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Elizabethkingia in Children: A Comprehensive Review of Symptomatic Cases Reported from 1944–2017

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Abstract

Elizabethkingia species often exhibit extensive antibiotic resistance and result in high morbidity and mortality, yet no systematic reviews exist that thoroughly characterize and quantify concerns for infected infants and children. We performed a review of literature and identified an initial 902 articles; 96 articles reporting 283 pediatric cases met our inclusion criteria and were subsequently reviewed. Case reports spanned 28 countries and ranged from 1944 to 2017. Neonatal meningitis remains the most common presentation of this organism in children, along with a range of other clinical manifestations. The majority of reported cases occurred as isolated cases, rather than within outbreaks. Mortality was high but has decreased in recent years, although neurologic sequelae among survivors remains concerning. Child outcomes can be improved through effective prevention measures and early identification and treatment of infected patients.

Keywords

Elizabethkingia ; *Chryseobacterium* ; *Flavobacterium* ; children; emerging infectious diseases

Introduction

Elizabethkingia species were first described by Elizabeth O. King at the Communicable Disease Center (CDC, now Centers for Disease Control and Prevention) in 1959. The genus was previously classified as *Flavobacterium* and then reclassified in 1994 as *Chryseobacterium* before receiving its current taxonomic designation in 2005. They are non-glucose-fermenting, nonmotile, catalase- and oxidase-positive gram-negative rods ubiquitous in the environment that can colonize hospital environmental surfaces, and are known to

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be widely resistant to many classes of antibiotics. They can colonize human hosts but also cause symptomatic disease in adults such as pneumonia, meningitis, and endocarditis [1]. Adult disease typically occurs in people who are immunocompromised, with a high mortality rate reported [2]. *E. meningoseptica* (formerly *F. meningosepticum* and then *C. meningosepticum*) is particularly known to cause neonatal sepsis and meningitis, especially in premature newborns, sometimes leading to outbreaks in neonatal intensive care units (NICUs) [3]. The other named species of the genus—*E. anophelis*, *E. endophytica*, and *E. miricola*—are less common as reported sources of pediatric infection. However, recent literature suggest that many previous cases reported as *E. meningoseptica* were actually *E. anophelis* as these two species are difficult to differentiate by traditional microbiological methods [4]; whether *E. endophytica* is a distinct species is currently in question [5].

Two unrelated outbreak clusters of *Elizabethkingia* spp. occurring in the Midwest United States among adults were recently reported in Illinois and Wisconsin, shepherding new attention to this pathogen [6,7]. A neonatal case occurred in the same period and was described in news accounts yet was not associated with these outbreak clusters, as demonstrated by genetic sequencing [8]. Little knowledge exists regarding infants' specific risks and needs, which is concerning given the elevated morbidity and mortality observed among neonatal cases of *Elizabethkingia.* Although a small number of reviews concerning this pathogen have been published in recent years, they have either not focused specifically on children [3] or did not employ a systematic review protocol [9]. In order to increase understanding of pediatric outbreak clusters and assist pediatric providers in being prepared for cases of this rare infection, we reviewed and characterized all cases of *Elizabethkingia* in children reported in the scientific literature dating back to the first instances of the bacterium's isolation.

Methods

In order to identify studies that examine case reports of *Elizabethkingia* spp. in pediatric patients, we performed a systematic review [10] of the peer-reviewed and gray literature tailored to four electronic databases (PubMed, Scopus, Embase, and Global Health) using title, abstract, keyword, and Medical Subject Headings (MeSH) terms (see Supplemental Appendix 1 for search strategies and limits used). The reference lists of all papers were also reviewed for inclusion of additional reports. Following abstraction of the original set of papers in May 2016, we duplicated our search strategy in February 2017 to account for new papers published in the interim.

