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Review Paper

Rational Use of Ceftriaxone in Therapeutics: Evidence-Based Prescribing and Resistance Concerns

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ABSTRACT

Ceftriaxone functions as a third-generation cephalosporin which hospitals use because it offers wide-ranging antimicrobial effects and it reaches high body tissue levels and its long-lasting effects enable medical staff to administer the drug once throughout the day. The drug functions as an essential treatment for severe bacterial infections yet its high usage patterns have brought about an increase in antimicrobial resistance which specifically drives the distribution of extended-spectrum beta-lactamase (ESBL) producing pathogens. This review evaluates the pharmacological profile of ceftriaxone, its evidence-based indications, and the urgent need for antimicrobial stewardship. The drug serves as the main treatment option for meningitis and community-acquired pneumonia and gonorrhea but it does not work against Pseudomonas aeruginosa and MRSA. The drug presents two different safety issues which involve the development of biliary pseudolithiasis and its prohibition in neonates because of kernicterus dangers and calcium precipitation dangers. The resistance crisis worsens through the widespread wrong use of surgical prophylaxis and treatment for viral diseases. Healthcare systems need to establish alignment with World Health Organization "Watch" group classifications while implementing stewardship programs that require doctors to restrict their prescription practices and perform IV-to-oral transitions without delaying. The medical effectiveness of ceftriaxone depends on medical staff following proper dosage methods and local resistance patterns during antibiotic drug reduction procedures.

INTRODUCTION

Third-generation cephalosporins became widely used after their discovery which changed how doctors treated serious bacterial infections. Among these, ceftriaxone stands out as one of the most frequently prescribed antibiotics globally [1]. The drug became popular because it effectively treats multiple Gram-negative and Gram-positive

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bacterial infections while its high tissue penetrability and extended elimination half-life enable doctors to prescribe it as a single daily dose treatment [2]. The current state of medical treatment is undergoing major transformations. The world now faces two health crises which include infectious diseases and the hidden spread of antimicrobial resistance (AMR). The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have flagged third-generation cephalosporin resistance as a critical priority [3]. Healthcare facilities use ceftriaxone as an all-purpose treatment for undiagnosed fever cases which results in harmful effects on the microbiome and enables the development of drug-resistant bacteria [4]. The misuse of ceftriaxone presents significant problems because Enterobacterales bacteria become infected after encountering this antibiotic which leads to the development of extended-spectrum β-lactamase (ESBL) producers and vancomycin-resistant enterococci (VRE) [3] , [5]. The drug excretes in the bile at high levels which creates dangerous safety hazards for medical practice because biliary pseudolithiasis develops as a result of this condition [6]. The review establishes a connection between pharmacological knowledge and its application in medical settings. The document provides a complete study of ceftriaxone pharmacological effects while it assesses the drug's evidence-based medical uses and explains how resistance develops with its resulting effects and describes methods for maintaining its long-term effectiveness.

2. Overview of Ceftriaxone

2.1 Classification and Chemical Properties

Ceftriaxone functions as a third-generation semi-synthetic cephalosporin antibiotic which exhibits broad-spectrum antibacterial activity. The chemical structure of the compound contains a methoxyimino group which enables it to resist hydrolysis by various beta-lactamases that Gram-negative bacteria produce [7]. The disodium salt of the compound dissolves easily in water enabling intravenous (IV) and intramuscular (IM) administration. The drug requires parenteral administration because it does not absorb from the gastrointestinal tract unlike other cephalosporins.

2.2 Mechanism of Action

All beta-lactam antibiotics use ceftriaxone to kill bacteria by stopping their ability to build cell walls. The drug establishes strong binding with penicillin-binding proteins (PBPs) through its interaction with PBP2 and PBP3 which exist on the bacterial cell wall inner membrane [8]. The binding process stops the transpeptidation reaction which represents the last stage of peptidoglycan production. Bacterial autolysins cause cell death through cell wall breakdown which occurs because cross-linkage inhibition prevents proper cell wall formation [7].

2.3 Antimicrobial Spectrum and Limitations

Ceftriaxone demonstrates strong antibacterial effects against three bacterial groups which include:

- Gram-positive aerobes: Streptococcus pneumoniae (including penicillin-intermediate strains), Streptococcus pyogenes, Streptococcus agalactiae, and methicillin-susceptible Staphylococcus aureus (MSSA).
- Gram-negative aerobes: Neisseria gonorrhoeae, Neisseria meningitidis, Haemophilus influenzae, Escherichia coli, Proteus mirabilis, and Salmonella species [9].
- Spirochetes: Borrelia burgdorferi (Lyme disease).

