A 73-year-old man treated with long-term hemodialysis, erythropoietin, and intravenous iron sucrose infusions developed *Vibrio vulnificus* infection after eating raw oysters harvested from the Alabama coast. Five of the 31 persons with cases of *V. vulnificus* infection reported to the Alabama Department of Public Health (Montgomery) during 1996–2002 (including the patient described here) also had renal disease. Persons with renal disease, especially those treated with long-term hemodialysis and intravenous iron infusions, may have an increased risk of infection with *V. vulnificus*.

*Vibrio vulnificus* infections often occur in persons with chronic liver disease, alcoholism, diabetes mellitus, immunodeficiencies, hemochromatosis or other iron overload disorders, or *HFE* mutations and in persons receiving iron chelation therapy [1–5]. Persons with chronic renal disease may also have increased susceptibility to *Vibrio* infection [6, 7], but there are few descriptions of such cases [4, 8, 9]. Here, we describe the occurrence of *V. vulnificus* infection in a man treated with long-term hemodialysis who also received periodic intravenous infusions of iron sucrose and erythropoietin for management of anemia. The pertinence of observations in the present case to the pathogenesis of, susceptibility to, and prevention of *V. vulnificus* infections is discussed.

**CASE REPORT**

A 73-year-old white man was treated with long-term hemodialysis, erythropoietin, and periodic infusions of iron sucrose (Venofer; American Regent Laboratories [10]) to maintain a serum transferrin saturation of ≥30% and a serum ferritin concentration of ≥300 ng/mL [11, 12]. On the third and second days before hospital admission, the patient ate raw oysters (but no other raw seafood) harvested in Alabama during April while he was on a visit to the Alabama coast, ~400 km south of his home. Six hours after consuming the second oyster meal, he awoke with shaking chills, a temperature of 40°C, and severe pain and swelling of his left arm distal to his arteriovenous graft.

Expanding hemorrhagic necrotic bullae and progressive tense edema were present in the left arm. The findings of a physical examination did not suggest the occurrence of chronic liver disease. Doppler studies of the left upper extremity revealed no evidence of impaired arterial or venous flow. The leukocyte count was 8200 leukocytes/mm³ (including 41% segmented and
METHODS

Laboratory methods. Blood cell counts, serum biochemistry analyses, and coagulation studies were performed using standard automated clinical methods. HLA-A and -B alleles were detected using low-resolution DNA-based typing (PCR/sequence-specific oligonucleotide probe) [13]. Genotyping for the common HFE missense mutations C282Y (exon 4; nt 845G→A) and H63D (exon 2; nt 187C→G) was performed using genomic DNA obtained from peripheral blood specimens [13]; evaluation for uncommon HFE alleles was not performed [14].

Review of V. vulnificus infections reported in Alabama. We requested information from the Alabama Department of Public Health (Montgomery) regarding reports of V. vulnificus infection and pertinent patient data, including age at diagnosis, sex, race, and reports of concurrent renal disease.

RESULTS

Data collected on Centers for Disease Control and Prevention Cholera and Other Vibrio Illness Surveillance Report forms (CDC 52.79; revised November 1998) by the Alabama Department of Public Health were returned for the years 1996–2002. There were a total of 31 reports of V. vulnificus infection, including the case described here. The mean age (±SD) of these patients at diagnosis was 56 ± 16 years (range, 24–86 years). Twenty-seven patients were men, and 4 were women. Twenty-six patients were white, 3 were Asian, and 2 were African American. Thirteen patients died of V. vulnificus infection, 13 survived the infection, and the survival status was unknown or unreported for 5 patients.

Renal disease of an otherwise unspecified type was reported to be present in 4 of the 31 patients, including the patient described here. It was reported that a 63-year-old white man with renal disease died as a consequence of V. vulnificus infection of a leg wound. A 41-year-old white man with renal disease was infected via a facial wound and survived. A 46-year-old white man with renal disease survived V. vulnificus bacteremia associated with eating raw oysters. The present patient is presumed to have had bacteremia, because this is the most common manifestation of V. vulnificus infection associated with eating raw oysters and the usual primary site of infection in patients with bullae. Renal disease was reported to be absent in 17 cases; the presence or absence of renal disease was not indicated for 10 cases.

DISCUSSION

Infections with V. vulnificus are reported frequently in states adjacent to the Gulf of Mexico in the United States and in other geographic areas, many of which are also contiguous to warm seas [15, 16]. In the southeastern United States, onset of illness with V. vulnificus infection usually occurs during March through November, with the peak number of cases occurring in May [17]. The median ages of patients who develop Vibrio septicemia or wound infections in this geographic area are 63 and 61 years, respectively [7]. These observations are consistent with the month of disease onset and ages of the present patient and of additional cases reported to the Alabama Department of Public Health in the period of 1996–2002.

