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Case Report

A case of necrotizing fasciitis following *Edwardsiella tarda* septicemia with gastroenteritis☆

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ABSTRACT

Edwardsiella tarda is an uncommon pathogen that causes gastroenteritis in humans and is found in the aquatic environment. In rare cases, it also causes fatal infections, including sepsis and necrotizing fasciitis. However, it remains unknown whether *E. tarda* gastroenteritis could lead to these lethal diseases via hematogenous spread. Here we have reported a previously healthy 64-year-old woman with necrotizing fasciitis consecutively caused by *E. tarda* septicemia with gastroenteritis. The patient was transferred to the emergency department due to disturbance of consciousness and hypotension after suffering from diarrhea for a month. As whole-body computed tomography (CT) revealed an edematous change in the small intestine, septic shock following gastroenteritis was suspected, and the patient was immediately started on empiric antibiotic therapy and provided critical care. Her general physical conditions gradually began improving, but, on day 7, rapidly appearing blisters on both the lower limbs were noted, and she was accordingly examined again by conducting a CT scan. Based on the results, she was diagnosed with necrotizing fasciitis in both lower extremities, and surgical debridement was rapidly performed. Microbiological analysis of the specimens revealed *E. tarda* bacteremia, which suggested that *E. tarda* caused a series of infections in this patient. Finally, she fully recovered and was discharged within 3 months. Cumulatively, we proposed that gastroenteritis by *E. tarda* could directly result in fatal infections through the blood stream.

1. Introduction

Edwardsiella tarda (*E. tarda*) is a gram-negative rod whose genus *Edwardsiella* was originally identified in 1962 [1], and this genus includes a human pathogenic species, *E. tarda*, and non-human pathogenic species, including *E. ictaluri* and *E. hoshinae* [2]. *E. tarda* is usually found in an aquatic environment, including in fish, amphibians, or reptiles [3]. In humans, *E. tarda* is rarely isolated from the feces of healthy individuals [4]; however, it can cause several infections. Whereas gastroenteritis is the most frequent manifestation of *E. tarda* infection, extraintestinal infections, such as soft tissue infection or septicemia, by *E. tarda* are exceedingly rare albeit potentially life-threatening diseases [5]. Among these, *E. tarda*-necrotizing fasciitis has quite a high mortality rate [6], which suggests the importance of understanding the pathogenesis of this infection.

Necrotizing fasciitis is a severe and fatal infection of the subcutaneous tissue that was first described by Hippocrates and has been long considered a great threat to the human health [7]. Despite the recent advances in medical treatment, the mortality rate due to necrotizing fasciitis remains 20–25% [8,9]. Necrotizing fasciitis can be categorized into polymicrobial infection, monomicrobial gram-positive infection, and monomicrobial gram-negative infection [10], which predicts the chances of survival [9]. Polymicrobial infection is the most common (55%) [11] and is most closely associated with mortality [9]. However, necrotizing fasciitis by *E. tarda* has only been reported in Japanese literature [6,12]; therefore, its clinical character is insufficiently defined. Furthermore, although some reviews of necrotizing fasciitis mention that bacteria invade the soft tissues via disruption of the skin surface or through hematogenous spread from another infection site [13,14], the direct evidence of how bacteria, especially *E. tarda*, reach the subcutaneous tissues remains elusive.

☆ All authors meet the ICMJE authorship criteria.

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Table 1
Results of blood tests.

