



REVIEW NEPHROLOGY

Yersinia enterocolitica Infection in Patients Undergoing Intermittent Hemodialysis

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Abstract

End-stage renal disease is the last stage of chronic kidney disease and affects more than 2 million patients worldwide. The infection-related hospitalization is an important cause of excess morbidity and mortality in this group of patients. *Yersinia enterocolitica* (YE) is one of the bacteria that hemodialysis (HD) patients can occasionally be infected with. The most common symptoms are fever and mild diarrhea, which is self-limited. However, in HD patients, especially in iron-overloaded cases, severe watery or bloody diarrhea can occur. The consumption of undercooked food by patients should sensitize the physician to the possibility of YE infection. Clinically, YE is difficult to diagnose due to nonspecific symptoms and the relatively low prevalence of yersiniosis, compared to other causative pathogens in dialysis patients. There is little information about yersiniosis in HD patients. For this reason, this review aims to summarize the current knowledge on YE infection in HD patients, with the main objective of expounding the problems in identifying, diagnosing, and treating yersiniosis in HD patients.

Keywords: end-stage renal disease; enteric yersiniosis; hemodialysis; *Yersinia enterocolitica*

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Introduction

Yersinia enterocolitica (YE) is a gram-negative bacillus that can cause a zoonotic disease called enteric yersiniosis. YE is characterized by acute diarrhea, mesenteric adenitis, terminal ileitis, and appendicitis-like syndrome, which usually manifests as right lower quadrant abdominal pain, fever, vomiting, elevated white blood cells count, and diarrhea (1). Enteric Yersiniosis occurs more frequently in Europe (1.8 cases per 100,000 population) than in North America (0.28 per 100,000) (2, 3). However, the epidemiology of

yersiniosis remains unclear and poorly understood (4, 5). Children are more exposed to the risk of complications of YE infection (3). YE can cause sepsis in immunocompromised patients, including those with end-stage renal disease (ESRD) undergoing hemodialysis (HD) (1, 6). It is well-known that patients receiving HD have a lot of immunological changes (7, 8). Over the past decades, extensive research has expanded the insights into those changes. It showed a decrease in lymphocytes count, significant increase of natural killer (NK) cells, with high levels of cytokine factors that stimulate monocyte and granulocyte production (9).

Furthermore, it has been demonstrated that uremic toxins, restricted diet, hypervolemia, and hypertension can cause an increase in the number of reactive oxygen species (ROS).

A decrease in antioxidant defense causes disturbances in the intestinal barrier, resulting in the translocation of endotoxins (10). All factors previously mentioned clarify why HD patients are more prone to be infected than the general population. Intravenous iron and deferoxamine therapy also largely increase the susceptibility of HD patients to YE infection (11–13).

Method

Electronic and manual searches were performed in PubMed, Google Scholar, EMBASE, WHO guidelines, and Science Direct using the keywords, “hemodialysis, *Yersinia enterocolitica*, and yersiniosis.” Currently, there is no review regarding this noteworthy topic of YE infection in HD patients. This review summarizes the current knowledge on identifying, diagnosing, and treating YE infection in HD patients, with the principal objective of improving the understanding of the pathogenesis and the clinical features of yersiniosis in HD patients.

Yersinia enterocolitica

YE, one of the members of the Yersiniaceae family under the Enterobacteriaceae order, possesses biochemically heterogeneous strains, and they are classified into six bio-groups (1A,1B,2,3,4,5), with more than 57 O serogroups. However, only strains belonging to bio-groups 1B,2,3,4,5 are pathogenic (8, 14). Serogroups are specific to different geographical areas; for example, bio-serogroups 4/O:3 and 2–3/O: 9 are prevalent in Europe, while 2–3/O:5,27 are prevalent in Japan (14, 15). Temperature is crucial for YE pathogenesis. To infect, YE possesses some virulence factors that help it to colonize the intestinal tract and resist the host defense mechanisms; most of them are temperature-regulated (14, 16–20). The epidemiology of YE infection is poorly understood; most sporadic cases of yersiniosis are reported without apparent sources and a lack of investigation into the sources of contamination (4, 5). Large outbreaks of enteric yersiniosis have been reported from North America (Canada), Europe (The Netherlands, Finland, Norway, and Germany), and Asia (Japan, Bangladesh) (21–27). However, among developed countries, incidences of yersiniosis outbreak appeared to be lower than in less developed countries (4). Several sources and routes of YE infection have been identified, with meats (especially pork), raw milk, and fish being most commonly involved in YE transmission (4, 28, 29). Eating undercooked meat and drinking untreated water are considered to be the main causes of acquiring yersiniosis (29).

