lionel Hon-Wai Lum[1,3] and David Michael Allen[1,3,4*]

Abstract

Background Bloodstream infections with the non-fermenting Gram-negative organisms *Stenotrophomonas maltophilia*, *Elizabethkingia* spp. or *Chryseobacterium* spp. are observed in nosocomial settings. Comparative description of their clinical presentation, microbiological characteristics, treatment options and outcomes remain to be investigated.

Methods We performed a retrospective single-centre analysis of bloodstream infections with the abovementioned three organisms from 1 Jan 2012 to 30 Jun 2024.

Results A total of 349 distinct encounters (from 322 unique patients) were identified with bacteraemia. *Stenotrophomonas maltophilia* was the commonest (197/349, 56.4%), followed by *Elizabethkingia* spp. (127/349, 36.4%) and *Chryseobacterium* spp. (25/349, 7.2%). Prior carbapenem exposure was observed in 59.9% of cases. The majority were related to central lines (58.2%). Most cases were nosocomial in onset (82.5%), and a third were from the intensive care unit (32.1%). A significant proportion of our *Stenotrophomonas maltophilia* (32.8%) and *Chryseobacterium* spp. (22.7%) isolates were resistant to levofloxacin, while a majority of the organisms retained

*Correspondence:
Jinghao Nicholas Ngiam
Nicholas_ngiam@nuhs.edu.sg
Ka Lip Chew
Ka_lip_chew@nuhs.edu.sg
David Michael Allen
mdcdma@nus.edu.sg

Full list of author information is available at the end of the article

susceptibility to trimethoprim-sulfamethoxazole (TMP-SMX) and minocycline. Dual antibiotics were used in a minority of encounters (23/349, 6.6%). Mortality was high across infections with the three organisms, but highest amongst those with *Stenotrophomonas maltophilia* bacteraemia (41.6%), followed by *Elizabethkingia* spp. (29.9%) and *Chryseobacterium* spp. (20.0%).

Conclusions *Stenotrophomonas*, *Elizabethkingia or Chryseobacterium spp* bacteraemia was associated with significant mortality. Most cases were nosocomial in acquisition, with prior carbapenem exposure or indwelling central catheters. Fluoroquinolone resistance was common for *Stenotrophomonas maltophilia* and *Chryseobacterium* spp., but less prevalent in *Elizabethkingia* spp., while TMP-SMX and minocycline retained susceptibility. Monitoring these trends would be critical in guiding empiric therapy for these organisms.

Keywords Stenotrophomonas maltophilia, Elizabethkingia spp., Chryseobacterium spp., Clinical outcomes, Bacteraemia

Introduction

Three non-fermenting carbapenem resistant Gram-negative organisms – *Stenotrophomonas maltophilia*, *Elizabethkingia* spp. and *Chryseobacterium* spp. may cause invasive bloodstream infections in certain clinical contexts. These three organisms share common risk factors for the development of infection including prior carbapenem exposure, indwelling central catheters, immunocompromised states or critical illness in the intensive care [1–3]. Historically, there are also specific infections that are associated with each of these organisms. For example, *S. maltophilia* typically causes infections of the respiratory tract and bloodstream infections, while *Elizabethkingia* spp. is an important cause of meningitis in the paediatric population, and *Chryseobacterium* spp. is known to cause nosocomial bloodstream infections, often in the context of indwelling devices [4–6]. These organisms are frequently difficult to treat because they are intrinsically resistant to carbapenems and most beta-lactam antibiotics [1, 7]. They thus require therapy with other antimicrobial agents such as fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX) or tetracyclines (minocycline in particular). In fact, due to difficulty in predicting susceptibility patterns in patients with severe *S. maltophilia* infections, guidance from the Infectious Diseases Society of America (IDSA) recommends dual antimicrobial therapy [8]. However, clinical data is scarce. Similarly, invasive *Elizabethkingia* spp. infections may be fulminant, and some experts also recommend combination therapy initially [9]. Invasive infections with *Chryseobacterium* spp. are less frequent, but can also confer significant mortality and morbidity [4].

From a global perspective, infections with these three organisms are on the rise, with evolving trends in antimicrobial susceptibility. Unfortunately, optimal treatment remains ill-defined and clinical outcomes remain poor. In part, clinical outcomes are poor for patients with bacteraemia with these organisms as they present as invasive infections in immunocompromised hosts [10–12]. In patients with haematologic malignancies, *S. maltophilia* often causes a severe haemorrhagic pneumonia [13]. In other hosts, these organisms can cause invasive infection in those critically ill and also present as part of a co-infection with additional virulent pathogens [3, 4, 8, 14]. Therefore, we aimed to describe and examine the comparative characteristics of the background, clinical presentation of bloodstream infections with *S. maltophilia*, *Elizabethkingia* spp. and *Chryseobacterium* spp., in addition to describing trends in antibiotic treatment regimens and clinical outcomes. This would be informative to guide optimal treatment of infections with these organisms and also form the basis for future prospective study.

Methods

We performed a retrospective single-centre cohort study to describe the clinical characteristics, antimicrobial susceptibility patterns and treatment outcomes for bloodstream infections with *S. maltophilia*, *Elizabethkingia* spp. and *Chryseobacterium* spp. This study included distinct patient encounters with positive blood cultures identifying any of the three organisms from 1st January 2012 to 30th June 2024. All patients were adults (age $\geq$ 21 years old) hospitalised in our tertiary specialist institution (National University Hospital, Singapore). The positive blood cultures were identified through the laboratory information system, for which species level identification was performed using Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry (MALDI-TOF MS) (Bruker MALDI Biotyper, Bruker, Massachusetts, US). We excluded positive cultures from other sites (e.g. respiratory samples) and only examined positive blood cultures. We excluded duplicate blood culture isolates from the same patient hospitalisation encounter within the study period. Relapse of bacteraemia or recurrent bloodstream infection was tabulated separately, if it occurred in a different hospitalisation encounter. Susceptibility testing was performed by Etest. The tested antimicrobials varied during the included time period with the most frequently tested antimicrobials being trimethoprim-sulfamethoxazole (TMP-SMX), levofloxacin,

and minocycline. Ceftazidime testing for *S. maltophilia*, and piperacillin-tazobactam testing for *Elizabethkingia spp.* and *Chryseobacterium* spp. was also performed. The laboratory uses the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints. However, EUCAST breakpoints were only available for *S. maltophilia* testing for TMP-SMX [15]. Non-species PK/PD breakpoints were used for levofloxacin, ceftazidime, and piperacillin-tazobactam interpretation. As there are no EUCAST non-species breakpoints for minocycline and TMP-SMX (other than for *S. maltophilia)*, Clinical and Laboratory Standards Institute (CLSI) breakpoints were used.

