THE DRUG UTILIZATION REVIEW OF CEFTRIAXONE IN TERTIARY CARE HOSPITAL, PESHAWAR

Abdur Rahman[1], Anwar Ul Wahab[1], *Muhammad Hasnain[1], Saud Khan Sahil[1], Mohsin Raziq[1], Safa Bakhtawar[1]

[1] Department of Pharmacy, University of Peshawar, Pakistan

Corresponding Author:
Muhammad Hasnain

ABSTRACT:

Drug Utilization Evaluation (DUE) represents a continuous and systematic approach aimed at fostering the proper and efficient utilization of medications. Its fundamental aim is to pinpoint the potential issues and the exploration of corresponding resolutions. A retrospective study was employed to assess the judicious utilization of ceftriaxone. The investigation involved a thorough examination of medication records pertaining to 158 patients who underwent ceftriaxone treatment during their hospitalization at medical wards A, B, C, D, and Pulmonology wards of Tertiary Care Hospitals in Peshawar from May 10, 2023, to June 10, 2023. A drug use evaluation was executed to ascertain whether the application of ceftriaxone aligned with the established protocol for its rational use. Seven criteria, specifically indication for use, dosage, prescription type, frequency of administration, treatment duration, treatment type, and the conduction of culture & sensitivity tests, were employed to appraise its utilization. Data was systematically collected using a structured format and assessed against the drug use evaluation clinical guidelines provided by Médecins Sans Frontières (MSF).

A comprehensive review was conducted on 158 patient records receiving ceftriaxone, revealing a notably high prescribing rate (45.01% point prevalence). Ceftriaxone use was predominantly empiric, accounting for 77.8% of cases, with the primary indications being fever workup (14.6%), chronic obstructive pulmonary disease (5.1%), and enteric fever (5.1%). The most prevalent daily administration frequency and mean treatment duration were 2 g (71.5%) and 8.56 days, respectively. Unfortunately, inappropriate utilization of ceftriaxone was prevalent, particularly concerning the duration of drug administration (64.55%) and the absence of culture and sensitivity tests (85.4%). The study underscores the overall inappropriate use of ceftriaxone, attributed to factors such as indications for use, continued empiric use for suspected infections, and empiric fever therapy. This tendency may stem from the practice of administering empiric antibiotics for fever without clear clinical, biochemical, radiological, or microbiological evidence of bacterial infection. Such unwarranted use not only incurs additional medical costs for patients with viral illnesses but also places a financial burden on hospitals. Despite this, the study found that the dose, frequency, and duration of ceftriaxone were generally appropriate. To address these issues, adherence to evidence-based guidelines is crucial, and the presence of clinical pharmacists in all wards is recommended to monitor and ensure the judicious use of ceftriaxone and other antibiotics.

1 INTRODUCTION:

Ceftriaxone, a frequently used third-generation cephalosporin antibiotic, is a compelling choice for medical use across various settings, including the emergency department (ED), outpatient clinic, and at hospital. Due to its substantial protein binding and prolonged half-life, it is primarily administered intravenously, though intramuscular administration is also an option. Importantly, ceftriaxone is excreted through the biliary tract, obviating the necessity for dosage adjustments in cases of renal or hepatic impairment. It is active against many commonly encountered gram-positive and gram-negative pathogens, such as Streptococcus pneumonia and Escherichia coli, respectively [1]. This antibiotic is widely employed due to its remarkable antibacterial potency, low potential for toxicity, excellent tolerance, and expansive range of effectiveness against a wide array of infections. It is the preferred initial treatment for conditions such as acute bacterial meningitis, severe community-acquired pneumonia, mild to moderate complicated intra-abdominal infections, severe complicated intra-abdominal infections, hospital-acquired pneumonia, Neisseria gonorrhoeae infections, and severe cases of pyelonephritis or prostatitis. In cases of acute invasive bacterial diarrhoea/dysentery, bone and joint infections, mild to moderate pyelonephritis or prostatitis, and sepsis in neonates and children, it is considered a secondary treatment option [2]. Meningitis, streptococcal endocarditis, severe lime disease [3].

