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A study of the third generation of cephalosporin ceftriaxone, uses and precautions

A Research Project

Submitted to Council of College of Pharmacy / university of Babylon in Partial Fulfillment of the Requirements for the Graduation in Pharmacy.

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

" وَقُل رَّبِّ زِدْنِي عِلْمًا "

صدق الله العلي العظيم

سورة طه الآية (114)

Certification

I certify that this research has been prepared under my supervision at the College of Pharmacy /University of Babylon.

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Approved by the Council of the College of Pharmacy/University of Babylon

DEDICATION

Dedicated to,

Our parents who taught us to believe in ourselves

our teachers who used to lead us to light,

to our Al-hashed and army men who spread peace,

and finally, to our supervisor who helped us along the project work time,

Assist. Prof. Dr. Lena Fadhil Hamza

Acknowledgement

Owing to the blessing of The Almighty God, we finished this research project.

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Abstract

Ceftriaxone is a third generation semi-synthetic cephalosporin, part of a group of broad-spectrum antimicrobials. This includes gram-positive and gram-negative aerobic bacteria, as well as minimal anaerobic action.

Method:

A randomized sample of 70 patient was selected from Marjan Teaching Hospital –Al Hayat Microbiology Laboratory , Imam Al-Sadiq Teaching Hospital- Main Microbiology Laboratory.The data has been collected from the microbiology laboratory records of antibiotic susceptibility test .This is a case study carried out from November 2022 to May 2023. The study was taken place and data collected in Babylon province of Iraq at Marjan Teaching Hospital -Al Hayat Microbiology Laboratory , Imam Al-Sadiq Teaching Hospital - Main Microbiology Laboratory.

Results: Conclusion:

In our study in many healthcare organizations we found that the most common bacteria that show resistance to cefteriaxone is streptococcus ,E.coli ,citrobacter and staphylo - coccus this is likely due to the frequent uses of cefteriaxone without real indication to it. Bacterial sensitivity test is very much negligited in the healthcare facilities and the wrong time of doing bacterial culture where the patient is already on antibiotic therapy.The development of bacterial resistance is due to the mechanism of resistance in this bacterial strain where:Streptococcus has multiple morphology to change resistance mechanisms through gene mutation E.coli can cause biofilm formation which can't overcome by cefteriaxone .Citrobacter often overcome cefteriaxone through over expression of their chromosomal beta lactamase. And finally staphylococcus Resistance mechanisms include enzymatic inactivation of the antibiotic, alteration of the target with decreased affinity for the antibiotic.

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1.1. Introduction

Ceftriaxone is a third generation semi-synthetic cephalosporin, part of a group of broad-spectrum antimicrobials. This includes gram-positive and gram-negative aerobic bacteria, as well as minimal anaerobic action(1). It is mainly known for its bactericidal action against gram-negative pathogens (1,2).The bactericidal activity of ceftriaxone results from the inhibition of cell wall synthesis and is reportedly mediated through ceftriaxone's binding to penicillin-binding proteins(3). Ceftriaxone is stable to beta-lactamases and displays good activity against most gram-negative bacteria including the Enterobacteriaceae. Its long half-life is unique among third-generation cephalosporins (4). It can be given either intravenously or intramuscularly (5). Ceftriaxone is 100% bioavailable following intramuscular injections and is eliminated by biliary and renal excretion. It is primarily indicated in gram-negative meningitis and for multi-antibiotic resistant infections. It is a drug of choice for gonorrhea and for community acquired pneumonia(4). Ceftriaxone is generally well tolerated, adverse events can include diarrhea, nausea, abdominal pain, dyspepsia, headache, and rash. Rare but potentially severe adverse events include Clostridium difficile-associated diarrhea, hypersensitivity reactions, angioedema, anaphylaxis and Stevens Johnson syndrome/toxic epidermal necrolysis(5).

1.2 Aim of the Research Project

The aim of this research project is:

1. To gain a comprehensive understanding of ceftriaxone properties, mechanisms of action, pharmacokinetics, pharmacodynamics, indications, and potential adverse effects.
2. Assess the susceptibility and resistance patterns of different bacterial strains to ceftriaxone to guide appropriate antibiotic therapy and combat the spread of resistant organisms.

3. By studying ceftriaxone comprehensively, researchers and healthcare professionals can enhance its rational use, improve patient outcomes, and contribute to the development of new treatment guidelines and therapeutic strategies.

2.1. Historical Review

2.1.1 History of Cephalosporins

Cephalosporins, along with penicillin, belong to the beta-lactam Group of bactericidal antibiotics(6). Historically, cephalosporins have been discovered by the Italian scientist Giuseppe Brotzu (1895-1976) in 1945, who isolated a mixture of compounds from the mold Acremonium (previously called Cephalosporium)(7). Later on, in 1955, the British scientists Edward Abraham (1913–1999) and Guy Newton (1919-1969) discovered, purified, and described the structure of cephalosporin C as a minor component of the mixture of antibiotics produced by Acremonium(8) .Cephalosporin C possessed only modest antibacterial activity and was produced in negligible quantities until 1960 when the era of semisynthetic cephalosporins began.Structurally, these antibiotics contain a six-member dihydrothiazine ring fused to the beta-lactam portion. The substituents at C3, C4, and C7 are key factors for their antimicrobial activity. Furthermore, the carboxyl group at C4 needs to remain unchanged, and the acylamido side chain at C7 (7-aminocephalosporanic nucleus) has a pivotal role in the hydrophilic/hydrophobic features of these compounds.Cephalosporins are produced by structural modification in the laboratory. Based on the timeline of drug development and their antimicrobial properties, these antibiotic agents are grouped into different generations, first through fifth(9).The distinction concerns the structure of the molecules and implies important therapeutic implications. In general, moving from the first to the third generation, the microbicidal activity of cephalosporins decreases against gram-positive organisms but increases against gram-negative bacilli. Notably, the resistance against beta-lactamases increases from the first to the fifth generation(10).In terms of antibacterial activity, first-generation cephalosporins such as cefadroxil, cefazolin, and cephalexin are solely active against gram-positive organisms. Furthermore, second-generation (e.g., cefaclor, cefotetan, cefamandole, and loracarbef) has improved activity against gram-negative and some anaerobes, although there is less activity against gram-positive microbes.The third-generation class of cephalosporins is the most commonly prescribed group. These

