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Update on Treatment of Enteric Fever in Pediatric Patients According to Current Multidrug Resistance

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ABSTRACT

Introduction: Enteric fever is a severe systemic disease caused by a gram-negative bacillus, Salmonella Enterica serotype Typhi. It commonly occurs in children and young adults. The aim of the research is to address the treatment of enteric fever in pediatric patients including multidrug resistance to first-line drugs.

The treatment of enteric fever has been complicated by the worldwide spread of typhoid organisms resistant to ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol. Ceftriaxone damages the germ structure that can kill Salmonella typhi, germ resistance is limited and there are no harmful side effects when administered to children.

Discussion: The interest in this pathogen is based on Salmonella typhi strains that have become multiresistant to antibiotics such as some cephalosporins, fluoroquinolones, etc. The importance in terms of antimicrobial resistance lies in the failure of conventional treatments, which causes a delay in effective therapeutic management.

Conclusion: Cephalosporins are currently the first line against enteric fever, specifically ceftriaxone and cefixime. In order for the treatment to conclude satisfactorily, it is necessary to observe the disappearance of fever and the decrease of accompanying symptoms.

KEYWORDS: Enteric, fever, salmonella, pediatrics

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INTRODUCTION

Enteric fever is a disease that mainly presents with fever and abdominal pain, this condition is caused by a gram-negative, non-encapsulated, flagellated, facultative anaerobic, non-lactose-fermenting bacillus, member of the Enterobacteriaceae family, which infects the epithelial cells of the small intestine, Salmonella Enterica serotype Typhi (formerly S. typhi). It usually causes systemic involvement and can sometimes lead to serious complications such as intestinal perforation and intestinal hemorrhage.

There are several serotypes of Salmonella that produce a similar syndrome; the main ones are S. enterica serotypes Paratyphi A, B or C; these are collectively referred to as typhoidal serovars of Salmonella and infection with either can result in the clinical syndrome of enteric fever, although it is not possible to reliably predict the causative organism based on clinical findings. Pathogens restricted to humans are S. enterica, S. Typhi and Paratyphi which outside of the acute picture can lead the patient to an asymptomatic chronic carrier state. The term "enteric fever" is a collective term that refers to both typhoid and paratyphoid fever, "typhoid fever" and "enteric fever" are often used interchangeably.

Enteric fever usually occurs predominantly in children and young adults as opposed to older patients. Worldwide it represents a major health problem; apparently the high incidence of infections by the pathogen S. Typhi is closely related to the low socioeconomic level with overpopulation, in some regions of the world are important vehicles for seafood from areas with contaminated water. There are several factors that influence the evolution of the disease such as duration of illness before initiation of treatment, choice of antimicrobial treatment, age, previous exposure to the agent, history of vaccination, virulence of the bacterial strain, amount of inoculum ingested and host factors.

It is recommended to consider a probable case of typhoid fever when the following clinical data are present: fever

higher than 39º C for more than 3 days, headache, general malaise, dry cough.

Therefore, it is important to perform an adequate clinical evaluation in order to give the ideal follow-up to our patients; thus, the objective of the research is to address the treatment of enteric fever in pediatric patients, including multidrug resistance to first-line drugs.