Immune Dysfunction in HD Patients

Infections are a major cause of morbidity and mortality in dialysis patients, second only to cardiovascular disease. One of the major predisposing factors for susceptibility to infection in this group of patients is uremia-associated immunodeficiency. It is a dysfunction in which both immune activation and immune suppression coexist. Due to the reduction of the kidney’s clearance, uremic toxins are accumulated and directly or indirectly stimulated by receptors on immune cells. This leads to different aspects of inflammation, including overproduction of ROS and nitrogen species as well as inflammatory cytokines by phagocytes, endothelial cells, and monocyte chemotactic stimulation (30–32). It is important to note that uremia-associated immune dysfunction in HD patients affects both innate and adaptive immunity (31). The innate immunity system helps with recognition and phagocytosis, and the induction of inflammation, while adaptive immunity is associated with the production of antibodies and memory cells. It has been reported that in this group of patients, their neutrophils, macrophages, T-lymphocytes, and B- lymphocytes undergo increased apoptosis (33). Such leukopenia along with the compromised microbicidal ability and nitric oxide synthesis inhibition of innate immune cells attenuate their responsiveness to infections. Furthermore, decreased lymphocytes counts and dendritic cell depletion, which break the messenger bridge between innate and adaptive immune systems in HD patients, weaken the efficiency of both systems’ response to bacterial infections (30, 32). Interestingly, it is worth mentioning that contrary to the mechanisms of immunosuppressive conditions in HD patients, post-renal transplantation patients acquire infections mainly due to the use of immunosuppression drugs rather than their own immunity level post-transplantation (34).

The Role of Iron Overload in YE Infection

Anemia is a major problem in most patients receiving chronic dialysis. It is characterized not only by erythropoietin (EPO) deficiency but also by iron deficiency from poor intestinal iron absorption and low ferritin levels. Almost all HD patients treated with EPO receive parenteral iron (Fe) to ensure sufficient Fe during therapy (35–37). Intravenous Fe therapy helps to maintain Fe stores and decreases EPO demand in patients undergoing chronic HD. While it is generally believed that restoration of hemoglobin toward the target range is a good outcome of Fe therapy, it has been noticed that Fe overload and Fe toxicity may be the adverse consequences of this treatment (38, 39). Long-term prescription of Fe can potentially lead to Fe overload, where it accumulates in organs such as the liver, myocardium, and joints (40, 41). Fe overload has been associated with

reduced phagocytic function and oxidative burst, as well as impaired bacterial killing (42–45). Furthermore, several studies have also demonstrated the close relationship between the availability of Fe and bacterial virulence, including YE (14, 46–48). Most bacteria acquire Fe by producing and releasing high-affinity chelators called siderophores that help to bind and solubilize ferric iron. The Fe/siderophore complexes then enter bacterial cells after binding to specific receptors. Deferoxamine is a bacterial siderophore that is used as a chelating agent in the treatment of Fe toxicity or of chronic Fe overload states. YE requires Fe for growth and has receptors for siderophores, and it is different from other bacteria in that it cannot produce siderophores endogenously (14, 49). In Robins-Browne et al. (11), experiment suggested that iron dextran and deferoxamine exert an adverse influence on the course of experimental yersiniosis, and the effect of this chelating agent probably accounts in part for the increased susceptibility of humans with iron overload to systemic yersiniosis and possibly to other infections. Abcarian et al. (12) reported that systemic YE infection occurs almost exclusively in patients with Fe overload treated with chelating agents. Other researchers also suggest that the administration of deferoxamine against iron overload predisposes to YE sepsis by stimulating bacteria growth (13). It is worth mentioning that iron-chelators are rarely used in the EPO era, but the use of EPO may help protect against such infection.

