Open Forum Infectious Diseases

REVIEW ARTICLE

Far East Scarlet-Like Fever: A Review of the Epidemiology, Symptomatology, and Role of Superantigenic Toxin: *Yersinia pseudotuberculosis*-Derived Mitogen A

A. Amphlett

Department of Microbiology, Derriford Hospital, Plymouth, United Kingdom

Far East scarlet-like fever (FESLF) is a severe inflammatory disease that occurs sporadically and in outbreaks in Russia and Japan. Far East scarlet-like fever is caused by *Yersinia pseudotubuclosis* infection, an organism that typically causes self-limiting gastroenteritis in Europe. Studies suggest the ability of Far Eastern strains to produce superantigen toxin *Y pseudotuberculosis*-derived mitogen A is integral to FESLF pathogenesis.

In Europe, human Y pseudotuberculosis infection typically occurs sporadically, in the form of a self-limiting gastroenteritis. In Russia and Japan, outbreaks of Y pseudotuberculosis infection cause severe systemic inflammatory symptoms. This disease variant is called FESLF. Geographical heterogeneity exists between virulence factors produced by European and Far Eastern Y pseudotuberculosis strains, implicating superantigen Y pseudotuberculosis-derived mitogen A (YPMa) in the pathogenesis of FESLF. This article describes the epidemiology and clinical features of FESLF, and it presents the evidence for the role of YPMa in FESLF pathogenesis.

Keywords. Far East scarlet-like fever; *Yersinia pseudotuberculosis*; *Yersinia pseudotuberculosis* mitogen A.

Yersinia pseudotuberculosis was first isolated in 1883 [1] from tuberculosis-like lesions in guinea pigs. The organism is 1 of 3 species within the genus pathogenic for humans. *Yersinia pseudotuberculosis* is a fecal-oral pathogen adept at contaminating chilled food stores due to the organisms ability to proliferate at temperatures as low as 4°C [2].

In Europe, human *Y pseudotuberculosis* infection typically occurs sporadically, in the form of a self-limiting gastroenteritis. In Russia and Japan, outbreaks of infection cause severe systemic inflammatory symptoms. This disease variant is called Far East scarlet-like fever (FESLF). In Russian and Japan, *Y pseudotuberculosis* infection is recognized as a national health problem and was added to the national notification system in 1988 [3].

Geographical heterogeneity exists between virulence factors produced by European and Far Eastern *Y pseudotuberculosis* strains. *Yersinia pseudotuberculosis*-derived mitogen A (YPMa) is a superantigenic toxin produced almost exclusively by Far Eastern strains [4]. Numerous studies have implicated YPMa as a key player in the pathogenesis of FESLF.

The epidemiological and clinical dichotomy of *Y pseudotuberculosis* disease has stimulated an exciting body of research. This review summarizes the impact of FESLF across the globe and at the bedside, additionally exploring the role of YPMa in the pathogenesis of this fascinating disease.

Epidemiology of Far East Scarlet-Like Fever

Yersinia pseudotuberculosis has a large animal reservoir, causing epizootic disease in European brown hares in Northern Europe, sheep in Australia, and farmed deer in New Zealand. The organism has been isolated in healthy pigs, dogs, cats, cattle, horses, rabbits, and birds. Human transmission arises due to fecal contamination of soil, water, and fresh produce by infected animals [5–10].

Human *Y pseudotuberculosis* infection has primarily been reported in the Northern hemisphere in Europe, North America, Russia, and Japan, but infection occurs at low incidences on all continents. Disease may arise sporadically or in the form of outbreaks. Most cases are sporadic. Sporadic infection is underreported because stool cultures are not routinely requested in patients presenting with mild clinical features, such as diarrhea. Small outbreaks have been reported in Europe, but large-scale outbreaks have only occurred in Canada, Finland, Russia, and Japan [11, 12]. Far East scarlet-like fever has primarily been observed in Russia and Japan.

In Russia, the first reported epidemic of *Y pseudotuberculosis* infection occurred in Vladivostok in 1959. Initial disease was characterized by clinical features that led to a misdiagnosis of scarlet fever. A few days later, patients developed different clinical features, and the disease was named FESLF [13].

Received 13 September 2015; accepted 15 December 2015.

Correspondence: A. Amphlett, Department of Microbiology, Derriford Hospital, Plymouth, UK (alexander.amphlett@nhs.net).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofv202

Between 1959 and 1980, *Y pseudotuberculosis* infection occurred sporadically and epidemically in the Russian Far East only: the Voronezsh, Lipetsk, and Stavropol regions; Sverdlovsk, Novosibirsk, and Kemerovo. Of the reported cases, 50%–85% were from outbreaks of FESLF [14].