cephalosporins are semisynthetic analogs with different chemical substitutions on the C7 acylamido chain. The class includes ceftriaxone, cefdinir, cefixime, cefixime, cefditoren, cefpodoxime, ceftazidime, cefoperazone, ceftizoxime, ceftibuten, and others. They are broad-spectrum antimicrobial agents with activity against both gram-negative and gram-positive organisms. Nevertheless, they are more active against gram-negative bacteria and organisms resistant to the first and second regeneration cephalosporins. Furthermore, these agents seem to be less active against several gram-positive bacteria, such as *Streptococcus* and *Staphylococcus* species. In other words, they are active against some gram-positive strains, although not as active as the first-generation cephalosporins. Interestingly, third-generation cephalosporins show more stability to beta-lactamases than first or second generations, especially those produced by Klebsiella, Haemophilus influenzae, and Escherichia coli.Cefoperazone and ceftazidime are active against Pseudomonas aeruginosa, while the rest of the class is not. Despite the rising prevalence of gram-positive organisms in spontaneous bacterial peritonitis (SBP), third-generation cephalosporins appear to furnish adequate empirical treatment in patients with healthcare-associated and community-acquired SBP without hepatocellular carcinoma(11).

2.1.2 History of Ceftriaxone

A research programme on cephalosporins was conducted in the author's laboratory with the aim of creating compounds with improved antibacterial and pharmacokinetic properties. In the first phase of this programme, great attention was paid to the study of how the structure of a 3-heterocyclic-thiomethyl side chain is capable of influencing antibiotic activity within a large series of model compounds possessing the same acyl side chain (2-thienylacetyl) as cephalothin. Several structural and physico-chemical features of the heterocyclic thiols used and the corresponding cephalosporins were correlated with in vitro and in vivo activity. As a result of these studies, the enolic 2-methyl-6-hydroxy-5-oxo-as-triazine-3-thiol was identified as the most interesting

substituent, since the corresponding cephalosporin showed a valuable resistance breakthrough against several cephalothin-resistant Proteus strains. Consequently, further studies involving the use of different acyl side chains were performed. The introduction of the basic 2-(2-amino-4-thiazolyl)-2-(Z)-methoxyimino-acetyl side chain finally led to ceftriaxone, which has a very long elimination half-life of 8 hours, high beta-lactamase stability and extremely high chemotherapeutic efficacy against a broad spectrum of Gram-positive and Gram-negative pathogens. Owing to these properties, ceftriaxone is the first beta-lactam antibiotic suitable for once-daily administration(12).Ceftriaxone was patented in 1978 and approved for medical use in 1982(13).It is on the World Health Organization's List of Essential Medicines(14).

2.2. Chemistry

Ceftriaxone is a third-generation cephalosporin compound having 2-(2-amino-1,3-thiazol-4-yl)-2-(methoxyimino)acetylamino and [(2- methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)sulfanyl]methyl side-groups. It has a role as an antibacterial drug, an EC 3.5.2.6 (beta-lactamase) inhibitor and a drug allergen. It is a cephalosporin, a member of 1,2,4-triazines, a member of 1,3- thiazoles and an oxime O-ether. It is a conjugate acid of a ceftriaxone(1-)(15,16).

Ceftriaxone sodium is a white to 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 sodium solutions ranges from light yellow to .amber, depending on the length of storage, concentration and diluent used Each vial contains ceftriaxone sodium equivalent to 250 mg, 500 mg, 1 gram or 2 grams of ceftriaxone activity. Ceftriaxone sodium contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity(17,18).

2.3.Pharmacodynamics

Ceftriaxone is a cephalosporin/cephamycin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually grampositive, organisms(19).Ceftriaxone has in vitro activity against grampositive aerobic, gram-negative aerobic, and anaerobic bacteria(20).The bactericidal activity of ceftriaxone results from the inhibition of cell wall synthesis and is mediated through ceftriaxone binding to penicillinbinding proteins (PBPs)(21).Ceftriaxone is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended-spectrum beta-lactamases(19).However, resistance to ceftriaxone usually occurs through beta-lactamase hydrolysis, altered PBPs, or reduced bacterial cell permeability(21). Ceftriaxone is often used in combination with macrolide and aminoglycoside antibiotics for the treatment of pneumonia. It is also a choice drug for treatment of bacterial meningitis. In pediatrics, it is commonly used in febrile infants between 4 and 8 weeks of age who are admitted to hospital in order to exclude sepsis. Ceftriaxone has also been used to treat Lyme disease, typhoid fever, and gonorrhea (22). Ceftriaxone should not be mixed with or giving in the same IV line as diluents/products containing calcium as they may cause ceftriaxone to precipitate(19).Ceftriaxone use may also cause biliary sludge or gallbladder pseudolithiasis(19,23).

2.3.1. Mechanism of action

Ceftriaxone works by inhibiting the mucopeptide synthesis in the bacterial cell wall (19,21).The beta-lactam moiety of ceftriaxone binds to penicillin-binding proteins (PBP) (carboxypeptidases, endopeptidases, and transpeptidases) located in the bacterial cytoplasmic membrane. PBPs participate in the terminal stages of assembling the bacterial cell wall, and in reshaping the cell wall during cell division. Inactivation of PBPs interferes with the cross-linkage of peptidoglycan chains necessary for bacterial cell wall strength and rigidity. Therefore, binding of ceftriaxone to these enzymes causes the enzyme to lose activity and the bacteria to produce defective cell walls, causing cell death. Compared to the second and first generation cephalosporins, ceftriaxone is more

active against gram-negative bacteria and less active against gram-positive bacteria. Ceftriaxone also crosses the blood-brain barrier and reaches therapeutic concentrations in the central nervous system (24).

2.4. Pharmacokinetic

Ceftriaxone is a third-generation cephalosporin that exhibits saturable plasma protein binding, which influences its pharmacokinetic parameters depending on the dose. Systemic clearance and volume of distribution of total drug show dependence on both concentration and time, whereas for unbound drug these parameters remain constant. The decrease in renal or non-renal clearance with age or in the presence of disease states is often compensated by the concurrent increase in free fraction, resulting in no apparent changes in half-life and no need for dose adjustment. Because of its unusually long plasma half-life, the availability of intramuscular administration and its high intrinsic activity against many organisms, ceftriaxone has become a popular agent in once-daily therapy of infections in pediatric patients, gonococcal infections and outpatient management of pneumonia and osteomyelitis(25).