Baseline clinical data was tabulated, including the clinical presentation, demographics, past medical history and outcome data. Nosocomial onset of bacteraemia was defined as bacteraemia occurring ≥ 48 hours into the hospitalisation. We defined prior carbapenem exposure as having received a carbapenem within one month prior to the episode of bacteraemia. Microbiological findings included the speciation of each organism, as well as the antibiotic resistance patterns. Laboratory markers were tabulated if obtained from the same blood draw, or the closest results that were obtained within 48 h of the positive blood culture, including the full blood count, kidney function, liver function testing, and C-reactive protein levels. For each episode of bloodstream infection, antibiotic choice and duration was recorded. The initial empiric antibiotic choice was defined as the antibiotic that was chosen in response to the identification of one of these three organisms in blood culture, prior to antibiotic susceptibility testing results. The empiric antibiotic choice was labelled as an "appropriate" choice, if the clinical isolate eventually demonstrated susceptibility to one or more of the chosen agents. Clinical outcomes such as the length of hospital stay, need for intensive care, mechanical ventilation, vasopressor support, recurrence of bacteraemia within a year from the index episode and in-hospital all-cause mortality were also evaluated. We recorded all episodes of bloodstream infection (bacteraemia). If the same individual had two separate hospital encounters with bacteraemia, they were recorded as two distinct episodes. Co-infection with other pathogens were also recorded if they were concomitantly isolated from blood cultures in the same setting as the positive blood culture with *S. maltophilia*, *Elizabethkingia* spp. or *Chryseobacterium* spp. Adequate source control of infection was recorded if patients had undergone a procedure such as central line removal, debridement of infected tissues, or abscess drainage, where appropriate.

We then stratified the patients into three groups (*S. maltophilia*, *Elizabethkingia* spp. and *Chryseobacterium* spp.) and compared them across clinical, demographic, laboratory parameters as well as clinical outcomes. Continuous parameters were examined by one-way analysis of variance and presented as means ± one standard deviation. Categorical variables were presented in frequencies and percentages, and compared by Chi-squared tests. Where statistical significance across the three groups was observed, post-hoc pairwise comparisons between the groups were conducted, with Bonferroni correction. A p-value of < 0.05 was considered significant. All data analyses for this study were carried out on SPSS version 20.0 (SPSS, Inc., Chicago, Illinois). This study had been approved by the National Healthcare Group Domain Specific Review Board (DSRB 2024–3132) prior to its conduct. The study was done in accordance with the principles laid out by the Declaration of Helsinki. All data was anonymised and a waiver of written informed consent had been obtained from the institutional review board prior to the conduct of the study, as this was a retrospective study and did not involve the human participants directly.

Results

A total of 349 distinct patient encounters involving 322 patients with bloodstream infections caused by *S. maltophilia*, *Elizabethkingia* spp., and *Chryseobacterium* spp. were analyzed. The majority of these infections were attributed to *S. maltophilia* (56.4%), followed by *Elizabethkingia* spp. (36.4%), then *Chryseobacterium* spp. (7.2%) (Fig. 1).

Demographics and clinical presentation

Patients with *Elizabethkingia* spp. bacteremia were significantly older. Immunocompromised status was most common in patients with *S. maltophilia* (62.4%) compared with the other two organisms (*Elizabethkingia* spp. (37.8%) or *Chryseobacterium* spp. (48.0%). Additionally, prior carbapenem exposure within the preceding month was reported in 59.9% of cases, with no significant differences observed among the three pathogens. Central lines were present in most patients, particularly those with *S. maltophilia* (89.8%). Total parenteral nutrition was rare (2.9%) and predominantly associated with *S. maltophilia* as well, although this was not statistically significant. Most infections were nosocomial in onset (82.5%), and 32.1% of cases occurred in the intensive care unit (Table 1).

Microbiological characteristics

Co-infections were observed in 25.8% of cases, most commonly with *Chryseobacterium* spp. (44.0%). Enterococci ($n = 14$) and Coagulase negative Staphylococci were the most common co-pathogens ($n = 13$), followed by *Pseudomonas* spp. ($n = 11$), *Candida* spp. ($n = 7$), and *Acinetobacter* spp. ($n = 7$). Catheter-related infections accounted for a majority (58.2%) of cases. Amongst these

