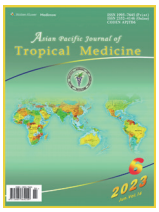

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Chryseobacterium/Elizabethkingia species infections in children

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ABSTRACT

Objective: To investigate the clinical and epidemiological features and outcome of *Chryseobacterium* and *Elizabethkingia* spp. infections in children, together with antimicrobial susceptibilities.

Methods: This retrospective study was conducted at a tertiary pediatric hospital in Turkey. All patients infected with *Chryseobacterium/Elizabethkingia* spp. among those presenting to Ankara City Hospital between March 2014 and March 2022 were included.

Results: A total of 49 cases were included and 29 cases were identified as *Elizabethkingia*. The median age was 14 (0.2-185.0) months. The majority (89.8%) of these patients had an underlying disease, including malignancy (42.9%). Bacteremia (46.9%) and central line-associated bloodstream infection (28.6%) were the most common infections. The thirty-day all-cause mortality rate was 12.2%. The most commonly used antibiotics were ciprofloxacin and trimethoprim-sulfamethoxazole (TMP-SMX). Forty-five (91.8%) isolates were susceptible to ciprofloxacin, 44 (91.6%) to TMP-SMX, and 21 (87.5%) to levofloxacin.

Conclusions: *Chryseobacterium* and *Elizabethkingia* spp. are emergent, nosocomial pathogens and the majority of cases were older than the neonatal period. They were mainly seen in patients with long hospital stays, indwelling devices, and those who have received antibiotics within the last month, especially carbapenems. In addition, they were associated with bloodstream infection and malignancy. The most commonly useful antibiotics according to the resistance patterns were ciprofloxacin and TMP-SMX.

KEYWORDS: *Chryseobacterium*; *Elizabethkingia*; Flavobacteriaceae; Weeksellaceae

1. Introduction

Chryseobacterium and *Elizabethkingia* are rare pathogens in children from the Weeksellaceae family[1]. The taxonomy of these organisms is confusing because of frequent changes. Some species, including *Flavobacterium meningosepticum*, were reclassified as *Chryseobacterium* in 1994[2]. In 2005, *Chryseobacterium* (*C.*) *meningosepticum* and *C. miricola* were transferred to a new genus on the basis of phylogenetic characteristics named *Elizabethkingia* after the microbiologist who first described them[3]. While *Chryseobacterium* and *Elizabethkingia* species are considered from the Flavobacteriaceae family, they have been transferred to the family Weeksellaceae[1]. *C. indologenes*, *C. odoratum*, *C.*

Significance

Elizabethkingia and *Chryseobacterium* infections are resistant to many antibiotics used in empirical therapy and have high mortality. Contrary to the literature, most of our cases were sporadic and were older than the newborn age group. Most of the patients were long-term hospitalized patients with an underlying disease. They had taken antibiotics, especially carbapenems, in the last month. According to the antibiogram resistance patterns, the most commonly used antibiotics were ciprofloxacin and trimethoprim-sulfamethoxazole.

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multivorum, *C. breve*, *C. gleum*, *Elizabethkingia* (*E.*) *meningoseptica*, and *E. anophelis* are frequently reported pathogenic members of the *Weeksellaceae* species. *Chryseobacterium* and *Elizabethkingia* species are aerobic, nonfermenting, oxidase-positive, Gram-negative rods commonly found in the water, soil, and environment[2,3].

C. indologenes and *E. meningoseptica* are the most common pathogenic species and can cause a wide range of clinical presentations and a high mortality rate[2]. Although *E. meningoseptica* most commonly causes neonatal meningitis, it can also cause many other diseases such as sepsis, pneumonia, endocarditis, septic arthritis, and skin infection[4]. *C. indologenes* can cause serious infections such as ventilator-associated pneumonia, bacteremia, and catheter-related blood-stream infections, as well as multidrug-resistant nosocomial infections and hospital outbreaks in pediatric and adult patients[5,6].

Identifying these microorganisms is important due to inherent resistance to multiple antibiotics that are typically prescribed for empiric treatment of Gram-negative bacterial infections, including extended spectrum β-lactam agents and aminoglycosides, and the high mortality rates of inadequately or improperly treated infections[4]. Unfortunately the data on infections related to these microorganisms, especially in pediatric patients, is currently inadequate.

The aim of the current study was to document the clinical patterns, risk factors, and outcomes of pediatric patients infected with *Chryseobacterium* and *Elizabethkingia* spp. at our hospital, as well as the antimicrobial susceptibility of the strains isolated from these patients, so as to reveal the different characteristics of these two microorganisms which are of the same family.