CEFTRIAXONE COVERAGE:

Ceftriaxone exhibits a wide-ranging effectiveness against numerous gram-negative and gram-positive bacteria, including, but not limited to, Citrobacter species, Escherichia coli, various Haemophilus species, Klebsiella pneumonia, Neisseria gonorrhoeae, Proteus mirabilis, Salmonella typhi, Serratia marcescens, Staphylococcus species, Streptococcus pneumonia, Streptococcus pyogenes, and Treponema pallidum. Notably, these bacterial strains often demonstrate resistance to earlier-generation antibiotics [4]. The report indicates that in addition to its antibacterial properties, ceftriaxone exhibits antitumor activity both in vitro and in vivo. The results of kinase profiling have suggested that Aurora B could potentially be "off" target protein affected by ceftriaxone. This prediction was confirmed by pull-down assay data, which demonstrated that ceftriaxone can indeed bind to Aurora B in vitro and within A549 cells. Furthermore, at a concentration of 500 μM, ceftriaxone was observed to inhibit anchorage-independent cell growth by targeting Aurora B in lung cancer cells, specifically A549, H520, and H1650. Importantly, findings from in vivo xenograft animal models showed that ceftriaxone effectively curtailed the growth of A549 and H520 lung tumors by inhibiting Aurora B. These compelling results indicate that ceftriaxone holds promise as an anticancer agent for the treatment of lung cancers, achieved through its inhibition of Aurora B [5]. Ceftriaxone is ineffective against certain bacterial types, such as Enterobacter species, Listeria monocytogenes, Pseudomonas aeruginosa, and Methicillin-resistant Staphylococcus aureus (MRSA). In cases of infections caused by these pathogens, fourth-generation cephalosporin antibiotics like cefepime may be considered as an alternative treatment [6].

INTERPRETATION OF SUSCEPTIBILITY TESTING OF CEFTRIAXONE:

The susceptibility of various bacterial isolates to ceftriaxone was determined through two methods: Kirby-Bauer assays using 30 micrograms ceftriaxone disks and microdilution (MIC) assays following standard procedures. A regression equation was used to express the relationship between zones of inhibition and MICs, which is represented as follows: zone diameter = 22.98 - 2.653 In (MIC). Based on this regression line and breakpoints estimated from ceftriaxone concentrations in plasma 12 to 24 hours after 1- and 2-g doses, the susceptibility of a pathogen to ceftriaxone was categorized as follows:

- **Susceptible**: zone diameter of 16 mm or greater, MIC of 16 micrograms/ml or less.
- **Moderately susceptible**: zone diameter of 13 to 15 mm, MIC of 17 to 63 micrograms/ml.
- **Resistant**: zone diameter of 12 mm or less, MIC of 64 micrograms/ml or greater.

These defined breakpoints were applied to assess the susceptibility of organisms isolated during clinical studies in the United States. The study examined the correlation between in vitro results and bacteriologic outcomes to evaluate the appropriateness of these chosen breakpoints. The findings revealed that the results of the disk assays accurately predicted bacteriologic responses in 91.7 percent of the cases (1,388 out of 1,513 organisms), while the dilution assays correctly predicted the response in 95.3 percent of cases (897 out of 941 organisms). Importantly, the correlation between in vitro results and bacteriologic outcomes in patients treated with ceftriaxone was on par with or even superior to that achieved in patients treated with the comparative agent's cefamandole and cefazolin. Therefore, the selected cutoff points for indicating susceptibility and resistance to ceftriaxone appear to be appropriate and highly predictive of clinical success [7].

OVER USE AND RESISTANCE:

The excessive use of antibiotics and the consequent development of antibiotic resistance represent a significant threat to global public health. Infections caused by bacteria that have become resistant to specific antibacterial drugs not only consume more healthcare resources but are also linked to a higher risk of unfavourable clinical outcomes and mortality. Low and middle-income countries (LMICs) are disproportionately affected by antibiotic resistance due to a combination of factors, including a high prevalence of infectious diseases, limited resources, and fewer antibiotic treatment options. As a response to the growing issue of resistance, cephalosporin, a class of antibiotics, have become a primary target for evaluation and management in antibiotic stewardship programs. However, findings from a global antimicrobial stewardship effort conducted by the World Health Organization (WHO) across its six regions revealed alarming resistance patterns. In particular, Escherichia coli (E. coli) displayed resistance rates of 50% or higher to third-generation cephalosporin in five of the regions, indicating widespread resistance. Additionally, Klebsiella pneumoniae (K. pneumonia) showed resistance in 50% or more of the cases in all six regions, and Neisseria gonorrhoea exhibited resistance of 25% or more to third-generation cephalosporin in three of the regions. The rise of extended-spectrum beta-lactamases, often associated with the overuse of third-generation cephalosporin, has further complicated the treatment of infections caused by certain bacteria, such as Enterobacter and Enterobacteriaceae species. This highlights

the urgent need for enhanced antibiotic stewardship and measures to combat the growing problem of antibiotic resistance on a global scale [8].