After 1980, FESLF outbreaks were reported in Central and Western Russia. This change in geographical distribution was facilitated by the following: the intensive socioeconomic development of Eastern and Northern Russia, urbanization, centralization of harvesting, transportation development, and novel fresh produce storage methods. *Yersinia pseudotuberculosis* infection was recognized as a Russian national health problem and included in the national notification system in 1988 [3].

In Russia, between 2000 and 2010, the total mean number of newly registered cases was 6024 per year, and the mean incidence was 4.2 per 100 000 population. Cases differ in their geographical distribution within Russia, with 67.2% of cases being diagnosed in Siberia, 2.6% in the European region, and 7.4% in the Far East [3].

Russia can be subdivided into 4 areas regarding the incidence of *Y pseudotuberculosis* infection: (1) high-level epidemic territories with incidences greater than 15 per 100 000 (St. Petersburg, Tyumen, Tomsk, Kemerovo, Novosibirsk, Kamchatka, Khakassiya, and Chukotka); (2) middle-level epidemic territories with incidences between 4 and 14 per 100 000 (Arkhangel, Murmansk, Leningrad, Magadan, Sakhalin, Altai, and Republic of Altai, Nenetskii, and Khanty-Mansiiskii autonomous districts, Primorsky Krai); (3) low-level epidemic territories with sporadic cases and incidences less than 3.9 per 100 000 (all central Russian provinces, Ural and Volga areas, 5 territories of Siberia, and 4 territories of the Russian Far East); and (4) territories without reported cases (Tyva, Astrakhan, and North Caucasus).

Yersinia pseudotuberculosis infection is primarily a disease of children. In Russia, between 2000 and 2010, the incidence of infection in children 14 years and under was 17 per 100 000; the incidence in adults was 1.4 per 100 000, 12.5 times lower. In Russia, human *Y pseudotuberculosis* infection occurs with equal sex distribution, but in Japan male children are more commonly affected [15].

The incidence of *Y pseudotuberculosis* disease is seasonal. Incidence increases during the winter, peaks in April–May and ends in June–July. In Russia, this specific intra-annual distribution may be due to the harvest of local vegetables in Northern and Eastern Russia for long-term storage during the winter and the supply of early vegetables from the warm Southern provinces in May–June. In Northern Russian vegetable stores, a study found that 1.6%–2.4% of vegetables were contaminated with *Y pseudotuberculosis* in December and 16.3%–28.3% in April–June. The supply of infected vegetables to centralized kitchen or restaurant facilities led to outbreaks, whereas distribution via food markets led to sporadic cases [3].

In 1977, an epidemic of *Y pseudotuberculosis* infection in Japan also gave rise to FESLF. The disease was given a different name, Izumi fever [16]. Between 1977 and 1989, epidemics in Japan were primarily associated with the consumption of contaminated water and contact with infected animals [17]. Between 1989 and 1995, foodborne epidemics occurred almost annually in Japan [15].

Clinical Features of *Yersinia pseudotuberculosis* Infection

In Europe, the symptoms of *Y pseudotuberculosis* infection are typically gastrointestinal only. The presentation ranges from mild gastroenteritis to pseudoappendicular syndrome. Enterocolitis is the typical manifestation in children, whereas terminal ileitis and mesenteric lymphadenitis (the cause of pseudoappendicitis) are the typical clinical manifestations in adults; both are self-limiting. Sepsis is uncommon, predominantly occurring in patients with preexisting comorbidities such as the following: diabetes mellitus, liver cirrhosis, or hemochromatosis [18]. During sepsis, bacteria spread preferentially to the liver, spleen, kidney, and lungs forming tuberculosis-like granulomatous abscesses [19]. Postinfective complications are rare but include the following: reactive arthritis, erythema nodosum, iritis, and glomerulonephritis [2]. *Yersinia pseudotuberculosis* has also been implicated in the etiology of Kawasaki disease [20].

In 1959, an epidemic of *Y pseudotuberculosis* infections in Vladivostok gave rise to severe inflammatory symptoms. The epidemic involved more than 300 people, with 200 of them being hospitalized in a specially organized facility and studied carefully. At disease onset, the majority of patients presented with punctuate rash, hyperemic skin, tonsillitis, pale nasolabial triangle, submandibular lymphadenopathy, and hyperemic tongue. These symptoms led to an initial erroneous diagnosis of scarlet fever. After a few days, the symptoms subsided and new features emerged causing the disease to be named FESLF [13].