2. Subjects and methods

2.1. Study design and population

This retrospective study was conducted at the Ankara City Hospital, which is a tertiary pediatric hospital in Turkey. Patients under 18 years of age with isolates of *Chryseobacterium* and *Elizabethkingia* spp. between March 2014 and March 2022 were included in the study. Each case was reviewed by a pediatric infectious disease specialist; isolates discarded due to contamination or colonization, as determined according to the clinical picture, were excluded from the study (Figure 1). The clinical samples collected were blood (either from a peripheral vein or through a central venous catheter), endotracheal aspirate, sputum, cerebrospinal fluid, pus, and urine. Data obtained from the records included age, sex, unit, duration of hospitalization (before culture positivity), presence of prior antibiotic treatment, history of surgery in the last month, underlying diseases, presence of colonization with resistant microorganisms, the use of indwelling catheters (such as central venous catheter, mechanical ventilation, urinary catheterization, tracheostomy, or percutaneous endoscopic gastrostomy tube), trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, time to negative culture, laboratory results, microbiology data, antibiotic treatment, and outcome. In infected patients, the empiric treatment was changed according to the antibiotic susceptibility test results after the detection of *Chryseobacterium* and *Elizabethkingia* spp. The data were evaluated separately for the two microorganisms and a comparison was made.

2.2. Definitions

Colonization was defined as the first stage of microbial infection at the appropriate portal of entry. The presence of microorganisms in or on a host together with growth and multiplication but without clinical symptoms of infection was accepted as colonization. Colonized patients were not included in the study[6].

Significant bacteremia was defined as growth of *Chryseobacterium* and *Elizabethkingia* spp. in blood cultures as well as the clinical manifestation of signs of the systemic inflammatory response syndrome. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, and classified according to laboratory and clinical findings[7]. Catheter-related bloodstream infection, nosocomial pneumonia, urinary tract infection, surgical site infection, and skin and soft tissue infection were defined according to the Centers for Disease Control and Prevention guidelines[8].

2.3. Microbiologic identification

Samples were inoculated on routine 5% Sheep Blood agar and MacConkey agar 5% Sheep Blood agar (BioCell, Turkiye) and MacConkey agar (BioCell, Turkiye). After 16-24 hours of incubation at 37 ℃, the growing isolates were identified with VITEK® MS (bioMérieux, France). Antimicrobial susceptibility profiles of the isolates of *Chryseobacterium* and *Elizabethkingia* were determined by VITEK® 2 Compact (bioMérieux, France), and interpreted based on the Clinical and Laboratory Standards Institute's criteria for other non-Enterobacteriaceae[9].

2.4. Ethical approval

The Ethics Committee of Ankara City Hospital approved the study with reference number 2022/E2-22-1566.

2.5. Statistical analyses

All statistical analyses were conducted using SPSS software (version 25; IBM, Chicago, IL). The data of the patients were collected retrospectively from the hospital records. Normality of distribution of the continuous variables was measured with the One-Sample Kolmogorov-Smirnov Test. The continuous variables with a normal distribution were expressed as mean±SD and compared using Student's *t*-test, while the variables with a non-normal distribution were expressed as median (min-max) and compared using the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher's exact test. In all analyses, a *P* value <0.05 was considered to indicate statistical significance.

3. Results

3.1. Population

Chryseobacterium and *Elizabethkingia* spp. were isolated in 49 patients. Twenty-two of these patients were female (44.9%), and 27 were male (55.1%). The median age was 14 (0.21-185.0) months. Of the 49 cases, 29 (59.2%) were identified as *Elizabethkingia* and 20 (40.8%) as *Chryseobacterium*. There was no outbreak during the study period.

An underlying disease was present in 44 (89.8%) of these patients. These diseases consisted of malignancies in 21 patients, cardiovascular disorders in 13 patients, neuromotor disorders in 5 patients, chronic lung diseases in 3 patients, and renal disorders in 2 patients. Eighteen (36.7%) patients were hospitalized in the pediatric hematology oncology unit, 16 (32.7%) in the infant unit, 10 (20.4%) in the intensive care unit, 3 (6.1%) in the toddler unit, and 2 (4.1%) in the neonatal service. There were 33 patients with a central venous catheter and 9 with a urinary catheter; 8 patients who were hospitalized in the intensive care units were mechanically ventilated; 6 patients had a tracheostomy and 12 patients had a percutaneous endoscopic gastrostomy tube. Of the 29 patients with *Elizabethkingia* infection, 25 had a central venous catheter, while only 8 of the 20 patients with a *Chryseobacterium* infection had a central venous catheter (86.2% *vs.* 40.0%, *P*=0.001). None of the patients were receiving total parenteral nutrition. Fifteen (30.6%) patients had undergone surgery in the last month. Twenty-one patients (42.9%) diagnosed with leukemia were receiving TMP-SMX prophylaxis and this rate was significantly higher in patients with *Elizabethkingia* infections (55.2% *vs.* 25.0%, *P*=0.036).