	Admission	Discharge	Reference
WBC	1500/μL	5600/μL	4000–9000/μL
RBC	249 × 10^4/μL	306 × 10^4/μL	3.8–5.4 × 10^4/μL
Hb	10.3g/dL	10.2g/dL	11.5–15g/dL
Plt	6.6 × 10^4/μL	13.5 × 10^4/μL	15–35 × 10^4/μL
Na	133 mEq/L	140 mEq/L	136–147 mEq/L
K	1.7 mEq/L	4.2 mEq/L	3.5–5 mEq/L
Cl	80 mEq/L	103 mEq/L	98–110 mEq/L
T-Bil	5.9 mg/dL	0.6 mg/dL	0.2–1.2 mg/dL
AST	169 U/L	21 U/L	12–35 U/L
ALT	49 U/L	9 U/L	30/05/2019 U/L
LDH	461 U/L	U/L	110–240 U/L
BUN	13.2 mg/dL	14.1 mg/dL	20/08/2019 mg/dL
Cr	2.05 mg/dL	0.47 mg/dL	0.4–0.8 mg/dL
UA	9.2 mg/dL	5.5 mg/dL	2.6–7.0 mg/dL
Ca	6.9 mg/dL	mg/dL	2.5–11.0 mg/dL
AMY	12 U/L	U/L	30–120 U/L
CPK	1541 U/L	U/L	13–187 U/L
TP	5.4 g/dL	7.8 g/dL	6.1–8.1 g/dL
Alb	2.1 g/dL	3.6 g/dL	3.2–5 g/dL
Glu	11 mg/dL	mg/dL	72–106 mg/dL
CRP	18.4 mg/dL	0.1 mg/dL	0.3 ≧ mg/dL

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Plt, platelets; Na, sodium; K, potassium; Cl, chloride; T-Bil, total-bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; Ca, calcium; AMY, amylase; CPK, creatine phosphokinase; TP, total protein; Alb, albumin; Glu, glucose; CRP C-reactive protein.

Here, we have reported a case of necrotizing fasciitis consecutively caused by *E. tarda* gastroenteritis in a previously healthy person. We propose that *E. tarda* gastroenteritis directly results in extraintestinal manifestations, independent of the host immune status. We believe that our findings can provide an insight into the pathogenic mechanisms of necrotizing fasciitis.

2. Case report

A previously healthy 64-year-old woman presented with anorexia and green diarrhea for a month. She was transferred to our emergency department when she lost consciousness. Her initial Glasgow Coma Scale score was E4V1M1. On her physical examination, her vital signs were found to be as follows: blood pressure 52/33 mmHg, heart rate 92 bpm, SpO2 100% on 6 L/min oxygen, respiratory rate 18 bpm, and body temperature 35.7 °C. Her present history and physical examination results suggested the disturbance of consciousness, resulting from septic shock following gastroenteritis. Consistent with this preliminary diagnosis, her blood test revealed pancytopenia, high C-reactive protein (CRP) level, hepatic disorder, renal dysfunction, hypoglycemia, and coagulation disorder (Table 1). Whole-body computed tomography (CT) scanning revealed an edematous change in the small intestine (Fig. 1), which supported the theory that gastroenteritis led to septicemia. Therefore, we immediately started norepinephrine perfusion accompanied by mechanical ventilation and empiric antibiotic therapy consisting of Meropenem (MEPM) 750 mg/day, Vancomycin (VCM) 500 mg/day, and Ciprofloxacin (CPFX) 300 g/day in

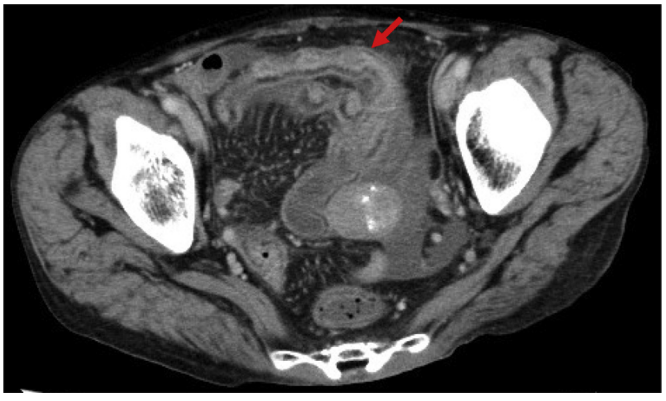

Fig. 1. An edematous change in the small intestine wall indicated enteritis. Contast-enhanced abdominal CT scan on admission.