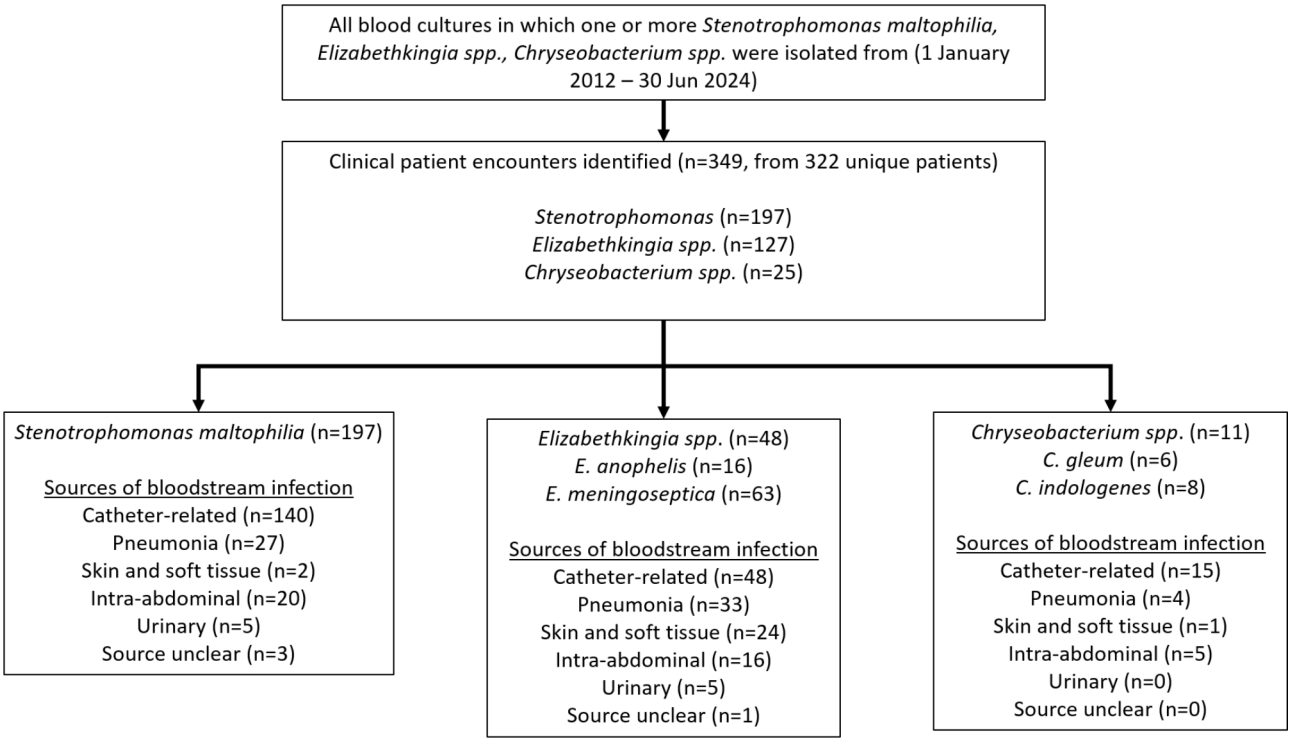

Fig. 1 Flowchart describing patient population by organism and sources of bloodstream infection

three organisms, the organism to present most frequently with skin and soft tissue infection as its source of infection was *Elizabethkingia* spp. A majority of these skin and soft tissue infections were a result of recent peripheral intravenous cannulation and subsequent thrombophlebitis. Intra-abdominal infection had the highest frequency with *Chryseobacterium* spp. (Table 1). Intraabdominal infections tended to occur after surgery or an endoscopic procedure, such as endoscopic retrograde cholangiopancreaticography for biliary obstruction. All episodes of urinary infection were associated with urological procedures or stenting.

Across the three organisms, 23% of isolates were resistant to levofloxacin, and 4.2% were resistant to TMP-SMX. Eight of the 349 isolates (2.3%) were resistant to both TMP-SMX and levofloxacin. Of these, 7 were *S. maltophilia* isolates and the remaining one was a *Chryseobacterium* isolate. Amongst the *S. maltophilia* isolates, resistance to levofloxacin in our institution was high (32.8%), although a majority retained susceptibility to TMP-SMX (93.1%) and minocycline (98.8%). Similarly, amongst the *Chryseobacterium* spp. isolates, 22.7% were resistant to levofloxacin, while a majority remained susceptibile to TMP-SMX (95.7%) and minocycline (100%). For *Elizabethkingia* spp., levofloxacin resistance was observed in 7.9%, while no isolates were resistant to TMP-SMX or minocycline. (Table 2).

Antimicrobial treatment and clinical outcomes

Initial antibiotic regimens commonly included TMP-SMX (37.0%) or levofloxacin (39.0%), with dual therapy used in only 6.6% of cases. Empiric therapy was appropriate in 84.2% of encounters, though 17.5% required regimen changes due to antibiotic intolerance or inappropriate initial choices. Patients received an average of 12 (±7) days of appropriate antibiotics, with no significant differences among the three pathogens (Table 2).

The overall mean length of hospital stay was 48 ± 107 days. Most patient encounters required a procedure for source control (219 out of 349, 62.8%). Of these procedures, 208 patients underwent central line removal, and the remaining 11 patients either had debridement of infected issues, or drainage of intra-abdominal abscesses. In-hospital mortality was high in this cohort at 35.8% (125 out of 349). Mortality was highest amongst patients with *S. maltophilia* bacteraemia (41.6%) versus *Elizabethkingia* spp. (29.9%). and *Chryseobacterium* spp. (20.0%, $p = 0.023$). Recurrence of bacteraemia within 1 year of the index episode was observed in 12 out of 349 patient encounters (3.4%), and a majority of these were in patients with *S. maltophilia* (Table 2).

Discussion

Overall, we described important trends in hospitalised patients presenting with bloodstream infection with *S. maltophilia*, *Elizabethkingia* spp. or *Chryseobacterium*