Incidence and Prevalence of YE Infection in Dialysis Units

There is little information about YE infection in dialysis units. However, the available data suggest that the incidence of yersiniosis in dialysis units is rare, compared to other causative pathogens commonly found in HD patients (50, 51). Most HD patients infected by YE were found to be overloaded with Fe (52–55). However, there is also a report of an HD patient infected with YE without being overloaded with Fe (56). Some studies have suggested that ESA therapy might help in the treatment of YE, as it lowers serum ferritin and transferrin saturation, and improves phagocytosis (57–59). Septicemia due to YE infection has been reported sporadically. Some reported cases were associated with the administration of deferoxamine (60–62), and one case was reported due to eating undercooked meat (56). Table 1 summarizes the reported YE infections in HD patients.

Nosocomial Transmission of YE Infection in Dialysis Units

Several studies have suggested that HD patients are most susceptible to nosocomial infections among all other hospitalized patients (63–65). There are reports of YE spread in hospital dialysis units (21, 66–68), although nosocomial transmission of YE infection is not a major risk for HD patients (69–71).

Table 1: Summary of reported yersinia enterocolitica infection in hemodialysis patients.

Authors	Year of publication	Number of patients	Administration of Deferoxamine	Systemic infection	Iron overloaded	Country	Reference in this review
Waterlot Y et al.	1985	?	Yes	Yes	Yes	France	62
Boyce N et al.	1985	1	Yes	Yes	Yes	Australia	61
Hoen B et al.	1988	1	Yes	Yes	Yes	France	60
Hoen B et al.	1991	?	No	?	Yes	France	55
Gaughan WJ et al.	1992	12	3 of them	Varies	Varies	The United States	54
Fakir M et al.	1992	1	No	Yes	No	France	53
Stoffel et al.	1998	1	No	Yes	No	Germany	6
Mergenhagen et al.	2011	1	No	Yes	Yes	The United States	52
Intra et al.	2017	1	No	Yes	No	Italy	56
Delicou et al.	2017	1	Yes	Yes	Yes	Greece	79

Nosocomial transmission modes of YE are typically through the fecal–oral route; they occur by contact spread between patients, patients and healthcare workers (HCWs) (either direct or indirect), or through contaminated water, food, medications, or devices and equipment (66–68). Although the clinical significance and the contribution of YE to nosocomial transmission in dialysis units are unclear, it is important to strictly enforce all recommendations in universal precautions and HD procedures to prevent YE along with other gastrointestinal infections among all patients in dialysis units. Furthermore, a segregation policy can be considered for HD patients with severe diarrhea to prevent direct or indirect contact transmission (66, 72). Figure 1 summarizes the nosocomial transmission routes and the prevention of YE infection in dialysis units (73–76).

Clinical Presentations and Outcomes of YE Infection in HD Patients

Under most circumstances, YE infection presents with enterocolitis, mild fever, and pseudo-appendicitis. However, HD patients have high-grade fever (up to 40°C), chills, severe abdominal pain, watery or bloody diarrhea, and some extra-intestinal manifestations, such as lymphadenitis, erythema nodosum, reactive arthritis, uveitis, and septicemia, due to their compromised immunity, especially in those treated with deferoxamine (6, 61, 77–79). Clinically, it is not easy to distinguish infections of YE from that of other enteric pathogens. However, if the patient has diarrhea for several days with the pain localized to the right lower quadrant, and has a recent history of consuming undercooked food, especially pork, soft cheese, or unpasteurized milk, YE involvement has to be suspected. In this case, laboratory tests along with computed tomography (CT) imaging can be used to confirm the diagnosis. Although reactive arthritis, erythema nodosum, liver and splenic abscess are major complications of YE infection (78, 80), currently there are no reports on the natural histological progress regarding complications of YE infection in HD patients.

Diagnostic Approaches for YE Complications

There are no specific chemical, radiological, or hematological findings that can confirm the diagnosis of YE infection in HD patients. Multiple approaches are preferred for diagnosis, which can be established by culture isolation from the stool, mesenteric lymph nodes, peritoneal fluid or blood (in case of sepsis), or through CT scan and ultrasonography (81, 82). Nevertheless, there are some special considerations in the use and interpretation of the results in HD patients.