Inclusion/exclusion criteria

Papers were included if they reported on at least one human pediatric symptomatic infection (i.e., less than 18 years old) with bacteria currently classified as *Elizabethkingia* spp. Given the evolving taxonomy of *Elizabethkingia* spp. [5], we also examined studies that reported on cases of *Flavobacterium meningosepticum* and *Chryseobacterium meningosepticum*. Notably, we excluded studies in which the infectious organism was only specified to the genus level (e.g., *Flavobacterium spp.*) for genera other than *Elizabethkingia*. Only English-

language papers were considered. No restrictions based on publication date or date of diagnosis were applied.

Reviews, commentaries, and other papers that described only non-primary data sources were excluded from data extraction to reduce the threat of duplicate publication bias, but we did examine their reference lists for additional articles. In some instances, papers contained some cases that we included because they were novel and others that we excluded because they had already been reported elsewhere; reviewers extracted data from the oldest reference.

Cases of colonization with *Elizabethkingia* spp. bacteria without clinical symptoms of infection were excluded, and only symptomatic cases from those papers, if any, were abstracted. Adult case reports of *Elizabethkingia* infection and non-human studies (e.g., analyses of microbiological isolates, animal studies) were all excluded.

Study selection

Once all identified bibliographic records from the four electronic databases were consolidated, with duplicates removed, the list of papers was divided evenly between two reviewers (MS and JLF) and another reviewer (EJD) separately reviewed all of them. These reviewers independently screened titles and abstracts using the aforementioned eligibility criteria, and iteratively discussed points of confusion. Finally, additional papers identified from reference lists during the data extraction process described below or additional searches were also subject to screening for inclusion criteria.

Data extraction

For the included papers, two reviewers (EJD and MS, JLF, or DB) independently extracted data by a standardized process, with discussions to resolve discrepancies on study parameters. The following information was extracted from each paper: publication year, country (and state, if U.S.), number of pediatric cases, age and sex of cases, clinical presentation, bacterial species, and outcomes of cases (recovered, died, or unknown). Reports were studied to identify which cases were documented as outbreak clusters and further describe those settings. For children who recovered from infection, reviewers noted documentation and descriptions of complications. For children who did not recover from infection, the number of days from onset of symptoms until death was recorded, if reported. If patients were reported to leave against medical advice, their outcome was classified as unknown. Notably, it was sometimes not possible to link unique cases with their respective outcomes due to how findings were reported in each paper. We opted not to assess information pertaining to antibiotic treatment, as this would likely be more of a function of evolving treatment options over time rather than information of clinical value.

No individual or cumulative assessments for risk of bias (e.g., selection, reporting, performance biases) among included papers were conducted.

Analytic approach

All included studies were entered into a database, and basic descriptive statistics were generated. We did not perform extensive analyses to determine statistically meaningful differences between groups, due to inconsistencies in reporting observations. The two exceptions were determining whether there were differences in mortality before vs. after 1990 (which was evaluated with Wilcoxon rank-sum tests) and whether there were differences in likelihood of death across age groups among patients with known outcomes (evaluated using Fisher's exact tests). These tests were selected after determining that the dataset was not normally distributed.

Results

Overall findings

A total of 902 articles were retrieved from the initial May 2016 search (Figure 1). Five additional papers were identified during the abstraction process by examining the reference lists of included articles, and 14 papers were identified during the February 2017 iteration of the original search.

Ninety-six reports describing 283 cases of *Elizabethkingia* infection in children met our inclusion criteria and were subsequently analyzed (Supplemental Appendix 2). Over three-quarters of cases were in neonates (less than one month of age), with smaller numbers in infants (one month to less than one year of age), children (one year to less than 18 years of age), and children of unknown age (Table 1). Of the 178 (62.9%) cases for which sex was reported, 97 (54.5%) were in males and 81 (45.5%) in females.

