La bactériémie à *Edwardsiella tarda*. Une infection d’origine hydrique et alimentaire, mais fatale : analyse bibliographique et cas cliniques dans un seul centre

**BACKGROUND:** *Edwardsiella tarda* bacteremia (ETB) can be a fatal disease in humans.

**OBJECTIVES:** To determine the significant risk factors associated with death caused by ETB, and to examine the geographical, seasonal, environmental and dietary factors of the disease.

**METHODS:** A retrospective, observational, case control study was performed. The PubMed MEDLINE and Japanese Medical Abstract Society (www.jamas.or.jp) databases were searched for ETB case reports and meeting abstracts. In addition, retrospective chart reviews of patients with ETB at the Tokyo Women’s Medical University Hospital (Tokyo, Japan) were conducted to evaluate the risk factors associated with death using multivariate analyses.

**RESULTS:** The literature search yielded 46 publications, comprising 72 cases from the English (n=30), French (n=1), Spanish (n=1) and Japanese (n=14) literature. Five cases at the Tokyo Women’s Medical University Hospital were also included. Of the included 77 cases, the mean age was 61 years and 39% of patients were female; 77.2% of the cases occurred between June and November, and 45.5% were reported in Japan. Dietary factors (raw fish/meat exposure) were reported for 10.4% of patients and 12.9% reported environmental (ie, brackish water) exposure. The overall mortality rate was 44.6%; however, this rate increased to 61.1% for ETB patients with soft tissue infections. Liver cirrhosis was determined to be an independent risk factor associated with death (OR 12.0 [95% CI 2.46 to 58.6]; P=0.00213) using multivariate analyses.

**DISCUSSION:** To our knowledge, the present analysis was the first and largest multi-language review of ETB. Clinical characteristics of ETB resemble those of *Aeromonas*, typhoid fever and *Vibrio* vulnificus infections, in addition to sharing similar risk factors.

**CONCLUSION:** ETB should be categorized as a severe food- and waterborne infection, which results in high mortality for patients with liver cirrhosis.

**Key Words:** Bacteremia; *Edwardsiella tarda*; Foodborne infection; Food habits; Liver cirrhosis; Risk factors; Waterborne infection

---

*Edwardsiella tarda* is a motile, facultatively anaerobic, Gram-negative rod that is categorized as a member of the family Enterobacteriaceae. The genus *Edwardsiella* was first recognized by Trabulsi et al (1) in 1962, followed by a description of *E. tarda* in the mid-1960s. These organisms have subsequently been named the “Bartholomew group” by King and Adler (2), the “Asakusa group” by Sakazaki (3) and “Edwardsiella” by Ewing et al (4).

*E. tarda* is typically isolated from fresh or brackish water environments such as river mouths. It has also been isolated from the intestines of humans (after eating fresh water food sources such as catfish [5] or eels [6]) and from animals, including reptiles and freshwater fish.

*E. tarda* rarely causes infections in humans. The colonization rate in humans ranges from 0.0073% in the Japanese (7) to 1% in Panamanians (8). Approximately 80% of *E. tarda* infections in humans are characterized
as gastroenteritis and E. tarda is primarily isolated from stool samples. Extraintestinal infections, such as endocarditis, empyema, hepatobiliary infections, peritonitis, intra-abdominal abscesses, osteomyelitis, wound infections and meningitis, have been reported less frequently.

While E. tarda bacteremia (ETB) occurs relatively rarely (<5%), it can be fatal in humans (9). However, little is known about the clinical epidemiology of ETB. Therefore, we aimed to document the clinical epidemiology of ETB, including independent risk factors associated with death, the geographical and seasonal distributions, as well as environmental and dietary risks, based on previous reports and recent clinical cases of ETB at our institution (Tokyo Women’s Medical University [TWMU] Hospital [Tokyo, Japan]).