INAPPROPRIATE USE:

Survey findings indicate that a significant proportion of antibiotic prescriptions, ranging from 22% to 65%, are either inappropriate or incorrect [9]. Despite extensive efforts to regulate and encourage the proper use of antibiotics, much of this misuse is attributed to healthcare practitioners who lack a comprehensive understanding of pharmacology and pathophysiology. This, in turn, affects their ability to make accurate diagnoses and choose the most effective and appropriate treatment strategies. As a consequence of this, there is a heightened risk of antimicrobial resistance and adverse medication reactions. Additionally, the length of hospitalization may be prolonged, and the commencement of successful therapy can be delayed, serving as notable side effects associated with ceftriaxone and other antibiotics [10]. Patient-related factors contributing to the issue of irrational antibiotic use encompass instances such as patients failing to complete their prescribed antibiotic doses, non-compliance with treatment regimens, and self-medication without proper guidance. On the other hand, drug-related factors include the use of ineffective or substandard antibiotics, which can further exacerbate the problem of irrational antibiotic use.

In Uganda, there have been reports of clinician practices that heighten the risk of irrational antibiotic utilization. These practices include the over-the-counter sale of antibiotics without a prescription, which is associated with under-dosing and the prescription of antibiotics to patients who do not clinically require them. Such prescribing practices often result from insufficient medical knowledge or personal financial motivations, rather than a patient's genuine need for antibiotic therapy [11]. The excessive use of antibiotics in low and middle-income countries (LMICs) has led to alarmingly high rates of antimicrobial resistance. For instance, a study conducted in private hospitals in Lahore, Pakistan, revealed that out of 93 Escherichia coli isolates, a striking 82% displayed resistance to beta-lactam antibiotics, with a significant portion also resistant to fluoroquinolones and trimethoprim-sulfamethoxazole. These high resistance rates are primarily attributed to the overuse and misuse of antibiotics in the region. It's worth noting that concerns regarding antimicrobial prescribing practices in LMICs are not uniform. For instance, in Namibia, approximately 62% of antibiotic prescriptions comply with national guidelines, demonstrating that responsible prescribing is possible. However, the frequent and unnecessary use of antibiotics in Pakistan has undoubtedly contributed to the surge in antimicrobial resistance rates, as documented by various studies highlighting the improper use of antibiotics in ambulatory care settings in the country [12]. While the rates of ceftriaxone use may not fully align with international guidelines, it's noteworthy that Ghana reported the highest level of appropriate ceftriaxone utilization at 93%. In contrast, Sudan exhibited the lowest rate of appropriate ceftriaxone use, with only 6.7% compliance with recommended guidelines. These disparities highlight the variation in antibiotic prescribing practices and adherence to international standards in different countries, with Ghana demonstrating a relatively high level of appropriate ceftriaxone use in comparison to Sudan [13]. The empirical use of ceftriaxone is prevalent, with estimates as high as 80-90% in

hospitalized patients in certain countries. In a cross-sectional survey conducted at Mubende Regional Referral Hospital in Uganda, concerning the clinical use of ceftriaxone, it was found that 81% of administrations were inappropriate, and culture and sensitivity testing were lacking in over 93% of the patients sampled. Similar findings have been reported in studies conducted in various countries across Africa, the Middle East, and Asia.

Notably, the mortality rates are elevated in surgical cases, particularly among patients who have undergone maternal cesarean sections in low- and middle-income countries (LMICs). The heightened mortality in these patients can be attributed to the development of post-surgical site infections, occurring in 2-24% of cases, primarily due to the inappropriate use of antibiotics. Patients who miss their post-cesarean section antibiotic doses are 2.5 times more likely to develop post-surgical site infections, and these infections can lead to fatalities in over 5.3% of affected patients [14].

RESISTANCE STATISTICS:

Twenty-five years ago, a study was conducted to investigate the incidence of bacterial species and their susceptibilities to ceftriaxone and other beta-lactam antibiotics in patients with community-acquired infections. The study revealed that all bacterial strains resistant to other antibiotics were fully susceptible to ceftriaxone at that time. However, over the years, the landscape of antibiotic resistance has changed significantly. Resistance to ceftriaxone by the FC428 ceftriaxone-resistant Neisseria gonorrhoeae strain was first reported in Japan in January 2015. Subsequently, in 22% of the countries participating in the Gonococcal Isolate Surveillance Project, reduced susceptibility to ceftriaxone among patients with N. gonorrhoeae infection was reported. In 2018, the world's first gonorrhea strain resistant to ceftriaxone was reported in England, and it also exhibited high-level resistance to azithromycin.

In another study conducted at Jimma Teaching Referral Hospital in Ethiopia, clinical isolates of Staphylococcus aureus and Escherichia coli showed alarming resistance rates, with 73% and 65% resistance to ceftriaxone and ceftazidime, respectively. Among the bacterial strains that were resistant to both ceftriaxone and ceftazidime, 44% of Staphylococcus aureus and 43.5% of Escherichia coli were resistant to both drugs.