For 98 cases (34.6%), there was reported evidence demonstrating that cases were part of an outbreak cluster. In total, 19 different outbreak clusters were described across 15 published reports, some exclusively in children and others including adults as well. Some clusters included colonized patients; however, the majority of the literature did not distinguish exposures or risk factors between colonized and symptomatic cases. Thirteen of the 15 reports (86.7%) describe cases in NICU or related settings (e.g., postnatal hospital nurseries). Another report described three outbreak clusters in the same pediatric hospital, with an index case from the NICU and spreading across five different units [11]. The remaining report described an outbreak in an intensive care unit where all affected patients (all but one being adults) were on bedside hemodialysis [12]. The remaining 185 (65.4%) cases occurred sporadically, or at least did not have reported evidence of connection to any outbreak cluster. In one case there was evidence of perinatal or intrauterine transmission [13].

Nearly all cases (277 [97.9%], from 92 reports) were described as *E. meningoseptica*. We identified only three reports of *E. anophelis* in children, representing five cases, all in reports since 2013. All but one occurred in Hong Kong; the other occurred in the Central African Republic, which also had a second case report of *E. anophelis* in a child but which was not included because the report was not in English [14,15]. All included cases of *E. anophelis* were in newborns and two (40%) died. There was only one identified pediatric case of *E.*

miricola: a two-year-old child in Switzerland with a urinary tract infection whose outcome was not reported [16].

Time and location

Cases were described starting with a 1959 article identifying the new *E. meningoseptica* species (then *F. meningosepticum*), and retrospective analysis identified cases published back to 1944. A report of neonatal meningitis from 1922 was later postulated to potentially be *Elizabethkingia* species, but was not included because this identification was never confirmed [17,18]. Every decade from the 1940s onward included reported cases, with more pediatric cases reported after 2010 than in any previous decade despite the fact that our analysis included only papers published through February 2017. Analyzing the 47 reports (165 children) published prior to 1990 compared to the 49 reports (118 children) following, there is higher reported mortality prior to 1990 among all children with known outcomes (47.1% vs. 26.4%, $p<0.001$), with a similar result when limiting the comparison to neonates only (51.2% vs. 31.0%, $p=0.004$) or when including all children with any known or unknown outcome in the denominator (40.0% vs. 19.5%, $p<0.001$).

Reports originated in 28 countries. The United States had the largest number (71 cases from 23 reports), followed by India (35 cases from 14 reports), Taiwan (35 cases from nine reports), and Malaysia (32 cases from four reports). There were cases from all six inhabited continents, with the majority (165, 58.3%) arising from Asia. The 71 U.S. cases originated from 16 states and Puerto Rico. Local context of cases and outbreak clusters were described for some reports, including several originating from healthcare settings, but these data were reported inconsistently and could not be adequately quantified for this review.

Clinical presentation

Clinical presentation was described for 275 (97.2%) cases. Two hundred nine (73.9%) presented with meningitis. Sixty-seven (23.7%) presented with sepsis (with some overlap with diagnoses of meningitis), with 20 (7.1%) other cases having report of bacteremia. Symptoms at presentation included expected findings of meningitis or sepsis, including fever, lethargy, cyanosis, and apneic episodes. Forty-four (15.5%) were noted to have seizures and 19 (6.7%) with jaundice. Nineteen (6.7%) were reported to present with pneumonia, and seven (2.5%) with gastroenteritis or diarrhea, with bloody diarrhea in one case [19]. Other presentations less frequently reported were ventriculitis, pneumothorax, cellulitis, septic arthritis, urinary tract infection, peritonitis, sinusitis, and subdural abscess. Only one report described a rash, which was pustular and covered the genital region of the neonate, but it is unclear whether this was related to the *Elizabethkingia* infection [20]. Three cases had inflammatory eye findings described (conjunctivitis, discharge) while another had keratitis and corneal ulcer as the presenting infection in a teenaged wearer of contact lenses [21]. A number of cases, particularly nonneonatal ones, occurred in children with pre-existing medical conditions leading to immune suppression (e.g., leukemia, liver transplant), exposure to extensive invasive procedures (e.g., abdominal surgeries, shunt placements, peritoneal dialysis), or prolonged hospitalizations that increased exposure time to hospital-acquired infections, and some attributed the source of infection to hospital water supplies or medical equipment [22,23]. However, some cases were noted to be community-

acquired [24–26] or even foodborne [27] infections, and a number of cases occurred in previously healthy children without known risk factors.

