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CEFTRIXONE SERIOUS INFECTION DISEASE IN SEPTICEMIA

A brief introduction of sepsis epidemiology, ceftriaxone, ceftriaxone doses, infection site pathogen, managements, pathophysiology, treatment.

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Abstract

Ceftriaxone belongs to the class of medicines known as cephalosporin antibiotics. It works by killing bacteria or preventing their growth. It is generally recognized as safe and effective when used as a single drug in the therapy of septicemia and other serious infections involving bacteremia in both adults and children. An advantage of ceftriaxone over other third-generation cephalosporins is its long serum half-life, which allows the drug to be given every 12 hours in children or less frequently in adults also Two potent third generation cephalosporins with similar antibacterial spectra, but different pharmacokinetics were compared in patients suffering from septicemia due to different organisms Sepsis is a life-threatening organ dysfunction syndrome caused by a dysregulated host response to infection, associated with a mortality rate over 25%, that has been designated a global health priority. Most of the sepsis is community-acquired, and progression can be insidious, making diagnosis difficult. Prognosis depends on early administration of broad-spectrum antibiotics and effective source control. Certain factors which are major determinants in the survival of the septic patient - age, underlying disease, infecting organism - are beyond the physician's control. Others, however, we can have some impact on. These include initial vigorous supportive treatment, early and appropriate antibiotic administration and timely surgical intervention. In the following discussion current understanding of the pathophysiology of sepsis is outlined, together with a practical approach to the problem of patient management. Risk factors for the development of septicemia, which are similar to those associated with any urinary tract infection, are reviewed. The "ABCs of Management" are outlined. Early recognition and effective management including selection of an effective antimicrobial agent for empiric therapy can have a direct impact on the patient's survival. Potential infecting type of bacteria are reviewed, and specific empiric therapies are described. In addition to antibiotic administration, rapid resuscitation and surgical drainage or debridement of the source of infection are integral parts of immediate treatment for sepsis. The importance of locating and draining (or removing) the source of infection is emphasized. Since sepsis is a systemic infection, patients must be monitored closely for failure of vital physiologic

functions. Suggestions are offered for dealing with lack of response to antibiotic and supportive measures. Rapid diagnosis and effective management can improve the prognosis for septic patients.

Ceftriaxone sodium

MW: 552.600 g/mol MF: C18H16N8O7S3-2

IUPAC name: (7R)-7-[(2E)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoace.

Keywords: Ceftriaxone; Dose; Pharmacokinetics; Sepsis SEPSIS EPIDOMILOGY; INFECTION SITE; PATHOGEN;

INTRODUCTION

Septicemia is a clinically significant form of bacteremia complicated by toxemia, fever, malaise, and often shock (see Table 3-5). Septicemia is characterized by the multiplication of microorganisms within the bloodstream and "seeding" into blood from fixed microcolonies present in one or more tissues. Ceftriaxone belongs to the class of medicines known as cephalosporin antibiotics. It works by killing bacteria or preventing their growth Sepsis is a clinical syndrome characterized by systemic inflammation due to infection. **Sepsis**, also known as **septicemia**, **septic**, septic shock or **blood poisoning, is** a potentially life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs. This initial stage of sepsis is followed by suppression of the immune system. Common signs and symptoms include fever. increased heart rate, increased breathing rate and confusion. There may also be symptoms related to a specific infection, such as a cough with pneumonia or painful urination with a kidney infection. The very young, old, and people with a weakened immune system may have no symptoms of a specific infection, and the body temperature may be low or normal instead of having a fever. Severe sepsis causes poor organ function or blood flow. The presence of low blood pressure, high blood lactate, or lower unit may suggest poor blood flow. Septic shock is low blood pressure due to sepsis that does not improve after fluid replacement. There is a continuing severity ranging from sepsis to septic shock. Although wide-ranging and dependent upon the population studied, mortality has been estimated to be greater than 10 percent and greater 40 percent when shock is present in this topic review, the management of sepsis and septic shock is discussed. Our approach is consistent for the most part with 2021 guidelines issued by the Surviving Sepsis and septic operation

Ceftriaxone -

Ceftriaxone (ceftriaxone sodium and dextrose) Injection is an antibacterial drug used to treat conditions such as lower respiratory tract infections, skin and skin structure infections urinary tract infections, pelvic inflammatory bacterial Septicemia bone and joint infections, and meningitis.