2.4.1. Absorption

Ceftriaxone is only given as an injection, either intramuscularly or intravenously(26). It is rapidly and completely absorbed following intramuscular administration(26). Ceftriaxone is less than 1% bioavailable if given orally(27).Ceftriaxone is normally poorly absorbed through the mucosal membrane of the intestine and is thus ineffective when administered by the oral route. One method to improve the its permeability is to use permeation enhancers. The need of high doses of enhancer is closely related to the fact that most permeation enhancers deliver drug into the bloodstream not by increasing the permeability of the drug itself but by perturbing the biological membrane and consequently allowing drug absorption nonspecifically. Permeation enhancers reversibly and specifically or nonspecifically increases permeation of drug across the GIT epithelia(28,29). Polyoxyethylene ether, mixed micelles containing sodium

taurocholateand glycerol monooleate or oleic acid were reported to enhance the absorption of cephalosporins. The effect of selected permeation enhancers on the lipophilicity of the drug was investigated using the octanol/buffer system. The experimental results on the partition coefficient were confirmed using in vitro transport model (static Franze diffusion cell) with excised intestinal membrane of animal(30) .The results indicated that there is significant improvement in the permeability of the drug and the extent of enhancement was highly dependent on the type of used absorption enhancer. The results obtained from this study indicate that ceftriaxone sodium could be successfully delivered orally when formulated with permeation enhancers(31).

2.4.2. Volume of Distribution

The apparent volume of distribution of an intravenous or intramuscular dose in healthy patients is 5.78 to 13.5 L(26). Ceftriaxone has good enough CSF penetration to be used as an effective treatment of bacterial meningitis(33). Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1-2 g; concentrations well above the minimal inhibitory concentrations of most pathogens responsible for infection are detectable for more than 24 hours in over 60 tissues or body fluids including lung, heart, biliary tract/liver, tonsil, middle ear and nasal .The volume of distribution and the plasma clearance of ceftriaxone in pediatric patients were threefold greater than those in adults(26).

2.4.3. Protein Binding

Ceftriaxone is 95% protein bound. It is reversibly bound to albumin, and the binding decreases with the increase in the concentration, e.g. from 95% binding at plasma concentrations of <100 mg/L to 85% binding at 300 mg/L. Owing to the lower albumin

content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma(26).

2.4.4. Metabolism

Metabolism of ceftriaxone is negligible. Ceftriaxone is not metabolized systemically; only the intestinal flora transforms the agent into inactive metabolites(34).

2.4.5. Route of elimination

Ceftriaxone is primarily eliminated unchanged in urine (33-67%)(26). The remainder is eliminated through secretion in the bile and removed from the body via the feces as microbiologically inactive compounds(26,35).

Multiple dosing of ceftriaxone with doses ranging from 0.5 to 2 g at 12- or 24-hour intervals by intravenous and intramuscular routes resulted in 15 to 36 percent accumulation of ceftriaxone in plasma and no change in its elimination half-life(35).

2.4.6.Half-life

In human subjects, ceftriaxone exhibits an exceptionally long elimination half-life (5.8 to 8.7 hours) and a small degree of nonlinearity in its pharmacokinetics which can be ignored in its clinical applications(26)[2] The half-life of ceftriaxone in the middle ear fluid has been estimated to be 25 hours(26,36).

2.4.7.Clearance

The plasma clearance of ceftriaxone in healthy adults receiving a 0.15-3g dose is 0.58 to 1.45 L/hour(26). The renal clearance of ceftriaxone is 0.32 to 0.73 L/hour(26). In intensive care unit patients, ceftriaxone's total drug clearance was 0.96L/h (0.55-1.28 L/h), and unbound drug clearance was 1.91 L/h (1.46-6.20 L/h) (37).

2.4.8. Special populations

- Neonates and elderly patients

In neonates, urinary recovery accounts for about 70% of the dose. Renal or hepatic dysfunction In infants aged less than eight days and in elderly persons aged over 75 years, the average elimination half-life is usually 2 to 3 times that in the young adult group.

- Renal or hepatic dysfunction

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half-life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

2.5.1. Ceftriaxone Dosage

Ceftriaxone is available as intravenous and intramuscular injection(39).

Adult and Pediatric Dosage Forms and Strengths:

1-Injectable solution

- 1 g/50 mL
- 2 g/50mL

2-Powder for injection

- 250 mg
- 500 mg
- 1 g
- 2 g

2.6.Indication and uses:

Ceftriaxone injection is used to treat certain infections caused by bacteria such as gonorrhea (a sexually transmitted disease), pelvic inflammatory disease (infection of the

female reproductive organs that may cause infertility), meningitis (infection of the membranes that surround the brain and spinal cord), and infections of the lungs, ears, skin, urinary tract, blood, bones, joints, and abdomen. Ceftriaxone injection is also sometimes given before certain types of surgery to prevent infections that may develop after the operation. Ceftriaxone injection is in a class of medications called cephalosporin antibiotics. It works by killing bacteria. Ceftriaxone and other third-generation antibiotics are used to treat organisms that tend to be resistant to many other antibiotics(42).

1-Gonorrhoea:

Ceftriaxone is the recommended treatment for gonorrhea, a sexually transmitted infection caused by the bacteria Neisseria gonorrhoeae. According to the Centers for Disease Control and Prevention (CDC) guidelines, ceftriaxone should be given as a single intramuscular injection of 250 mg for the treatment of uncomplicated gonorrhea(43). Ceftriaxone is subsidised if prescribed for the treatment of confirmed ciprofloxacinresistantgonorrhoea(42).Research shows that ceftriaxone attains the optimal concentrations to prevent the development of step-wise mutations and resistance in Neisseria gonorrhoea.Standard treatment with ceftriaxone has been shown to be greater than 95% effective.Therefore a repeat test to ensure cure is not usually required as long as the patient is asymptomatic after treatment. Azithromycin (oral) is also routinely given when treating gonorrhoea, because co-infection with chlamydia is common(43,44).