There were 3 (6%) coinfections with other bacteria in the entire study group. No repetitive culture positivity was detected. The median duration of hospitalization before culture positivity was 25 days (1-204 days). *Elizabethkingia* infections were significantly more common than *Chryseobacterium* infections (*P*=0.007). The median length of hospital stay (before culture positivity) of patients infected with *Elizabethkingia* was longer than patients infected with

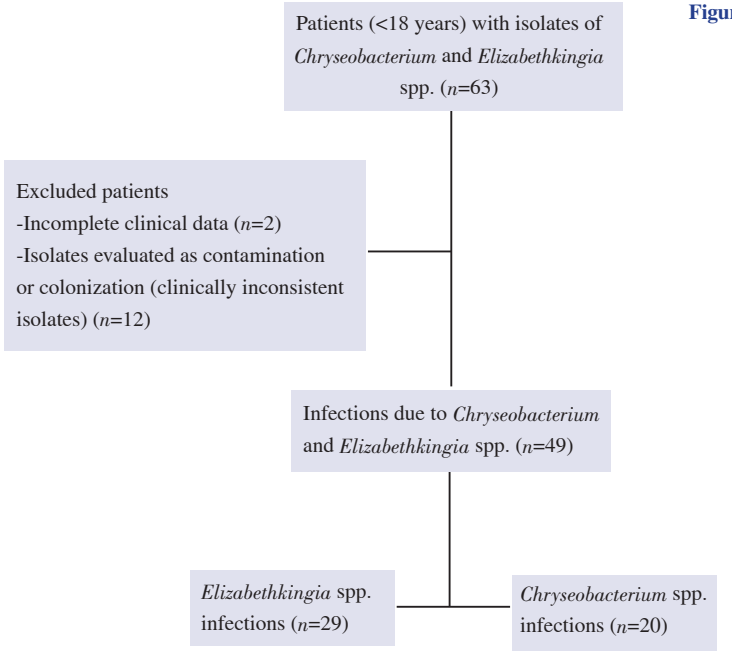

Figure 1. Flowchart of the selection process.

Table 1. Patients characteristics, underlying diseases and risk factors with *Chryseobacterium* and *Elizabethkingia* infections.

Characteristics	Total (*n*=49)	*Elizabethkingia* spp. (*n*=29)	*Chryseobacterium* spp. (*n*=20)	*P*
Sex, male/female, *n*	27/22	15/14	12/8	0.567
Age, month, median (min-max)	14 (0.21-185)	15 (0.21-185)	11 (1-172)	0.911
Duration of hospitalization (before culture positivity), d, median (min-max)	25 (1-204)	28 (3-204)	9.5 (1-204)	0.007*
Underlying disease, *n* (%)				0.405
None	5 (10.2)	2 (6.9)	3 (15.0)	
Malignancy	21 (42.9)	16 (55.2)	5 (25.0)	
Cardiovascular disorder	13 (26.5)	6 (20.7)	7 (35.0)	
Neuromotor disorder	5 (10.2)	2 (6.9)	3 (15.0)	
Chronic lung disease	3 (6.1)	2 (6.9)	1 (5.0)	
Renal	2 (4.1)	1 (3.4)	1 (5.0)	
Wards of patients, *n* (%)				0.632
Hematology oncology department	18 (36.7)	13 (44.8)	5 (25.0)	
Pediatric intensive care unit	10 (20.4)	5 (17.2)	5 (25.0)	
Infant unit	16 (32.7)	9 (31.0)	7 (35.0)	
Toddler unit	3 (6.1)	1 (3.4)	2 (10.0)	
Neonatal intensive care unit	2 (4.1)	1 (3.4)	1 (5.0)	
Indwelling devices of patients, *n* (%)				
Central venous catheter	33 (67.3)	25 (86.2)	8 (40.0)	0.001*
Mechanical ventilation	8 (16.3)	5 (17.2)	3 (15.0)	0.835
Tracheostomy	6 (12.2)	1 (3.4)	5 (25.0)	0.024*
Urinary catheter	9 (18.4)	4 (13.8)	5 (25.0)	0.319
Percutaneous endoscopic gastrostomy	12 (24.5)	7 (24.1)	5 (25.0)	0.945
Surgery in the last one month, *n* (%)	15 (30.6)	9 (31.0)	6 (30.0)	0.938
Receiving TMP-SMX prophylaxis, *n* (%)	21 (42.9)	16 (55.2)	5 (25.0)	0.036*
History of antibiotic use in the last one month, *n* (%)	42 (85.7)	28 (96.6)	14 (70.0)	0.009*
Yes				
Carbapenems	31 (63.3)	23 (79.3)	8 (40.0)	0.007*
Glycopeptides	18 (36.7)	13 (44.8)	5 (25.0)	0.230
Aminoglycosides	21 (42.9)	12 (41.4)	9 (45.0)	0.900
Cephalosporins	17 (34.7)	10 (34.5)	7 (35.0)	0.920
β-lactam- β-lactamase inhibitors	17 (34.7)	11 (37.9)	6 (30.0)	0.761
Colistin	10 (20.4)	4 (13.8)	6 (30.0)	0.279
Colonization with resistant microorganisms	11 (22.4)	8 (27.6)	3 (15.0)	0.299

*indicates significant difference.