CLINICAL MANIFESTATIONS

Enteric fever (formerly known as typhoid fever) is a serious systemic disease commonly caused by Salmonella Typhi[13] (Gram-negative bacteria) and represents a major global threat to public health. Although the incidence of enteric fever has declined markedly in developed countries, it remains high in developing countries[2] , in Mexico is no exception, since only in 1970 there was an outbreak of more than 10,000 cases, in fact, only today, worldwide, it was shown that each year there are 27 million cases and 200,000 deaths caused by S Typhi[6] . Ingestion of food or water contaminated with human feces is the common mode of transmission. Waterborne disease outbreaks due to poor sanitation and direct fecal-oral spread due to poor personal hygiene are the most common[2] and the incubation period is usually 10 to 14 days, however, it can vary from 3 to 60 days depending, in part, on the size of the inoculum[9] . Once exposed to the agent, salmonellae reach the small intestine, where they pass through the epithelium into the specialized M cells that line Peyer's patches, and then enter the intestinal lymph nodes and enter the bloodstream, whereby salmonellae spread to many other organs, e.g. bone marrow, lungs, kidneys, central nervous system and gallbladder, the latter known as the primary site of chronic carriage[13] . Symptoms in patients may vary, however, fever was the main one (100%) followed by abdominal pain (57.14%), vomiting (50%), anorexia (30.61%) and cough (13.26%). Body pain (4.08%), headache (3.06%), constipation (2.04%), irritability (1.02%), aphasia (1.02%), and seizures (1.02%) were present in a small number of patients. Physical examination is an important part, the most common signs in pediatric patients were toxic appearance (92.85%), coated tongue (66.32%), pallor (39.79%), hepatomegaly (36.73%), and splenomegaly (20.40%). Most of the clinical signs are mostly more common in patients older than 5 years, however, pallor was more commonly observed in patients (51.61%) younger than 5 years[2]

It is recommended to request blood cytometry and investigate the presence of anemia, leukopenia (20- 25%), eosinopenia (70-80%) and thrombocytopenia (usually within the second week in 10-15%) as data associated with typhoid fever[12] . It is recommended to request Widal's agglutination test (febrile reactions) from the second week of onset of clinical data; it will be considered positive when the titers of both antibodies (O and H) are ≥ 1:160. However, a negative test result does not rule out the disease. The isolation of S typhi from bone marrow tissue (myeloculture) has a sensitivity of 80-95% and a specificity of 100%; it is considered the gold standard (reference study) for the diagnosis of typhoid fever[11] , in addition an antimicrobial sensitivity study is also recommended in order to have a broad framework about treatment[10] .

TREATMENT

The treatment of enteric fever has been complicated by the development and rapid global spread of typhoid organisms resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol. In addition, the development of increasing resistance to fluoroquinolones is a growing challenge.Multidrug-resistant (MDR) strains (i.e., those resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol) are prevalent worldwide, although they have declined as other antibiotics have become more widely used for the treatment of enteric fever. MDR strains of S. Typhi and S. Paratyphi have caused numerous outbreaks in endemic regions. Because of this, ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol fell out of favor as first-line drugs for the treatment of enteric fever.

Ceftriaxone is considered an effective antibiotic for the short-term treatment of typhoid fever. Ceftriaxone can selectively damage the germ structure which can kill Salmonella typhi, has a broad spectrum, does not interfere with human body cells, limited germ resistance and no harmful side effects when administered to children. This is very important to take into account, since chloramphenicol can cause leukopenia, agranulocytosis, anemia, neurological, intolerance or hyperergic reaction. [1]Ceftriaxone and cefixime appeared to be the first line of antibiotic treatment for typhoid fever. Despite susceptibility, clinical nonresponse was observed in about 10 percent of patients requiring antibiotic combinations[1] . Using chloramphenicol the body temperature decreases on average 3.5 days and on average using ceftriaxone at 2.3 days. This shows that typhoid fever patients using ceftriaxone have fever faster than chloramphenicol.[4]

Early and effective treatment requires a good medical history, as treatment may vary if the patient acquired the strain somewhere endemic for multidrug-resistant strains. The prevalence of MDR strains varies in Africa, the Middle East and Central Asia, from 10 to 80 percent, depending on the country. Genome sequencing and analysis of international isolates has identified a predominant S. Typhi MDR strain, H58, which has spread throughout Asia and Africa, displacing more susceptible strains and causing ongoing MDR epidemics. As of 2018, approximately 75 percent of strains in Africa remain MDR, with no significant change over the past 15 years. In endemic locations outside Asia, empiric treatment with ceftriaxone is suggested. If ceftriaxone is not available, cefotaxime is a reasonable alternative. Although some studies have shown slower defervescence time with cephalosporins (compared with fluoroquinolones), frank resistance to third-generation cephalosporins is rare in most locations, so ceftriaxone is

likely to be an effective empiric agent. Aztreonam has been effective in small trials and can be used in people who cannot take cephalosporins because of allergies. In situations where the risk of decreased susceptibility to fluoroquinolones is low, a parenteral fluoroquinolone is also a suitable alternative.