2-Treatment failure:

Treatment for gonorrhea failed in nine cases. In all nine cases, researchers analysed the genetic information from strains of gonorrhea isolated from the men. The researchers were not able to find genetic markers of resistance to ceftriaxone in any of these cases. They therefore re- treated all the men with another round of ceftriaxone (without any oral antibiotics) .at a dose of 1 gram given as a single intravenous dose Subsequently, the researchers found that eight of the nine men were cured. Again, investigation found that the ninth man did not have ceftriaxone- resistant gonorrhea, so he was given a third

course of this drug and was cured(43). Another researches shows that treatment efficacy different from country to another : Research describe a gonorrhoea case with combined high-level azithromycin resistance and ceftriaxone resistance. In February 2018, a heterosexual male was diagnosed with gonorrhoea in the United Kingdom following sexual intercourse with a locally resident female in Thailand and failed treatment with ceftriaxone plus doxycycline and subsequently spectinomycin. Resistance arose from two mechanisms combining for the first time in a genetic background similar to a commonly circulating strain. Urgent action is essential to prevent further spread(45). Another one describe a gonorrhoea case with ceftriaxone plus high-level azithromycin resistance. In April 2022, an Austrian heterosexual male was diagnosed with gonorrhoea after sexual intercourse with a female sex worker in Cambodia. Recommended treatment with ceftriaxone (1 g) plus azithromycin (1.5 g) possibly failed. Worryingly, this is the second strain in an Asian Neisseria gonorrhoeae genomic sublineage including high-level azithromycinresistant strains that developed ceftriaxone resistance(47).

3-Pelvic inflammatory disease:

Ceftriaxone is an antibiotic that has been used in the treatment of pelvic inflammatory disease (PID). PID is a serious infection of the female reproductive organs that can cause long-term complications such as chronic pain, infertility, and ectopic pregnancy. Ceftriaxone is typically used in combination with other antibiotics to provide broad-spectrum coverage against the bacteria that commonly cause PID. One study published in the International Journal of Gynecology & Obstetrics evaluated the efficacy of ceftriaxone in the treatment of PID. The study found that the combination of ceftriaxone (250mg) with doxycycline(100mg) and metronidazole(400mg) was highly effective in resolving PID symptoms and preventing recurrence. The study concluded that this combination therapy should be considered as a first-line treatment for PID. In addition to

its use in treating PID, ceftriaxone has also been used for the prophylaxis of sexually transmitted infections (STIs) that can lead to PID, such as gonorrhea and chlamydia(42).

4- Meningitis:

Ceftriaxone is one of the preferred antibiotics for the treatment of bacterial meningitis, which is an infection of the membranes surrounding the brain and spinal cord. According to the Infectious Diseases Society of America (IDSA) guidelines, ceftriaxone is recommended as the initial therapy for meningitis in adults and children, as it is effective against several types of bacteria that can cause meningitis.Cefteriaxone has produced high cure rates in patients with meningitis caused by meningococci, pneumococci, or H. influenzae(49).The use of ceftriaxone in the treatment of bacterial meningitis is supported by numerous studies. For example, a randomized controlled trial published in the New England Journal of Medicine compared the efficacy of ceftriaxone with that of another antibiotic, cefotaxime, in the treatment of bacterial meningitis. The study found that both antibiotics were equally effective, with no significant difference in clinical outcomes or adverse effects(49).

5-Community-acquired pneumonia (CAP):

Ceftriaxone is often used as a first-line treatment for CAP caused by Streptococcus pneumoniae, Haemophilusinfluenzae, and other bacteria. According to a 2021 systematic review and metaanalysis, ceftriaxone is one of the most effective antibiotics for the treatment of CAP and is associated with lower mortality rates compared to other antibiotics. In addition to its use in treating CAP, ceftriaxone has also been used for the empiric treatment of hospital-acquired pneumonia (HAP) and ventilator- associated pneumonia (VAP) caused by multidrug resistant organisms(47).

6-treatment of urinary tract infection:

UTIs are one of the most common bacterial infections in humans, and ceftriaxone has been shown to be effective against a wide range of organisms that cause UTIs, including Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis. Ceftriaxone is primarily used for the treatment of complicated UTIs, such as pyelonephritis (infection of the kidney), as well as for the treatment of infections caused by multi-drug resistant organisms. In addition, ceftriaxone has been used for the empiric treatment of UTIs in patients with complicated medical histories or who are at risk for drug-resistant infections. One study published in the Journal of Antimicrobial Chemotherapy found that ceftriaxone was highly effective in the treatment of complicated UTIs caused by extended-spectrum betalactamase (ESBL)-producing E. coli. The study concluded that ceftriaxone should be considered as a first-line treatment for these types of infections. Another study published in the journal BMC Infectious Diseases compared the efficacy of ceftriaxone and ciprofloxacin (another commonly used antibiotic for UTIs) in the treatment of uncomplicated UTIs. The study found that ceftriaxone was as effective as ciprofloxacin in treating these infections, with a lower risk of adverse effects(50).

7-Sepsis:

Ceftriaxone is used as a treatment for sepsis, which is a life- threatening condition caused by a bacterial infection that has spread to the bloodstream. According to a 2020 review, ceftriaxone is a recommended first- line antibiotic for the treatment of sepsis in both adults and children, as it has a broad spectrum of activity against many types of bacteria(51).

7-Other uses for this medicine:Ceftriaxone injection is also sometimes used to treat sinus infections, endocarditis (infection of the heart lining and valves), chancroid (genital sores caused by bacteria), Lyme disease (an infection that is transmitted by tick bites that may cause problems with the heart, joints, and nervous system), relapsing fever (an infection that is transmitted by tick bites that causes repeated episodes of fever), shigella (an infection that causes severe diarrhea), typhoid fever (a serious infection that is common

in developing countries), salmonella (an infection that causes severe diarrhea), and Whipple's disease (a rare infection that causes serious problems with digestion). Ceftriaxone injection is also sometimes used to prevent infection in certain penicillin-allergic patients who have a heart condition and are having a dental or upper respiratory tract (nose, mouth, throat, voice box) procedure, patients who have fever and are at high risk for infection because they have very few white blood cells, close contacts of someone who is sick with meningitis, and in people who have been sexually assaulted or who have been bitten by humans or animals(42).