Table 2. Clinical and laboratory findings, treatment and outcome of patients with *Chryseobacterium* and *Elizabethkingia* infection.

	Total (*n*=49)	*Elizabethkingia* spp. (*n*=29)	*Chryseobacterium* spp. (*n*=20)	*P*
Infection site of patients, *n* (%)				
Bacteremia and sepsis	23 (46.9)	12 (41.4)	11 (55.0)	0.179
Central line-associated bloodstream infection (CLABSI)	14 (28.6)	12 (41.4)	2 (10.0)	
Ventilatory- associated pneumonia	5 (10.2)	2 (6.9)	3 (15.0)	
Urinary tract	3 (6.1)	1 (3.4)	2 (10.0)	
Skin-soft tissue	4 (8.2)	2 (6.9)	2 (10.0)	
Time between initiation of treatment and duration of fever, d, median (min-max)	2 (0-6)	2 (0-5)	1 (0-6)	0.447
Time to provide culture negativity, d	4 (2-9)	4 (2-8)	5 (2-9)	0.153
Median central venous catheter time, d	28 (3-180)	28 (3-100)	27 (5-180)	0.850
Need for catheter removal, *n* (%)	16 (32.7)	13 (44.8)	3 (15.0)	0.029*
Duration of the treatment, d	12 (4-24)	12 (4-24)	10 (10-16)	0.334
Time to clinical improvement, d	3 (1-12)	3 (1-7)	5 (2-12)	0.044*
Initial C-reactive protein value, mg/dL	32.4 (3-52)	38.8 (3-64)	18.6 (2-39)	0.004*
Initial leukocyte count, mm	4 280 (350-19 550)	3 260 (350-19 080)	6 355 (1 710-19 550)	0.022*
Initial neutrophil count, mm	2 050 (40-16 000)	1 910 (40-16 000)	3 140 (700-15 080)	0.053

*indicates significant difference.

Chryseobacterium (28 days *vs.* 9.5 days, *P*=0.007). There were 42 (85.7%) patients with a history of antibiotic use in the last month, and the rate was significantly higher with *Elizabethkingia* infections (96.6% *vs.* 70.0%, *P*=0.009). A total of 31 (63.2%) patients had used carbapenem antibiotics in the last month, and this was again significantly more common with *Elizabethkingia* infections (*P*=0.005) (Table 1). There was no significant difference between the other antibiotic groups regarding infections due to the two microorganisms.

The body fluid specimens of the patients where *Elizabethkingia* and *Chryseobacterium* were isolated consisted of blood (*n*=37), endotracheal aspirate (*n*=5), urine (*n*=3), and pus (*n*=4). There was no CSF, sputum, or swab cultures among the isolates included in the study. Eleven patients (22.4%) had colonization with resistant microorganisms. Eight patients were colonized with carbapenem resistant *Klebsiella pneumoniae*, two with carbapenem resistant *Acinetobacter baumannii*, and one patient with carbapenem resistant *Pseudomonas aeruginosa*. Patient characteristics, underlying diseases and risk factors, which vary according to the microorganisms, are shown in Table 1.

3.2. Clinical manifestation, treatment and outcome

Fever was present in 38 (77.5%) patients, and 15 of these patients had febrile neutropenia. A nosocomial infection was found in 44 (89.7%) of the 49 patients. The clinical presentation was bacteremia and sepsis in 23 patients, central line-associated bloodstream infection (CLABSI) in 14 patients, ventilator-associated pneumonia in 5 patients, skin and soft tissue infection in 4 patients, and urinary tract infection in 3 patients. Two patients who had sepsis also needed circulatory support. *Elizabethkingia* was the causative agent in most (85.7%) CLABSI. The median central venous catheter duration was 28 (3-180) days. The catheter had to be removed during the infection in 16 patients, and this event was found to be significantly more common in *Elizabethkingia* infections (81.2%, 44.8% *vs.* 15.0%, *P*=0.029).

