decreasing bacterial killing. *Y. pseudotuberculosis* and *Y. pestis* make other siderophores in addition to yersiniabactin.

CLINICAL MANIFESTATIONS

Self-limiting diarrhea is the most common reported presentation in infection with pathogenic *Y. enterocolitica*, especially in children under the age of 4, who form the single largest group in most case series. Blood may be detected in diarrheal stool. Older children and adults are more likely than younger children to present with abdominal pain, which can be localized to the right iliac fossa—a situation that often leads to laparotomy for presumed appendicitis (pseudoappendicitis). Appendectomy is not indicated for *Yersinia* infection causing pseudoappendicitis. Thickening of the terminal ileum and cecum is seen on endoscopy and ultrasound, with elevated round or oval lesions that may overlie Peyer's patches. Mesenteric lymph nodes are enlarged. Ulcerations of the mucosa are noted on endoscopy. Gastrointestinal complications include granulomatous appendicitis, a chronic inflammatory condition affecting the appendix that is responsible for ≤2% of cases of appendicitis; *Yersinia* is involved in a minority of cases. *Y. enterocolitica* infection can present as acute pharyngitis with or without other gastrointestinal symptoms. Fatal *Y. enterocolitica* pharyngitis has been recorded. Mycotic aneurysm can follow *Y. enterocolitica* bacteremia, as can focal infection (abscess) in many other sites and body compartments (liver, spleen, kidney, bone, meninges, endocardium).

In all age groups, *Y. pseudotuberculosis* infection is more likely to present as abdominal pain and fever than as diarrhea. A superantigenic toxin—*Y. pseudotuberculosis* mitogen (YPM)—is produced by strains seen in eastern Russia in association with Far Eastern scarlet-like fever, a childhood illness with desquamating rash, arthralgia, and toxic shock. A similar illness is recognized in Japan (Izumi fever) and Korea. Similarities have been noted with Kawasaki disease, the idiopathic acute systematic vasculitis of childhood. There is an epidemiologic link between exposure of populations to superantigen-positive *Y. pseudotuberculosis* and an elevated incidence of Kawasaki disease.

Y. enterocolitica or *Y. pseudotuberculosis* septicemia presents as a severe illness with fever and leukocytosis, often without localizing features, and is significantly associated with predisposing conditions such as diabetes mellitus, liver disease, and iron overload. Hemochromatosis combines several of these risk factors. Administration of iron chelators like desferrioxamine, which provide iron accessible to *Yersinia* (and have an inhibitory effect on neutrophil function), may result in *Yersinia* septicemia in patients with iron overload who presumably have an otherwise mild gastrointestinal infection. HIV/AIDS has been associated with *Y. pseudotuberculosis* septicemia. The unusual phenomenon of transfusion-associated septicemia is linked to the ability of *Y. enterocolitica* to multiply at refrigerator temperature (*psychrotrophy*). Typically, the transfused unit has been stored for >20 days, and it is believed that small numbers of yersiniae from an apparently healthy donor with subclinical bacteremia are amplified to very high numbers by growth inside the bag at ≤4°C, with consequent septic shock after transfusion. A method for preventing this very rare event (i.e., a range of 1 case in 500,000 to 1 case in several million transfused units in countries such as the United States and France) without unacceptable restriction in the blood supply has not yet been devised.

POSTINFECTIVE PHENOMENA

Like other invasive infections of intestinal origin (salmonellosis, shigellosis), reactive arthritis (articular arthritis of multiple joints developing within 2–4 weeks of a preceding infection) results from autoimmune activity initiated by the deposition of bacterial components (not viable bacteria) in joints in combination with the immune response to invading bacteria. The majority of individuals affected by reactive arthritis due to *Yersinia* are HLA-B27 positive. Myocarditis with electrocardiographic ST-segment abnormalities may occur with *Yersinia*-associated reactive arthritis. Most *Yersinia*-associated cases follow *Y. enterocolitica* infection (presumably because it is more common than infection with other species), but *Y. pseudotuberculosis*–associated reactive arthritis is also well documented in Finland, where sporadic and outbreak infections with *Y. pseudotuberculosis* are more common than in other countries. Of infected individuals identified in a recent *Y. pseudotuberculosis* serotype O:3 outbreak in Finland, 12% developed reactive arthritis affecting the small joints of the hands and feet, knees, ankles, and shoulders and lasting >6 months in most cases. Erythema nodosum **(see Fig. 25e-40)** occurs after *Yersinia* infection (more commonly in women) with no evidence of HLA-B27 linkage.