Based on the clinical observations of 570 patients Zalmover [21] identified 6 stages of FESLF. The first stage is the Incubation Period, which is asymptomatic and lasts 7–10 days. The second stage is Initial Onset, in which pyrexia, rigors, and more generalized symptoms (such as headache, myalgia, arthralgia, weakness, and appetite loss) occur. Hyperemia of the face and neck, pale nasolabial triangle, hyperemia of the conjunctiva, and swelling of the scleral vessels, coryza, and abdominal pain may also occur at this stage. The third stage is the Accrual Stage. It most commonly occurs 3 days after disease onset. Generalized symptoms, abdominal pain, and arthralgia increase during this stage, and pyrexia is maximal. The scarlet fever-like rash characterizes this stage. The rash has variable presentations being punctuate (rubella or measles-like) or confluent (erythematous-like). Gastrointestinal manifestations are variable, usually manifesting as follows: acute gastritis, gastroenteritis, mesenteric adenitis, or terminal ileitis. Some patients also experience acute cholecystitis. Abdominal pain in the lower right quadrant may mimic appendicitis, and caused up to 40%

Table 1. Clinical Features of Far East Scarlet-Like Fever

System	Occurring at Disease Onset and Persisting With Variable Severity Throughout the Disease	Occurring During the Accrual Stage	Occurring Later in the Disease Course
General	Pyrexia, rigors, headache, appetite loss	–	–
Neurological	–	Hypertonia, photophobia, insomnia, meningism[a]	–
Respiratory	Coryza	–	–
Cardiovascular	–	Syncope[a], muffled heart sounds[a], arrthymia[a]	
Gastrointestinal	Abdominal pain	Nausea, vomiting, diarrhea	–
Hepatobiliary	–	–	Jaundice
Musculoskeletal	Myalgia, athralgia	–	–
Dermocutaneous	Hyperemia of the face, neck and/or conjuctiva. Pale nasolabial triangle.	Punctuate/confluent rash	Desquamation

[a] Uncommon clinical feature.

of FESLF patients to receive appendectomies in the 1960s. Approximately half of patients develop hepatic lesions exhibiting the features of acute parenchymatous hepatitis. However, morphological liver changes do not persist after symptoms subside. The central nervous system is also commonly affected during the accrual stage: ie, weakness, hypotonia, headache, photophobia, vomiting, and insomnia. Meningism was observed in some patients. Cardiovascular symptoms are uncommon but include the following: syncope, muffled heart sounds, and arrhythmia. The fourth stage is Remission. This usually occurs 6 days after disease onset. During this stage, there is a decrease in the severity of most symptoms, most notably pyrexia, with persistence of rash and increased jaundice. The fifth stage is Recurrence with Exacerbation. This typically occurs 8 days after disease onset. During this stage, there is an increase in symptom severity, with the exception of pyrexia, and desquamation occurs and jaundice is maximal. The sixth stage is Convalescence. The disease course commonly lasts for 12 days, after which there is gradual resolution of all symptoms including rash, desquamation, and jaundice (Table 1).

Based on the frequency and combination of symptoms Zalmover [21] proposed 5 forms of FESLF, listed in order of decreasing frequency: scarlet fever-like, abdominal, icteric, arthralgic, and generalized. In accordance with this classification, common initial misdiagnoses of FESLF are as follows: scarlet fever, gastroenteritis, appendicitis, viral hepatitis, polyarthritis, tonsillitis, and upper respiratory tract infection.

Serotyping of *Yersinia pseudotuberculosis*

Serotyping is a common *Y pseudotuberculosis* typing method, dividing *Y pseudotuberculosis* into 15 O-serotypes (O:1–O:15) and 10 subtypes (O:1a–O:1c, O2a–O2c, O:4a–O:4b, and O:5a–O5:b) based on variability in lipopolysaccharide O-antigen profiles. Most European *Y pseudotuberculosis* isolates are of serotypes O:1–O:3, whereas serotypes O:4–O:15 are primarily found in Asia. All *Y pseudotuberculosis* strains are considered potentially pathogenic, but only *Y pseudotuberculosis* serotypes O:1–O:6 and O:15 have been clinically isolated. The most common clinical serotypes are O:1a, O:1b, and O:3 in Europe and O:4b and O:5b in the Far East. Serotypes O:7–O:14 have only been isolated from environmental and animal sources in Asia (Table 2) [4, 22].

Genotyping of *Yersinia pseudotuberculosis*

Fukushima et al [4] divided *Y pseudotuberculosis* into 6 genetic groups (G1–G6) based on the presence of 3 key virulence factors: the *Y pseudotuberculosis* virulence plasmid (pYV), the high pathogenicity island (HPI), and the subtype of *Y pseudotuberculosis*-derived mitogen produced (YPMa/YPMb/YPMc) (Table 3).