More recently, Dr. Moopans' Aster Hospital in Doha, Qatar, reported the first cases of ceftriaxone-resistant Salmonella Typhi in the Middle East. These examples underscore the growing concern of microbial strains developing resistance to ceftriaxone, which poses a significant threat to its effectiveness. Like other first-line antibiotics, the emergence of resistance to ceftriaxone has become a major worry for many countries, considering its historical performance, tolerability, and affordability. As indicated in Figure 1, a 10-year surveillance study in the United States demonstrated that ceftriaxone has become one of the top 10 antibiotics with increasing resistance rates among Enterobacteriaceae strains.

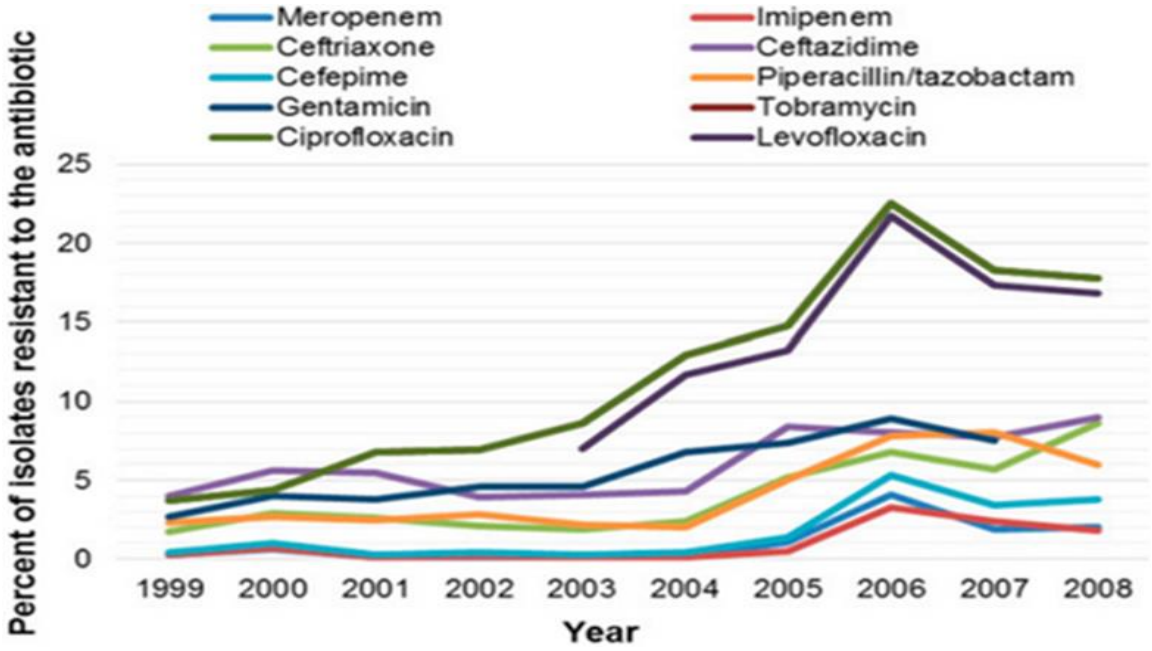

FIGURE 1: The Percentage of Enterobacteriaceae strains resistance from a US surveillance study

STRATEGIES TO MINIMIZE RESISTANCE:

Addressing antimicrobial resistance (AMR) requires a multifaceted approach, and several strategies have been proposed to mitigate its impact. These strategies include the integrated use of antimicrobial stewardship programs (ASPs), a deep understanding of the pharmacokinetic and pharmacodynamics profile of antibiotics, the utilization of data from diagnostic testing and antimicrobial susceptibility testing, and surveys that monitor the clinical response to antimicrobial treatments. These approaches work together to minimize the emergence and spread of AMR. The scientific and public health communities advocate for the development of new antibiotics. Simultaneously, there is a growing emphasis on the rational and responsible use of existing antibiotics at all levels of healthcare. Combating AMR is an ongoing effort that necessitates both the expansion of treatment options and the preservation of existing antimicrobial resources. In addition to traditional antimicrobial drugs, novel strategies are emerging for the treatment of microbial diseases. One such approach is the use of nanotechnology, which has gained considerable attention for enhancing the effectiveness of existing antimicrobial agents. Nanomaterials (NMs) are being explored for targeted drug delivery, where they can transport antimicrobials to specific sites of action. Moreover, NMs themselves may possess intrinsic antimicrobial activity, which can work synergistically with traditional drugs to combat microbial infections more effectively. These diverse strategies underscore the need for a comprehensive and innovative approach to address the growing threat of AMR and ensure the continued effectiveness of antimicrobial therapies [15]. Host defense peptides, bacteriophages, vaccines, immunoglobulins, and probiotics are various approaches and therapies used in the field of

medicine to combat bacterial infections and promote better health. Here's a brief explanation of each:

- **Host Defense Peptides**: These are small, naturally occurring molecules produced by the human body as part of the innate immune system. They possess antimicrobial properties and can target and kill bacteria. Host defense peptides play a crucial role in the body's first line of defense against pathogens.
- **Bacteriophages:** Bacteriophages are viruses that specifically infect and kill bacteria. They are used in phage therapy to combat bacterial infections. Phage therapy involves using bacteriophages to target and eliminate harmful bacteria while sparing beneficial ones.
- **Vaccines:** Vaccines are preventive measures that stimulate the immune system to produce an immune response against specific bacteria or viruses. This helps the body recognize and fight off the pathogen more effectively if encountered in the future. Vaccines have been instrumental in preventing bacterial infections such as tetanus, diphtheria, and whooping cough.
- **Immunoglobulins:** Immunoglobulins, also known as antibodies, are proteins produced by the immune system to target and neutralize invading pathogens, including bacteria. In some cases, specific immunoglobulins may be administered as therapy, such as immunoglobulin therapy for certain immune deficiencies.
- **Probiotics:** Probiotics are live microorganisms, primarily beneficial bacteria that can help maintain a healthy balance of microbes in the gut. While they are more commonly associated with promoting gastrointestinal health, probiotics may also contribute to overall immunity and help prevent certain bacterial infections.

Each of these approaches has a specific role in managing bacterial infections or promoting overall health, and they are often used in combination with traditional antibiotic treatments or other therapies to improve outcomes in various medical contexts [16]. Recent research has highlighted the potential of a rational approach to antibiotic use through fixed-dose combinations (FDC) to help delay or even prevent the emergence of antimicrobial resistance (AMR). Specifically, antibiotic combinations that exhibit pharmacodynamic synergism, as well as the incorporation of non-antibiotic adjuvants (NAAs), have demonstrated the ability to combat antibacterial resistance effectively. In one such example, a combination of ceftriaxone, sulbactam, and the NAA ethylenediaminetetraacetate (EDTA), with the EDTA present in a concentration considered low enough to qualify as an excipient, was developed. This FDC approach is designed to address antibacterial resistance (ABR) by eradicating biofilms, inhibiting conjugal transfer of resistance genes, preventing bacterial adhesion, and reducing the expression of efflux transporters.

This FDC demonstrates efficacy comparable to meropenem, particularly against extended-spectrum beta-lactamase (ESBL) strains, and it remains active against metallo-beta-lactamase (MBL) strains. As a result, it has the potential to serve as a valuable alternative to carbapenem antibiotics, helping to spare the use of these critical drugs while still effectively combating challenging bacterial infections [17].

EXTRA COST ON HEALTHCARE SYSTEM DUE TO RESISTANCE:

Antimicrobial drug resistance has substantial economic implications, with projections estimating that it could add anywhere from $100 million to $30 billion annually to healthcare costs. To illustrate the financial impact of inappropriate antibiotic use, it was reported that the global annual cost related to infections caused by antibiotic-resistant bacteria due to the inappropriate use of ceftriaxone ranged from $4 million to $5 million. A separate study conducted in Spain focused on the use of third-generation cephalosporin, with ceftriaxone being the most commonly prescribed agent. This study revealed that the cost of inappropriate antibiotic use was twice as high for patients who were not treated in compliance with international guidelines and appropriately. These findings underscore the economic burden of antimicrobial resistance and the importance of prudent antibiotic use in reducing both healthcare costs and the development of resistance [18].

POSSIBLE ADVERSE DRUG REACTIONS WITH CEFTRIAXONE:

Adverse drug reactions (ADRs) represent a significant risk in modern medicine, and cutaneous ADRs are a particularly important clinical concern as they can pose a threat to a patient's well-being. Cephalosporin, a class of antibiotics, can, in some cases, trigger severe or life-threatening IgE-mediated reactions in individuals. One distinctive type of cutaneous drug reaction is known as a Fixed Drug Eruption (FDE). FDE presents a unique pattern, characterized by skin lesions that consistently recur at the same site or sites whenever the causative drug is administered. These lesions typically manifest as round or oval, well-defined erythematous plaques that may develop central blisters. They tend to appear on the lips and genitalia, although they can affect any skin or mucosal surface. The eruption typically occurs within hours of the drug's administration and resolves on its own without causing permanent scarring within a few weeks of onset [19]. Severe cases of hemolytic anaemia have been reported in individuals undergoing ceftriaxone therapy. Hemolytic anemia is a condition characterized by the rapid destruction of red blood cells, outpacing the body's ability to produce new ones. In cases where a patient develops anemia while receiving ceftriaxone, it is crucial to discontinue the treatment immediately. Further administration of ceftriaxone should be suspended until the underlying cause of the anemia is identified and appropriately addressed [20]. Ceftriaxone, while generally considered safe, can, in very rare cases (with a frequency of less than 1%), lead to central nervous system (CNS) adverse drug reactions (ADRs). These reactions may manifest as signs of encephalopathy, such as delirium, altered mental status, or even convulsions, and they often occur during hospitalizations. As the use of antibiotics, including ceftriaxone, becomes more crucial in combating increasingly antibiotic-resistant bacteria, it is essential to enhance our understanding of and prevent ADRs associated with these medications, especially those affecting the CNS. Clinicians may have limited knowledge regarding the relationship between neurotoxicity and antibiotics, even though CNS ADRs can potentially lead to life-threatening issues and, in severe cases, even death. In many instances, neurotoxicity can be prevented through dose adjustments based on the patient's renal function.

