ORIGINAL RESEARCH PAPER

Pharmaceutical Science

# THE SYSTEMIC DRUG REVIEW OF CEFTRIAXONE

KEY WORDS:

| | |
|---|---|
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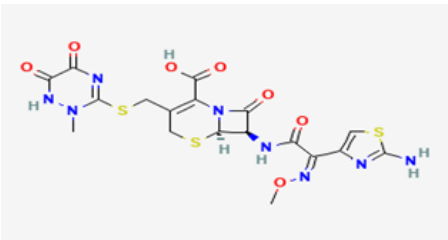
## INTRODUCTION



Ceftriaxone is the most commonly preferred antibiotic drug,its well known for its potency,effectiveness and broad range of activity with minimal risk of harm to the body.Ceftriaxone is a kind of third generation cephalosporin that can resist lactamase and was patented back in 1979; it works well against gram bacteria and most gram negative bacteria.This antibiotic can easily enter the fluid when there's no inflammation, in the meninges. Thus it has been implemented to abort many infections affecting different organs of the body such as the CNS (central nervous system) and lungs, skin and soft tissue; bone and joints; urinary tract infections; pneumonia; abdominal infections; respiratory tract infections; bacteremia/septicemia; meningitis; infections, in immunosuppressed patients; acute bacterial otitis media; genital infections;Lyme disease; surgical prophylaxis of infections; gonorrhea (Neisseria);sepsis; bronchitis and endocarditis. Ceftriaxone is used as a broad spectrum antibacterial drug medically. It has a very long half life and shows good penetration into meninges, eye and inner ear.It works as a beta lactamase inhibitor which works well against multi drug resistant entereobacteraiceae. Ceftriaxone has broader and stronger gram-negative coverage then first or second-generation cephalosporins, ceftriaxone acts as a bactericidal agent by inactivating penicillin-binding proteins in the outer cytoplasmic membrane and hampering bacterial cell wall synthesis leading to breakdown of the bacterial cell wall.Ceftriaxone is mainly utilised for suppressing the infections of respiratory tract,skin,soft tissue,Urinary tract etc. Ceftriaxone is mainly administered intravenously or intramuscularly for a variety of infections Clostridium difficile and certain types of Bacteroides bacteria, like B.fragilis show sensitivity or resistance, to ceftriaxone; however certain other anaerobic bacteria are affected by this medication. Inappropriate and unfit practice of ceftriaxone accelerates the chance of antimicrobial resistance, rockets the costs of treatment, affects productivity, and exposes patients to certain side effects, and can also result in death[1]. Efficacy and safety were comparable to multiple-dose cefazolin. Antimicrobials like Ceftriaxone demands special attention because it rather has a lenghty half-life, such that they can be administered infrequently in comparison to other classes of drugs. The viability of utilizing this antibiotic derives from the truth that monumental expenses might be lowered when used suitably .Ceftriaxone is a type of aminothiazolyl-oxyimino cephalosporin. It possesses the typical in-vitro and outside the womb activity of a third-generation cephalosporin with excellent activity against majority of gram-negative aerobic bacilli: Escherichia coli; species of Proteus, Klebsiella, Morganella, Providencia and Citrobacter; and Enterobacter.agglomerans. Ceftriaxone also has a better bactericidal action against pneumococcus, group B streptococci, meningococcus, gonococcus and Hemophilus influenzae[2]. This present study showed a very high level of non-uniform ceftriaxone use which may lead to the development of drug resistant organisms thus results in failure and poor results of treatment and high cost of treatment. Empiric treatment with ceftriaxone and the presence of co-administered drugs was significantly associated with its inappropriate use[3]. Resistance to ceftriaxone is primarily through hydrolysis by beta-lactamase, alteration of Proteins bound to penicillin(PBP), and decreased permeability.

In general, prescribers should follow the current evidence based practice and use ceftriaxone only for the confirmed or highly suspected cases. The constant and time to time assessment is also advised in an effort to minimize the irrational use of ceftriaxone. To sustain and practice the rational use of antibiotics the hospital was also taught to adopt the concept of antimicrobial guardianship program.

### Clinical Pharmacology And Pharmacokinetics

- Following an intravenous injection, ceftriaxone was

completely absorbed into the bloodstream and reached its concentration in the plasma. It binds to human plasma proteins reversibly, with the binding percentage dropping from 95 at plasma concentrations below 25 mcg/ml to 85 at 300 mcg/ml.