Stool culture

In case of digestive disorders, stool culture is the best way to confirm the diagnosis of YE (83, 84), as the stool shedding

of the organisms could continue for weeks after the onset of syndromes. YE grows more slowly than Enterobacteriaceae and needs selective media such as *Cefsulodin-irgasan-novobiocin* (CIN) agar. Identification and bio-grouping of YE are performed after 48 h on the suspected colonies, and most results are available in 72 h (85). However, because of the compromised immunity of HD patients, their stool cultures are rarely positive; instead, *nucleic acid amplification test* (NAAT) *gastrointestinal multiplex panel* (GIMP) is especially useful for this group of patients because it targets only pathogenic YE strains and has a faster turnaround time (86).

Serological tests

To detect IgG, IgA, and IgM antibodies, and for the diagnosis of YE, common serological tests like *enzyme-linked immunosorbent assays* (ELISA) and immunoblotting have been used in Europe and Japan but not in the United States, because of the lack of guidelines to interpret agglutinin titers (87). Agglutinin titers in the range of 1:128 are considered positive for YE infection; however, in HD patients, negative or minimal titers ($\geq 1:32$) cannot rule out yersiniosis (88).

Imaging studies

As the pain of YE infection is localized to the right lower quadrant, it is easily mistaken for acute appendicitis. Ultrasonography and CT scan are useful in distinguishing true appendicitis from pseudo-appendicitis, especially in HD patients. CT imaging can be used to further confirm or rule out intrahepatic or splenic abscesses (89).

Treatment of YE in HD Patients

YE infection is a self-limiting disease in the general population. Most of the time, patients are treated symptomatically with intravenous fluids in the case of severe dehydration. Nevertheless, HD and other immunocompromised patients are at a higher risk of developing septicemia; thus, they often require treatment with antibiotics (79). As these are beta-lactamase-producing bacteria, penicillin, and first- and second-generation cephalosporins are ineffective (1). The combination of doxycycline and an aminoglycoside is most recommended. Trimethoprim-sulfamethoxazole, fluoroquinolones, chloramphenicol, and third-generation cephalosporins have also been proven to be effective. However, the choice of antibiotics and doses are largely dependent on the initiation time of treatment and the degree of severity of the disease (90–92). In complicated gastrointestinal infections or focal extra-intestinal infections, Cover et al. (77) suggested doxycycline or trimethoprim-sulfamethoxazole as an alternative to fluoroquinolones. Previous study had shown that using third-generation cephalosporins with or without other antibiotics; fluoroquinolones alone or with other medications to be effective in the case of YE septicemia (93).