**METHODS**

A retrospective, observational, case control study was performed. The present analysis comprised literature and retrospective chart reviews. A search was conducted for case reports and case series involving ETB, published between January 1968 and December 2013, with the PubMed MEDLINE and Japanese Medical Abstracts Society ICHUSHI (www.jamas.or.jp) databases using the following keywords: “Edwardsiella tarda”, “E. tarda” and “infection”. An episode of ETB was defined as ≥1 positive blood cultures yielding E. tarda from the same patient. Results meeting the following criteria were included: published case reports or abstracts from scientific meetings; patients of any age; and articles published in any language including English, French, Spanish and Japanese. Exclusion criteria included: negative blood culture; no description of E. tarda infection; animal cases; experimental studies; and review articles.

In addition, the medical records of patients, regardless of age, with ETB admitted to the TWMU (a 1423-bed university hospital in Tokyo, Japan) between April 2000 and December 2013, were included in the retrospective chart review.

The following data were obtained from both published and TWMU-admitted cases that fulfilled the inclusion criteria: age; sex; underlying disease; antibiotic treatment; complications related to the ETB; geographical area; month of ETB onset; history of exposure to antimicrobial agents; behavior/dietary risk factors; and period of time from onset to patient dying.

**TABLE 1**

**Clinical characteristics of 77 patients with Edwardsiella tarda bacteremia (ETB)**

| Cases, n | Overall n (%) | Survived, n | Died, n | Univariate analysis | Multivariate analysis |
|----------|---------------|-------------|---------|---------------------|----------------------|
| **Age, years, mean (range) OR mean ± SD** | 77 | 44 | 33 | | 0.75 |
| >65 years of age | 31 (40.3) | 17 | 14 | 0.818 |
| <1 year of age | 6 (7.8) | 3 | 3 | 1 |
| Female sex | 30 (39.0) | 20 | 10 | 0.166 |
| **Underlying diseases** | | | | | |
| Cancer | 29 (37.7) | 13 | 16 | 1 |
| Hepatobiliary cancer | 17 (22.1) | 6 | 11 | 0.0531 |
| Gastric/colon cancer | 5 (6.5) | 3 | 2 | 1 |
| **Noncancer** | | | | | |
| Liver cirrhosis | 13 (16.9) | 2 | 11 | 0.000567 |
| Gallbladder stone, cholecystitis | 21 (27.3) | 16 | 5 | 0.0434 |
| Diabetes | 7 (9.1) | 2 | 5 | 0.131 |
| **Complication of ETB** | | | | | |
| Meningitis | 4 (5.2) | 1 | 3 | 0.308 |
| Liver abscess | 10 (13.0) | 7 | 3 | 0.502 |
| Diarrhea | 19 (24.7) | 13 | 6 | 0.295 |
| Soft tissue infection | 18 (23.4) | 7 | 11 | 0.103 |
| Intrauterine infection | 3 (3.9) | 3 | 0 | 0.3498 |
| No complication | 35 (45.5) | 21 | 14 | 0.817 |
| **Antimicrobial agents** | | | | | |
| Penicillins | 19 (24.7) | 12 | 7 | 0.398 |
| Cephalosporins | 26 (33.8) | 15 | 11 | 0.781 |
| Carbapebens | 8 (10.4) | 4 | 4 | 1 |
| Others (eg, aminoglycosides) | 16 (20.8) | 10 | 6 | 0.104 |
| **Behavior/dietary risk factors** | | | | | |
| Alcoholism | 5 (6.5) | 3 | 2 | 1 |
| Exposure | | | | | |
| To raw food | 8 (10.4) | 6 | 2 | 0.454 |
| To fresh or marine water, animal feces | 10 (13.0) | 6 | 4 | 1 |
| **Geographical area** | | | | | |
| Japan | 35 (45.5) | 19 | 16 | 0.653 |
| United States (US) | 12 (15.6) | 9 | 3 | 0.216 |
| States around the Gulf of Mexico | 5 (6.5) | 4 | 1 | 1 |
| Republic of China (Taiwan) | 10 (13.0) | 6 | 4 | 1 |
| Other region (Not Japan, US, Taiwan) | 19 (24.7) | 9 | 10 | 0.104 |
| **Season of onset (northern hemisphere)** | | | | | |
| Summer (June to November) | 18 (23.4) | 13 | 5 | 0.117 |
| **Period of time from onset to patient dying** | 20 h – 61 days (median 8 days) | | | | |
TABLE 2
Antimicrobial susceptibility of *Edwardsiella tarda* isolated from blood culture; five cases from Tokyo Women’s Medical University (TWMU; Tokyo, Japan) and eight cases from the literature