- Concentrations can be observed between 2 to 3 hours after taking the dose of the medication Multiple IV) or intramuscular (IM) doses, varying between 0.the range given at intervals of 12 to 24 hours led to an increase of 15 percent, to 36 percent, in the ceftriaxone levels compared to a single dose.
- When the patient receives an injection of ceftriaxone, with or without lignocaine (lidocaine) its bioavailability is comparable to that of a dose despite having slightly lower average peak plasma levels observed after administration via injection, into the muscle tissue. Peak plasma concentrations typically reach their levels between 1 to 3 hours after receiving the injection.
- Additionally, ceftriaxone is able to cross the blood-placenta barrier.Average plasma concentrations of ceftriaxone following a single 30-minute intravenous (IV) infusion of a 0.5, 1 or 2 gm dose and intramuscular (IM) administration of a single 0.5 (250 mg/mL or 350 mg/mL concentrations) or 1 gm dose in healthy subjects are presented in Table 1.

**Table.1. Ceftriaxone Plasma Concentrations After Single Dose Administration**[4]

| DOSE/ROUTE | Average plasma concentration(mcg/mL) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.5 hr | 1 hr | 2 hr | 4 hr | 6 hr | 8 hr | 12 hr | 16 hr | 24 hr |
| 0.5gm IV* | 82 | 59 | 48 | 37 | 29 | 23 | 15 | 10 | 5 |
| 0.5gm IM 250 mg/mL | 22 | 33 | 38 | 35 | 30 | 26 | 16 | ND | 5 |
| 0.5 gm IM 350 mg/mL | 20 | 32 | 38 | 34 | 31 | 24 | 16 | ND | 5 |
| 1gm IV* | 151 | 111 | 88 | 67 | 53 | 43 | 28 | 18 | 9 |
| 1 gm IM | 40 | 68 | 76 | 68 | 56 | 44 | 29 | ND | ND |
| 2 gm IV* | 257 | 192 | 154 | 117 | 89 | 74 | 46 | 31 | 15 |
| ND=not determined | | | | | | | | | |

*IV doses were infused at a constant rate over 30 minutes.

- About 33% to 67% of a ceftriaxone dose is eliminated through the urine as unchanged drug, while the rest is secreted into the bile and eventually appears in the feces as microbiologically inactive compounds. In healthy adult subjects, the elimination half-life varied between 5.8 and 8.7 hours for doses ranging from 0.15 to 3 grams. The apparent volume of distribution was found to be between 5.78 and 13.5 liters, while plasma clearance ranged from 0.58 to 1.45 liters per hour. Additionally, renal clearance was observed to be between 0.32 and 0.73 liters per hour.the urinary concentrations of ceftriaxone after single dose administration is described in the table 2.

**Table.2. Urinary Concentrations Of Ceftriaxone After Single Dose Administration**

| Dose/Route | Average Urinary Concentrations (mcg/mL) | | | | | |
|---|---|---|---|---|---|---|
| | 0 - 2 hr | 2 - 4 hr | 4-8 hr | 8-12 hr | 12-24 hr | 24-48 hr |
| 0.5 gm IV | 516 | 356 | 139 | 82 | 65 | 14 |
| 0.5 gm IM | 109 | 419 | 305 | 119 | 100 | 30 |
| 1 gm IV | 980 | 860 | 281 | 139 | 108 | 28 |
| 1 gm IM | 504 | 628 | 418 | 228 | N.D | N.D |
| 2 gm IV | 2692 | 1976 | 757 | 274 | 198 | 40 |
| **N.D**-Not defined | | | | | | |

- In critically ill patients with normal renal function, inadequate plasma concentrations may result following od bolus dosing of ceftriaxone. Drug accumulation may occur in critically ill patients with renal failure[5].
- Ceftraixone are mainly excreted unchanged and in a non-metabolised form through by either glomerular filtration or tubular secretion .Unlike Cefotaxime, a compound which is the only one to get deacetylated in the body before excretion.
- The pharmacokinetics of ceftriaxone showed only slight changes in elderly individuals and those with renal impairment or liver dysfunction compared to healthy adults (see Table 3). As a result, there is no need to adjust the dosage for these patients, even when administering up to 2 grams of ceftriaxone per day. Additionally, hemodialysis did not significantly remove ceftriaxone from the plasma