Median treatment duration was 12 (4-24) days. The duration of treatment varied according to the agent and the type of infection. The duration of treatment was 10 (4-15) days in bacteremia and sepsis, 14 (10-21) days in CLABSI, 14.5 (10-18) days in pneumonia, 16 (10-24) days in skin and soft tissue infection, and 10 days in urinary tract infection. Median time to clinical improvement was 3 (1-12) days and this was higher in *Chryseobacterium* infections (*P*=0.044). While median time to clinical improvement with treatment was longer in pneumonia (9 days) and skin and soft tissue infections (8 days), it was 3 days in the other infections. Median time to culture negativity was 4 (2-9) days. The median C-reactive protein level was 32.4 (3-52) mg/L and this value was significantly higher in *Elizabethkingia* infections (*P*=0.004). Median C-reactive protein levels were significantly higher in *Elizabethkingia* infections compared to *Chryseobacterium* infections (38.8 mg/L *vs.* 18.6 mg/L, *P*=0.004). The median leukocyte count was 4 280/mm^3 (350-19 550). The median neutrophil count was 2 050/mm^3 (40-16 000). Table 2 presents the clinical and laboratory findings, treatment, and outcome of patients with *Chryseobacterium* and *Elizabethkingia* infection.

Four patients could not receive treatment. Bacteremia and sepsis were most commonly treated with ciprofloxacin (14/23, 60.9%). TMP-SMX monotherapy (5/14, 35.7%) or combined (1/14, 7.1%) treatment was frequently used in the treatment of CLABSI. Ciprofloxacin was the second most frequently used treatment for CLABSI (4/14, 28.6%). TMP-SMX therapy (single and combined therapy) was the most commonly used treatment in pneumonia (3/5, 60.0%). Ciprofloxacin monotherapy was used for all urinary tract infections. In skin and soft tissue infections, vancomycin and ciprofloxacin monotherapy or combination treatment was administered. Considering the treatment of all patients, the most commonly used antibiotic was ciprofloxacin (25/49, 51.0%) (22/49, 44.9% ciprofloxacin alone and 3/49, 6.1% in combination with vancomycin). TMP-SMX was given by itself at a rate of 14.3% (7/49) and in combination with ciprofloxacin in 6.1% (3/49). The other antibiotics used were vancomycin (5/49, 10.2%), cefepime (2/49, 4.1%), teicoplanin (2/49, 4.1%), and piperacillin-tazobactam (1/49, 2.0%). Combination therapy was used when there was no clinical improvement after 48-72 hours of monotherapy.

The 30-day mortality rate was 12.2% (*n*=6). Infection-related death occurred in 4 *Elizabethkingia* infections and 2 *Chryseobacterium* infections. Four patients died before effective treatment for *Elizabethkingia* and *Chryseobacterium* could be started although they had already received broad-spectrum empirical treatment. The underlying disease was a malignancy in 4 patients and cardiovascular disease in 2 patients. Four patients had bacteremia, sepsis, or catheter-related bloodstream infection, while one patient had ventilator-associated pneumonia and one patient had skin infection of the surgical site. The infection site, underlying diseases, antibiotic treatments in the last month, and colonization with resistant microorganisms were not related to mortality. Four patients were on mechanical ventilation, 5 patients had urinary catheters, and 4 patients had undergone surgery in the last month.

3.3. Bacterial isolates, antimicrobial susceptibility

Of the 49 cases, 29 (59.2%) were identified as *Elizabethkingia* and 20 (40.8%) as *Chryseobacterium*. While 3 (15.0%) of the *Chryseobacterium* species were *C. gleum*, 17 (85.0%) were *C. indologenes*. Antibiotic susceptibility of the *Elizabethkingia* and

Chryseobacterium species is shown in Table 3. According to these findings, *Elizabethkingia* and *Chryseobacterium* spp. were found to be susceptible to ciprofloxacin in 91.8% (45/49), TMP-SMX in 91.6% (44/48), and levofloxacin in 87.5% (21/24). When the evaluations of antibiotic susceptibility were performed separately for *Chryseobacterium* and *Elizabethkingia*, *Chryseobacterium* isolates seemed to be more susceptible than *Elizabethkingia* isolates to cefepime, ceftazidime, gentamicin, imipenem and piperacillin-tazobactam and tetracycline. *Elizabethkingia* isolates were resistant to amikacin, netilmicin, gentamicin, and piperacillin-tazobactam, and weakly sensitive to cephalosporins and carbapenems.

Table 3. Antimicrobial susceptibility rates of *Chryseobacterium* and *Elizabethkingia* isolates [*n* (%), *N*=49)].