| Age/years/sex | Underlying disease(s) | Complication | Exposure/dietary risk | Minimum inhibitory concentration (MIC), mg/L | Antibiotic susceptibility | Case reference | Country | Year |
|---------------|-----------------------|--------------|-----------------------|---------------------------------------------|--------------------------|---------------|---------|------|
| 67/female     | NHL                   | SCA          | ND                    | <2                                         | AMK (Cefazolin)           | TWMU-4        | Japan   | 2011 |
| 21/male       | NS                    | Liver abscess| ND                    | <2                                         | AMK (Cefazolin)           | TWMU-5        | Japan   | 2013 |
| 46/female     | none                  | Liver abscess| ND                    | <2                                         | AMK (Cefazolin)           | TWMU-1        | Japan   | 2004 |
| 60/male       | LC,HCC                | EC           | ND                    | <2                                         | AMK (Cefazolin)           | TWMU-2        | Japan   | 2004 |
| 84/male       | BCa                   | Cholecystitis| ND                    | <2                                         | AMK (Cefazolin)           | TWMU-3        | Japan   | 2010 |
| 80/female     | PCA                   | Liver abscess| ND                    | <2                                         | AMK (Cefazolin)           | TWMU-4        | Japan   | 2013 |
| 46/female     | Ce-Ca                 | EC           | Sushi                 | <2                                         | AMK (Cefazolin)           | TWMU-5        | Japan   | 2013 |

The mean age of the patients was 61 years (range two days to 101 years) and 30 cases (30 of 77 [39%]) involved women. Underlying diseases included cancer (29 of 77 [37.6%]); hepatobiliary cancer (17 of 77 [20.8%]) and liver cirrhosis (13 of 77 [16.8%]). Six (6.5%) cases involved neonatal patients. Thirteen (16.9%) cases occurred in healthy individuals without any underlying disease and there were 35 (45.5%) cases of uncomplicated ETB. Eighteen (23.4%) cases involved soft tissue infections, 24.7% involved diarrhea, 13.0% involved liver abscess and 3.9% involved meningitis. Despite appropriate antimicrobial therapy, the overall mortality rate was 44.6% (33 of 74, no mortality data available for three cases [14,46,49]); however, this rate increased to 61.1% (11 of 18) for patients with soft tissue infections.

Treatment using the following antimicrobial agents was described in 51 cases (66.2%): cefalosporin (n=26), penicillin (n=19) and carbapenems (n=8). Although no significant differences were found with respect to age, sex, complications of ETB, geographical area or season of onset among cases in which the patient died compared with those in which the patient survived, liver cirrhosis (OR 12.0 [95% CI 2.46 to 58.6]; P=0.02213) was considered to be an independent risk factor associated with death in multivariate analyses (Table 1). Antibiotic susceptibility of the *E. tarda* strains that were isolated from the blood cultures was tested retrospectively in accordance with the standards of the Clinical and Laboratory Standards Institute using E-test (bioMérieux, France).

Continuous data were compared using a t-test and categorical data were compared using Fisher’s exact tests; P<0.05 was considered to be statistically significant. Multivariate analyses were used to determine the independent risk factors associated with mortality using forward stepwise logistic regression. All variables with P<0.1 in univariate analyses were entered into the multivariate model. Statistical analyses were performed using R version 3.0.3 (www.r-project.org).