**Table.3.mean Pharmacokinetic Parameters Of Ceftriaxone In Humans**

| Subject Group | Elimination Half-Life (hr) | Plasma Clearance (L/hr) | Volume of Distribution (L) |
|---|---|---|---|
| Normal Subjects | 5.9 - 8.5 | 0.58 - 1.45 | 5.4 – 12.7 |
| Geriatric patients (mean age-65 yr) | 8.2 | 0.82 | 10.3 |
| Patients With Liver Disease* | 8.8 | 1.1 | 13.6 |
| *Patients with Liver disease might show impairment in metabolism | | | |

**Main Uses Of Ceftraixone**

Ceftriaxone is mainly used in the following infectious cases caused by bacteria

- **Upper respiratory tract and lung infections such as bronchitis or pneumonia**(S.pneumoniae)
- **Skin infections**(Atopic dermatitis)
- **Urinary tract infections(UTI)**
- **Gonorrheal infections**
- **Sepsis**
- **Bone and joint infections**(S.aureus osteomyelitis )
- **Meningitis** (N.meningitidis)
- **Pelvic inflammatory disorders**(Chlamydia)
- **Infections caused due to surgical prophylaxis**
- **Abdominal infections**(salmonella,shigella etc)

Along with these bacteriae ceftraixone also works well against E.coli,B.fragilis,H.influenzae and K.pneumoniae

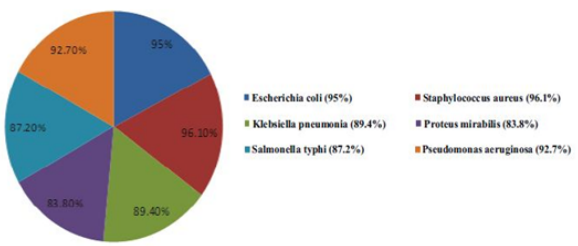



**Figure.1.** Susceptibility of different bacteria towards Ceftriaxone[6].

**Dosage Forms Of Ceftriaxone**

- 250 mg injection
- 500 mg injection
- 1 g injection
- 2 g injection
- 10 g injection

**Adverse Drug Effects**

- **Hypersensitivity**- The most common and most widely found adverse drug effect of ceftriaxone wherein certain allergic reactions like skin rashes,urticaria can be seen along with anaphylaxis in rare cases. Temporary escalate in transaminases can also be seen.
- **GI disturbances**-The GIT might be completely disturbed with increased diarrhea,vomiting and anorexia
- **Pain**- Pain at the site of injection might also be seen in

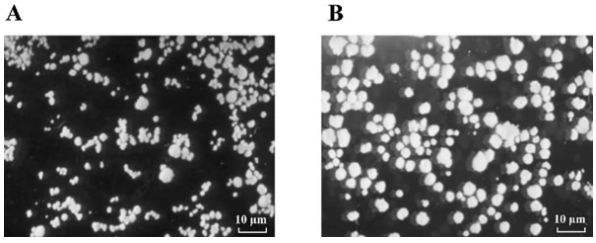
some cases.Lidocaine is given to numb the pain at the site of injection

- **Nephrotoxicity-** The risk of nephrotoxicity is seen in Ceftriaxone administration
- **Intolerance Towards Alcohol-**The patient is advised to not consume alcohol for 48 hours after receving a dose of ceftriaxone or else there might be palpitations, diaphoresis, vertigo, nausea etc(disulfiram like reactions)
- **Neurological Effects-** Neurotoxicity has been reported with both third-generation and fourth-generation cephalosporins including ceftriaxone. Epileptogenic activity of -lactam antibiotics was first shown in 1945, when seizures were reported in experimental animals following intraventricular injection of penicillin , particularly in the settings of renal failure and excessive dosage[7].
- **Haemolysis-** Extensive haemolysis can be seen after administration of ceftriaxone in rare cases
- **Paediatric ADR-** Ceftriaxone-associated biliary adverse events in pediatrics cause biliary pseudolithiasis and scarcely nephrolithiasis often happens in children less than eighteen years who receive overdoses of ceftriaxone[8]. Hyperbilirubinemia is notably contraindicated for neonates who have been administered ceftriaxone (especially premature infants), because this can lead to the displacement of bilirubin from its albumin-binding sites, which in turn increases the concentrations of free bilirubin in the blood. A child older than one month and a child younger than twelve months in special circumstances are at considerable risk of adverse outcomes, particularly due to the potential for bilirubin encephalopathy. However, the implications of this condition necessitate careful monitoring and intervention. Although the risks are pronounced, proper management can mitigate some of the dangers associated with elevated bilirubin levels.