Table 2. Serotyping Scheme and Isolation Source of *Yersinia pseudotuberculosis*

O Groups	O Subgroups	Clinically Isolated	Location Isolated
1	1a	Yes[a]	Europe
	1b	Yes[a]	Europe and Far East
	1c	No	Far East
2	2a	Yes	Europe and Far East
	2b2c	Yes	Europe and Far East
		No	Far East
3		Yes	Europe and Far East
4	4a	Yes	Far East
	4b	Yes[b]	Far East
5	5a	Yes	Europe and Far East
	5b	Yes[b]	Far East
6		Yes	Europe
7		No	Far East
8		No	Far East
9		No	Far East
10		No	Far East
11		No	Far East
12		No	Far East
13		No	Far East
14		No	Far East
15		Yes	Far East

[a] Most common clinically isolated *Y pseudotuberculosis* serotypes in Europe.

[b] Most common clinically isolated *Y pseudotuberculosis* serotypes in Russia and Japan.

Table 3. Geographical Heterogeneity Between Europe and the Far East Regarding the Prevalence of pYV, HPI, YPM Among Wild *Yersinia pseudotuberculosis* Strains

Genetic Group	Presence of			Pathogenic Type	Serotypes From		% Strains From			No. of Isolates
	pYV	HPI Variant	YPM Variant		Europe	Far East	Humans	Animals	Environment	
1	+	Complete	YPMa	Pathogenic	–	1b, 3, 5a	44	56	None	9
2[a]	+	Complete	–	European gastroenteric	1a, 1b	1a, 3, 5b, 13, 14	16	84	None	99
3[b]	+	–	YPMa	Far East systemic (except O:1c and O:7)	4a	1b, 1c, 2a, 2b, 2c, 3, 4a, 4b, 5a, 5b, 6, 7, 10	39	42	19	1, 589
Yersinia similis	–	–	YPMb	Nonpathogenic	–	1b, 5a, 5b, 6, 7, 9, 10, 11, 12	None	54	46	93
5	+	Truncated	YPMc	European Low Pathogenicity	3	3	2	98	–	235
6	+	–	–	Pathogenic	1b, 2a, 2b, 3, 5a	1b, 2a, 2b, 2c, 3, 4a, 4b, 5a, 5b, 6, 7, 10, 11, 13	8	74	18	210

Abbreviations: HPI, high pathogenicity island; YPM, *Y pseudotuberculosis*-derived mitogen.

[a] Most common clinically isolated *Y pseudotuberculosis* genotype in Europe.

[b] Most common clinically isolated *Y pseudotuberculosis* genotype in the Far East (adapted from [4]).

Multilocus Sequence Typing of *Yersinia pseudotuberculosis*

Serotyping and genotyping are products of classic taxonomic criteria, which include pairwise DNA-DNA reassociation and biochemical testing. However, considerable genetic diversity exists within *Yersinia* species. Multilocus sequence typing has been used to further delineate the population genetic structure of *Y pseudotuberculosis*.

Multilocus sequence typing reveals that the "*Y pseudotuberculosis* complex" comprises of 3 distinct populations: the *Yersinia pestis/Y pseudotuberculosis* group, *Yersinia similis*, and the Korean group. This distinction has been confirmed by D-raffinose and D-melibiose fermentation and pyrazinamidase activity [23, 24].

Yersinia similis expresses *Y pseudotuberculosis*-derived mitogen B and lacks pYV and HPI. Isolates belong to genetic type G4. The strain is thought to be apathogenic in humans and has only been isolated in Japan and Germany from small mammals and the environment. *Yersinia similis* may cause diagnostic problems due to being biochemically indistinct from *Y pseudotuberculosis* by commercial test kits [25].

The Korean group resemble *Y pseudotuberculosis* but are genetically more distinct and may be in the process of becoming a different species. Isolates belong to genetic types G3 and G6, which are considered pathogenic. Korean groups' strains have been isolated from humans, suggesting clinical relevance [23].

Yersinia pseudotuberculosis Virulence Plasmid

The presence of the pYV is requisite for pathogenicity in *Yersinia* species; therefore, the presence or absence of this plasmid divides strains into pathogenic (G1–G3, G5–G6) and nonpathogenic subgroups (G4). Subgroups G2 and G3 comprise the majority of clinical isolates, and subgroups G1, G2, and G6 comprise the minority.

The major virulence factors encoded by pYV are a type III secretion system and effector proteins termed *Yersinia* outer proteins (Yops). The YopE is a GTPase-activating protein, and YopH is a protein tyrosine phosphatase, both of which are antiphagocytic. The YopO/YpkA is a serine threonine kinase. The YopM can transit to the host cell nucleus. The YopJ/P inhibits the production of proinflammatory cytokine tumor necrosis factor-α (TNF-α) and induces macrophage apoptosis. The YopT is a cytotoxin that causes actin filament disruption. All Yops have additionally been shown to disrupt intracellular signaling or result in cytoskeletal changes that interfere with phagocytosis [26]. The pYV also encodes proteins involved in the control and translocation of the effector Yops to the target cell: YopN, YopB, YopD, TyeA, lcrG, and lcrV. Pathogenic *Yersinia* species preferentially target the cells of the innate immune system (neutrophils, macrophages, and dendritic cells) for injection of Yops, attenuating the innate immune response [27].