Table 1 Demographics and clinical characteristics by organism

Parameter	Overall cohort (*n* = 349)	*Stenotrophomonas maltophilia* (*n* = 197)	*Elizabethkingia* spp. (n = 127)	*Chryseobacterium* spp. (n = 25)	*p*-value
Age (years)	63.7 (± 5.0)	60.7 (± 14.9)	68.7 (± 14.2)[#]	61.9 (± 13.1)	< 0.01
Age < 60 years, n	131 (37.%)	87 (44.2%)	34 (27.0%)[#]	10 (40.0%)	0.008
Male sex, n	227 (65%)	125 (63.5%)	84 (66.1%)	18 (72.0%)	0.664
Smoking, n	27 (7.8%)	11 (5.6%)	13 (10.2%)	3 (12.0%)	0.225
Hypertension, n	184 (52.7%)	92 (46.7%)	80 (63.0%)	12 (48.0%)	0.015
Hyperlipidaemia, n	144 (41.3%)	71 (36.0%)	66 (52.0%)[#]	7 (28.0%)	0.007
Diabetes mellitus, n	120 (34.4%)	63 (32.0%)	47 (37.0%)	10 (40.0%)	0.537
End-stage kidney disease, n	63 (18.1%)	35 (17.8%)	21 (16.7%)	7 (28.0%)	0.398
Chronic liver disease, n	31 (8.9%)	17 (8.6%)	11 (8.7%)	3 (12.0%)	0.851
Ischaemic heart disease, n	97 (27.8%)	40 (20.3%)	49 (38.6%)[#]	8 (32.0%)	0.001
Immunocompromised host, n	183 (52.4%)	123 (62.4%)	48 (37.8%)[#]	12 (48.0%)	< 0.001
Type of immunocompromised host					< 0.001
Solid organ transplant	7 (2.0%)	5 (2.5%)	2 (1.6%)	0 (0.0%)	
Bone marrow transplant	17 (4.9%)	11 (5.6%)	2 (1.6%)	4 (16.0%)	
Haematological disorder	76 (21.8%)	59 (29.9%)	15 (11.8%)	2 (8.0%)	
Solid tumours	76 (21.8%)	44 (22.3%)	27 (21.3%)	5 (20.0%)	
Rheumatological disorders	8 (2.3%)	6 (3.0%)	2 (1.6%)	0 (0.0%)	
Others	3 (0.9%)	2 (1.0%)	0 (0.0%)	1 (4.0%)	
Prior carbapenem exposure within one month of bacteraemia, n	209 (59.9%)	128 (65.0%)	68 (53.5%)	13 (52.0%)	0.086
Duration of prior carbapenem exposure (days)	9 (± 7)	10 (± 7)	8 (± 5)	9 (± 7)	0.089
Presence of central line, n	263 (75.4%)	177 (89.8%)	68 (53.5%)[#]	18 (72.0%)	< 0.001
Total parenteral nutrition, n	10 (2.9%)	9 (4.6%)	1 (0.8%)	0 (0.0%)	0.093
Nosocomial onset of bacteraemia, n	288 (82.5%)	155 (78.7%)	114 (89.8%)	19 (76.0%)	0.025
Onset of bacteraemia in Intensive Care Unit, n	112 (32.1%)	78 (39.6%)	30 (23.6%)[#]	4 (16.0%)	0.002
Co-infection (bacteraemia) with other organisms	89 (25.8%)	60 (30.8%)	18 (14.4%)[#]	11 (44.0%)[@]	< 0.001
Source of bacteraemia					< 0.001
Catheter-related	203 (58.2%)	140 (71.1%)	48 (37.8%)	15 (60.0%)	
Pneumonia	64 (18.3%)	27 (13.7%)	33 (26.0%)	4 (16.0%)	
Skin and soft tissue	27 (7.7%)	2 (1.0%)	24 (18.9%)	1 (4.0%)	
Intraabdominal	41 (11.7%)	20 (10.2%)	16 (12.6%)	5 (20.0%)	
Urinary	10 (2.9%)	5 (2.5%)	5 (3.9%)	0 (0.0%)	
Unclear source	4 (1.1%)	3 (1.5%)	1 (0.8%)	0 (0.0%)	
Temperature (℃)	38.3 (± 0.7)	38.2 (± 0.8)	38.3 (± 0.7)	38.4 (± 0.5)	0.502
Duration of fever (days)	4.6 (± 3.7)	5.3 (± 4.3)	3.7 (± 2.6) [#]	3.2 (± 1.9) [#]	< 0.001
Respiratory rate (per minute)	22 (± 6)	22 (± 7)	22 (± 3)	21 (± 3)	0.766
Pulse rate (per minute)	94 (± 20)	95 (± 20)	93 (21)	95 (± 16)	0.500
Systolic blood pressure (mmHg)	121 (± 25)	119 (± 26)	122 (± 23)	131 (± 29)	0.054
Diastolic blood pressure (mmHg)	69 (± 16)	66 (± 14)	71 (± 17) [#]	77 (± 19) [#]	0.001
Oxygen saturations (%)	98 (± 3)	98 (3)	98 (3)	97 (± 3)	0.643
Haemoglobin (g/dL)	9.6 (± 2.1)	9.1 ± 1.9)	10.2 (± 2.2) [#]	10.3 (± 2.0) [#]	< 0.001
Total white cell count (x10^9/L)	9.8 (± 8.1)	8.1 (± 7.2)	12.3 (± 8.8) [#]	11.1 (± 7.9)	< 0.001
Absolute neutrophil count (x10^9/L)	8.2 (± 7.3)	6.7 (± 6.6)	10.3 (± 7.9) [#]	8.2 (± 7.3)	< 0.001
Absolute lymphocyte count (x10^9/L)	0.81 (± 0.69)	0.69 (± 0.65)	0.97 (± 0.71) [#]	0.95 (± 0.71)	0.001
Platelet count (x10^9/L)	171 (± 136)	143 (± 124)	205 (± 139) [#]	223 (± 165) [#]	< 0.001
Serum creatinine (μmol/L)	173 (± 186)	155 (± 175)	196 (± 197)	196 (± 206)	0.129
Aspartate aminotransferase (AST, U/L)	151 (± 758)	89 (± 241)	259 (± 1214)	99 (± 309)	0.145
Alanine aminotransferase (ALT)	118 (± 780)	61 (± 109)	215 (± 1287)	88 (± 206)	0.229
Lactate dehydrogenase (U/L)	960 (± 2221)	802 (± 1213)	1272 (± 3341)	615 (± 280)	0.197
C-reactive protein (mg/L)	106 (± 91)	116 (± 100)	95 (± 79)	85 (± 74)	0.089

[#]post-hoc pairwise comparison against *Stenotrophomonas maltophilia, where p < 0.05*