Limitations : Ceftriaxone has essential restrictions because it provides no treatment against

Pseudomonas aeruginosa, Acinetobacter baumannii, Enterococcus species, Listeria monocytogenes, and methicillin-resistant Staphylococcus aureus (MRSA) [2] ,[8]. The drug becomes ineffective against bacteria that produce these enzymes because ESBLs and AmpC β-lactamases hydrolyze it [10].

3. Pharmacokinetics and Pharmacodynamics

Apprehension of the pharmacokinetics (PK) and pharmacodynamics (PD) of ceftriaxone is critical for making rational dosing decisions and is particularly demanded when special populations are concerned.

3.1 Absorption and Distribution

Following IM administration, ceftriaxone reaches its maximum plasma levels after it enters the bloodstream within 2 to 3 hours. The drug demonstrates superior body tissue and body fluid distribution which includes lung tissue, bone tissue, joint spaces, and peritoneal space fluid [11].

- CSF Penetration: Ceftriaxone penetrates the inflamed meninges well, achieving cerebrospinal fluid (CSF) concentrations which exceed the minimum inhibitory concentrations (MICs) for common meningeal pathogens, which makes it a first-line agent for bacterial meningitis treatment [12].
- Protein Binding: The drug demonstrates strong binding to serum albumin with a binding range between 85 and 95 percent. The total drug concentration affects binding because higher concentrations result in increased free fraction levels. In patients who have severe hypoalbuminemia from nephrotic syndrome or severe malnutrition or liver failure, ceftriaxone free fraction will become elevated, which might result in increased drug clearance and modified treatment effectiveness [13].

3.2 Metabolism and Elimination

Ceftriaxone does not undergo metabolic processes within human beings. The drug has two distinct pathways for elimination which include:

1. Approximately 33 to 67 percent of the drug gets removed from the body through urine as it passes through glomerular filtration.
2. The remainder of the substance gets excreted through bile into feces [14].

The dual elimination pathways enable physicians to maintain standard drug dosages for patients who have either renal impairment or hepatic impairment because their other organ system functions properly [11].

3.3 Half-life and Dosing Rationale

Ceftriaxone demonstrates an extended elimination half-life which lasts between 6 and 9 hours in healthy adults, while most cephalosporins have a half-life that ranges from 1 to 2 hours [2]. This supports once-daily (q24h) dosing for most infections.

3.4 PK/PD Determinants of Efficacy

Ceftriaxone functions effectively as a time-dependent antibiotic when its drug concentration remains above the minimum inhibitory concentration (MIC) of the targeted pathogen for specific duration [15]. The bactericidal effect reaches its maximum when the drug concentration remains above the minimum inhibitory concentration (MIC) for 50 to 60 percent of the dosing period. The target minimum inhibitory concentration (MIC) needs to be sustained through more frequent dosing intervals which require administration every 12 hours in cases of severe infections or when treating pathogens with elevated MICs [15].

3.5 Evidence-Based Therapeutic Indications

Rational prescribing would reserve for ceftriaxone only those infections where it enjoys clear benefits over narrower-spectrum agents.

4. Guideline-Approved Indications

4.1 Community-Acquired Pneumonia (CAP)

Current IDSA/ATS guidelines recommend ceftriaxone in combination with a macrolide (or doxycycline) for patients with CAP requiring hospitalization (non-ICU) [16]. The treatment offers protection against S. pneumoniae and H. influenzae, which serve as the main infectious agents. Monotherapy is generally insufficient because it does not target Legionella and Mycoplasma, which are classified as atypical pathogens [16].

- **Meningitis**

Ceftriaxone (in combination with vancomycin) is the empiric treatment of choice for acute bacterial meningitis in children and adults [12]. Vancomycin needs to be added because it provides coverage against S. pneumoniae strains that show resistance to penicillin and cephalosporins. The medical team can reduce the intensity of treatment after they verify the patient's susceptibility to drugs.

- **Typhoid Fever:**

The resistance of Salmonella Typhi to fluoroquinolones forces medical professionals to use ceftriaxone as their main antibiotic for treating enteric fever cases which occur in South Asia [17]. The rising number of extensively drug-resistant S. Typhi strains which show ceftriaxone resistance has become a dangerous emergency that needs carbapenem treatment [17].

- **Sepsis and Intra-abdominal Infections:**

The medical community treats community-acquired sepsis cases which doctors suspect originate from urinary or abdominal sources by using ceftriaxone together with metronidazole which treats anaerobic infections. The drug provides effective treatment for E. coli and Klebsiella spp. infections but local resistance patterns need to determine its use for treatment without prior testing [18].