High Pathogenicity Island

The most common clinical genotype in Europe is G2, a strain that possesses pYV and the HPI. The HPI is a 36-kb chromosomal DNA fragment that carries the biosynthetic gene cluster for yersiniabactin, a molecule involved in siderophore-mediated iron acquisition [28]. Iron uptake is a prerequisite for successful bacterial growth and dissemination. The presence of HPI and yersiniabactin production has been shown to increase virulence [29].

Yersiniabactin is produced by almost all European strains causative of non-FESLF disease (serotypes: O:1a, O:1b, O:2b, and O:3) and is absent from almost all Far Eastern strains causative of FESLF (O:1b, O:2, O:3, O:4, and O:5).

Yersinia pseudotuberculosis-Derived Mitogen A

The most common clinical genotype in Russia and Japan is G3, a strain possessing pYV and producing the superantigenic toxin YPMa. The YPMa is produced by all Far East clinical strains

causative of FESLF and is absent from almost all European strains causative of non-FESLF disease. The HPI is absent from most Far Eastern strains, which may represent divergent phylogenetic origin rather than secondary loss [4].

Superantigenic activity in *Y pseudotuberculosis* was first reported in 1993 [30, 31]. The identified toxin was named YPM after it was observed that the toxin had a mitogenic effect on T-cell populations. The YPM is the only superantigenic toxin identified in Gram-negative bacteria. Superantigens are also produced by *Staphylococcus aureus*, *Staphylococcus pyrogenes*, and some retroviruses. Three YPM variants have been detected: YPMa, YPMb, and YPMc, encoded by chromosomal genes of the same name (*ypmA*, *ypmB*, and *ypmC*) [32].

Patients with severe FESLF have higher titers of anti-YPMa, immunoglobulin G, and YPMa-responsive T cells [30]. In the intravenous mouse model of infection, a strain in which *ypmA* had been inactivated caused prolonged mean time to death in comparison to the wild type. However, no significant difference was observed between the Δ*ypmA* mutant and the wild type via the intragastric route [33].

The term "superantigen" refers to YPMa possessing 3 additional properties, in addition to those of a conventional antigen: (1) YPMa is able to bind directly to major histocompatibility complex (MHC) class II molecules on antigen presenting cells [34]; (2) YPMa has a specificity for a set of Vβ elements, the variable region on the beta chain of a T-cell receptor, and this interaction is independent of antigen specificity [35]; and (3) YPMa is able to activate T cells, which are $CD4^+$ or $CD8^+$, including T cells from donors with different MHC class II allotypes [36, 37].

The pathological implication of these properties are that YPMa is able to bind directly to MHC class II molecules, activating T cells as rapidly as conventional antigens activate innate immune cells [34]. In addition, YPMa is able to interact with a subset of T cells containing Vβ elements: Vβ3, Vβ9, Vβ13.1, and Vβ13.2, activating between 5% and 20% of the entire T-cell population [38].

The resultant effect is that a large proportion of active T cells produce TNF-α [39], interferon (IFN)-γ [40], and interleukin (IL)-2 [41]. These cytokines stimulate macrophages, natural killer cells, vascular endothelial cells, and fibroblasts to produce a variety of inflammatory cytokines and chemokines such as the following: IL-1 [42], IL-6, TNF-α [43], IL-12 [44], IL-8 [45], macrophage inflammatory protein (MIP)-1α, MIP-2α [46], monocyte chemoattractant protein (MCP)-1 [47], and MCP-2 [48]. These mediators promote pyrogen and acute reactive protein release and increase vascular permeability.

Diseases caused by superantigenic toxin-producing bacteria share clinical features such as the following: high-grade fever, conjunctival inflammation, pharyngeal inflammation, and latent development of an erythematous skin rash followed by desquamation in the convalescent phase [49, 50]. Superantigens have been shown to enhance susceptibility to lipopolysaccharide-induced shock [51].

DISCUSSION

The differing clinical manifestation of *Y pseudotuberculosis* infection in Europe, compared with that of Russia and Japan, has been recognized since 1959 [13], but only within the last 10 years have FESLF-associated genomic elements been identified. The superantigenic properties of YPMa were first recognized in 1993 [30, 31], and a strong association was established between the presence of gene *ypmA* and strains causative of FESLF in 2001 [4].