Antibiotics	*Elizabethkingia*	*Chryseobacterium*	*P*
Aztreonam			-
Sensitive	-	-	
Resistant	2 (100.0)	13 (100.0)	
Cefepime			0.029
Sensitive	2 (7.1)	6 (31.6)	
Resistant	26 (92.9)	13 (68.4)	
Ceftazidime			0.001
Sensitive	1 (3.7)	8 (42.1)	
Resistant	26 (96.3)	11 (57.9)	
Ciprofloxacin			0.690
Sensitive	27 (93.1)	18 (90.0)	
Resistant	2 (6.9)	2 (10.0)	
Gentamicin			0.040
Sensitive	-	3 (15.8)	
Resistant	25 (100.0)	16 (84.2)	
Imipenem			0.023
Sensitive	1 (6.7)	6 (42.9)	
Resistant	14 (93.3)	8 (57.1)	
Meropenem			0.545
Sensitive	3 (12.0)	1 (6.3)	
Resistant	22 (88.0)	15 (93.7)	
Levofloxacin			0.642
Sensitive	10 (90.9)	11 (84.6)	
Resistant	1 (9.1)	2 (15.4)	
Netilmicin			0.523
Sensitive	-	1 (7.7)	
Resistant	5 (100.0)	12 (92.3)	
Piperacillin-tazobactam			0.010
Sensitive	-	4 (22.2)	
Resistant	27 (100.0)	14 (77.8)	
Tetracycline			0.129
Sensitive	1 (14.3)	5 (50.0)	
Resistant	6 (85.7)	5 (50.0)	
Tobramycin			0.423
Sensitive	1 (50.0)	3 (23.1)	
Resistant	1 (50.0)	10 (76.9)	
Amikacin			0.240
Sensitive	-	1 (5.0)	
Resistant	27 (100.0)	19 (95.0)	
Trimethoprim-sulfamethoxazole			0.090
Sensitive	25 (86.2)	19 (100.0)	
Resistant	4 (13.8)	-	

4. Discussion

Elizabethkingia and *Chryseobacterium* species are rare, emerging, aerobic, Gram-negative bacteria that cause nosocomial infections, and data on these species in the pediatric population is scarce. To our knowledge, this is the largest pediatric data reported, with 49 patients[3–6,11–21]. During the 5-year period of the SENTRY Surveillance Program (1997-2001), which showed the results of 50 cultures with *Elizabethkingia* and *Chryseobacterium* spp., only 0.03% (50/155 811) of all bacterial isolates in children and adolescents were found to be *Chryseobacterium* and *Elizabethkingia* spp[11]. Our hospital is the biggest tertiary pediatric hospital in Turkey, and we identified 49 patients with symptomatic disease due to *Elizabethkingia* and *Chryseobacterium* spp. in eight years. *Elizabethkingia* and *Chryseobacterium* infections were also uncommon in our study.

In the 1944-2017 review of Dziuban *et al.* on pediatric patients with *E. meningoseptica* infections, 76% were neonates and 34.6% of the cases were part of an outbreak cluster[2]. Similarly, 30% of the patients were neonates in the study of Chan *et al*. with 13 pediatric invasive *E. meningoseptica* infections between 2010 and 2017[20]. Contrary to most previous data, our study reported only two neonatal patients and there were no outbreaks or clusters. The median age was 14 months in the current study, and was similar to the study showing bacteremias in children due to *C. indologenes* and *E. meningoseptica*[4]. In the study of Alyami *et al*., in which *Chryseobacterium/Elizabethkingia* spp. infections were reviewed recently, the rate of newborns among the pediatric patients was similar to our study (1/11), although the number of patients was limited[17].

In the SENTRY study, 52% of the isolates were from the respiratory tract, 46% from the bloodstream isolates, and only one from skin and soft tissue[11]. In our study, only 10.2% of the samples were from the respiratory tract, 75.5% from the bloodstream, 8.2% from skin and soft tissue, and 6.1% from the urinary tract. Some studies have shown that *Chryseobacterium* and *Elizabethkingia* spp. can be rapidly cleared by the immune system when introduced into the bloodstream or respiratory tract of a healthy human host[11,17]. This difference in results may be related to the fact that our study was generally conducted with pediatric patients who had an underlying disease.

Consistent with previous studies, most (89.8%) patients had an underlying disease, an indwelling device, history of recent surgery, and previous treatment with broad-spectrum antibiotics in the last month[3,4,6,17]. Our carbapenem resistance rate was high, similar to previous data[3,10]. In support of previous data, our results show that

the use of carbapenem group antibiotics was significantly higher in the last month and the TMP-SMX prophylaxis rate was significantly higher in *Elizabethkingia* infections.

Chryseobacterium and *Elizabethkingia* spp. infections were more common in long-term hospitalized patients[3,16]. The majority of the patients in the current study were hospitalized in the hematology-oncology services with a diagnosis of malignancy, and infections were frequently nosocomial with a median duration of hospitalization before infection of 25 days. These characteristics were more prominent in *Elizabethkingia* infections.