The study protocol was approved by the TWMU Hospital Medical Ethics Committee (No. 3052).

RESULTS
The literature search resulted in 234 articles from the PubMed MEDLINE database and 68 articles from the ICHUSHI database, published between January 1968 and December 2013. Of these, 202 and 54 publications were excluded, according to inclusion criteria, from the PubMed MEDLINE and ICHUSHI databases, respectively. The resulting 46 publications, published between 1968 and 2013, were retrieved from the English (n=30) (8-37), French (n=1) (38), Spanish (n=1) (39) and Japanese (n=14) literature (40-53). A total of 72 cases were described in the retrieved publications and five cases diagnosed at the TWMU were also included, resulting in 77 cases for analysis.
DISCUSSION

To our knowledge, the present study was the first and largest multi-language review of ETB. The results indicate that the overall mortality related to ETB is 44.6%, and ETB may be more likely to occur in the humid and subtropical climates of Eastern Asia and the Gulf of Mexico in the US, particularly during summer and autumn months. Furthermore, environmental and dietary risk factors, such as exposure to brackish water and raw food consumption, may play a role in ETB.

ETB occurs infrequently (<5%) (9), and the risk factors are not well established. Investigating similarities with other species may provide some clues regarding the mechanisms related to ETB. Previous case series suggest that up to 50% of ETB patients also had hepatobiliary diseases, including alcoholic cirrhosis (9). Interestingly, the authors indicated that conditions resulting in iron overload, such as cirrhosis, sickle cell anemia, leukemia and the neonatal state, are also considered to be risk factors for ETB (9). In the present analysis, 66.2% of the cases involved hepatobiliary diseases, including cancer. Twenty-one (27.3%) of these cases involved gallbladder stones with recurrent episodes of cholecystitis. The rate of underlying diseases may be higher in ETB than in other E tarda infections; this may indicate that the presence of underlying disease increases the risk for developing ETB. However, the results of our multivariate analyses suggest, for the first time, that liver cirrhosis is an independent risk factor associated with death in ETB. Cholecystitis with gallbladder stones may increase the risk for ETB in a way similar to that of human typhoid fever. Moreover, the overall rate of underlying diseases in ETB may be higher than in other E tarda infections, potentially indicating that the presence of underlying disease increases the risk for ETB and subsequent high mortality from ETB.

In addition, reservoir-related Aeromonas species are similar to E tarda. Both can cause a wide spectrum of diseases among warm- and cold-blooded animals, including fish, reptiles, amphibians, mammals and humans. Population sizes of both species can grow quite large, generally peaking in the warmer temperatures of the summer months in temperate freshwater lakes and chlorinated drinking water, and have been associated with contact with reptiles, including those kept as pets (54). Vibrio vulnificus can also cause severe disseminated infection associated with exposure to seawater and brackish water. Severe V vulnificus infections in humans are also responsible for liver cirrhosis. Therefore, clinical characteristics of E tarda infections in humans resemble those of Aeromonas, typhoid fever and V vulnificus infections, and share similar environmental risks. It is well known that necrotizing fasciitis type 3, which is known as a marine infection and can be fatal within 48 h, is caused by Vibrio or Aeromonas species. Therefore, it should be recognized that E tarda can also result in necrotizing fasciitis type 3. In addition, previous reports indicate that the mortality rate of ETB is nearly 50%, which is similar to that of V vulnificus or severe infections caused by Aeromonas species (56,57). E tarda infections, including ETB, are considered to be foodborne. Despite this, dietary risk factors for ETB have not been well established or documented. In addition, most of the cases of ETB are suspected to occur endogenously through primary colonization and infection in the human intestinal tract. However, documented E tarda infections in humans have resulted from the consumption of infected or contaminated food such as fish (58). According to the Food and Agriculture Organization of the United Nations Statistics Division (FAOSTAT) Food Balance Sheet 2006 (http://faostat.fao.org/), Japan has one of the world’s highest per capita seafood consumption rates. E tarda has been isolated from raw flounder in Japanese fish farms (58). Interestingly, E tarda has been reported to result in a 60% to 90% mortality rate among Japanese eels (59), and a traditional custom in Japan, dating from the 18th century, is to eat cooked eel at the end of July. Furthermore, 71% of the eels from the eel farms in Korea (60) have been reported to carry E tarda.