However, ceftriaxone exhibits an atypical pharmacokinetic profile compared to other cephalosporin antibiotics. It features extended albumin binding, mixed biliary and renal clearance,

and a prolonged elimination half-life, which justifies its once-daily dosing regimen. Encephalopathy is not a well-known ADR of ceftriaxone, but it has been reported in rare cases. Its management typically involves close monitoring of the patient during hospitalization, particularly for any signs of CNS-related ADRs. This underscores the importance of healthcare providers' vigilance when administering ceftriaxone and monitoring patients for any adverse reactions [21].Less common side effects include headaches, dizziness, itching, fever, nausea, vomiting and diarrhoea [22].

DRUG INTERACTIONS AND THEIR MANAGEMENT:

The risk of calcium-ceftriaxone precipitation in the gallbladder is a notable concern, and ceftriaxone should not be used with calcium-containing solutions in individuals of any age. This interaction should be avoided without exception in newly born child. The calcium-containing solutions that should not be used in conjunction with ceftriaxone include:

- Calcium acetate.
- Calcium chloride.
- Calcium gluceptate.
- Calcium gluconate.
- Lactated Ringer's solution.

In situations where these calcium-containing solutions are necessary, such as during pregnancy or surgery, it is important to separate the administration of ceftriaxone from that of the calcium-containing product to minimize the risk of precipitation.

Additionally, ceftriaxone can interact with other medications, including:

- AMSACRINE: A chemotherapy drug used to treat certain types of lymphoma.
- Aminoglycoside antibiotics: This includes drugs like GENTAK (gentamicin) and TOBREX (tobramycin).
- DIFLUCAN (fluconazole): An antifungal medication.
- VANCOCIN (vancomycin): A glycopeptide antibiotic.

These drug interactions should be taken into consideration when prescribing or administering ceftriaxone to avoid potential complications or reduced effectiveness of the medications involved. It is advisable for healthcare providers to be aware of these interactions and to carefully manage medication regimens accordingly [23].

COMBINE USE OF CEFTRIAXONE WITH OTHER ANTIBIOTICS FOR INFECTION NEISSERIA GONORRHOEAE:

The use of ceftriaxone in combination with azithromycin or gentamicin for the treatment of Neisseria gonorrhoeae infection is an important strategy to address the issue of drug resistance to ceftriaxone, a critical antibiotic for managing this sexually transmitted infection. The combination of azithromycin and ceftriaxone, often referred to as dual therapy, is recommended by treatment guidelines developed in the United States, Europe, and by the World Health Organization (WHO) for the effective treatment of gonorrhea. In the context of Neisseria gonorrhoeae resistance

patterns, studies have shown variations in susceptibility to different antibiotics. In your provided data, 36.60% of the isolates were fully susceptible to gentamicin, while 61.30% of the strains exhibited intermediate susceptibility. Given the evolving landscape of antibiotic resistance, the combination therapy approach, including the addition of gentamicin, can be a valuable strategy. It's essential to carefully consider the local antibiotic resistance profiles and treatment guidelines when choosing the most appropriate therapy. By using gentamicin as an adjunct in combination therapy (azithromycin and ceftriaxone), healthcare providers can help ensure effective treatment while minimizing the progression of drug resistance to ceftriaxone [24].

2 METHODOLOGY:

1. STUDY DESIGN:

Retrospective study is used to assess the rational use of ceftriaxone.

2. STUDY SETTING:

This study conducted in medical A, B, C, D and Pulmonology wards of the Tertiary Care Hospital, Peshawar.

3. PATIENT POPULATION:

A total of 158 patients data is collected, all those patients who ≥18 years of age and receive ceftriaxone were included in the study, both the gender male and female data is collected.

3.1. Inclusion criteria:

Study comprise of patients ≥18 years of age. The study comprise of both the genders male and female. There is no area limitation in this study.

3.2. Exclusion criteria:

All those subjected were excluded from the study having incomplete record.
Out patients were excluded from study as it is not convenient to make a follow-up study.