2.7. Adverse Effects

1.Gastrointestinal Effects: The most common side effect of ceftriaxone is gastrointestinal discomfort, which includes nausea, vomiting, diarrhea, and abdominal pain. These symptoms are usually mild and transient and do not require discontinuation of therapy. However, in rare cases, ceftriaxone may cause severe colitis, which can lead to dehydration, electrolyte imbalances, and even death(52).

2. Hypersensitivity Reactions : Ceftriaxone can cause allergic reactions in some individuals, ranging from mild rashes to severe anaphylactic shock. Symptoms of hypersensitivity reactions may include hives, itching, wheezing, difficulty breathing, and swelling of the face, lips, or tongue. Patients with a history of allergies to cephalosporins or penicillins are at higher risk of developing an allergic reaction to ceftriaxone.(53)

3. Hematologic Effects: Ceftriaxone can affect the blood-forming cells in the bone marrow, leading to a decrease in the number of white blood cells, red blood cells, and platelets. This condition is known as hematologic toxicity and can increase the risk of infections, anemia, and bleeding disorders. Patients with renal impairment and those receiving high doses of ceftriaxone are at higher risk of developing hematologic toxicity.(54)

4. Hepatobiliary Effects:Ceftriaxone can cause liver function abnormalities, including elevations in serum transaminases, bilirubin, and alkaline phosphatase. These changes are

usually reversible and asymptomatic, but in rare cases, they may progress to liver failure. Patients with preexisting liver disease or those receiving high doses of ceftriaxone are at higher risk of developing hepatobiliary toxicity.(55)

5.Renal: elevations of the BUN (1.2%). Less frequently reported (<1%) were elevations of creatinine and the presence of casts in the urine.

6.Central nervous system : headache or dizziness were reported occasionally (<1%).(52)

7.Genitourinary : moniliasis or vaginitis were reported occasionally (<1%).(52)

8.Miscellaneous: diaphoresis and flushing were reported occasionally (<1%).(52)

Other rarely observed adverse reactions (<0.1%) include abdominal pain, agranulocytosis, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, flatulence, gallbladder sludge, glycosuria, hematuria, jaundice, leukocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.(52)

The adverse effects of ceftriaxone are generally dose-dependent and reversible. Most of the adverse effects can be managed by reducing the dose or discontinuing the medication. However, in some cases, the adverse effects can be severe and life-threatening, requiring immediate medical attention. Therefore, healthcare professionals should monitor patients receiving ceftriaxone for any signs of adverse effects and intervene promptly when necessary.(52)

2.8.Toxicity

the toxicity are likely similar to the adverse effects of the medication. If overdose of ceftriaxone occurs, treat with symptomatic and supportive treatment, as ceftriaxone levels will not be reduced by dialysis(56)

2.8.1.Hepatotoxicity

Parenteral administration of ceftriaxone has been associated with development of biliary sludge in 3% to 46% of patients. The incidence may be higher in children than adults and is associated with higher doses and longer courses of treatment and possibly with fasting or dehydration. The syndrome is referred to as “pseudolithiasis” as the sludge and stones consist largely of ceftriaxone and they resolve spontaneously when the drug is stopped, indicating that surgery can be avoided. Most cases occur with minimal or no symptoms. Frank symptoms of cholecystitis are reported in up to 5% of patients who develop pseudo-lithiasis. Typically, serum enzymes and bilirubin levels remain normal even with biliary colic, but in rare instances there is cholestatic jaundice or gallstone pancreatitis that can be severe and require surgical intervention. Sludge and symptoms of gallbladder disease can arise within a few days of starting therapy, but typically resolve rapidly once ceftriaxone is stopped, although sludge and gallstones may be detectable by ultrasound for several months.(56).

2.9. Contraindication

2.9.1.Contraindicationdefinition

A contraindication is a specific situation in which a drug, procedure, or surgery should not be used because it may be harmful to the person.

2.9.2.Types of contraindication

There are two types of contraindications:

1. Relative contraindication means that caution should be used when two drugs or procedures are used together. (It is acceptable to do so if the benefits outweigh the risk.)
2. Absolute contraindication means that event or substance could cause a life-threatening situation. A procedure or medicine that falls under this category must be avoided.

Some treatments may cause unwanted or dangerous reactions in people with allergies, high blood pressure, or pregnancy. For example, isotretinoin, a drug used to treat acne, is absolutely contraindicated in pregnancy due to the risk of birth defects. Certain decongestants are contraindicated in people with high blood pressure and should be avoided.

Many medicines should not be used together by the same person. For instance, a person who takes warfarin to thin the blood should not take aspirin, which is also a blood thinner. This is an example of a relative contraindication (57).

2.9.3. Ceftriaxone Contraindications:

2.9.3.1.Hypersensitivity

Ceftriaxone is contraindicated in patients with known hypersensitivity to Ceftriaxone, any of its excipients or to any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin and other beta lactam antibacterial agents may be at greater risk of hypersensitivity to Ceftriaxone(59).

2.9.3.2.Neonates

- Premature neonates: Ceftriaxone is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).
- Hyperbilirubinemicneonates:Hyperbilirubinemic neonates should not be treated with Ceftriaxone. Ceftriaxone can displace bilirubin from its binding to serum albumin, leading to a risk of bilirubin encephalopathy in these patients.
- Neonates Requiring Calcium Containing IV Solutions

  Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of Ceftriaxone-calcium

  Cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Ceftriaxone and calcium-containing fluids(60,61).

In some of these cases, the same intravenous infusion line was used for both Ceftriaxone and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. There have been no similar reports in patients other than neonates(58).

2.9.3.3.Lidocaine

Intravenous administration of Ceftriaxone solutions containing lidocaine is contraindicated. When lidocaine solution is used as a solvent with Ceftriaxone for intramuscular injection, exclude all contraindications to lidocaine. Refer to the prescribing information of lidocaine(58).

2.8.3.4. Clostridium difficile associated diarrhea (CDAD):

has been reported with use of nearly all antibacterial agents, including ceftriaxon, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated(62).

2.8.3.5.Hemolytic Anemia

An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including ceftriaxone . Severe cases of hemolytic anemia, including fatalities, have been reported during treatment in both adults and children. If a patient develops anemia while on ceftriaxone, the diagnosis of a

cephalosporin associated anemia should be considered and ceftriaxone stopped until the etiology is determined(63).