Outcomes

Among the 283 cases, 56 (19.8%) had an unknown outcome. Of the remainder, 138 were reported to have survived: 48.8% of all cases, and 60.8% of those with known outcome. Of these 138 known survivors, 66 (47.8%) were reported to have recovered completely with typical development, although length of follow-up was varied. Of the remaining surviving children, forty-two (30.4% of all survivors) were reported to have developed hydrocephalus following their infection, excluding a small number of cases where hydrocephalus was present prior to *Elizabethkingia* infection. Some additional cases had further details reported about the sequelae of infection, such as motor or cognitive deficits, spasticity, or ongoing seizures. At least nine (6.5%) surviving children had some degree of hearing loss specifically reported as a sequela. Nineteen (13.8%) surviving children did not have any further information on their outcomes.

Among all cases, 89 (31.4%) children were reported to die prior to recovery from *Elizabethkingia* infection; rates of death were different across age groups with highest mortality observed among neonates relative to all other age categories (37.7%; p=0.006) (Table 1). Of 45 (50.6%) cases where time from onset of symptoms to death was reported, the range was one to 192 days, with a mean of 27.7 days and median of 16 days.

Discussion

This review captures all identified cases of *Elizabethkingia* infection in children published in the English language literature, providing the most current source of information regarding the clinical aspects of this rare yet emerging infection. Numbers of reported cases are increasing in recent years, possibly associated with improved diagnostic capabilities in low-resource areas, and geographic distribution is widespread. Our results show that neonatal meningitis remains the most common presentation of this infection in children, but a variety of other clinical manifestations were also reported. *Elizabethkingia* infections in children are often fatal, and higher mortality than seen in this analysis has been described in earlier reviews [28,29]. Deaths were reported most commonly in our review among infected neonates, although some occurred among infected older children as well. The decreased mortality in more recent cases may be due to newer antibiotic options and increasing use of antimicrobial susceptibility testing, given the widespread antimicrobial resistance that frequently occurs in this genus; improved conditions of intensive care units; or differences in delay to diagnosis over time. However, the frequent reports of severe morbidity among survivors, especially hydrocephalus, developmental deficits, and hearing loss, also reinforce the importance of early identification and treatment before progression of neurologic damage can occur [3,26,30].

While outbreaks of *Elizabethkingia* spp. are concerning and can lead to poor outcomes, it is worth noting that the majority of cases reported in children occurred sporadically. Cases of *Elizabethkingia* spp. infection are typically avoidable, regardless of whether they are sporadic or in a cluster. Many cases were hospital-acquired infections from sources such as

water supplies or medical equipment, making this an important nosocomial infection. Many children in hospitals have immune systems weakened by intensive medical interventions, malnourishment, prematurity, or any of a number of other chronic or infectious conditions, and are vulnerable to opportunistic pathogens. Proper infection control protocols are essential to avoid contaminated sources introducing these bacteria to children who may be at greatest risk of disease.

Retrospective analysis of isolates from cases described as *E. meningoseptica* have shown many infections to have been caused by *E. anophelis*. Using newer advanced molecular identification techniques may provide further insights into clinical differences between these species and possibly identify *E. anophelis* as the causative agent in more pediatric infections [31]. The single case of *E. miricola* in a two-year old child with a urinary tract infection did not have a reported outcome, and more experience with this species will be necessary to determine its relative pathogenicity [16].

Several unusual presentations of *E. meningoseptica* in children have been reported that may be useful for clinicians to keep in mind. Gunnarsson, et al. reported a rare case in Iceland of a 17-year-old with septic arthritis following a puncturing injury to the knee [32]. A rare case of keratitis in Singapore was presented in a 14-year-old contact lens user, a condition previously reported in an adult [33]. Other unusual reports often occurred in immune-compromised children, such as sinusitis and bacteremia in a 16-year-old in the U.S. with Shwachman-Diamond syndrome [34] and a two-year-old in Singapore with acute lymphoblastic leukemia who developed septic shock from the bacteria after eating sushi [27]. Ratnamani and Rao described *E. meningoseptica* as an emerging nosocomial pathogen among patients on hemodialysis, including a three-year-old child [12].