For patients with severe or complicated enteric fever acquired in Pakistan (e.g. recent travel to Pakistan), empiric therapy with a carbapenem (Meropenem) is suggested. This is due to an ongoing outbreak of XDR S. Typhi in this region.

DISCUSSION

Typhoid fever was shown to be common among rural and urban populations. In the study of Modi, R et. al, patients with enteric fever were identified in the age group of 6 to 10 years, they concluded that this was probably due to exposure to unhygienic food that the children were exposed to outside, this finding is comparable with the studies of Bano-Zaidi, M et. al in which the patients' ages ranged from 1 to 70 years, and 80% of the patients were between 5 and 29 years old. al in which the ages of the patients ranged from 1 to 70 years, and 80% of the patients were between 5 and 29 years, while Mogasale V et. al the median age of the cases were 29 years, which is higher than the median age reported in several other typhoid endemic areas. Although no age is exempt from typhoid fever, contaminated drinking water continues to be identified as the major risk factor for typhoid fever in all studies.

Improving sanitation facilities and increasing access to safe drinking water and cleaning products for rural populations presents a major challenge for developing countries, where there is a higher prevalence of cases and overcrowding. Poor hygiene practices also appear to increase the likelihood of contracting typhoid fever.

Identifying prolonged febrile syndrome is often difficult to diagnose in pediatrics due to the low specificity of its symptoms, and it tends to be confused with malaria, dengue, influenza and other febrile diseases in countries where the latter pathologies are endemic.(7)

Interest in the presentation of this pathogen is based on Salmonella typhi strains that have become multidrug resistant to antibiotics such as some cephalosporins, fluoroquinolones, etc;(1) associating this with a more severe disease, with high mortality rates, especially in children under two years of age. Resistance to fluoroquinolones is alarming because they are commonly used in the treatment of chronic carrier state.(1)

The importance in terms of antimicrobial resistance lies in the failure of conventional treatments, which causes a delay in effective therapeutic management that leads to the patient worsening in symptoms, increasing morbimortality, as well as in the study of Modi, R. hospitalized patients presented a therapeutic failure in treatment of ciprofloxacin and ceftriaxone, which later developed seven of them developed severe complications.

In the study by Dahiya, S. te. in concluding that at present the ideal drug for the treatment of typhoid fever are the third generation cephalosporins, ceftriaxone and cefixime are currently the drug of choice for treating these infections. In case the patient is hospitalized and the fever does not remit with monotherapy, combined therapy is recommended.

CONCLUSIONS

As first-line physicians it is of utmost importance to diagnose enteric fever in pediatric patients effectively, so it is necessary to take a detailed clinical history in order to continue with the pharmacological approach, in which there are currently different bibliographies where they mention the presence of multidrug resistance in the most previously used drugs, as is the case of chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole; which, in addition to not acting against gram-negative bacteria, their administration can cause an aggravation of the disease until it becomes a deadly enteric fever. Because of this, the use of new antibiotics as treatment in this pathology continues to be investigated; among which are the cephalosporins as first line against enteric fever, specifically ceftriaxone and cefixime, because there is very little evidence of the presence of multiresistances in these antibiotics and there are no data that talk about side effects specifically in children. For the treatment to conclude satisfactorily in pediatric patients, it is necessary to observe their temperature changes, i.e. the disappearance of fever and the decrease of the accompanying symptoms present in enteric fever.

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