2.10. Interactions

It is important to be aware of potential drug interactions with ceftriaxone to ensure safe and effective treatment. Here are some notable drug interactions:

2.10.1.Calcium-containing medications:

Ceftriaxone should not be mixed or administered simultaneously with any calcium-containing intravenous solutions, such as calcium-containing electrolyte solutions or total parenteral nutrition (TPN) solutions. The formation of ceftriaxone-calcium precipitates can occur, leading to potentially life-threatening lung and kidney complications(64).

2.10.2. Nonsteroidal anti-inflammatory drugs (NSAIDs):

Concurrent use of ceftriaxone and NSAIDs, such as ibuprofen or naproxen, may increase the risk of bleeding or bruising. This combination should be used with caution, especially in individuals with a history of bleeding disorders or those taking anticoagulant medications(65).

2.10. 3.Warfarin:

Ceftriaxone may enhance the anticoagulant effect of warfarin, increasing the risk of bleeding. Close monitoring of the International Normalized Ratio (INR) is recommended when these medications are used together. Dose adjustments of warfarin may be necessary(66).

2.10.4.Probenecid:

Probenecid may increase the blood levels and prolong the elimination half-life of ceftriaxone. This combination is sometimes used to enhance the effectiveness of ceftriaxone in the treatment of certain infections(67).

2.10. 5. Aminoglycosides:

Concurrent use of ceftriaxone with aminoglycoside antibiotics, such as gentamicin or tobramycin, may increase the risk of kidney damage. Monitoring of kidney function is advised when these medications are used together(68).

There is no food interaction observed with ceftriaxone found yet.

2.11.Resistance

2.11.1.Introduction to Resistance:

With the discovery of antibiotics, the healthcare community thought that the battle with infectious diseases was won. However, now that so many bacteria have become resistant to multiple antimicrobial agents, the war has seemingly escalated in favor of the bacteria. Infectious diseases are currently a significant cause of morbidity and mortality worldwide. An assessment of these diseases by the World Health Organization (WHO) found that lower respiratory infection, diarrheal diseases, HIV/AIDS, and malaria are in the top ten contributors to morbidity and mortality (69). The advent of antimicrobial resistance has added significantly to the impact of infectious diseases, in number of infections, as well as added healthcare costs. Even though we have a very large number of antimicrobial agents from which to choose for potential infection therapy, there is documented antimicrobial resistance to all of these, and this resistance occurs shortly after a new drug is okayed for use. These concerns prompted the WHO to launch a Global Action Plan on antimicrobial resistance in 2015(69,70).Antibiotic resistance is set to be one of this century's major public health challenges. Few people are aware of this issue, which is also poorly documented. A report commissioned by the British government in 2016 estimated that as many as 10 million people could die from an antibiotic resistant infection by the year 2050(70).

2.11.1.Introduction to Resistance:

Antimicrobial agents can be divided into groups based on the mechanism of antimicrobial activity. The main groups are: agents that inhibit cell wall synthesis, depolarize the cell membrane, inhibit protein synthesis, inhibit nuclei acid synthesis, and inhibit metabolic pathways in bacteria. improper stewardship of antimicrobial agents has helped lead to the tremendous resistance issue that we now face. Factors that have contributed to the growing resistance problem include: increased consumption of antimicrobial drugs, both by humans and animals; and improper prescribing of

antimicrobial therapy. Overuse of many common antimicrobials agents by physicians may occur because the choice of drug is based on a combination of low cost and low toxicity . There may also be improper prescribing of antimicrobials drugs, such as the initial prescription of a broad-spectrum drug that is unnecessary, or ultimately found to be ineffective for the organism(s) causing the infection . The danger is that excessive use of antibiotics in humans leads to emergence of resistant organisms . In addition, prior use of antimicrobial drugs puts a patient at risk for infection with a drug resistant organism, and those patients with the highest exposure to antimicrobials are most often those who are infected with resistant bacteria(72,74).

2.11.3 Cefteriaxone bacterial resistance:

Ceftriaxone is an extended-spectrum third-generation cephalosporin with a 72%–97% cure rate. It is a greatly effective antibaterial with high potency covering wide variety of gram-negative and gram-positive specious and has been extensively prescribed in healthcare facilities including for empirical treatment. Twenty five years back, a study was conducted to investigate the incidence of bacterial species and their susceptibilities to ceftriaxone and other β-lactams from patients with communityacquired infections. The report indicated that all bacterial strains resistant to other antibiotics were found to be fully susceptible to ceftriaxone.7 Resistance to ceftriaxone by FC428 ceftriaxone-resistant N. gonorrhoeae strain was first reported in January 2015 in Japan,9 22% of the Gonococcal Isolate Surveillance Project member countries reported reduced susceptibility to ceftriaxone among patients with N. gonorrhoeae infection(73).The world's first gonorrhea strain resistant to ceftriaxone was reported in 2018 in England and showing high-level resistance to azithromycin was isolated from a man who sought care in early 2018.22 A study conducted in Jimma Teaching Referral Hospital, Ethiopia using clinical isolates reported S. aureus and E. coli reported that 73% and 65% of the clinical isolates were resistant to ceftriaxone and ceftazidime, respectively. The study also demonstrated that among the bacterial strains that were resistant to ceftriaxone and ceftazidime, 44% of S. aureus and 43.5% of E. coli were found to be resistant to both drugs.3 Recently, Dr.

Moopans' Aster Hospital in Doha, Qatar reported the first cases of ceftriaxone-resistant Salmonella Typhi in the Middle East.11 Over the years, an increasing number of microbial strains have become resistant to ceftriaxone threatening its use.23-25 Like other first-line antibiotics, resistance to ceftriaxone has become worrisome for many countries in consideration of its historical performance, tolerability, and affordable price. A10-year period surveillance study in US revealed that ceftriaxone has become one of the 10 increasing antibiotic resistances by Enterobacteriaceae strains(74).