- **Urinary Tract Infections (UTIs):**

Ceftriaxone serves as an effective treatment solution for complicated urinary tract infections and pyelonephritis. The emergency department uses it as a parenteral bridge therapy before patients switch to oral antibiotics [19].

- **Sexually Transmitted Infections (STIs) :**

For uncomplicated gonorrhea, a single IM dose of ceftriaxone (500 mg or 1 g depending on weight and guidelines) is the gold standard [20]. Due to rising azithromycin resistance, previous dual-therapy recommendations have shifted in some jurisdictions to high-dose ceftriaxone monotherapy [20].

4.2 Empirical vs Targeted Therapy

The empirical use of ceftriaxone functions as a valid treatment for patients with severe community-acquired infections. The implementation of "targeted therapy" should begin after the laboratory results become accessible. The ongoing administration of ceftriaxone for bacteria that respond to specific treatments such as oxacillin for S. aureus or cefazolin for E. coli is deemed an unreasonable practice that contributes to the development of bacterial resistance [21].

4.3 Dosing Strategies and Administration

Adult Dosing

- Standard infections: The recommended intravenous or intramuscular dosage ranges

from 1 to 2 grams which should be administered once per day.

- Meningitis: The administration of 2 grams through intravenous injection should occur every 12 hours which leads to a total daily dosage of 4 grams to reach necessary cerebrospinal fluid levels [12].
- Gonorrhea: The patients who weigh less than 150 kilograms should receive a single injection of 500 milligrams while those who weigh 150 kilograms or more should receive a single injection of 1 gram [20].

Pediatric and Neonatal Dosing

- Children: The recommended dosage ranges from 50 to 75 milligrams per kilogram which should be taken once each day. The recommended dosage for meningitis treatment requires 80 to 100 milligrams per kilogram to be taken every 12 to 24 hours [22].
- Neonates: The use of extreme caution is necessary because ceftriaxone causes bilirubin to separate from albumin which results in an increased danger of bilirubin encephalopathy (kernicterus). The drug remains prohibited for use in neonates who experience hyperbilirubinemia and for premature infants [23].

Renal and Hepatic Impairment

No dose adjustment is needed for renal failure or hepatic dysfunction alone. The patient requires serum concentration monitoring because they have severe renal and hepatic failure, and their maximum dosage should not exceed 2 grams per day according to reference [11].

IV and IM Routes

The pain of IM injection can be reduced through the application of 1% lidocaine which helps to reconstitute the powder [24]. The administration of IV medications should be conducted through either slow injections which take 2 to 4 minutes or through infusions which last 30 minutes to avoid causing vein irritation.

5. Safety Profile and Drug Interactions

5.1 Adverse Drug Reactions (ADRs)

Ceftriaxone is generally well-tolerated, but specific ADRs warrant attention:

- **Hypersensitivity :** The skin reaction to penicillin allergies shows cross-reactivity to penicillins at a rate of 1 to 3 percent which requires caution when treating patients who have experienced severe penicillin allergies before [25].
- **Biliary Pseudolithiasis:** Ceftriaxone-calcium complexes can precipitate in the gallbladder, forming sludge or "pseudostones." This condition occurs in 3 to 46 percent of children who receive high doses but usually becomes reversible after treatment stops [6] [26].
  - **Hematologic:** Eosinophilia, thrombocytosis, and rare cases of immune-mediated hemolytic anemia have been reported [25].

5.2 Serious Toxicities

- **Kernicterus:** Displacement of bilirubin from blood stream results in brain damage for neonates who show vulnerability to this condition. [23]
- **Calcium Precipitation:** Neonates experience fatal reactions which occur when calcium-ceftriaxone precipitates block their lungs and kidneys. Ceftriaxone must not be mixed or administered simultaneously with calcium-

containing IV solutions (including Ringer's lactate and parenteral nutrition) [27].

6. Irrational Use of Ceftriaxone

6.1 Common Misuse Patterns

Studies consistently demonstrate that hospital environments experience their highest levels of ceftriaxone misuse because it stands as one of the most frequently misused antibiotics.

- **Surgical Prophylaxis:** The application of ceftriaxone for surgical prophylaxis should not be done because it leads to unreasonable outcomes. Narrower spectrum agents like cefazolin are preferred. The extended duration of ceftriaxone creates a situation where doctors continue to prescribe ceftriaxone beyond what is medically necessary [28].
- **Viral Infections:** Doctors commonly prescribe the medication for viral upper respiratory tract infections which it does not help treat [28].