The mechanism by which YPMa causes FESLF is likely to be multifactorial. A study that injected purified YPMa subcutaneously into mice found that toxic shock did not occur when monoclonal antibodies were used against TNF-γ, IFN-γ, or CD4, implicating these cytokines and T-cell subtype in the pathogenesis of YPMa-induced toxic shock syndrome [52]. In addition, a variation in susceptibility of mice to *Yersinia* infection has been reported due to variable IFN-γ production [53]. Superantigens have been shown to potentiate the toxicity of endotoxins, such as lipopolysaccharide, and this synergistic action may additionally contribute to morbidity [54].

The majority of Far East *Y pseudotuberculosis* strains produce YPMa, but not all cases of *Y pseudotuberculosis* infection cause FESLF, suggesting interplay between the superantigen and other virulence factors. Genome sequencing of a FESLF causing *Y pseudotuberculosis* strain has implicated additional virulence factors that may be involved in the pathogenesis of the disease [55]. These genomic elements include the following: plasmid VM82, *Yersinia* adhesion pathogenicity island (YAPI), which encodes and type IV pilus [56], and the genes *aec64* and *helic* contained within a horizontally acquired pathogenicity island. It would be useful to additionally inactivate these genes in a Δ*ypmA* mutant and use the resultant stain in the mouse model of infection. Survival data could be analyzed to discern whether any of these genomic elements potentiate the pathogenicity of YPMa.

Patient factors may also play a role in whether YPMa-producing strains give rise to FESLF. The FESLF typically affects children <14 years old [3], and in Japan male children are 1.5 times more commonly affected than females [15]. An exploration of patient factors from a public health and immunological perspective would be useful to further understand the relationship between YPMa-producing strains and FESLF.

CONCLUSIONS

Human *Y pseudotuberculosis* infection occurs sporadically in Europe, but in Russian and Japan epidemiological outbreaks and more severe clinical manifestations significantly contribute to national morbidity. An explanation for this dichotomy is the geographical heterogeneity of virulence factors produced.

Emerging evidence suggests that YPMa is likely to be a key player in the pathogenesis of FESLF. However, the nature of this association is complicated by interactions with other virulence factors and host immunology.