2.11.4.Mechanism of ceftriaxone resistance development

Infectious microbes use different mechanisms to resist antimicrobials such as mutational adaptations, acquisition of genetic materials, alteration of gene expression, limiting drug uptake, alteration of drug targets, inactivation of drugs, and active drug efflux .Other more complex phenotypes, such as biofilm formation and quorum are also related to tolerance to antibiotics in bacteria. reported biofilm formation and pathogenesis as major mechanism of resistance by E. coli. The most active fractions of bacteria have been recognized to occur as biofilm where cells are adhered to each other on surfaces within a selfproduced .matrix of extracellular polymeric substance (EPS) The EPS provides the bacterial a barrier that inhibits antibiotic penetration into the cell which further promotes the emergence of antibiotic resistance; which is referred as quorum sensing (bacterial communication for the biofilm integrity). In β-lactam antibiotics(74,75),gonococci develop resistance through two mechanisms: the first is (high level, quickly acquired and easy to transfer among strains) mediated by a resistance plasmid that produces β-lactamase; and the second mechanism is mediated by chromosomal genes which takes a relatively long time for the gradual accumulation of multiple resistance- .related gene mutations(74).[6] The production of extended-spectrum β-lactamase has been recognized as the most important mechanism of resistance development against ceftriaxone by E. coli. A molecular analysis study in Taiwan also reported that the emergence of ceftriaxone resistance in Salmonella isolates was associated with the production of CMY_2(64%) and CTX_M beta_lactamases(27%) . On

the other hand, the mechanism of resistance to ceftriaxone by N. gonorrhoeae strains was found to be due to chromosomally mediated mutations in the three loci of penA, mtrR, and penB. Generally, the following mechanisms are presumed to majorly contribute to the development and spread of resistance against cephalosporins including cefteriaxone(73,76).

2.11.5.Strategies to counter ceftriaxone resistance

over the last few years, ceftriaxone resistance has become growing and extremely worrisome challenge to the global healthcare system and several strategies have been initiated to contain the spread of antimicrobial drug resistance. Its extended use for therapeutic or preventative measures in humans and farm animals resulted in the development and spread of resistance. Recent advances in nanotechnology also offer novel formulations based on distinct types of nanostructure particles with different sizes and shapes, and flexible antimicrobial properties. For ceftriaxone, several nanostructured formulations through conjugation, intercalation, encapsulation with lipid carrier, and polymeric films have been investigated by different groups with promising results in combating the development of resistance. This review addressed the existing knowledge and practice on the contribution of nano-based delivery approaches in overcoming ceftriaxone resistance(71,72).

3. Patient,Materials and Methods

3.1.Study groups

A randomized sample of70 patient was selected from Marjan Teaching Hospital –Al Hayat Microbiology Laboratory , Imam Al-Sadiq Teaching Hospital- Main Microbiology Laboratory.

3.2.Data collections

The data has been collected from the microbiology laboratory records of antibiotic susceptibility test .

3.2.Data collections

This is a case study carried out from November 2022 to May 2023.

3.4.Place of study

The study was taken place and data collected in Babylon province of Iraq at Marjan Teaching Hospital -Al Hayat Microbiology Laboratory , Imam Al-Sadiq Teaching Hospital - Main Microbiology Laboratory.

3.5.Data study

The samples were analyzed according to the following tables:

Table (3.1): **Male and Female Count**

Gender	**Count**
Male	30
Female	40
Total	**70**

Table(3.2): The count of Sample Type

NO.	Sample	Count
1	Urine	29
2	Blood	1
3	Stool	2
4	Wound	9
5	Sputum	18
6	Vaginal swap	2
7	Throat swap	3
8	Pulmonary fluid	4
9	Urethral	2
	Total	**70**

Table(3.3): Count of Bacterial Types

NO.	Bacterial Type	Count
1	Streptococcus	21
2	E.Coli	12
3	Staphylococcus aureus	11
4	Citrobacter	10
5	Candida	7
6	Klebsilla	7
7	Salmonella	2

3.6. Statistical analysis

The percentage of bacteria resistant to ceftriaxone was used to determine the percentage of non-resistant bacteria

4.1. Sample Type Count

Types of bacteria collected from various samples of the body were studied to investigate ceftriaxone-resistant bacteria, which are shown in Figure (3.1).

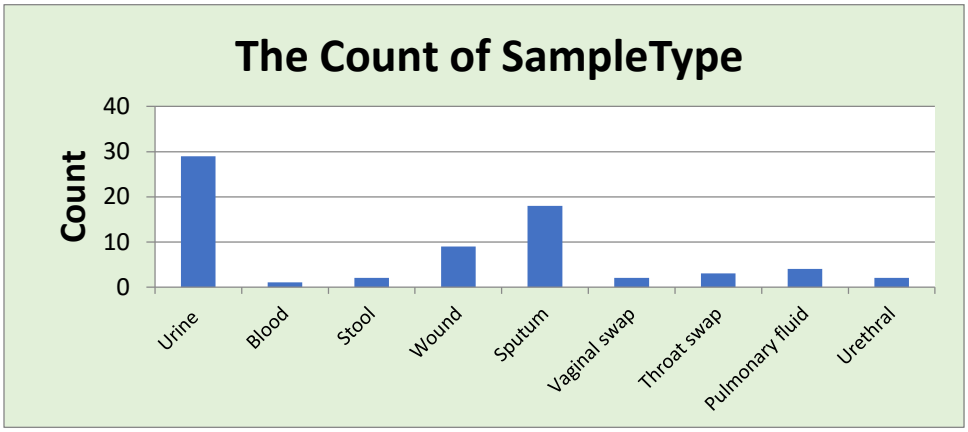

Figure (3.1): The number of bacteria according to the type of samples

4.2. Percentage of bacteria resistant to ceftriaxone

The results of the current study indicated in Table (3.1) that the highest percentage of resistance to ceftriaxone appeared in Citrobacter bacteria, followed by Candida bacteria, while the lowest percentage appeared in Streptococcus bacteria.