4. SAMPLING TECHNIQUE:

The study employed a non-probability, convenience sampling technique consistently throughout the research. Convenience sampling is a method chosen by researchers to collect data from a readily available pool of respondents. It is the most frequently utilized technique due to its simplicity and cost-effectiveness.

5. DATA COLLECTION:

Data were gathered through a comprehensive review of patients' medication charts during the study period, employing a standardized format for patient data collection. The format was structured to capture patient identification details, demographics, disease condition, admission and discharge dates, working diagnosis, past medical history, chief complaints, a general review of systems,

abnormal laboratory tests, unusual diagnostic outcomes, culture and sensitivity (C&S) results, and specifics related to the administration of ceftriaxone. This encompassed details such as its indication, dosage, frequency of administration, duration of therapy, and information about concurrently administered antibiotics.

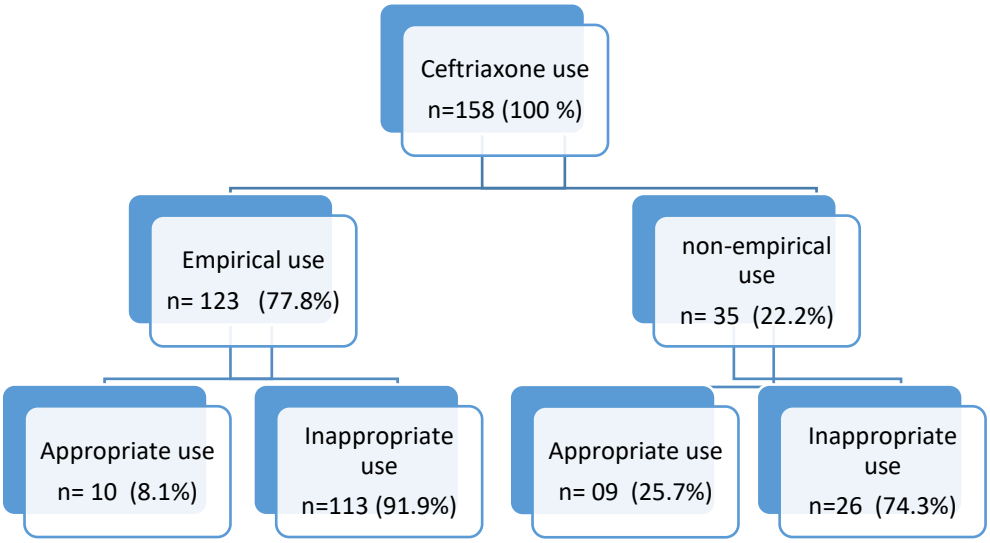

Figure 02: The evaluation of the appropriateness of ceftriaxone indicators.

A. Empirical therapy:

- **Appropriate empirical antibiotic therapy:**
  Defined as applying the antibiotic agent which matches in vitro susceptibility of the isolated bacteria or C-reactive protein greater than 30mg/L, but was initially provided without evidence on the causative pathogen or C-reactive protein test.
- **Inappropriate empirical antibiotic therapy:**
  Defined as applying the antibiotic agent which doesnot matches in vitro susceptibility of the isolated bacteria or C-reactive protein less than 30mg/L, but was initially provided without evidence on the causative pathogen or C-reactive protein test.

B. Non-empirical therapy:

- **Appropriate non-empiric therapy:**
  Applying antibiotic agent which matches in vitro susceptibility of the isolated bacteria or C-reactive protein greater than 30mg/L, and was provided with evidence on the causative pathogen or C-reactive protein test.
- **Inappropriate non-empiric therapy:**

Applying antibiotic agent which matches in vitro susceptibility of the isolated bacteria or C-reactive protein less than 30mg/L, and was provided with evidence on the causative pathogen but the antibiotic given in disease not present in guidelines.

6. DATA ANALYSIS:

The drug utilization assessment aimed to determine the appropriateness of ceftriaxone usage, following the established protocol governing its rational utilization. We utilized seven criteria namely indications for use, dosage, prescription type, administration frequency, treatment duration, treatment type, and the performance of culture and sensitivity tests to evaluate its application. We inputted and analyzed the outcomes of these evaluations using SPSS version-22. To assess the overall appropriateness of ceftriaxone utilization, compliance with each of the seven criteria was determined for every patient, following the guidelines outlined in the Médecins Sans Frontières (MSF) protocol.

3 RESULTS:

Sociodemographic characteristics:

A total of 158 patients were included in this study of which 60.1 % were males and 39.3 were females. Most of the study participants were adults in the age group of 18-65 (81.01 %) with mean age of 48.38 . The socio-demographic characteristics of the participants were summarized below (Table 1 and Table 2).

Charactristic	Category	Frequency	Percent
Gender	Female	63	39.9
	Male	95	60.1
	Total	158	100.0

TABLE 1: The sociodemographic characteristics of patients.