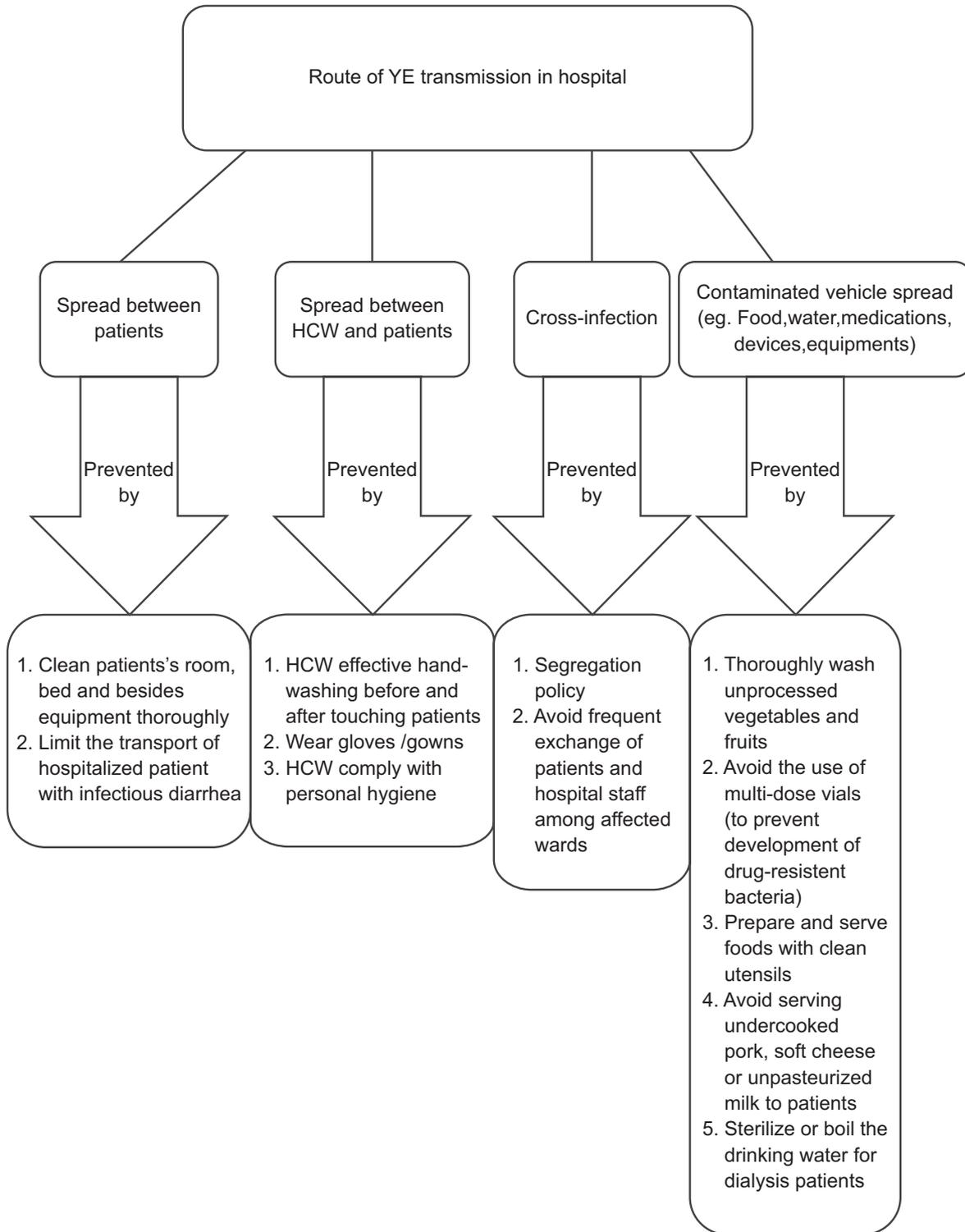


Figure 1: The nosocomial transmission routes and prevention of *Yersinia enterocolitica* infection in dialysis units. YE: *Yersinia Enterocolitica*; HCW: healthcare workers.