[@]post-hoc pairwise comparison against *Elizabethkingia* spp., where *p* < 0.05

Table 2 Microbiology and treatment outcomes of patients by organism

Parameter	Overall cohort (*n* = 349)	*Stenotrophomonas maltophilia* (*n* = 197)	*Elizabethkingia* spp. (*n* = 127)	*Chryseobacterium* spp. (*n* = 25)	*p*-value
Microbiology					
Resistant to levofloxacin	79/344 (23.0%)	64/195 (32.8%)	10/127 (7.9%)[#]	5/22 (22.7%)	< 0.001
Resistant to TMP-SMX*	14/336 (4.2%)	13/189 (6.9%)	0/124 (0.0%)[#]	1/23 (4.3%)	0.012
Resistant to minocycline	1/194 (0.5%)	1/92 (1.1%)	0/85 (0.0%)	0/17 (0.0%)	0.573
Resistant to piperacillin-tazobactam	15/90 (16.7%)	-	12/75 (16.0%)	3/15 (20.0%)	0.704
Resistant to ceftazidime	40/78 (51.3%)	25/62 (40.3%)	12/12 (100.0%)	3/4 (75.0%)	< 0.001
Therapeutic strategies					
Initial empiric antibiotic choice in response to bacteraemia					< 0.001
TMP-SMX* containing	129 (37.0%)	93 (47.2%)	32 (25.2%)	4 (16.0%)	
Levofloxacin containing	136 (39.0%)	77 (39.1%)	52 (40.9%)	7 (28.0%)	
Minocycline containing	11 (32.0%)	5 (2.5%)	3 (2.4%)	3 (12.0%)	
Piperacillin-tazobactam containing	39 (1.1%)	0 (0.0%)	34 (26.8%)	5 (20.0%)	
Others	34 (9.7%)	22 (11.2%)	6 (4.7%)	6 (24.0%)	
Initial dual antibiotics regimen	23 (6.6%)	13 (6.6%)	8 (6.3%)	2 (8.0%)	0.952
Initial antibiotic choice appropriate	294 (84.5%)	163 (83.2%)	112 (88.2%)	19 (76.0%)	0.227
Required switch in antibiotics from empirical regimen	61 (17.5%)	33 (16.8%)	24 (18.9%)	4 (16.0%)	0.866
Final antibiotic regimen choice					< 0.001
TMP-SMX* containing	144 (41.3%)	95 (48.2%)	43 (33.9%)	6 (24.0%)	
Levofloxacin containing	137 (39.3%)	66 (33.5%)	64 (50.4%)	7 (28.0%)	
Minocycline containing	19 (5.4%)	13 (6.6%)	3 (2.4%)	3 (12.0%)	
Piperacillin-tazobactam containing	15 (4.3%)	0 (0.0%)	11 (8.7%)	4 (16.0%)	
Others	34 (9.7%)	23 (11.7%)	6 (4.7%)	5 (20.0%)	
Final dual antibiotics regimen	20 (5.7%)	12 (6.1%)	6 (4.7%)	2 (8.0%)	0.767
Final antibiotic choice effective	305 (87.6%)	169 (86.2%)	116 (91.3%)	20 (80.0%)	0.191
Duration of appropriate antibiotics (days)	12 (± 7)	12 (± 7)	13 (± 7)	11 (± 4)	0.216
Appropriate antibiotic duration two weeks or longer, n	194 (56.1%)	99 (50.8%)	83 (65.9%)[#]	12 (48.0%)	0.020
Required procedure for source control (e.g. central line removal, debridement of infected tissues, drainage of abscesses)	219 (62.8%)	141 (71.6%)	58 (45.7%)[#]	20 (80.0%)[@]	< 0.001
Clinical outcomes					
Length of hospital day (days)	48 (± 107)	48 (± 76)	53 (± 148)	27 (± 30)	0.534
Length of intensive care unit stay	24 (± 27)	28 (± 29)	16 (± 23)	11 (± 6)	0.087
Required vasopressor support	107 (30.7%)	73 (37.1%)	29 (22.8%)[#]	5 (20.0%)	0.012
Required mechanical ventilation	104 (29.8%)	68 (34.5%)	31 (24.4%)	5 (20.0%)	0.082
Required intensive care	115 (33.0%)	80 (40.6%)	30 (23.6%)[#]	5 (20.0%)	0.002
In-hospital mortality	125 (35.8%)	82 (41.6%)	38 (29.9%)	5 (20.0%)	0.023
Recurrence of bacteraemia within 1 year	12 (3.4%)	11 (5.6%)	0 (0.0%)[#]	1 (4.0%)	0.026

*TMP-SMX: trimethoprim-sulfamethoxazole

[#]post-hoc pairwise comparison against *Stenotrophomonas maltophilia, where p < 0.05*

[@]post-hoc pairwise comparison against *Elizabethkingia* spp., where $p < 0.05$

spp. over the 13 years from 2012 to 2024. Broadly, the risk factors for acquisition of these organisms were similar. A majority (> 80%) were nosocomial in acquisition, and a third were acquired in critically ill patients in the intensive care unit. Furthermore, close to 60% had prior carbapenem exposure before developing bacteraemia with these organisms. Prolonged carbapenem exposure has been associated with invasive infections with these organisms as they are intrinsically resistant to carbapenems. Selection pressure from prolonged carbapenem exposure likely eradicates normal flora and allows for proliferation of these opportunistic non-fermenting intrinsically carbapenem-resistant Gram negative organisms [2–4, 16].

Nevertheless, there were sizeable number of catheter-related bloodstream infections amongst patients with end-stage kidney disease on haemodialysis that presented from the community. Given that they were community acquired infections, a majority of these patients did not have carbapenem exposure prior to infection. Compared with *Staphylococcus aureus* and coagulase negative *Staphylococci*, *S. maltophilia*, *Elizabethkingia* spp. and *Chryseobacterium* spp. are generally thought to be uncommon causes of catheter-related bloodstream

infections patients on dialysis. However, outbreaks in dialysis centres have been reported, which may be related to contaminated water sources [17, 18]. In our cohort these episodes appeared to be sporadic and did not appear to cluster to any specific timeframe. We also did not observe recurrence of bacteraemia in the same patients who would return to visit the same dialysis centre after hospital admission, which may more clearly suggest a contaminated water source.

Solid organ tumours also formed an important risk factor for bloodstream infections with these organisms, accounting for approximately 20% of encounters. These patients often have central lines for delivery of chemotherapy, or biliary obstruction and endoscopic procedures which have been stented. Translocation of bacteraemia from the biliary tree into the bloodstream has been reported after biliary procedures, particularly when the procedure was performed in the context of biliary obstruction [19]. Carbapenem or broad-spectrum antibiotic use peri-procedurally then may have subsequently pre-disposed to bacteraemia with one of these three organisms.