Age can influence pharmacodynamic changes, leading to a higher risk of serious central nervous system (CNS) adverse drug reactions (ADRs) and alterations in pharmacokinetics, such as reduced protein binding. In elderly patients, the unbound fraction of ceftriaxone increases due to lower albumin levels. Additionally, renal impairment, which often is related with age, impacts the elimination of the unbound portion of the drug. While some patients may have pre-disposing renal issues, they can also experience acute renal impairment during treatment due to their underlying medical conditions. This prolonged elimination can lead to ceftriaxone accumulation, resulting in clinical manifestations hindering the CNS. Recent population pharmacokinetic studies have identified serum creatinine and estimated glomerular filtration rate as an Important factor influencing ceftriaxone levels. These findings align with other pharmacokinetic research indicating that the daily dose of ceftriaxone should be decided and adjusted based on renal function and body weight to prevent toxic and abnormal plasma concentrations in patients with meningitis. Another hypothesis linked to renal impairment is an accumulation of toxic organic acids or an alteration of pH contributing to impair active transport of the molecule from cerebrospinal fluid to blood, promoting neurotoxicity. Excessive dosage is also considered as a risk factor[9].

**Contraindications**

- Ceftriaxone is contraindicated in newborns younger than 28 days and is primarily contradicted in preterm neonates up to 41 weeks postmenstrually. Ceftriaxone and calcium infusion should not be combined, especially in newborns, since this can result in calcium-ceftriaxone precipitates, a dangerous side effect. The product label has long warned of ceftriaxone's incompatibility with calcium and the potential for precipitate formation. Ceftriaxone is highly soluble as a sodium salt but much less soluble as a calcium salt.
- Incompatibility of ceftriaxone with calcium and the possible formation of precipitates have been stated in the product label from early on[10].
- There were 259,149 newborns found in all. Out of 79,038 newborns, 3.8% of patients who received IV calcium and ceftriaxone within 48 hours died, compared to 2.03% for parenteral feeding, 1.95% for IV calcium, 0.3% for ceftriaxone, and 1.54% for IV fluids. Ceftriaxone with IV calcium within 48 hours accounted for 5.47% of the fatalities of 102,456 newborns, while IV calcium accounted for 0.45%, ceftriaxone for 0.15%, IV fluids for 0.39%, and parenteral nutrition for 5.5%. Regardless of age, multivariate analysis revealed higher chances of death for infants who received IV calcium and ceftriaxone within 48 hours, and propensity score-matched analysis revealed a risk of mortality that was more than doubled[11].




Stereomicroscope Photographs of Insoluble Microparticles Insoluble microparticles in the solution of ceftriaxone isotonic sodium chloride solution (10 mg/ml) mixed with 2% (w/v) calcium chloride solution (A), or 8.5% (w/v) calcium gluconate solution (B), stored at 25°C for 6 h[12]

The above photographs show how the calcium-ceftriaxone crystals look like when observed under light obscuration particle counter.

Calcium-ceftriaxone precipitates rarely form in adults but FDA always advices not to infuse calcium along with ceftriaxone

**Drug-drug Interaction**

In general, ceftriaxone is quite safe, however there is one problem – the drug should not be administered together with compunds containing calcium. When administered together with intravenous calcium salts the ceftriaxone is capable of forming precipitates in the lungs as well as in the kidneys, especially in newborns. In addition, it may have an effect on anticoagulant medications such as warfarin increasing the likelihood of bleeding. It can also interfere with specific lab tests, particularly ones involving the liver product called bilirubin. Therefore, even though ceftriaxone has minimal side effects, it is important to recognize certain forms of drug interaction, particularly in cases, where patients use a number of medicines. The accompanying medications should not be taken while the patient is on ceftriaxone-