Toward the end of the 1960s in the US, E tarda was linked to catfish, mainly in the waters of Arkansas, Mississippi, Texas and Louisiana (61). Despite the small number of cases in the current study, approximately one-half of the cases occurred around the Gulf of Mexico, which receives a supply of nutrient-rich water from several rivers. Individuals residing in these areas may be exposed to high concentrations of E tarda through the water or contaminated food. According to data from the National Fisheries Institute, tilapia, pangasius and catfish are consumed in the US. They are farmed in fresh water and 79% of already-dressed catfish in the US carry E tarda (62). Given the collective findings of the available literature, we suspect that dietary exposures also affect the risk for ETB.

Little is known about the recent prevalence of E tarda colonization in healthy individuals; no recent data are available from large-scale studies in any country. A study conducted in the 1970s (7), is one of the few to report that only 26 of 353,600 Japanese individuals were healthy carriers of E tarda. We suspect that the rate of colonization in stool appears to be high among individuals in areas with a high consumption of raw fish contaminated with E tarda. The colonization rate in humans may be affected by changes in dietary habits and increased travel, and the use of novel techniques, such as matrix-assisted laser desorption ionization–time of flight mass spectrometry, may improve identification of E tarda, which was previously underestimated.

Trimethoprim/sulfamethoxazole-resistant E tarda has been clinically isolated in a pediatric patient with X-linked chronic granulomatous disease and osteomyelitis in Japan (63). Nine multidrug-resistant strains of E tarda were found in the current study. There are several studies showing at least 90% of E tarda strains to be colistin resistant. Natural resistance of E tarda to colistin or polymyxin B has been suggested, but its mechanism was unelucidated (64). Feedstuffs for domesticated animals are exposed to colistin in Japan (65) and some European countries. Antibiotic resistance in E tarda may emerge as an issue related to environmental antibiotic exposure in food production. Geographical differences among the Republic of China (Taylor)
and the US in the antimicrobial susceptibility of E. tarda, isolated from food-producing animals, have been previously described (66). Seasonal distribution of human E. tarda gastroenteritis has not been previously demonstrated (9). In addition, information has not been available regarding the time of year for extraintestinal E. tarda infections in previously reported cases. The results of the current review suggest that there may, in fact, be a seasonal distribution of ETB, and exposure to higher concentrations of E. tarda in the warmer temperatures of the summer months may increase the risk for ETB (61).

For example, Eastern Asia, which includes Japan and the Republic of China (Taiwan), and the states of the US near the Gulf of Mexico, reported the highest rates of ETB and belong to climates that are similar – humid and subtropical. In addition, dietary customs vary according to geographical region. Therefore, dietary factors may play a role in the geographical or seasonal distributions of ETB.

Taking all of this into account, we propose two reasons for the high prevalence of ETB in Japan. The first is that Japan is geographically rich in brackish water areas and rivers. Second, the Japanese consume a relatively large amount of raw seafood, which may be contaminated with E. tarda.