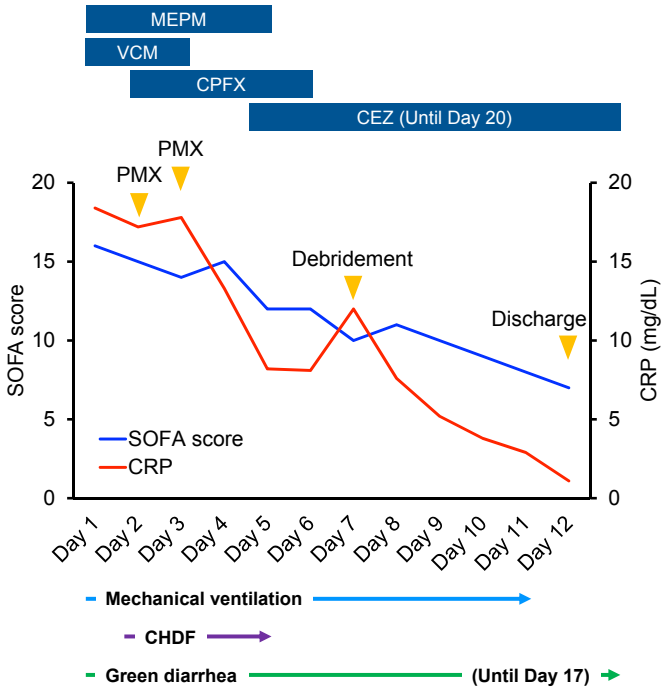

Fig. 2. Sepsis and inflammation gradually improved, but green diarrhea continued after ICU stay.

Table 2
Antibiotic susceptibility of *E. tarda* from blood culture.

Antibiotic	MIC (μg/mL)	Antibiotic	MIC (μg/mL)
ABPC	<4S	AMPC/CVA	<8S
PIPC	<8S	SBT/ABPC	<4S
CEZ	<4S	PIPC/TAZ	<8S
CTM	<8S	IPM/CS	<1S
CTX	<1S	MEPM	<1S
CAZ	<4S	DRPEM	<1S
CTRX	<1S	AMK	<4S
CFPM	<2S	TOB	<4S
CZOP	<4S	GM	<2S
CMZ	<16S	MINO	<2S
CCL	<8S	LVFX	<0.5S
CPDX-PR	<1S	CPFX	<0.25S
CFDN	<0.5S	STFX	<1S
CFPN-PI	<0.5S	FOM	<4S
FMOX	<4S	CL	>4R
AZT	<4S	ST	<2S

ABPC, Ampicillin; PIPC, Piperacillin; CEZ, Cefazolin; CTM, Cefotiam; CTX, Cefotaxime; CAZ, Ceftazidime; CTRX, Ceftriaxone; CFPM, Cefepime; CZOP, Cefozopran; CMZ, Cefmetazole; CCL, Cefaclor; CPDX-PR, Cefpodoxime Proxetil; CFDN, Cefdinir; CFPN-PI, Cefcapene Pivoxil; FMOX, Flomoxef; AZT, Aztreonam; AMPC/CVA; Amoxicillin/Clavulanic acid; SBT/ABPC, Sulbactam/Ampicillin; PIPC/TAZ, Piperacillin/Tazobactam; IPM/CS, Imipenem/Cilastatin sodium; MEPM, Meropenem; DRPEM, Doripenem; AMK, Amikacin; TOB, Tobramycin; GM, Gentamicin; MINO, Minocycline; LVFX, Levofloxacin; CPFX, Ciprofloxacin; STFX, Sitafloxacin; FOM, Fosfomycin; CL, Colistin; ST, Sulfamethoxazole-Trimethoprim.

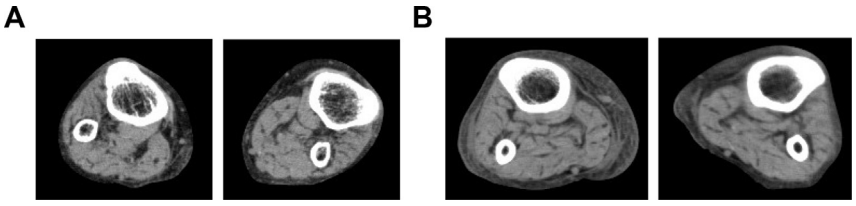

Fig. 3. Reticular patterns in the soft tissues indicated necrotizing fasciitis. A. Lower extremity CT scan on admission. B. Lower extremity CT scan on day 7.