Acknowledgments

Potential conflict of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Malassez L, Vignal W. On microorganisms of zoological tuberculoses [Sur le microorganisme de la tuberculose zoologique]. Arch Physiol Norm Pathol **1884**; 3 Ser. 4: 81–105.
2. Bottone EJ, Bercovier H, Mollaret HH. Genus XLI. Yersinia. In: Garrity GM, Brenner DJ, Krieg NR, Staley JT, ed. Bergey's Manual of Systematic Bacteriology. 2nd ed. Springer: New York; **2005**: pp 838–48.
3. Tseneva GY, Chesnokova MV, Timofeevich KV, et al. *Pseudotuberculosis* in the Russian Federation. Adv Exp Med Biol **2012**; 954:63–8.
4. Fukushima H, Matsuda Y, Seki R. Geographical heterogeneity between Far East and Western countries in prevalence of the virulence plasmid, the superantigen *Yersinia pseudotuberculosis* derived mitogen and the high-pathogenicity island among *Yersinia pseudotuberculosis* strains. J Clin Microbiol **2001**; 39:3541–7.
5. Wuthe HH, Aleksić S, Kwapil S. *Yersinia* in the European brown hare of Northern Germany. Contrib Microbiol Immunol **1995**; 13:51–4.
6. Slee KJ, Skilbeck NW. Epidemiology of *Yersinia pseudotuberculosis* and *Y. enterocolitica* infections in sheep in Australia. J Clin Microbiol **1992**; 30:712–5.
7. Wilson PR. Advances in health and welfare of farmed in New Zealand. N Z Vet J **2002**; 50(Suppl 3):105–9.
8. Nuorti JP, Niskanen T, Hallanvuo S, et al. A widespread outbreak of *Yersinia pseudotuberculosis* O:3 infection from iceberg lettuce. J Infect Dis **2004**; 189:766–74.
9. Rimhanen-Finne R, Niskanen T, Hallanvuo S, et al. *Yersinia pseudotuberculosis* causing a large outbreak associated with carrots in Finland, 2006. Epidemiol Infect **2009**; 137:342–7.
10. Fukushima H, Gomyoda M. Intestinal carriage of *Yersinia pseudotuberculosis* by wild birds and mammals in Japan. Appl Environ Microbiol **1991**; 57:1152–5.
11. European Food Safety Agency. Monitoring and identification of human enteropathogenic *Yersinia spp*. Scientific opinion of the panel of biological hazards. EFSA J **2007**; 595:1–30.
12. Pärn T, Hallanvuo S, Salmenlinna S, et al. Outbreak of *Yersinia pseudotuberculosis* O:1 infection associated with raw milk consumption, Finland, spring 2014. Euro Surveill; **2015**: 20(40).
13. Grunin II, Somov GP, Zalmover LU. [Far Eastern scarlatinoid fever]. Voen Med Zh **1960**; 8:62–6.
14. Somov GF. [Chief results of Far Eastern scarlatina-like fever (epidemic pseudotuberculosis) research]. Vestn Akad Med Nauk SSSR **1980**; 84–9.
15. Fukushima H, Gomyoda M, Tsubokura M, Aleksić S. Isolation of *Yersinia pseudotuberculosis* from river waters in Japan and Germany using direct KOH and HeLa cell treatments. Zentralbl Bakteriol **1995**; 282:40–9.
16. Sato K, Ouchi K, Taki M. *Yersinia pseudotuberculosis* infection in children, resembling Izumi fever and Kawasaki syndrome. Pediatr Infect Dis **1983**; 2:123–6.
17. Tsubokura M, Otsuki K, Sato K, et al. Special features of distribution of *Yersinia pseudotuberculosis* in Japan. J Clin Microbiol **1989**; 27:790–1.
18. Kaasch AJ, Dinter J, Goeser T, et al. *Yersinia pseudotuberculosis* bloodstream infection and septic arthritis: case report and review of the literature. Infection **2012**; 40:185–90.
19. Barnes PD, Bergman MA, Mecsas J, Isberg RR. *Yersinia pseudotuberculosis* disseminates directly from a replicating bacterial pool in the intestine. J Exp Med **2006**; 203:1591–601.
20. Vincent P, Salo E, Skurnik M, et al. Similarities of Kawasaki disease and *Yersinia pseudotuberculosis* infection epidemiology. Pediatr Infect Dis J **2007**; 26:629–31.
21. Zalmover LU. [Results of a 8-year study on clinical picture of Far East scarlatinoid fever]. Sov Med **1969**; 32:93–7.
22. Tsubokura M, Aleksić S. A simplified antigenic scheme for serotyping of *Yersinia pseudotuberculosis*: phenotypic characterization of reference strains and preparation of O and H factor sera. Contrib Microbiol Immunol **1995**; 13:99–105.
23. Laukkanen-Ninios R, Didelot X, Jolley KA, et al. Population structure of the *Yersinia pseudotuberculosis* complex according to multilocus sequence typing. Environ Microbiol **2011**; 13:3114–27.
24. Savin C, Martin L, Bouchier C, et al. The *Yersinia pseudotuberculosis* complex: characterization and delineation of a new species, *Yersinia wautersii*. Int J Med Microbiol **2014**; 304:452–63.
25. Sprague LD, Scholz HC, Amann S, et al. *Yersinia similis* sp. nov. Int J Syst Evol Microbiol **2008**; 58:952–8.
26. Dube P. Interaction of *Yersinia* with the gut: mechanisms of pathogenesis and immune evasion. Curr Top Microbiol Immunol **2009**; 337:61–91.
27. Marketon MM, DePaolo RW, DeBord KL, et al. Plague bacteria target immune cells during infection. Science **2005**; 309:1739–41.
28. Carniel E. The *Yersinia* high-pathogenicity island: an iron-uptake island. Microbes Infect **2001**; 3:561–9.
29. Carniel E, Guilvout I, Prentice M. Characterization of a large chromosomal "high-pathogenicity island" in biotype 1B *Yersinia enterocolitica*. J Bacteriol **1996**; 178:6743–51.