REFERENCES

1. Trabulsi LR, Ewing WH. Sodium acetate medium for the differentiation of Shigella and Escherichia cultures. Public Health Lab 1962;20:137-40.
2. King BM, Adler DL. A previously undescribed group of Enterobacteriaceae. Am J Clin Pathol 1964;41:230-2.
3. Sakazaki R. A proposed group of the family Enterobacteriaceae, the Asakusa group. Int Bull Bacteriol Nomencl Taxon 1965;15:45-7.
4. Ewing WH, McWhorter AC, Escobar MR, Lubin AH. Edwardsiella, a new genus of Enterobacteriaceae, based on a new species, E. tarda. Int Bull Bacteriol Nomencl Taxon 1965;15:33-8.
5. Wyatt LE, Nickelson R, Vanderzant C. Edwardsiella tarda in freshwater catfish and their environment. Appl Environ Microbiol 1979;38:710-4.
6. Joh SJ, KIM MJ, Kwon HM, Ahn EH, Jang H, Kwon JH. Characterization of Edwardsiella tarda isolated from farmed-cultural eels, Anguilla japonica, in the Republic of Korea. J Vet Med Sci 2011;73:7-11.
7. Omogawa T, Terayama T, Zenyoji H. Distribution of Edwardsiella tarda and hydrogen sulfide-producing Escherichia coli in healthy persons. J Jpn Assoc for Infect Dis (Kansenshogaku Zasshi) 1976;50:10-7.
8. Kounym M, Vasquez MA, Szent R. Escherichiosis in man and animals in Panama: Clinical and epidemiological characteristics. Am J Trop Med Hyg 1977;26:1183-90.
9. Janada JM, Sharon LA. Infections associated with the genus Edwardsiella: The role of Edwardsiella tarda in human diseases. Clin Infect Dis 1993;17:742-8.
10. Okubadejo OA, Alausa KO. Neonatal meningitis caused by Edwardsiella tarda. Br Med J 1968;3:357-8.
11. Sonnenwirth AC, Kallus BA. Meningitis due to Edwardsiella tarda. First report of meningitis caused by E. tarda. Am J Clin Pathol 1968;49:92-5.
12. Pankey GA, Seshul MB. Septicemia caused by Edwardsiella tarda. J La State Med Soc 1969;121:41-3.
13. Jordan GW, Hadley WK. Human infection with Edwardsiella tarda. Ann Intern Med 1969;70:283-8.
14. Bockemühl J, Pan-Urai R, Burkhardt F. Edwardsiella tarda associated with human disease. Pathol Microbiol 1971;37:393-401.
15. Sachs JM, Pacin M, Counts GW. Sickle hemoglobinopathy and Edwardsiella tarda meningitis. Am J Dis Child 1974;128:387-8.
16. Le Frock JL, Klinner AS, Zuckerman K. Edwardsiella tarda bacteremia. South Med J 1976;69:188-90.
17. Koshi G, Lalitha MK. Edwardsiella tarda in a variety of human infections. Indian J Med Res 1976;64:1753-9.
18. Claridge JE, Musher DM, Fainstein V, Wallace RJ Jr. Extraintestinal human infection caused by Edwardsiella tarda. J Clin Microbiol 1980;11:511-4.

The present review had limitations. One was the retrospective nature of the data, including the use of previously reported literature and only five recent cases from our institute. Fourteen of 72 cases from the literature were described only in the Japanese language. Therefore, publication and resource bias may have affected our results. The second limitation is that we focused on the results of blood cultures; however, sensitivity of blood cultures may vary during a long study period.

CONCLUSIONS

ETB may be categorized as a severe food- and waterborne infection similar to Aeromonas, Vibrio and Salmonella (typhoid fever) infections, which result in high mortality in patients with severe underlying diseases such as liver cirrhosis. Geographical and seasonal distributions may characterize ETB. The clinical epidemiology, including dietary risk factors and the current incidence of ETB should be further established.

DISCLOSURES: The authors have no financial relationships or conflicts of interest to declare.

ACKNOWLEDGEMENTS: Results from this study were presented, in part, as a poster (Presentation number 1263) at ID Week 2013, San Francisco, October 2 to 6, 2013.