intensive care unit (ICU) (Fig. 2). We found gram-negative rods in both the blood culture bottles and discontinued VCM. Due to the insufficient urinary output, we additionally started continuous hemodialysis (CHDF) and endotoxin adsorption therapy using polymyxin-B immobilized fiber (PMX) on day 2 and thereby achieved a gradual improvement in sepsis and inflammation (Fig. 2). On day 5, unexpectedly, we identified *E. tarda* in both the blood culture bottles by biochemical characterization using MicroScan WalkAway (Beckman Coulter). In addition, the sequence analysis of 16S rRNA gene revealed an almost-complete match between the sample and a *E. tarda* type strain ATCC 15947 (1263 bp/1265 bp), ensuring the identification. This finding indicated that septic shock with gastroenteritis was caused by *E. tarda*. Antibiotic sensitivity results by microbroth dilution method using MicroScan WalkAway (Beckman Coulter) (Table 2) recommended the cefazolin (CEZ) therapy (5 g/day). However, her serum CRP level increased again, and blisters on both the lower limbs rapidly appeared on day 7. Thus, soft tissues in the lower extremities were examined again by CT scanning and reticular patterns were detected in the soft tissues of the entire lower limbs (Fig. 3A,B). We diagnosed necrotizing fasciitis and immediately conducted surgical debridement. Although no bacteria were detected in the surgical or fecal specimens, green diarrhea continued until day 17 (Fig. 2), suggesting that *E. tarda* had still been in the digestive tract, regardless of the antibiotic therapy. Microbiological analysis might fail to detect *E. tarda* for some reasons. After surgical debridement, her general condition and inflammation slowly began improving again. On day 11, mechanical ventilation was discontinued and she was discharged from the ICU. After completion of wound care and rehabilitation treatment, the patient was finally discharged from the hospital on day 57 of her admission.

3. Discussion

E. tarda was named by Ewing et al. [1] and is described as gram-negative bacteria that exhibits the typical characteristics of the Enterobacteriacae family [2], including *Escherichia*, *Klebsiella*, and *Salmonella*. While *E. tarda* is often detected in aquatic environments [3], this pathogen occasionally causes human infections that consist of 80% *Salmonella*-like gastroenteritis and 20% extraintestinal diseases [2,15]. Necrotizing fasciitis is one of the most uncommon and life-threatening infections by *E. tarda* [6]; however, its virulence mechanism is poorly understood. In the present report, we have shown direct evidence that *E. tarda* gastroenteritis could progress to necrotizing fasciitis through hematogenous spread.

During *E. tarda* gastroenteritis, the bacteria migrate by using their flagella and attach to the epithelial cells in the gastrointestinal tract [16]. After binding to the host cells, *E. tarda* is endocytosed but uses a type III [17] or VI [18] secretion system to inject cytoplasm with effector proteins, which suppress the innate immunity or remodel the host cells to benefit bacterial survival [19]. Increasing bacteria further invade the adjacent epithelial cells and disrupt tissue homeostasis. Because host cells possess the antimicrobial system, such as xenophagy, in which cytosolic bacteria is selectively digested by lysosomal enzymes [20], gastrointestinal infection by *E. tarda* is usually restricted to a particular area. However, some situations, such as immunocompromised conditions, allow *E. tarda* to invade the deeper tissues and reach the blood stream or lymph node, leading to extraintestinal infections [16]. In this process, hepatic function is crucial for bacterial clearance from the blood stream [21]. A previous report has shown that liver-resident macrophages, Kupffer cells, contribute to bacterial clearance [22]. Type III secretion system-deficient *E. tarda* is efficiently killed by macrophages [17]. Consistently, liver diseases, such as hepatic cirrhosis, are closely associated with extraintestinal manifestations by *E. tarda* [5,6]. Furthermore, abdominal CT scan showed fatty liver in the present case (data not shown), which is again suggestive of the potential role of the liver immune system in necrotizing fasciitis by *E. tarda*.