Common side effects of Ceftriaxone include

- rash,
- diarrhea,
- nausea,
- vomiting,
- upset stomach,
- dizziness,
- headache,
- pain or swelling in your tongue,

- a lump where the medicine was injected,
- sweating,
- blood cloth
- vaginal itching or discharge,
- vaginal yeast infection,
- Anemia
- changes in taste, or
- Flushing.

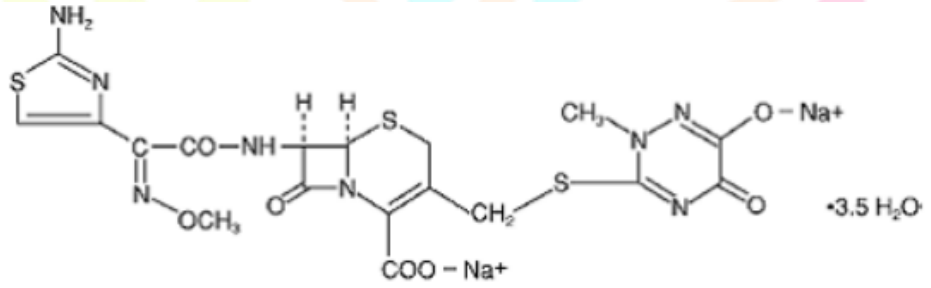
dosages

The recommended dose of Ceftriaxone is 1 to 2 grams once per day. Do not exceed 4 grams in one day. Talk to your doctor about your individual dosage recommendation.

Description -

Ceftriaxone for injection, USP is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is (6R,7R)-7-[2-(2-Amino-4- thiazolyl)glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl)Thio]methyl]- 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7^2 -(Z)-(O-methyl oxime), disodium salt, sesquaterhydrate.

The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$. It has a calculated molecular weight of 661.60 and the following structural formula:



Ceftriaxone sodium is white or yellowish, crystalline powder, which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 1% aqueous solution is approximately 6.7. The color of ceftriaxone solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

MANGMENT-

Sepsis epidemiology, infection site and pathogens

Sepsis is a life-threatening organ dysfunction syndrome caused by a dysregulated host response to infection, associated with a mortality rate over 25%, that has been designated a global health priority. Most of the sepsis is community-acquired, and progression can be insidious, making diagnosis difficult. Prognosis depends on early administration of broad-spectrum antibiotics and effective source control

Sepsis affects 1.7 million adults in the USA annually, with nearly 270,000 deaths, and between 19.4 and 31.5 million episodes annually, worldwide, with 5.3 million deaths. A global study reported a decrease of 18.8% in sepsis incidence worldwide from 60 million cases in 1990 to 49 million cases in 2017. However, sepsis-related Medicare hospital admissions increased from 811,644 to 1,136,889

from 2012 to 2018, with an associated increase in hospital and subsequent skilled nursing care cost from $27.7 to $41.5 billion. Mortality at 6 months remains high for septic shock at 60% and severe sepsis at 36%. Bacterial infections are the most common cause, but viruses and fungi may occur in patients with comorbid conditions and immunosuppression. The most common foci in hospitalized patients are infections of the lower respiratory tract, followed by intra-abdominal, bloodstream, intravascular line infections, and urinary tract infections