The treatment of *Elizabethkingia* and *Chryseobacterium* infections is challenging and there has been no consensus on the optimal antimicrobial therapy. They are resistant to most antibiotics used to treat Gram-negative bacteria, such as carbapenems, cephalosporins, and aminoglycosides[2–5]. However, they have shown susceptibility to agents used to treat Gram-positive infections. Rifampin has shown activity *in vitro* against *Elizabethkingia* and *Chryseobacterium* spp. and is usually used in combination with vancomycin[11, 22]. Vancomycin and rifampicin were not tested in our results. According to the SENTRY Antimicrobial Surveillance Program between 1997 and 2001, antibiotic susceptibility varies according to regions but susceptibility to the new quinolones, rifampin, TMP-SMX, ciprofloxacin and piperacillin-tazobactam was high while vancomycin showed poor potency[11]. Güngör *et al*. have reported that all their isolates in the outbreak were susceptible to ciprofloxacin *in vitro* but 3 patients did not respond to ciprofloxacin therapy. These patients survived when they switched the therapy to vancomycin and rifampin[21]. Vancomycin and ciprofloxacin monotherapy or combined treatments were used for skin and soft tissue infections in the current therapy. Chen *et al*. have demonstrated that all the *Elizabethkingia* spp. isolates were susceptible to piperacillin tazobactam and showed variable susceptibility to trimethoprim/sulfamethoxazole (78.6%), ciprofloxacin (33.3%), and levofloxacin (87.5%)[5]. In the study of Cooper *et al*. on children with *C. indologenes* and *E. meningoseptica* bacteremia, the bacteria were found to be highly sensitive to piperacillin tazobactam, TMP-SMX, and ciprofloxacin[4]. On the contrary, all *Elizabethkingia* isolates were resistant to piperacillin/tazobactam in our study while *Chryseobacterium* had low sensitivity, and ciprofloxacin had the highest potency. The majority of our patients were treated with ciprofloxacin, TMP-SMX, or a combination thereof, and most isolates were susceptible to those antibiotics. Our study suggests that ciprofloxacin and TMP-SMX use is adequate.

In previous studies, the mortality rates of *C. indologenes* and *E. meningoseptica* infections were high and variable. Such variable mortality rates have been reported (6.3%-31.4%), especially in studies where newborns were in the majority and had higher mortality rates[3,4,6,12–15,17,20,23]. Although most of our patients had a favorable outcome, the mortality rate in our study was significant. Only two patients were newborns and most of the deaths occurred before the culture was concluded and before effective antibiotic treatment could be started. The decreased mortality in more recent cases may be due to newer antibiotic options, increasing use of antimicrobial susceptibility testing, or differences in delay to diagnosis over time. Our relatively low mortality rates may be due to early and appropriate antimicrobial therapy, low number of newborn patients, and taking more cultures, as the majority were patients with malignancies.

This study has several limitations. Although the number of patients was higher than in the previous studies, the study is limited by its retrospective nature.

In summary, *Elizabethkingia* and *Chryseobacterium* infections are rare and nosocomial, and not necessarily part of outbreaks. The surveillance of *Chryseobacterium* and *Elizabethkingia* infections is still very important, and the clinicians should be aware of the changing epidemiology and increasing resistance of these microorganisms. To our knowledge, our study has the largest number of cases in pediatric patients. In addition, although *Elizabethkingia* and *Chryseobacterium* are different genera, we chose to include both in this study since they are in the same family and share common features, and also aimed to reveal any differences by comparing their clinical and laboratory features and antimicrobial susceptibilities with each other. Our study is one of the rare studies comparing these two agents. These infections are associated with younger age, but the majority of our cases were older than the neonatal period. They are mainly seen in patients with long hospital stays and indwelling devices (especially a central venous catheter) and in patients who have received antibiotics within the last month, especially carbapenems. They are resistant to most empirical antibiotics, and the best antibiotics are ciprofloxacin and TMP-SMX according to the resistance patterns.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Authors' contributions

AY contributed to the study conception and design. AY, G B implemented the study. AY, G B, AYG, BG, SKY, SÖ, TE, KK and AÖP analyzed and interpreted the data. AY and G B revised the work critically for intellectual content and granted final approval for publishing. All authors have reviewed the manuscript and consent was given to publish.

References

[1] García-López M, Meier-Kolthoff JP, Tindall BJ, Gronow S, Woyke T, Kyrpides NC, et al. Analysis of 1000 type-strain genomes improves taxonomic classification of *Bacteroidetes*. *Front Microbiol* 2019; **10**: 2083.

[2] Bender JM, Fisher RG. *Elizabethkingia* and *Chryseobacterium* species. In: Cherry J, Demmler-Harrison GJ, Kaplan SL, Steinbach WJ, et al, eds. *Feigin and Cherry's textbook of pediatric infectious diseases.* 8th ed. Philadelphia, PA: Elsevier Saunders Company; 2018, p. 1132-1134.