In the present case, although we had immediately administered broad-spectrum antibiotics for *E. tarda* septicemia on admission and confirmed an improvement in inflammation, necrotizing fasciitis in the lower limbs appeared on day 7. It should be noted as a limitation that *E. tarda* were not found in the wound culture. However, also other bacteria were not detected in the wound culture and green diarrhea continued until day 17. These clinical observations suggest that *E. tarda* caused both of gastroenteritis and necrotizing fasciitis. And thus, *E. tarda* can reside not only in the digestive tract but also in the subcutaneous tissues, regardless of the antibiotic therapy. Generally, bacteria adapt to various environments by using a two-component system (TCS), in which the histidine kinase receptor is activated by some environmental changes or signal molecules and activates the cognate response regulator via phosphorylation of aspartic acid to promote the gene expression of the virulence factor [23]. The several types of TCSs allow *E. tarda* to sense the change in phosphate concentration [24], magnesium concentration [25], osmolarity [26,27], host body temperature [25], or epinephrine [28] as well as to survive in the new environments. Because such statuses in the subcutaneous tissues should be dramatically changed in response to sepsis, *E. tarda* may use some types of TCSs to regulate the virulence factor expression for efficient invasion in severe environments.

In summary, we have described that gastroenteritis by *E. tarda* could progress to extraintestinal manifestations via the blood stream. This process, characterized by green diarrhea, took a month in the present case, suggesting that clinicians should carefully treat *E. tarda* gastroenteritis with suitable antibiotics to prevent development of extraintestinal infections.

Disclosure

The authors declare no conflict of interest associated with this research.

References

[1] 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. https://doi.org/10.1099/00207713-15-1-33.