TREATMENT -

Sepsis is a rare complication of an infection and occurs when an extreme immune system response triggers widespread inflammation throughout the body. Sepsis can be mild or severe. But regardless of severity, it's a potentially life-threatening illness that requires immediate medical attention. Timely administration of appropriate antibiotic therapy (i.e., with activity in vitro against the causative pathogens) is the cornerstone of the management of serious ICU infections. Observational, prospective and retrospective studies support the use of appropriate empiric antibiotic therapy in sepsis and septic shock. A retrospective cohort study of 21,608 adults with bloodstream infections from 131 US hospitals found that 4165 (19%) received discordant empiric antibiotic therapy (based on in vitro testing of blood culture isolates), which was independently associated with increased mortality risk. SYMPTOMS OF SEPSIS include high fever, high heart rate, and fast breathing rate. As the infection progresses, some people experience difficulty breathing, stomach pain, confusion, and dizziness. Sepsis can also lead to dangerously low blood pressure and organ failure. There isn't a single treatment for sepsis. Treatment varies and depends on the cause of the infection that led to sepsis, as well as the severity of symptoms. Because mild sepsis can rapidly progress to severe sepsis and then septic shock, doctors must work quickly to reduce inflammation. Although various organisms can cause an infection that turns into sepsis, such as bacteria, viruses, or fungi, the main treatment for sepsis is antibiotics since most cases are caused by a bacterial infection. Because the body demands more oxygen in this state, some patients with sepsis and septic shock are placed on mechanical ventilators to give their lungs and body some rest and the ability to heal, warns Brown. This therapy helps raise the amount of oxygen the lungs receive and the amount of oxygen that's delivered to your blood. There are different ways to receive oxygen therapy, such as through a nasal tube, a face mask, or mechanical ventilation (inserting a tube into the trachea). The administration of early appropriate therapy must be balanced against the unnecessary use of antibiotics, especially broad-spectrum agents, in the absence of proven infection, with excess mortality associated with this practice, and an increased risk of colonization and infection with antibiotic-resistant pathogens. Thus, the use of rapid, broad-spectrum empiric therapy, especially in emergency settings, must come with a commitment to de-escalation, meaning shorter duration, less broad-spectrum therapy and fewer drugs, once clinical and microbiologic data become available.

TREATMENT USING BY ANTIBIOTICS CEFTRIXONE -

Unbound ceftriaxone pharmacokinetics in adult patients have been poorly characterized. The objective of this study is to determine the ceftriaxone dose that achieves an unbound trough concentration ≥ 0.5 mg/L in > 90% of adult patients receiving once-daily dosing presenting to the emergency department (ED) with sepsis. We performed a prospective single-Centre pharmacokinetic study. A single unbound plasma ceftriaxone concentration was obtained from each patient using blood collected as part of routine clinical practice within the first dosing interval. Samples

were analyzed using a validated ultra-high pressure liquid chromatography method. Population pharmacokinetic analysis and Monte Carlo simulations (n = 1000) were performed using Metrics for R. A ceftriaxone concentration obtained throughout the first dosing interval was available for fifty adult patients meeting sepsis criteria. Using this concentration time-curve data, a pharmacokinetic model was developed with acceptable predictive performance per the visual predictive check. Ceftriaxone administered as a 1-g once-daily dose is unlikely to achieve a therapeutic exposure in > 90% of patients presenting to the ED with sepsis. Simulations show that a 1-g once-daily dose is unlikely to achieve the minimum therapeutic ceftriaxone exposure in > 90% patients with a creatinine clearance ≥ 60 mL/min. However, a 2-g once-daily dose will provide a therapeutic exposure for target pathogens infecting patients with a creatinine clearance ≤ 140 mL/min. Increasing the ceftriaxone dose to 2 g once daily will likely achieve the desired exposure against target pathogens. Future clinical trials are required to determine any potential clinical benefit of optimized ceftriaxone dosing.

Doses in Adults -

dosage in adults - Two potent third generation cephalosporins with similar antibacterial spectra but different pharmacokinetics were compared in patients suffering from septicemia due to different organisms. Sixty patients with a variety of underlying diseases were included in the study. They received either 2-4 g ceftriaxone (active ingredient of Rocephin) once a day or 1 g cefotaxime every 4 h for 10-15 days. Our data confirm that a single dose of 1 g twice a day of ceftriaxone should be sufficient to treat septicemia.