6.2 Prescribing Errors

- **Incorrect Dosing:** Meningitis treatment fails when doctors administer too little medication while excessive drug administration leads to higher chances of developing biliary sludge [6].
- **Failure to De-escalate:** The decision to maintain ceftriaxone treatment after culture results showed bacterial sensitivity to ampicillin and cefazolin represents a significant gap in stewardship practices [21].

7. Ceftriaxone and Antimicrobial Resistance

7.1 Mechanisms of Resistance

The main cause of ceftriaxone resistance occurs because bacteria produce β-lactamases which create this resistance:

- **ESBLs:** The CTX-M type enzymes function as hydrolytic enzymes which break down the oxyimino-β-lactam ring structure. Bacteria can exchange the genes which code for these enzymes because these genes exist on plasmids that allow for horizontal gene transfer between different bacterial species [10].
- **AmpC β-lactamases:** These enzymes exist either on chromosomal structures or plasmids and they provide bacteria with resistance against both cephamycins and third-generation cephalosporins [29].

8. Global Resistance Trends

The prevalence of ESBL-producing Enterobacterales has skyrocketed. In some regions of Southeast Asia and India, ESBL rates in E. coli exceed 60–70% [30]. The area requires carbapenems because ceftriaxone fails to treat most community-acquired UTIs and bacteremias.

9. Clinical and Economic Impact

Ceftriaxone resistance leads to:

- hospitals use "last-resort" antibiotics (carbapenems) more frequently.
- Patients stay in hospitals longer which results in higher death rates [31].
- The healthcare system incurs additional costs because patients need multiple treatment attempts.

10. Antimicrobial Stewardship and Rational Use

Rational use involves "the right drug, at the right dose, for the right duration, for the right patient." Stewardship Principles:

- Restrictive Policies:- Many hospitals limit ceftriaxone usage to particular medical conditions which require infectious disease (ID) approval after patients have received treatment for 72 hours [32].
- IV-to-Oral Switch (IVOS)- Patients who have reached stable medical conditions and do not have fever symptoms should receive their IV ceftriaxone treatment through oral medications which include cefixime cefpodoxime and cotrimoxazole to support their discharge process while minimizing IV line-related health risks [33].
- Audit and Feedback- The process of auditing ceftriaxone prescriptions together with delivering feedback to prescribers has proven effective in decreasing cases of improper prescription practices [32].

11. Rational Prescribing Guidelines

To curb resistance, clinicians must adhere to established guidelines:

- **WHO AWaRe Classification:** Ceftriaxone is classified under the "Watch" group, indicating it has higher resistance potential and should be prioritized as a key target of stewardship programs [34].
- **Local Antibiograms:** Empirical therapy choices must be informed by local resistance data. If local E. Coli resistance to ceftriaxone exceeds 20%, it may no longer be suitable for empirical monotherapy for severe sepsis [18].

12. Special Clinical Considerations

12.1 ICU and Critical Care

Patients with hyperdynamic sepsis require more frequent dosing of ceftriaxone because their body distribution and elimination rates change from normal patterns. The extended ceftriaxone half-life decreases its need for continuous infusion compared to other beta-lactam antibiotics [15].

12.3 De-escalation

A critical component of rational use is de-escalation. If a patient with CAP tests positive for penicillin-sensitive S. Pneumoniae, switching from ceftriaxone to penicillin G or ampicillin is mandatory to reduce selective pressure [16].

12.4 FUTURE PERSPECTIVES

The future of ceftriaxone therapeutics relies on preserving its utility.

The future of ceftriaxone therapeutics relies on preserving its utility.

- **Rapid Diagnostics:** Implementation of rapid molecular tests (e.g., PCR for mecA or CTX-M genes) can allow clinicians to avoid ceftriaxone in resistant cases or de-escalate sooner in susceptible ones .
- **New Formulations:** Research into combinations of ceftriaxone with novel beta lactamase inhibitors is ongoing to restore its activity against ESBL producers [35].

CONCLUSION

Ceftriaxone functions as an essential tool for doctors because it provides strong treatment results against dangerous infections, including meningitis and sepsis. The drug experiences two major threats which include doctors who prescribe it without medical justification and the increasing prevalence of ESBL-based resistance. The current system of empirical therapy which uses the "treat first, think later" method has reached its limits and needs to change. Rational use requires a complete system overhaul which needs diagnostic tests and correct treatment protocols and proper antibiotic management. The medical community can ensure ceftriaxone maintains its ability to save lives through proper use of the drug which includes

understanding its chemical boundaries and environmental effects.

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