[2] Janda JM, Abbott SL. Infections associated with the genus Edwardsiella: the role of Edwardsiella tarda in human disease. Clin Infect Dis 1993;17:742–8.
[3] Wyatt LE, Nickelson R, Vanderzant C. Edwardsiella tarda in freshwater catfish and their environment. Appl Environ Microbiol 1979;38:710–4.
[4] Onogawa T, Terayama T, Zen-yoji H, Amano Y, Suzuki K. Distribution of *Edwardsiella tarda* and hydrogen sulfide-producing *Escherichia coli* in healthy persons. J Jpn Assoc Infect Dis 1976;50:10–7. https://doi.org/10.11150/kansenshogakuzasshi1970.50.10.
[5] Wang IK, Kuo HL, Chen YM, Lin CL, Chang HY, Chuang FR, et al. Extraintestinal manifestations of Edwardsielia tarda infection. Int J Clin Pract 2005;59:917–21. https://doi.org/10.1111/j.1368-5031.2005.00527.x.
[6] Hara K, Ouchi H, Kitahara M, Shibano K, Miyauchi T, Ishiguro H. A case of fasciitis localized in the calf muscles associated with *Edwardsiella tarda* sepsis. Clin Neurol 2011;51:694–8. https://doi.org/10.5692/clinicalneurol.51.694.
[7] Descamps V, Aiteken J, Lee MG. Hippocrates on necrotizing fasciitis. Lancet 1994;344. 556–6.
[8] Khamnuan P, Chongruksut W, Jearwattanakanok K, Patumanond J, Yodluangfun S, Tantraworasin A. Necrotizing fasciitis: risk factors of mortality. Risk Manag Healthc Pol 2015;8:1–7. https://doi.org/10.2147/RMHP.S77691.
[9] Jabbour G, El-Menyar A, Peralta R, Shaikh N, Abdelrahman H, Mudali IN, et al. Pattern and predictors of mortality in necrotizing fasciitis patients in a single tertiary hospital. World J Emerg Surg 2016;11:40. https://doi.org/10.1186/s13017-016-0097-y.
[10] Sarani B, Strong M, Pascual J, Schwab CW. Necrotizing fasciitis: current concepts and review of the literature. Acs 2009;208:279–88. https://doi.org/10.1016/j.jamcollsurg.2008.10.032.
[11] Wong C-H, Chang H-C, Pasupathy S, Khin L-W, Tan J-L, Low C-O. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am 2003;85-A:1454–60. https://doi.org/10.2106/00004623-200308000-00005.
[12] Matsushima S, Yajima S, Taguchi T, Takahashi A, Shiseki M, Totsuka K, et al. A fulminating case of Edwardsiella tarda septicemia with necrotizing fasciitis. J Jpn Assoc Infect Dis 1996;70:631–6. https://doi.org/10.11150/kansenshogakuzasshi1970.70.631.
[13] Green RJ, Dafoe DC, Raffin TA. Necrotizing fasciitis. Chest 1996;110:219–29. https://doi.org/10.1378/chest.110.1.219.
[14] Salcido RS. Necrotizing fasciitis: reviewing the causes and treatment strategies. Adv Skin Wound Care 2007;20:288–93. https://doi.org/10.1097/01.ASW.0000269317.76380.3b. quiz294–5.
[15] Schlenker C, Surawicz CM. Emerging infections of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 2009;23:89–99. https://doi.org/10.1016/j.bpg.2008.11.014.
[16] Leung KY, Siame BA, Tenkink BJ, Noort RJ, Mok Y-K. Edwardsiella tarda – virulence mechanisms of an emerging gastroenteritis pathogen. Microb Infect 2012;14:26–34. https://doi.org/10.1016/j.micinf.2011.08.005.
[17] Tan YP. Role of type III secretion in Edwardsiella tarda virulence. Microbiology 2005;151:2301–13. https://doi.org/10.1099/mic.0.28005-0.
[18] Zheng J, Leung KY. Dissection of a type VI secretion system in Edwardsiella tarda. Mol Microbiol 2007;66:1192–206. https://doi.org/10.1111/j.1365-2958.2007.05993.x.
[19] Galán JE, Wolf-Watz H. Protein delivery into eukaryotic cells by type III secretion machines. Nature 2006;444:567–73. https://doi.org/10.1038/nature05272.
[20] Shibutani ST, Saitoh T, Nowag H, Münz C, Yoshimori T. Autophagy and autophagy-related proteins in the immune system. Nat Immunol 2015;16:1014–24. https://doi.org/10.1038/ni.3273.
[21] Ashare A, Stanford C, Hancock P, Stark D, Lilli K, Birrer E, et al. Chronic liver disease impairs bacterial clearance in a human model of induced bacteremia. Clin Trans Sci 2009;2:199–205. https://doi.org/10.1111/j.1752-8062.2009.00122.x.
[22] Wong CHY, Jenne CN, Petri B, Chrobok NL, Kubes P. Nucleation of platelets with blood-borne pathogens on Kupffer cells precedes other innate immunity and contributes to bacterial clearance. Nat Immunol 2013;14:785–92. https://doi.org/10.1038/ni.2631.
[23] Stock AM, Robinson VL, Goudreau PN. Two-component signal transduction. Annu Rev Biochem 2000;69:183–215. https://doi.org/10.1146/annurev.biochem.69.1.183.
[24] Chakraborty S, Sivaraman J, Leung KY, Mok Y-K. Two-component PhoB-PhoR regulatory system and ferric uptake regulator sense phosphate and iron to control virulence genes in type III and VI secretion systems of Edwardsiella tarda. J Biol Chem 2011;286:39417–30. https://doi.org/10.1074/jbc.M111.295188.
[25] Chakraborty S, Li M, Chatterjee C, Sivaraman J, Leung KY, Mok Y-K. Temperature and Mg 2+Sensing by a Novel PhoP-PhoQ two-component system for regulation of virulence in Edwardsiella tarda. J Biol Chem 2010;285:38876–88. https://doi.org/10.1074/jbc.M110.179150.
[26] Garmendia J. The roles of SsrA-SsrB and OmpR-EnvZ in the regulation of genes encoding the Salmonella typhimurium SPI-2 type III secretion system. Microbiology 2003;149:2385–96. https://doi.org/10.1099/mic.0.26397-0.
[27] Wang Q, Yang M, Xiao J, Wu H, Wang X, Lv Y, et al. Genome sequence of the versatile fish pathogen Edwardsiella tarda provides insights into its adaptation to broad host ranges and intracellular Niches. PLoS One 2009;4. https://doi.org/10.1371/journal.pone.0007646. e7646–16.
[28] Wang X, Wang Q, Yang M, Xiao J, Liu Q, Wu H, et al. QseBC controls flagellar motility, fimbrial hemagglutination and intracellular virulence in fish pathogen Edwardsiella tarda. Fish Shellfish Immunol 2011;30:944–53. https://doi.org/10.1016/j.fsi.2011.01.019.