Elizabethkingia spp. bloodstream infections were also observed amongst patients who were immunocompetent and not critically ill. The source of these infections was often pulmonary, in the form of hospital acquired pneumonias, or skin and soft tissue infection, in the context of thrombophlebitis after recent intravenous cannulation [20]. In our adult population, we did not identify meningitis or central nervous system infection, which had been commonly observed in the paediatric setting [5].

Overall, we found these three organisms to be important nosocomial pathogens. The in-hospital mortality in our cohort was high, consistent with data from other observational cohorts [3, 4, 14]. Amongst the three, mortality was highest in *S. maltophilia* bloodstream infections. Optimal treatment approaches for these infections remain unclear. In our centre, for infections with *S. maltophilia*, the first-line empiric antibiotic choice was TMP-SMX, due to the high rates of fluoroquinolone resistance.

S. maltophilia harbour beta lactamases that hydrolyse penicillins, cephalosporins, carbapenems and aztreonam [21–23]. In addition, they also demonstrate intrinsic resistance to aminoglycosides by chromosomal aminoglycoside acetyl transferase enzymes [24]. In addition to the intrinsic antimicrobial resistance, *S. maltophilia* is also known to develop resistance while on therapy, by upregulating efflux pumps [25–27]. Similarly, both *Elizabethkingia* spp. and *Chryseobacterium* spp. in addition to beta-lactamases, can also express efflux pumps which confer resistance to other antibiotics [28, 29]. As such, with the intention to avoid the development of antimicrobial resistance, some experts recommend the use of combination antibiotic therapy [8, 30]. The clinical evidence for this practice remains scarce and controversial. One reasonable approach may have been to stratify patients by disease severity, where it appeared that patients with more severe infection were more likely to demonstrate benefit from the use of combination antimicrobial therapy [31].

In contrast to *S. maltophilia*, clinical outcomes and characteristics are less well studied in *Elizabethkingia* spp. and *Chryseobacterium* spp., probably because they are less frequent causes of invasive infection. Consequently, there are no treatment guidelines for infections with *Elizabethkingia* spp. or *Chryseobacterium* spp. Dual antibiotic therapy is sometimes used for these infections, particularly, when the infection is severe and while susceptibility testing results are pending, to increase the likelihood of at least one appropriate empiric agent. In our retrospective review, dual therapy was rarely used for infections with these three organisms. Therefore, the numbers were too small to conclude or evaluate if outcomes associated with empiric dual therapy were better or worse than with monotherapy.

In addition to antibiotic choice, the optimal duration of antibiotic therapy for bloodstream infections with these organisms also remains to be elucidated. Duration of therapy is likely guided by the patient's clinical syndrome (e.g. pneumonia, skin and soft tissue infection, catheter-related infection, etc.), and clinical progress on antimicrobial therapy. The IDSA guidelines recommend line removal, and 7 to 14 days of antibiotics for catheter-related bloodstream infections with Gram negative organisms [32]. In most of the patients in our cohort, central lines were removed in a timely fashion, which likely provided an adequate degree of source control for the infection. The patients in our cohort received an average of 12 ± 7 days of appropriate antibiotics. With this, we observed that relapse of bacteraemia within a year was low in our cohort (3.4%). Future study is important to define appropriate antibiotic duration for this infection. To examine this, patients may have to be stratified by source of infection. For example, in clinical contexts in which the infection complicated and source control is less adequate (e.g. an infected biliary stent that cannot be removed), a longer duration of antibiotic therapy may be required.

Limitations

Our study reflects a single-centre experience of patients being managed for bloodstream infections with *S. maltophilia*, *Elizabethkingia* spp. or *Chryseobacterium* spp. MALDI-TOF MS could reliably identify *Elizabethkingia* spp. to a genus level, so this group was analyzed as a whole. Species-level identification to further comparing the differences in clinical characteristics and outcomes

among distinct species would require further diagnostic methods (for example, 16s rRNA sequencing) [33]. Source of infections were determined by the primary managing team, as documented in the clinical charts on retrospective review. The clinical and demographic data obtained therefore relied on the quality of documentation in the patients' electronic records. Importantly, this is a cross-sectional study, and we did not prospectively follow-up each of these patients. Furthermore, as this was a retrospective and observational cohort, treatment decisions, such as antibiotic choices and durations were left to the discretion of the managing physicians. As such, we could not systematically study the impact or difference of various treatment options on clinical outcomes as well. Most empiric antibiotics were administered intravenously, but we did not capture the timing of oral switch in therapy. We also only reported the antimicrobial susceptibility testing for the index episode of bacteraemia. There were some subjects with multiple blood cultures that returned positive over time. We did not capture if resistance to antibiotics had developed while on therapy.

Our findings were exploratory and descriptive. As such, we did not build a multivariable model to adjust for confounding variables that may have explained some of the observed trends. For example, although the prevalence of prior carbapenem exposure was common in bacteraemia with these three organisms, we did not have a control group of bacteraemia with other Gram-negative organisms to compare against. Nevertheless, we report real-world observational findings in terms of the clinical presentation and outcomes from these infections.

Furthermore, we also used all-cause in-hospital mortality as an outcome measure. It was not always possible to elucidate if the bacteraemia episode was the main contributor to an individual's mortality. Therefore, an individual's underlying co-morbidities such as underlying metastatic cancer may also have contributed to the adverse outcomes. We did not specifically study the trends in mortality over time. However, our study examined a long period of time (close to 13 years). The changes in critical care practices and other unmeasured factors may also have contributed to differences in clinical outcomes. Furthermore, in some immunocompromised hosts, fluoroquinolone or trimethoprim-sulfamethoxazole prophylaxis may have been used. Understanding the specific antibiotic therapy that the patient had been on prior to the bacteraemia episode may importantly influence the clinical outcomes, as well as the antimicrobial susceptibility profile of infections with these three organisms.