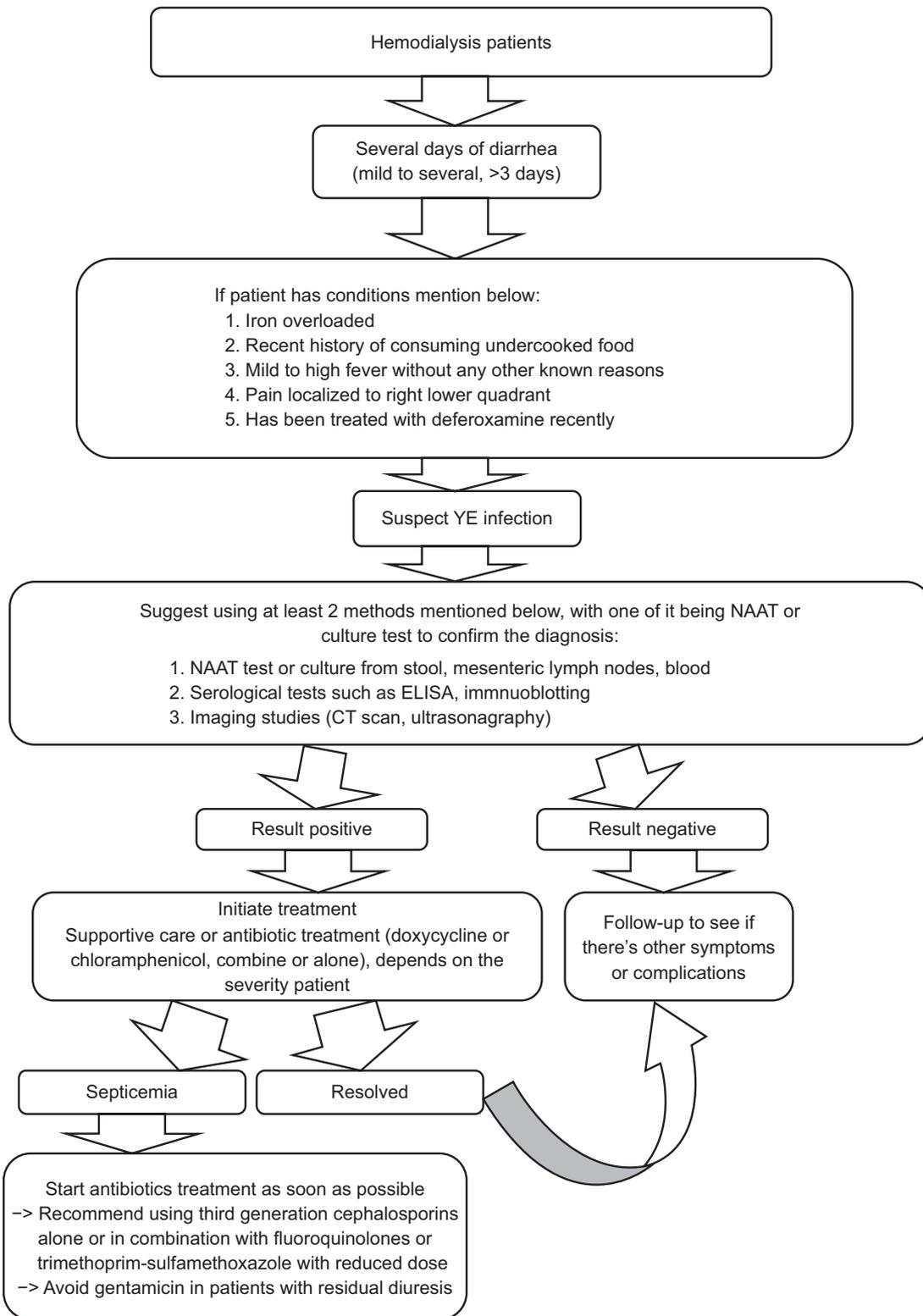


Figure 2: Suggested algorithm for the management of *Yersinia enterocolitica* infection in hemodialysis patients. YE: *Yersinia enterocolitica*; NAAT: nucleic acid amplification test; CT: computed tomography; ELISA: enzyme-linked immunosorbent assay.

Tauxe et al. (93) recommended YE septicemia patients being treated with intravenous third-generation cephalosporin such as ceftriaxone or ciprofloxacin (2 g per day in adults or 100 mg/kg per day in pediatric group, with the maximum dose of 4 g/day) along with gentamicin (5 mg/kg per day divided into one to three doses). As gentamicin can cause further nephrotoxicity in HD patients with residual diuresis, we recommend administering third-generation cephalosporins alone or in combination with fluoroquinolones or a reduced dose of trimethoprim-sulfamethoxazole for YE septicemia HD patients. For nonsepticemia, YE-infected HD patients with severe enterocolitis and extra-intestinal disorders, we recommend doxycycline or chloramphenicol either alone or in combination, depending on the severity. A suggested algorithm for the management of YE infection in HD patients is summarized in Figure 2.

Conclusion

YE infection is not commonly diagnosed in HD patients. However, in HD patients with an iron overload, having severe watery or bloody diarrhea for several days, especially with the recent consumption of undercooked food, should alert physicians to the possibility of YE infection. Stool culture or NAAT along with imaging tests (ultrasonography or CT scan) are recommended to confirm the diagnosis. Differential diagnosis should be made between appendicitis and liver or splenic abscess. In septicemia, antibiotic treatment with third-generation cephalosporins alone or in combination with fluoroquinolones or trimethoprim-sulfamethoxazole are recommended. For non-septicemia YE-infected HD adult patients with severe enterocolitis and extra-intestinal disorders, we recommend using doxycycline. Further studies of YE infection in HD patients may provide new methods of yersiniosis treatment for this group of patients.

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