On the other hand, the results of the current study indicate the spread of resistance to ceftriaxone among many types of bacteria important in human pathogenesis

Table (3.1): Bacterial Resistant Proportion

NO.	Bacterial Type	Total count	Susceptible	Resistant	ResistantPercentage
1	Streptococcus	21	14	7	33.3%
2	E.Coli	12	3	3	75%
3	Staphylococcus aureus	11	5	6	54.5%
4	Citrobacter	10	0	10	100%
5	Candida	7	1	6	85.7%
6	Klebsilla	7	2	5	71.42%
7	Salmonella	2	1	1	50%

4.1. Discussion

In our study in many healthcare organizations we found that the most common bacteria that show resistance to cefteriaxone is streptococcus ,E.coli ,citrobacter and staphylococcus this is likely due:

1_The frequent uses of cefteriaxone without real indication to it

2_ Bacterial sensitivity test is very much negligited in the healthcare facilities and the wrong time of doing bacterial culture where the patient is already on antibiotic therapy

3- The development of bacterial resistance is due to the mechanism of resistance in this bacterial strain where:

Streptococcus has multiple morphology to change resistance mechanisms through gene mutation E.coli can cause biofilm formation which can't overcome by cefteriaxone .

Citrobacter often overcome cefteriaxone through overexpression of their chromosomal beta lactamase.

And finally staphylococcus Resistance mechanisms include enzymatic inactivation of the antibiotic, alteration of the target with decreased affinity for the antibiotic

strategies to overcome cefteriaxone resistance:

1. Minimise unnecessary prescribing and overprescribing of antibiotics. This occurs when people expect doctors to prescribe antibiotics for a viral illness (antibiotics do not work against viruses) or when antibiotics are prescribed for conditions that do not require them.
2. Complete the entire course of any prescribed antibiotic so that it can be fully effective and not breed resistance.
3. Practice good hygiene such as hand-washing and use appropriate infection control procedures.

5.1. Recommendation

In our point of view ,When using ceftriaxone, it is important to follow the following recommendations provided by healthcare professionals.

1_Dosage: The appropriate dosage of ceftriaxone varies depending on the age, weight, and condition of the patient, as well as the type and severity of the infection being treated. It is essential to follow the prescribed dosage and schedule provided by your healthcare provider.

2_Route of Administration: Ceftriaxone is available for intravenous (IV) or intramuscular (IM) administration. The choice of administration route depends on the specific situation and the patient's condition. In most cases, IV administration is preferred for severe infections or when immediate therapeutic concentrations are required. IM administration may be suitable for certain less severe infections.

3_ Duration of Treatment: The duration of ceftriaxone treatment can vary depending on the type and severity of the infection. It is crucial to complete the full course of treatment as prescribed by healthcare provider, even if symptoms improve before the medication is finished. Premature discontinuation of antibiotics can lead to incomplete eradication of the infection and the risk of developing antibiotic resistance.

4_Allergies and Sensitivities: the healthcare provider must be infoemed about any known allergies or sensitivities to ceftriaxone or other antibiotics, particularly cephalosporins or penicillins. This information is crucial for selecting the appropriate antibiotic therapy and avoiding potential adverse reactions.

5_Monitoring and Follow-up: During ceftriaxone treatment, the healthcare provider may monitor the progress through clinical assessments, laboratory tests, or other diagnostic measures. It is important to attend follow-up appointments and report any changes in symptoms or adverse reactions promptly.

6_Drug Interactions: Ceftriaxone may interact with other medications or substances. the healthcare provider must be informed about any other medications, including over-the-counter drugs, herbal supplements, or recreational substances you are taking to avoid potential interactions.

5.2. Conclusion

ceftriaxone was an ideal antibiotic with broad spectrum antimicrobial activity toward gram positive and gram negative bacteria but due to in appropriate usage and neglication of sensitivity test and its availability as over the counter drug not just in prescription in Iraq it lead to that most bacteria developing resistance to the drug and render it with only modest susiptiplty

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قسم الأدوية

دراسة للجيل الثالث من السيفالوسبورين سيفترياكسون ، الاستخدامات والاحتياطات

بحث مقدم الى فرع الأدوية في كلية الصيدلة / جامعة بابل
كجزء من متطلبات الحصول على شهادة البكالوريوس في الصيدلة

من قبل

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

" وَقُلْ رَبِّ زِدْنِي عِلْمًا "

صدق الله العلي العظيم

سورة طه الآية (114)

الخلاصة

سيفترياكسون هومن الجيل الثالث من السيفالوسبورين شبه الاصطناعي ، وهو جزء من مجموعة واسعة من مضادات الميكروبات. والذي يشمل البكتيريا الهوائية موجبة الجرام وسالبة الجرام ، بالإضافة إلى بعض من البكتيريا اللاهوائية.

طرق العمل:

تم اختيار عينة عشوائية مكونة من 70 مريض من مستشفى مرجان التعليمي - مختبر الأحياء المجهرية و مستشفى الإمام الصادق التعليمي - مختبر الأحياء المجهرية الرئيسي ، وقد تم جمع البيانات من سجلات مختبر الأحياء المجهرية لاختبار الحساسية للمضادات الحيوية ، تم تنفيذ دراسة الحالة هذه من تشرين الثاني (نوفمبر) 2022 إلى أيار (مايو) 2023.حيث تم إجراء الدراسة وجمع البيانات في محافظة بابل العراقية في مستشفى المرجان التعليمي - مختبر الحياة للأحياء المجهرية ، ومستشفى الإمام الصادق التعليمي - محتبر الأحياء المجهرية الرئيسي.

النتائج و الأستنتاجات

في دراستنا في العديد من مؤسسات الرعاية الصحية ، وجدنا أن البكتيريا الأكثر شيوعًا التي تظهر مقاومة للسيفترياكسون هي المكورات العقدية والإشريكية القولونية والسيتروباكتر والمكورات العنقودية ، ويرجع ذلك على الأرجح إلى الاستخدامات المتكررة لسيفترياكسون دون إشارة حقيقية إليها. يتم إهمال اختبار الحساسية البكتيرية في مرافق الرعاية الصحية والوقت الخاطئ لإجراء الزراعة البكتيرية حيث يخضع المريض بالفعل للعلاج بالمضادات الحيوية ، ويعود تطور المقاومة البكتيرية إلى آلية المقاومة في هذه السلالة البكتيرية حيث: لتغيير آليات المقاومة من خلال الطفرة الجينية ، يمكن للإشريكية القولونية أن تتسبب في تكوين غشاء حيوي لا يمكن التغلب عليه بواسطة سيفتيرياكسون. وأخيرًا ، تشتمل آليات مقاومة المكورات العنقودية على التعطيل الأنزيمي للمضاد الحيوي ، وتغيير الهدف مع انخفاض تقارب المضاد الحيوي.