Doses in child -

For children with suspected sepsis but without clinical evidence of shock, the same management steps are recommended if an expedited diagnostic evaluation supports the diagnosis of sepsis. Both the expedited diagnostic evaluation, which includes additional laboratory and clinical testing to assess for infection and organ dysfunction, and initiation of the above management steps should occur within **three hours** of initial suspicion of sepsis Restoration of tissue perfusion and reversal of shock is identified by the following therapeutic endpoints (goals below in parentheses) Quality of central and peripheral pulses (strong, distal pulses equal to central pulses)

- ●Skin perfusion (warm, with capillary refill <2 seconds)
- ●Mental status (normal mental status)
- ●Urine output (≥1 mL/kg/hour, up to 40 mL/hour, once effective circulating volume is restored)
- ●Blood pressure (systolic pressure at least fifth percentile for age):
- •<1 month of age: 60 mmHg
- •1 month to 10 years of age: 70 mmHg + [2 x age in years]
- •10 years of age and older: 90 mmHg

However, blood pressure by itself is not a reliable end point for assessing the adequacy of resuscitation.

- ●Normal serum lactate (e.g., <2 mmol/L)
- ●Central venous oxygen saturation ($ScvO_2$) ≥70 percent, if available and appropriate (invasive monitoring may not be needed in patients who rapidly respond to initial resuscitation); this target is **not** applicable to children with congenital heart disease characterized by mixing lesions

Pathophysiology

Sepsis is caused by a combination of factors related to the invading pathogen(s) and to the status of the immune system of the host. The early phase of sepsis characterized by excessive inflammation (sometimes resulting in a cytokine storm) may be followed by a prolonged period of decreased functioning of the immune system. Either of these phases may prove fatal. On the other hand, systemic inflammatory response syndrome (SIRS) occurs in people without the presence of infection, for example, in those with burns, polytrauma, or the initial state in pancreatitis and chemical pentominoes. However, sepsis also causes similar response to SIRS. There are several

microbial factors that may cause the typical septic inflammatory to cascade to an invading pathogen is recognized by its pathogen- associated molecular patterns (PAMPs). Examples of PAMPs include lipopolysaccharides and flagellin in gram-negative bacteria, muramyl dipeptide in the peptidoglycan of the gram-positive bacterial cell wall, and CpG bacterial These PAMPs are recognized by the pattern recognition receptors (PRRs) of the innate immune system, which may be membrane-bound or cytosolic. There are four families of PRRs: the toll like receptor, the c type lectin receptors, the NOD-like receptors, and the RIG-like receptors Invariably, the association of a PAMP and a PRR will cause a series of intracellular signaling cascades. Consequentially, transcription factors such as nuclear factor-kappa Band activator protein-1 will up-regulate the expression of pro-inflammatory and anti-inflammatory cytokines. Upon detection of microbial antigens, the host systemic immune system is activated. Immune cells not only recognize pathogen-associated molecular patterns but also damaged-associated molecular patterns from damaged tissues. An uncontrolled immune response is then activated because leukocytes are not recruited to the specific site of infection, but instead they are recruited all over the body. Then, an immunosuppression state ensues when the proinflammatory T helper cell 1 (TH1) is shifted to TH2, mediated by interleukin 10 which is known as "compensatory anti-inflammatory response syndrome". The apoptosis (cell death) of lymphocytes further worsens the immunosuppression. Neutrophils, monocytes, macrophages, dendritic cells, CD4+ T cells and B cells all undergo apoptosis, whereas regulatory T cells are more apoptosis resistant. Subsequently, multiple organ failure ensues because tissues are unable to use oxygen efficiently due to inhibition of cytochrome c oxidase. The low blood pressure seen in those with sepsis is the result of various processes, including excessive production of chemicals that dilated blood vessels such as nitric oxide, a deficiency of chemicals that constrict blood vessels such as vasopressin and activation of ATP-sensitive potassium channels. In those with severe sepsis and septic shocks, this sequence of events leads to a type of circulatory shock known as distributive shocks.

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