Limitations and Strengths

Several limitations to this review merit consideration. As with any review, our selected protocol may have limited the full breadth of articles that could conceivably contain relevant case reports. Specifically, exclusion of studies written in non-English languages could result in our findings representing geographic bias and an undercount (we excluded 62 non-English articles out of 452 total reviewed reports). Another source of underestimation may have arisen from the several articles that we did not include due to a lack of explicit statement of our species of interest—for instance, those that described *Flavobacterium spp.* without specifying beyond the genus level.

The heterogeneity in reporting of clinical presentation and outcomes of patients may be a function of a variety of factors that is challenging to quantify, such as journal word limits or outcome reporting bias; patients may have experienced symptoms and sequelae that were not reported, and we often could not determine the temporality of events (e.g., pre-existing conditions). This limitation precluded us from investigating questions, such as the proportion of infected patients that were born premature or sustained permanent neurologic sequelae. Consistently reporting these types of features in future case reports of *Elizabethkingia* in children will improve understanding of these infections. Relatedly, it was not always possible to causally link outcomes with *Elizabethkingia* infection [35]. While clinical disease from *Elizabethkingia* infection in children is often severe, there were also reported

cases of asymptomatic colonization, even among neonates with *E. meningoseptica*, requiring no treatment and causing no sequelae [22,23]; this review was not intended to describe those cases. Finally, we acknowledge that included case reports may disproportionately represent locations with more resources (e.g., academic medical centers, NICUs, etc.) that could be more likely to have laboratory capacity to diagnose these infections and to seek dissemination of results in peer-reviewed outlets.

Although these limitations are notable, any other review protocol would be vulnerable to similar ones. To our knowledge, this is the first review that has investigated the literature on *Elizabethkingia* cases in pediatric patients using a systematic, reproducible protocol. Further, we note the strength of comprehensively including reported cases without restricting our search by geography, time, or evolving taxonomic classification. Further, although we were unable to identify gray literature that fulfilled our inclusion criteria, this review was not purposefully limited to peer-reviewed articles.

Conclusions

Elizabethkingia infections in children are often of high consequence and are associated with substantial morbidity and mortality, especially among neonates. In this review we identified pediatric cases, mostly sporadic but also in outbreak clusters, that go back over 70 years and span the globe, presenting predominantly as neonatal meningitis. We observed lower mortality in recent years, although neurologic sequelae among survivors remains concerning. More understanding of the evolving taxonomy of this genus is required to better characterize risks of individual species and target interventions appropriately.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points:

A comprehensive literature review of cases of *Elizabethkingia* infection in children characterizes the epidemiology, demographics, clinical presentation, and outcomes. Cases were reported from 1944–2017 (n=283) demonstrating high mortality that decreased in recent decades, and substantial morbidity among survivors, especially neonates.