- calcium acetate
- calcium carbonate
- calcium chloride
- calcium citrate
- calcium gluconate

- **Warfarin-** Administrating ceftriaxone with warfarin tend to increase effects of warfarin which may lead to anti-thrombosis like functions in the bloodstream which may lead to anti-coagulatory activity in the bloodstream leading to less venous thrombosis and thrombolytic functions
- **Probnecid**- The protein binding interaction between probenecid and ceftriaxone appears to be unique. The results are of limited clinical consequence for ceftriaxone but they emphasise the importance of evaluating the kinetics of the free drug when examining interactions involving probenecid[13]. Increased half-life means that

Probenecid provides enhancement at sustaining the antibiotic's serum concentrations above the MIC required to eliminate pathogens. Probenecid increases serum concentration of the ceftriaxone. Probenecid is useful in treating a range of infections, such as skin and soft tissue infections, gonorrhea, and staphylococcal infections[14].

- **Furosemide-** Ceftriaxone can enhance the toxicity of furosemide through pharmacodynamic co-ordination. The significance of this interaction is minor or unknown, but it does increase the risk of nephrotoxicity.
- **Azithromycin-** At times, doctors prescribe both azithromycin and ceftriaxone concurrently, since both these antibiotics are compatible with one another, and can synergistically handle the infection and the inflammation consequent to it. The rationale for this combination therapy is to provide coverage against a wider range of bacterial pathogens, at the same time limiting the Antibiotic Stewardship. Possible risks and side effects are as follows; Now when high doses of Azithromycin are administered as single-agent therapy, a bacteriostatic drug, it will exhibit a propensity to engender bacterial resistance with persistent use. That is why by including ceftriaxone into the mentioned treatment course, the possibility of such complication can be reduced to a minimum. In addition, the interaction of both therapeutic agents is mutually beneficial in the view that the dual approach increases the therapeutic impact by acting on the infection through the different mechanisms at the same time, while at the same time it contributes to the non-development of resistance to the use of azithromycin in the course of the patient's treatment eventually leading to increased therapeutic effectiveness.
- **Bcg Vaccine-** Ceftriaxone diminishes the efficacy of the live BCG vaccine through pharmacodynamic antagonism, meaning that the drug interferes with the vaccine's intended biological activity. As a result, concurrent administration of ceftriaxone and the BCG vaccine is contraindicated. It is recommended to postpone the administration of the live bacterial vaccine until the course of antibiotic treatment is fully completed, ensuring that the vaccine can achieve its optimal immunological effect without interference from the antibiotic therapy.
- **Cholera Vaccine-** The interaction of ceftriaxone with the cholera vaccine is pharmacodynamic; the antibiotic may neutralise or reduce the c hance of a positive response to the vaccine. The live attenuated strain in the cholera vaccine could be targeted by systemic antibiotic like ceftriaxone and therefore reduce the immune response the vaccine is supposed to create. For this reason, it is suggested to exclude using the cholera vaccine in patients with systemic antibiotics. In particular, the cholera vaccine should not be given for clients that have received oral or parenteral antibiotics during the past two weeks because administering the cholera vaccine weakens the purpose of vaccination since it is immunogenic. In the first case, other methods or deferring vaccination may be necessary for the necessary immune response to occur.
- **Typhoid Vaccine-** It competes with the live typhoid vaccine through pharmacodynamic antagonism since ceftriaxone alters the biological activity of the live bacteria. Thus, ceftriaxone should not be taken concurrently with the live typhoid vaccine because the antibiotic will depress the immune response that is created by the vaccine. If any of the vaccines require the use of a live bacterial typhoid vaccine, it should not be taken until all the antibiotics have been completed including ceftriaxone in order to allow the vaccine to mount its full immunological effect to offer enough protection to the body. It ensures that the antibiotic is cleared from the body to the barest level so that the vaccination takes place and would not be interfered with by the presence of the medication.

**Drug-food Interactions**

There has been no evidence of drug-food interactions when it comes to ceftriaxone as long as the person is not consuming two things-Calcium rich foods and alcohol.