[3] 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): 144-149.

[4] Cooper S, Levy I, Ben-Zvi H, Ashkenazi-Hoffnung L, Ben-Shimol S, Shachor-Meyouhas Y, et al. Flavobacteriaceae bacteremia in children: A multicenter study. *Pediatr Infect Dis J* 2019; **38**(11): 1096-1099.

[5] Chen FL, Wang GC, Teng SO, Ou TY, Yu FL, Lee WS. Clinical and epidemiological features of *Chryseobacterium indologenes* infections: Analysis of 215 cases. *J Microbiol Immunol Infect* 2013; **46**(6): 425-432.

[6] Aykac K, Ozsurekci Y, Tuncer O, Sancak B, Cengiz AB, Kara A, et al. Six cases during 2012-2015 and literature review of *Chryseobacterium indologenes* infections in pediatric patients. *Can J Microbiol* 2016; **62**(10): 812-819.

[7] Dani A. Colonization and infection. *Cent European J Urol* 2014; **67**: 86-87.

[8] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third ınternational consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; **315**(8): 801-810.

[9] Centers for Disease Control and Prevention (CDC). *Identifying Healthcare Associated Infections (HAI) for NHSN Surveillance.* [Online]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/2psc_identifyinghais_nhsncurrent.pdf. [Access on 18 October 2022].

[10]Clinical Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing: Twenty–fifth informational supplement M100–S25.* Wayne, PA: CLSI; 2015, p. 54.

[11]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): 445-448.

[12]Aydin Teke T, Oz FN, Metin O, Bayhan GI, Gayretli Aydin ZG, Oguz M, et al. *Chryseobacterium indologenes* septicemia in an infant. *Case Rep Infect Dis* 2014; **2014**: 270521.

[13]Corbella M, Brandolini M, Cambieri P, Decembrino N, Pagani M, Bottazzi A, et al. A catheter-related bloodstream infection caused by *Chryseobacterium indologenes* successfully treated with antibiotic-lock rescue therapy. *New Microbiol* 2017; **40**(3): 223-225.

[14]Ceylan A, Güdücüoğlu H, Akbayram S, Bekta A, Berktaş M. Sepsis caused by *Chryseobacterium indologenes* in a patient with hydrocephalus. *Mikrobiyol Bul* 2011; **45**(4): 735-740.

[15]Mehta R, Pathak A. Emerging *Chryseobacterium indologenes* infection in Indian neonatal intensive care units: A case report. *Antibiotics (Basel)* 2018; **7**(4): 109.

[16]Ceyhan M, Celik M. *Elizabethkingia meningosepticum* (*Chryseobacterium meningosepticum*) infections in children. *Int J Pediatr* 2011; **2011**: 215237.

[17]Alyami AM, Kaabia NM, AlQasim MA, Al Doghaim FS, Albehlal LB, Ahmed MA, et al. *Chryseobacterium/Elizabethkingia* species infections in Saudi Arabia. *Saudi Med J* 2020; **41**(3): 309-313.

[18]Srinivasan G, Muthusamy S, Raveendran V, Joseph NM, Easow JM. Unforeseeable presentation of *Chryseobacterium indologenes* infection in a paediatric patient. *BMC Res Notes* 2016; **12**(9): 212.

[19]Erinmez M, Büyüktas Manay A, Zer Y. Investigation of an outbreak of *Elizabethkingia meningoseptica* on a pediatric intensive care unit. *GMS Hyg Infect Control* 2021; **16**: 19.

[20]Chan JC, Chong CY, Thoon KC, Tee NWS, Maiwald M, Lam JCM, et al. Invasive paediatric *Elizabethkingia meningoseptica* infections are best treated with a combination of piperacillin/tazobactam and trimethoprim/sulfamethoxazole or fluoroquinolone. *J Med Microbiol* 2019; **68**(8): 1167-1172.

[21]Güngör S, Ozen M, Akinci A, Durmaz R. A *Chryseobacterium meningosepticum* outbreak in a neonatal ward. *Infect Control Hosp Epidemiol* 2003; **24**(8): 613-617.

[22]Wang L, Zhang X, Li D, Hu F, Wang M, Guo Q, et al. Molecular characteristics and antimicrobial susceptibility profiles of *Elizabethkingia* clinical ısolates in Shanghai, China. *Infect Drug Resist* 2020; **13**: 247-256.

[23]Paul SP, Heaton PA. *Chryseobacterium indologenes* bacteraemia: A potential cause of early-onset neonatal sepsis in a full-term baby. *J Coll Physicians Surg Pak* 2022; **32**(4): 535-537.

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