Most infections are attributable to ingestion of uncooked shellfish (typically raw oysters) or seawater contamination of superficial wounds [1, 8, 15–18]. The history of ingestion of raw oysters by the present patient is consistent with the occurrence of V. vulnificus in oysters harvested in Alabama coastal waters [19] and with other reports of persons with V. vulnificus infections in this geographic area [15, 20, 21]. The development of bullae is typical of V. vulnificus infection, although the results of blood cultures in the present case were negative. Because V. vulnificus can survive for 24 h on skin [21], the possibility that infection in the present patient was due to inoculation of areas of minor trauma by his handling of raw oysters or their shells cannot be excluded. It is also possible that the presence of the arteriovenous dialysis fistula increased the likelihood that the present patient would develop bullae due to Vibrio infection in the same extremity, although this is unproven.
Chronic liver disease, alcoholism, diabetes mellitus, immunodeficiencies, hemochromatosis or other iron overload disorders, inheritance of HFE mutations, and receipt of iron chelation therapy increase susceptibility to *Vibrio* infection [1–5, 16]. It is unknown whether the present patient had cirrhosis or other chronic liver disease, because liver biopsy was not performed; however, there was otherwise no evidence of chronic liver disease. He did not have a hemochromatosis phenotype [13], a common HFE mutation [13, 14], or an HLA immunophenotype typical of hemochromatosis in Alabama [22]; diabetes mellitus; a history of unusual, frequent, or severe infections; or subnormal concentrations of total serum IgG or IgG subclasses. We were unable to identify reports in which erythropoietin therapy was believed to increase susceptibility to infection. Taken together, these observations suggest that chronic renal insufficiency, chronic hemodialysis, or therapy to infection. This is consistent with reports of *V. vulnificus* infections in other persons in Alabama who had renal disease. Furthermore, there are reports of 2 other patients with chronic renal disease who had *V. vulnificus* infection [4, 9]. One also had transfusion iron overload [9], and the other had hypogammaglobulinemia due to nephrotic syndrome [4].

*V. vulnificus* does not grow in human serum or tissue unless iron is readily available [2, 16, 23, 24]. In the present patient, iron could have been available because of his low unbound iron–binding capacity of transferrin, receipt of infusions of iron sucrose, and hyperferritinemia. The serum unbound iron–binding capacity in patients who require hemodialysis is usually lower than that in persons without renal failure [11, 12, 25, 26]. Like the present patient, most persons treated with chronic hemodialysis receive intravenous iron infusions and erythropoietin for treatment of anemia [11, 12, 27]. In such patients, serum non–transferrin-bound iron is often detected before iron infusions, and the non–transferrin-bound iron level and transferrin saturation are increased significantly after infusions [28, 29]. Greater survival of *V. vulnificus* in the whole blood of patients who undergo hemodialysis is associated with greater serum transferrin iron saturation levels and greater serum ferritin concentrations [30]. Although these iron-related values were not measured in the present patient when his infection probably started, his serum transferrin saturation was maintained at >30% and his serum ferritin concentration at >300 ng/mL by iron sucrose infusions. Abnormal iron metabolism in persons treated with chronic hemodialysis is also associated with loss of ability of their serum to resist growth of *Staphylococcus epidermidis* in vitro [28] and with increased in vivo susceptibility to infection with *Yersinia* species [31]. In agreement with these observations, the risk of infections of all types in patients undergoing long-term hemodialysis has been directly related to the dose of intravenous iron [32].

Anemia associated with iron deficiency is common among persons treated with long-term hemodialysis [33–35]. Serum iron values in the present patient indicate that he was iron replete and had hyperferritinemia, although we did not measure his plasma concentrations of free hemoglobin. In mice, however, the lethality of intraperitoneal *V. vulnificus* was found to be directly related to the plasma concentration of hemoglobin, and increased susceptibility to *V. vulnificus* infection lasted beyond the time when hemoglobin levels had returned to normal [36]. *V. vulnificus* also produces a cytotoxic hemolysin [24] that could make hemoglobin iron more readily available in the blood or in a wound.

In vitro studies of blood neutrophils in persons treated with chronic hemodialysis have demonstrated several functional abnormalities that may decrease resistance to *V. vulnificus* infection. These include depressed phagocytosis [37, 38], impaired hydrogen peroxide production [37], and decreased chemiluminescence due to superoxide anion–independent mechanisms [39]. Furthermore, serum from patients undergoing long-term hemodialysis has been found to be less effective than serum from healthy subjects at opsonizing zymosan particles in a neutrophil phagocytosis assay system [38]. It is consistent with these reports that there was a significant negative correlation between the survival of *V. vulnificus* in the whole blood of persons treated with long-term hemodialysis and neutrophil phagocytosis in vitro, and there was evidence that *V. vulnificus* also resists phagocytosis by its possession of an antiphagocytic surface antigen [40].

There are several approaches to reducing the risk of *Vibrio* infection in persons treated with long-term hemodialysis and periodic intravenous iron infusions. It is prudent for nephrologists and other physicians to inform all such patients of the risk of *Vibrio* infection associated with eating raw shellfish and that they should avoid consumption of all uncooked shellfish harvested in warm seas. Forty-eight percent of persons treated with long-term hemodialysis in the Washington, D.C., area reported that they had eaten raw oysters after having kidney disease diagnosed [41]. Thus, education of patients undergoing long-term hemodialysis about *V. vulnificus* is likely to decrease their consumption of raw shellfish [41]. Advisories that persons with chronic renal disease should not eat uncooked shellfish may also be effective when displayed at all points of sale of uncooked oysters or other shellfish [1, 15]. Intravenous iron infusions are typically administered to patients who are being treated with long-term hemodialysis because they are relatively safe and effective [10–12, 27]. However, it seems prudent to maintain the lowest serum concentrations of iron, transferrin saturation, and ferritin that are consistent with an acceptable blood hemoglobin.
concentration. Finally, transfusion iron overload and the use of desferrioxamine should be avoided, if possible.

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References