Our study focused only on infections with these three organisms, and we were not able to compare the prevalence of these infections with bloodstream infections with other Gram-negative organisms., although our findings are exploratory, they may form the important basis for randomised controlled trials to evaluate optimal antimicrobial treatment regimens and duration in these infections. Additionally, to understand the evolution and development of antibiotic resistance, future prospective study on the mechanisms of resistance in these organisms are important.

Conclusions

Mortality and morbidity were high in our cohort, particularly in patients with *Stenotrophomonas maltophilia* bloodstream infection. Dual therapy was rarely used as part of the initial treatment regimen, and it remains unclear if this would have an impact on clinical outcomes. Fluoroquinolone resistance was common in *S. maltophilia* and *Chryseobacterium* spp., but was less frequently identified in *Elizabethkingia* spp. isolates. Understanding local trends in resistance patterns may thus help to guide empirical antibiotic choice for infections with these organisms. Monitoring local susceptibility patterns for these three organisms over time would be helpful to guide treatment protocols, and prospective studies evaluating optimal treatment regimens and duration, and evolving resistance mechanisms are warranted.

Abbreviations

CLSI	Clinical and Laboratory Standards Institute
DSRB	Domain Specific Review b\Board
EUCAST	European Committee on Antimicrobial Susceptibility Testing
IDSA	Infectious Diseases Society of America
MALDI-TOF MS	Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry
TMP-SMX	Trimethoprim-sulfamethoxazole

Acknowledgements

N/A.

Author contributions

MCYK, JNN contributed to the conception, data collection, data analysis, writing of the original draft and critical review of the manuscript. NS, KLC, LHWL and DMA contributed to the conception, data analysis, and critical review of the manuscript.

Funding

There is no funding to report for this study.

Data availability

Data will be made available on reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the hospital's institutional review board (National Healthcare Group (NHG) Domain Specific Review Board (DSRB) 2024–3132). A waiver of written informed consent was obtained from the hospital's institutional review board (National Healthcare Group (NHG) Domain Specific Review Board (DSRB) 2024–3132) prior to conduct. The study was carried out in accordance with the principles laid out by the Declaration of Helsinki.

Consent for publication

Not Applicable.

Competing interests
The authors declare no competing interests.

Clinical trial
Clinical trial number: not applicable.

Author details
[1]Division of Infectious Diseases, Department of Medicine, National University Health System, Singapore (City), Singapore
[2]Department of Laboratory Medicine, National University Hospital, 1E Kent Ridge Rd, NUHS Tower Block, Level 10, 119228 Singapore (City), Singapore
[3]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore (City), Singapore, Singapore
[4]National University of Singapore Centre for Population Health, Singapore, Singapore

Received: 21 December 2024 / Accepted: 13 February 2025
Published online: 25 February 2025