30. Abe J, Takeda T, Watanabe Y, et al. Evidence for superantigen production by *Yersinia pseudotuberculosis*. J Immunol **1993**; 151:4183–8.
31. Uchiyama T, Miyoshi-Akiyama T, Kato H, et al. Superantigenic properties of a novel mitogenic substance produced by *Yersinia pseudotuberculosis* isolated from patients manifesting acute and systemic symptoms. J Immunol **1993**; 151:4407–13.
32. Ramamurthy T, Yoshino K, Abe J, et al. Purification, characterization and cloning of a novel variant of the superantigen *Yersinia pseudotuberculosis*-derived mitogen. FEBS Lett **1997**; 413:174–6.
33. Carnoy C, Mullet C, Müller-Alouf H, et al. Superantigen YPMa exacerbates the virulence of *Yersinia pseudotuberculosis* in mice. Infect Immun **2000**; 68:2553–9.
34. Jardetzky TS, Brown JH, Gorga JC, et al. Three-dimensional structure of a human class II histocompatibility molecule complexed with superantigen. Nature **1994**; 368:711–8.
35. Kappler J, Kotzin B, Herron L, et al. V beta-specific stimulation of human T cells by staphylococcal toxins. Science **1989**; 244:811–3.
36. Dellabona P, Peccoud J, Kappler J, et al. Superantigens interact with MHC class II molecules outside of the antigen groove. Cell **1990**; 62:1115–21.
37. Scholl PR, Diez A, Karr R, et al. Effect of isotypes and allelic polymorphism on the binding of staphylococcal exotoxins to MHC class II molecules. J Immunol **1990**; 144:226–30.
38. Zippelius A, Pittet MJ, Batard P, et al. Thymic selection generates a large T cell pool recognizing a self-peptide in humans. J Exp Med **2002**; 195: 485–94.
39. Fast DJ, Schlievert PM, Nelson RD. Toxic shock syndrome-associated staphylococcal and streptococcal pyrogenic toxins are potent inducers of tumor necrosis factor production. Infect Immun **1989**; 57:291–4.
40. Jupin C, Anderson S, Damais C, et al. Toxic shock syndrome toxin 1 as an inducer of human tumor necrosis factors and gamma interferon. J Exp Med **1988**; 167:752–61.
41. Uchiyama T, Kamagata Y, Wakai M, et al. Study of the biological activities of toxic shock syndrome toxin-1: Proliferative response and interleukin 2 production by T cells stimulated with the toxin. Microbiol Immunol **1986**; 30:469–83.
42. Ikejima T, Dinarello CA, Gill DM, Wolff SM. Induction of human interleukin-1 by a product of *Staphylococcus aureus* associated with toxic shock syndrome. J Clin Invest **1984**; 73:1312–20.
43. Miethke T, Wahl C, Regele D, et al. Superantigen mediated shock: a cytokine release syndrome. Immunobiology **1993**; 189:270–84.
44. Leung DY, Gately M, Trumble A, et al. Bacterial superantigens induce T cell expression of the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen, via stimulation of interleukin 12 production. J Exp Med **1995**; 181:747–53.
45. König B, Köller M, Prevost G, et al. Activation of human effector cells by different bacterial toxins (leukocidin, alveolysin, and erythrogenic toxin A): generation of interleukin-8. Infect Immun **1994**; 62:4831–7.
46. Tessier PA, Naccache PH, Diener KR, et al. Induction of acute inflammation in vivo by staphylococcal superantigens. II. Critical role for chemokines, ICAM-1, and TNF-alpha. J Immunol **1998**; 161:1204–11.
47. Newman I, Wilkinson PC. The bacterial superantigen *Staphylococcal enterot*oxin B stimulates lymphocyte locomotor capacity during culture in vitro. Immunology **1996**; 87:428–33.
48. Neumann B, Emmanuilidis K, Stadler M, Holzmann B. Distinct functions of interferon-gamma for chemokine expression in models of acute lung inflammation. Immunology **1998**; 95:512–21.
49. Todd J, Fishaut M, Kapral F, Welch T. Toxic-shock syndrome associated with phage-group-I *Staphylococci*. Lancet **1978**; 2:1116–8.
50. Cone LA, Woodard DR, Schlievert PM, Tomory GS. Clinical and bacteriologic observations of a toxic shock-like syndrome due to *Streptococcus pyogenes*. N Engl J Med **1987**; 317:146–9.
51. Bohach GA, Fast DJ, Nelson RD, Schlievert PM. Staphylococcal and streptococcal pyrogenic toxins involved in toxic shock syndrome and related illnesses. Crit Rev Microbiol **1990**; 17:251–72.

52. Miyoshi-Akiyama T, Fujimaki W, Yan XJ, et al. Identification of murine T cells reactive with the bacterial superantigen *Yersinia pseudotuberculosis*-derived mitogen (YPM) and factors involved in YPM-induced toxicity in mice. Microbiol Immunol **1997**; 41:345–52.
53. Autenrieth IB, Beer M, Bohn E, et al. Immune responses to *Yersinia enterocolitica* in susceptible BALB/c and resistant C57BL/6 mice: an essential role for gamma interferon. Infect Immun **1994**; 62:2590–9.
54. Blank C, Luz A, Bendigs S, et al. Superantigen and endotoxin synergize in the induction of lethal shock. Eur J Immunol **1997**; 27:825–33.
55. Eppinger M, Rosovitz MJ, Fricke WF, et al. The complete genome sequence of *Yersinia pseudotuberculosis* IP31758, the causative agent of Far East scarlet-like fever. PLoS Genet **2007**; 3:e142.
56. Collyn F, Léty MA, Nair S, et al. *Yersinia pseudotuberculosis* harbors a type IV pilus gene cluster that contributes to pathogenicity. Infect Immun **2002**; 70:6196–205.