There is a long-standing association between antithyroid and anti-*Yersinia* antibodies. Antibody evidence of prior *Y. enterocolitica* infection in Graves' disease and increased levels of antithyroid antibody in patients with *Y. enterocolitica* antibodies were first noted in the 1970s. *Y. enterocolitica* contains a thyroid-stimulating hormone (TSH)–binding site that is recognized by anti-TSH antibodies from Graves' disease patients. Raised titers of antibodies to *Y. enterocolitica* whole cells and Yops have been found in some series of Graves' disease patients but not in others. One Danish study of twins found no evidence of an association between asymptomatic *Yersinia* infection (as evidenced by anti-Yop antibody titers) and antithyroid antibodies in euthyroid individuals, while another Danish study of twins with and without Graves' disease found that increased anti-Yop antibody titers were associated with Graves' disease. It remains unclear whether this cross-reactivity is significant in the etiology of Graves' disease.

LABORATORY DIAGNOSIS

Standard laboratory culture methods can be used to isolate enteropathogenic *Yersinia* species from sterile samples, including blood and cerebrospinal fluid. Culture on specific selective media (CIN agar), with or without pre-enrichment in broth or phosphate-buffered saline at either 4°C or 16°C, is the basis of most schema for isolation of yersiniae from stool or other nonsterile samples. Outside known high-incidence areas, specific culture may be carried out by laboratories only upon request. Virulence plasmid–negative strains of *Y. enterocolitica* can be isolated from cultures of stool from asymptomatic individuals, especially after cold enrichment. These strains usually differ in biotype (typically biovar 1a) from virulence plasmid–possessing strains; although some display apparent pathogenicity in a mouse model, virulence plasmid–negative strains are not commonly accepted as human pathogens. Because of the frequency with which the virulence plasmid is lost on laboratory subculture, combined biochemical identification (with biotyping according to a standard schema) and serologic identification are usually required to interpret the significance of an isolate of *Y. enterocolitica* from a nonsterile site. Most pathogenic *Y. enterocolitica* strains currently isolated from humans are of serogroup O:3/biovar 4 or serogroup O:9/biovar 2; this pattern holds even in the United States, where serogroup O:8/biovar 1B strains were previously predominant. Many self-validated multiplex PCR screens for detection of *Y. enterocolitica* in clinical samples—and rather more for its detection in food—have been described, but none of these assays is widely used outside its originating laboratory. Some CE-marked real-time PCR kits are now available in Europe for the diagnosis of yersiniosis in animals; as molecular diagnosis of enteric infection becomes more routine in human disease, it is likely that *Y. enterocolitica* will be included in diagnostic multiplex PCR screens of feces. Because of the presence of Ail in biovar 1a strains, this antigen cannot be used alone in diagnostic assays. A standard for PCR detection in food samples is being prepared by the International Organization for Standardization.

Agglutinating or ELISA antibody titers to specific O-antigen types are used in the retrospective diagnosis of both *Y. enterocolitica* and *Y. pseudotuberculosis* infections. IgA and IgG antibodies persist in patients with reactive arthritis. Serologic cross-reactions between *Y. enterocolitica* serogroup O:9 and *Brucella* are due to the similarity of their lipopolysaccharide structures. Multiple assays are required to cover even the predominant serogroups (*Y. enterocolitica* O:3, O:5,27, and O:9; *Y. pseudotuberculosis* O:1a, O:1b, and O:3), and these assays are generally available only in reference laboratories. ELISA and western blot tests for antibodies to Yops, which are expressed by all pathogenic strains of *Y. enterocolitica* and *Y. pseudotuberculosis*, are