References

1. Hafiz TA, Aldawood E, Albloshi A, et al. Stenotrophomonas maltophilia Epidemiology, Resistance Characteristics, and clinical outcomes: understanding of the recent three years' trends. Microorganisms. 2022;10(12):2506. https://doi.org/10.3390/microorganisms10122506.
2. Wang N, Tang C, Wang L. Risk factors for Acquired Stenotrophomonas maltophilia Pneumonia in Intensive Care Unit: a systematic review and Meta-analysis. Front Med (Lausanne). 2021;8:808391. https://doi.org/10.3389/fmed.2021.808391.
3. Choi MH, Kim M, Jeong SJ, et al. Risk factors for Elizabethkingia Acquisition and clinical characteristics of patients, South Korea. Emerg Infect Dis. 2019;25(1):42–51. https://doi.org/10.3201/eid2501.171985.
4. Chaudhary R, Kar M, Jamwal A, et al. Characteristics of Chryseobacterium bacteremia, associated risk factors and their antibiotic susceptibility pattern at a university hospital: a descriptive, retrospective study. Access Microbiol. 2023;5(11):000594v3. https://doi.org/10.1099/acmi.0.000594.v3.
5. Dziuban EJ, Franks JL, So M, Peacock G, Blaney DD. Elizabethkingia in children: a comprehensive review of symptomatic cases reported from 1944 to 2017. Clin Infect Dis. 2018;67(1):144–9. https://doi.org/10.1093/cid/cix1052.
6. Ebara H, Hagiya H, Haruki Y, Kondo E, Otsuka F. Clinical characteristics of Stenotrophomonas maltophilia bacteremia: a Regional Report and a review of a Japanese Case Series. Intern Med. 2017;56(2):137–42. https://doi.org/10.2169/internalmedicine.56.6141.
7. Rhoads DD. Stenotrophomonas maltophilia Susceptibility Testing challenges and strategies. J Clin Microbiol. 2021;59(9):e0109421. https://doi.org/10.1128/JCM.01094-21.
8. Pranita D, Tamma EL, Heil JA, Justo AJ, Mathers MJ, Satlin RA, Bonomo. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2024; Version 4.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed 14/07/2024.
9. Zajmi A, Teo J, Yeo CC. Epidemiology and characteristics of Elizabethkingia Spp. Infections in Southeast Asia. Microorganisms. 2022;10(5):882. https://doi.org/10.3390/microorganisms10050882.
10. AlFonaisan MK, Mubaraki MA, Althawadi SI, et al. Temporal analysis of prevalence and antibiotic-resistance patterns in Stenotrophomonas maltophilia clinical isolates in a 19-year retrospective study. Sci Rep. 2024;14(1). https://doi.org/10.1038/s41598-024-65509-z.
11. Hsu MS, Liao CH, Huang YT, et al. Clinical features, antimicrobial susceptibilities, and outcomes of Elizabethkingia meningoseptica (Chryseobacterium meningosepticum) bacteremia at a medical center in Taiwan, 1999–2006. Eur J Clin Microbiol Infect Dis. 2011;30(10):1271–8. https://doi.org/10.1007/s10096-011-1223-0.
12. Kirby JT, Sader HS, Walsh TR, Jones RN. Antimicrobial susceptibility and epidemiology of a Worldwide Collection of *Chryseobacterium* spp.: Report from the SENTRY Antimicrobial Surveillance Program (1997–2001). J Clin Microbiol. 2004;42(1):445–8. https://doi.org/10.1128/jcm.42.1.445-448.2004.
13. Huang C, Kuo S, Lin L. Hemorrhagic pneumonia caused by Stenotrophomonas maltophilia in patients with hematologic Malignancies—A systematic review and Meta-analysis. Medicina. 2024;60(1):162. https://doi.org/10.3390/medicina60010162.
14. Osawa K, Shigemura K, Kitagawa K, Tokimatsu I, Fujisawa M. Risk factors for death from Stenotrophomonas maltophilia bacteremia. J Infect Chemother. 2018;24(8):632–6. https://doi.org/10.1016/j.jiac.2018.03.011.
15. EUCAST: European Committee on Antimicrobial Susceptibility Testing. Clinical breakpoints - breakpoints and guidance. https://www.eucast.org/clinical_breakpoints (Date Accessed 19/7/2024).
16. Maraolo AE, Licciardi F, Gentile I, Saracino A, Belati A, Bavaro DF. Stenotrophomonas maltophilia infections: a systematic review and Meta-analysis of comparative efficacy of available treatments, with critical Assessment of Novel Therapeutic options. Antibiot (Basel). 2023;12(5):910. https://doi.org/10.3390/antibiotics12050910.
17. De Mauri A, Torreggiani M, Chiarinotti D, Andreoni S, Molinari G, De Leo M. Stenotrophomonas maltophilia: an emerging pathogen in dialysis units. J Med Microbiol. 2014;63(Pt 11):1407–10. https://doi.org/10.1099/jmm.0.076513-0.
18. Diniz Rocha VF, Cavalcanti TP, Azevedo J, et al. Outbreak of Stenotrophomonas maltophilia and Burkholderia cepacia Bloodstream Infections at a Hemodialysis Center. Am J Trop Med Hyg. 2020;104(3):848–53. https://doi.org/10.4269/ajtmh.20-1035.
19. Kwak MS, Jang ES, Ryu JK, Kim YT, Yoon YB, Park JK. Risk factors of post endoscopic retrograde cholangiopancreatography bacteremia. Gut Liver. 2013;7(2):228–33. https://doi.org/10.5009/gnl.2013.7.2.228.
20. Lin JN, Lai CH, Yang CH, Huang YH. Elizabethkingia Infections in humans: from Genomics to Clinics. Microorganisms. 2019;7(9):295. https://doi.org/10.3390/microorganisms7090295.
21. Crossman LC, Gould VC, Dow JM, et al. The complete genome, comparative and functional analysis of Stenotrophomonas maltophilia reveals an organism heavily shielded by drug resistance determinants. Genome Biol. 2008;9(4):R74. https://doi.org/10.1186/gb-2008-9-4-r74.
22. Gil-Gil T, Martínez JL, Blanco P. Mechanisms of antimicrobial resistance in Stenotrophomonas maltophilia: a review of current knowledge. Expert Rev Anti Infect Ther. 2020;18(4):335–47. https://doi.org/10.1080/14787210.2020.1730178.
23. Çıkman A, Parlak M, Bayram Y, Güdücüoğlu H, Berktaş M. Antibiotics resistance of Stenotrophomonas maltophilia strains isolated from various clinical specimens. Afr Health Sci. 2016;16(1):149–52. https://doi.org/10.4314/ahs.v16i1.20.
24. Okazaki A, Avison MB. Aph(3')-IIc, an Aminoglycoside Resistance Determinant from *Stenotrophomonas maltophilia*. Antimicrob Agents Chemother. 2007;51(1):359–60. https://doi.org/10.1128/AAC.00795-06.
25. Gould VC, Okazaki A, Avison MB. Coordinate hyperproduction of SmeZ and SmeJK efflux pumps extends Drug Resistance in Stenotrophomonas maltophilia. Antimicrob Agents Chemother. 2013;57(1):655–7. https://doi.org/10.1128/AAC.01020-12.
26. Bostanghadiri N, Ghalavand Z, Fallah F, et al. Characterization of phenotypic and genotypic diversity of Stenotrophomonas maltophilia strains isolated from selected hospitals in Iran. Front Microbiol. 2019;10:1191. https://doi.org/10.3389/fmicb.2019.01191.
27. Sánchez MB, Martínez JL. The Efflux Pump SmeDEF contributes to Trimethoprim-Sulfamethoxazole Resistance in Stenotrophomonas maltophilia. Antimicrob Agents Chemother. 2015;59(7):4347–8. https://doi.org/10.1128/AAC.00714-15.
28. Jian MJ, Cheng YH, Chung HY, et al. Fluoroquinolone resistance in carbapenem-resistant Elizabethkingia anophelis: phenotypic and genotypic characteristics of clinical isolates with topoisomerase mutations and comparative genomic analysis. J Antimicrob Chemother. 2019;74(6):1503–10. https://doi.org/10.1093/jac/dkz045.
29. Zhang L, Wang M, Qi R, et al. A novel major facilitator superfamily-type tripartite efflux system CprABC mediates resistance to polymyxins in Chryseobacterium sp. PL22-22A. Front Microbiol. 2024;15. https://doi.org/10.3389/fmicb.2024.1346340.
30. Prawang A, Chanjamlong N, Rungwara W, et al. Combination therapy versus Monotherapy in the treatment of Stenotrophomonas maltophilia infections: a systematic review and Meta-analysis. Antibiotics. 2022;11(12):1788. https://doi.org/10.3390/antibiotics11121788.
31. Chen L, Hua J, Hong S, et al. Assessment of the relative benefits of monotherapy and combination therapy approaches to the treatment of hospital-acquired Stenotrophomonas maltophilia pneumonia: a multicenter, observational, real-world study. Ann Intensive Care. 2023;13(1):47. https://doi.org/10.1186/s13613-023-01144-7.

32. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1–45. https://doi.org/10.1086/599376.
33. Chew KL, Cheng B, Lin RTP, Teo JWP. Elizabethkingia anophelis Is the Dominant Elizabethkingia Species Found in Blood Cultures in Singapore. Richter SS, ed. *J Clin Microbiol*. 2018;56(3):e01445-17. https://doi.org/10.1128/JCM.01445-17

Publisher's note