Consumption of alcohol can lead to disulfiram like effects on the person which might even lead to death in rare cases.Animals treated with ceftriaxone were found to consume significantly higher amounts of water post treatment.As it was found in a recent study that used the five-week ethanol drinking paradigm, the increase in water consumption might be a compensatory mechanism for the reduction in ethanol intake[15].A retrospective review conducted in China evaluated 78 cephalosporin-induced disulfiram-like reactions where drug hypersensitivity reactions were excluded via cephalosporin skin testing prior to intravenous cephalosporin receipt. Twenty (25.6%) of the reactions occurred in patients receiving ceftriaxone. Five patients died after consumption of alcohol after failed resuscitation attempts. Sweating was experienced by 63%, palpitations by 78%, dizziness by 56%, hypotension in 24%, tachycardia in 76%, premature atrial beat in 4%, and premature ventricular beat in 3%[16]. Also, doctors should keep in mind that ceftriaxone should not be prescribed for any alcoholics or heavy drinkers.

**In Pregnancy**

The studies indicated that exposure to ceftriaxone during pregnancy could significantly disrupt the maternal intestinal microbial health, resulting in monumental changes in the gut's microbial composition and gut microbial flora. These disruptions had serious implications for both maternal and neonatal health, particularly in terms of immune system function[17]. Namely, the change of microbiome was associated with flooding of pro-inflammatory factors in the system, which not only affected the mothers but also their offspring, thus,probably making their immune systems less reactive and potent. Further, the study has proposed a hypothesis of the presence of microbiome within the placenta which appear to be relatively infuriatingly insulated from the external environment and therefore, do not seem to be influenced by oral consumption of antibiotics such as ceftriaxone during pregnancy. These findings matter as they prompt further investigations of the role of these placental microbes in shaping the developing fetus and infants' immune system and overall wellbeing. In furthering our understanding of these intricate relationships, we suggest that future studies need to examine the role of placental microbiota in promoting fetal development and also the health impacts of early life gut microbial activity disruption in infants with altered placental microbiome.This field of study has significant potential to enhance our understanding of maternal-fetal health and the effects of antibiotic exposure during pregnancy.Ceftriaxone is prescribed in pregnant women who have contracted syphilis during or before pregnancy.Untreated or improperly treated syphilis in pregnancy has an 80% chance of fetal infection and is associated with miscarriage,stillbirth or neonatal death after delivery in 30% of cases[18] so keeping that in mind Ceftriaxone may be considered as an alternative for treatment of early syphilis in pregnancy[19] given the risks.

**CONCLUSION**

Ceftriaxone remains more or less a third-generation cephalosporin antibiotic with assured impact, wide-spectrum action and -lactamase malware vulnerability. Approved in 1979, the antibiotic has had success against almost all categories of gram positive and negative bacteria and is prescribed in treatment of infections of the nervous system, lungs, skin, urinary tract and others. Given intravenously or intramuscularly, it has good tissue penetration, including the meninges; it is used in various conditions, like meningitis, pneumonia, sepsis, and gonorrhea only if used correctly as it has concerns related to antimicrobial resistance, increased costs, and possible side effects. For instance, it is used to cure

upper respiratory infections, atopic dermatitis, UTIs, and abdominal infections attributable to bacteria such as Salmonella and Shigella. The injection comes in forms of 250 mg, 500 mg, 1 g, 2 g and 10 g in order for the physician to prescribe based on the condition of the patient and the severity of the infection.Ceftriaxone interacts with calcium products; therefore, this antibiotic should not be given with calcium-containing solutions especially in newborns for the formation of precipitate. Besides, it can improve the effects of anticoagulant and raise the risks of bleeding; and it can also interact with probenecid to extend the half-life of the latter. Its usage should be cautious especially when administered with furosemide because both are associated with nephrotoxicity. Furthermore, ceftriaxone interacts with live vaccines, including BCG, cholera, and typhoid, therefore vaccination should only be given after a certain period of time.During pregnancy, the maternal gut microbiotic balance is affected by ceftriaxone, which may affect maternal immune status, but it remains a syphilitic remedial intervention since the risks of under-treating the disease are more severe. Hence the importance of following guidelines in the use of the antimicrobials as well as practices such as antimicrobial stewardship to ensure the best returns and reduce development of resistance.Prescription of ceftriaxone: The most common violation of the recommended dosing regimen (20).The most common inappropriate use of ceftriaxone was deviation from the recommended treatment duration[20].

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