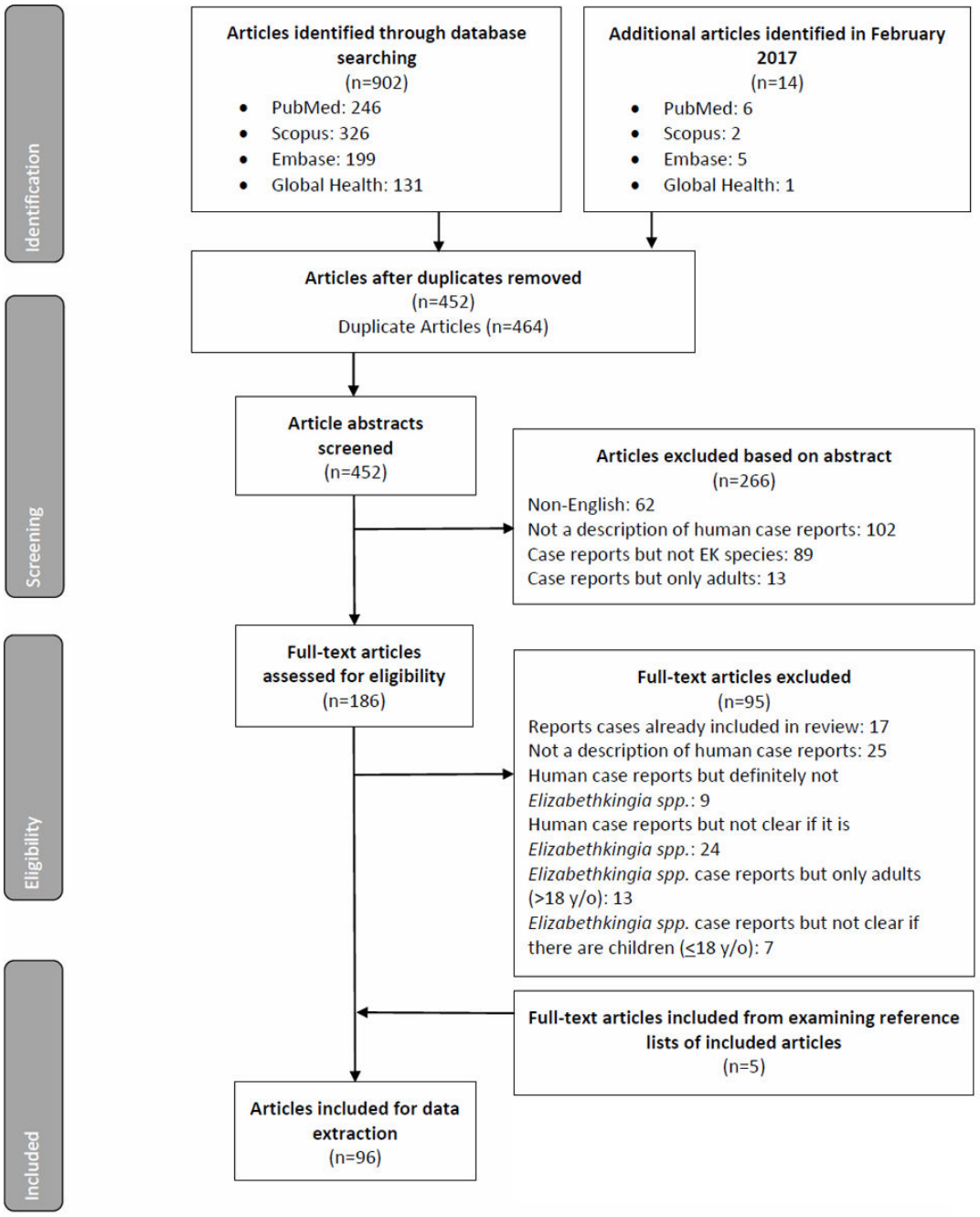

Figure 1.

PRISMA flowchart for review on *Elizabethkingia spp.* Infection in pediatric patients [10]

Note: Several articles fit multiple exclusion criteria, but only one main exclusion criterion was applied in accordance with a pre-determined exclusion hierarchy.

Table 1.

Reported outcomes of *Elizabethkingia spp.* case reports among patients aged 0–17 years reported in the peer-reviewed literature,[a] 1944–2017.

	Patient Outcomes, *N* (%)			Total
	Died	**Recovered**	**Unknown Outcome**	
Neonates (0–1 Months)	81 (37.7)	100 (46.5)	34 (15.8)	215 (76.0)
Infants (1–12 Months)	0 (0.0)	17 (94.4)	1 (5.6)	18 (6.4)
Older Children (1–17 Years)	6 (17.1)	18 (51.4)	11 (31.4)	35 (12.4)
Children of Unknown Age [a]	2 (13.3)	3 (20.0)	10 (66.7)	15 (5.3)
Total	89 (31.4)	138 (48.8)	56 (19.8)	283

[a] Includes cases from five studies reported to be in children <18 years of age but could not be categorized into a specific age category [36–40].