Charactristic	Category (Years)	%age	Minimum	Maximum	Average age	Std. Deviation
AGE	18-70	81.01	18	100	48.38	19.853
	≥70	18.99				

TABLE 2: The sociodemographic characteristics of patients.

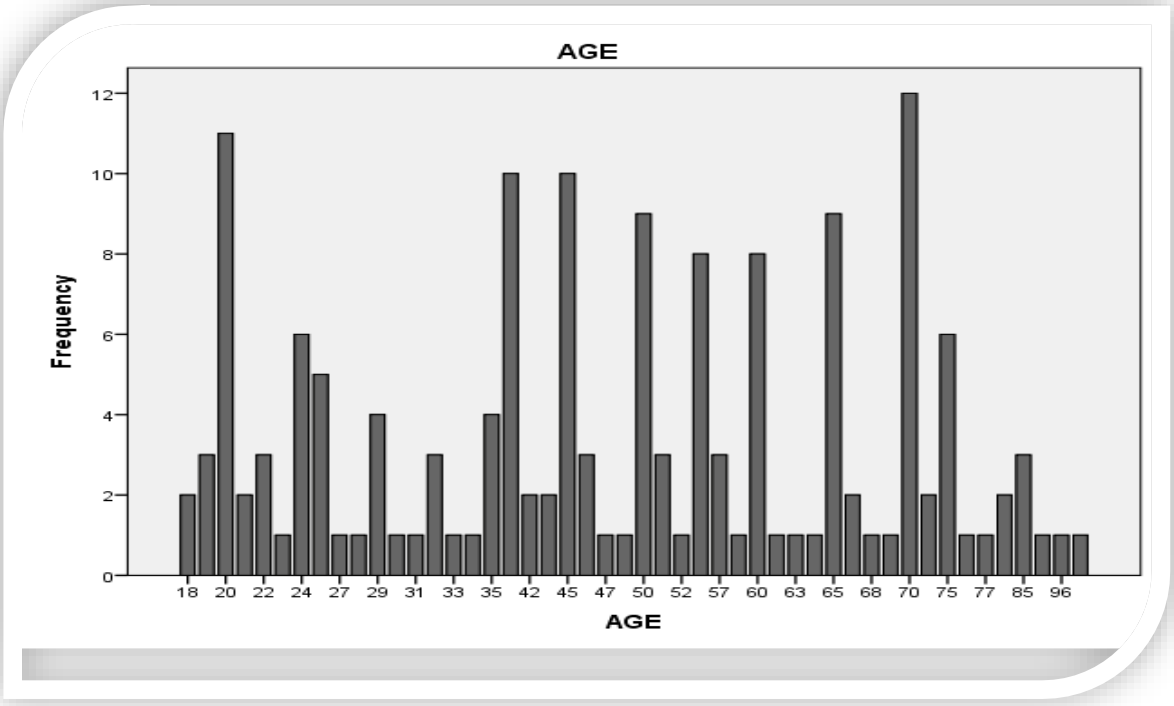

CHART 1: Patients sociodemographic traits.

Dosing of ceftriaxone use:

The most commonly prescribed dose of ceftriaxone was 2 g (78.5 %), the frequency of administration being once-daily dosing (20.9 %) and frequency of administration three a day is (0.6 %) which is summarized below in (Table 3).

Dose(g)	Frequency	Percent	Mean
1	33	20.9	
2	124	78.5	1.80
3	1	.6	
Total	158	100.0	

TABLE 03: Dosing of ceftriaxone for the study participants.

CEFTRIAXONE PRESCRIPTION TYPE:

The data shows that approximately 38.6% of prescriptions were brand-based, while the remaining 61.4% were generic. This is illustrated below in (Table 04).

Prescription	Frequency	Percent
BRAND	61	38.6
GENERIC	97	61.4
Total	158	100.0

TABLE 04: The prescription type for the study participants.

Frequency of ceftriaxone administration:

The most frequently prescribed dose was twice a day (BD) at 71.5%, followed by once a day (OD) at 28.5%, as indicated in Table 05.

Frequency	Frequency	Percent
BD	113	71.5
OD	45	28.5
Total	158	100.0

TABLE 05: Frequency pattern of ceftriaxone administration for the study participants.

DURATION OF CEFTRIAXONE USE

The mean duration of treatment was 8.56 days (range: 6-14 days). In most cases, practitioners used it for 7 days (49.4%), followed by 10 days (19.6%), and the lowest duration was 6 days (3.8%), as indicated in Table 06.

Duration(Days)	Frequency	Percent	Mean
6	6	3.8	8.56
7	78	49.4	
8	15	9.5	
9	6	3.8	
10	31	19.6	
12	11	7.0	
14	11	7.0	
Total	158	100.0	

Table 06: The duration of ceftriaxone use for the study participants.

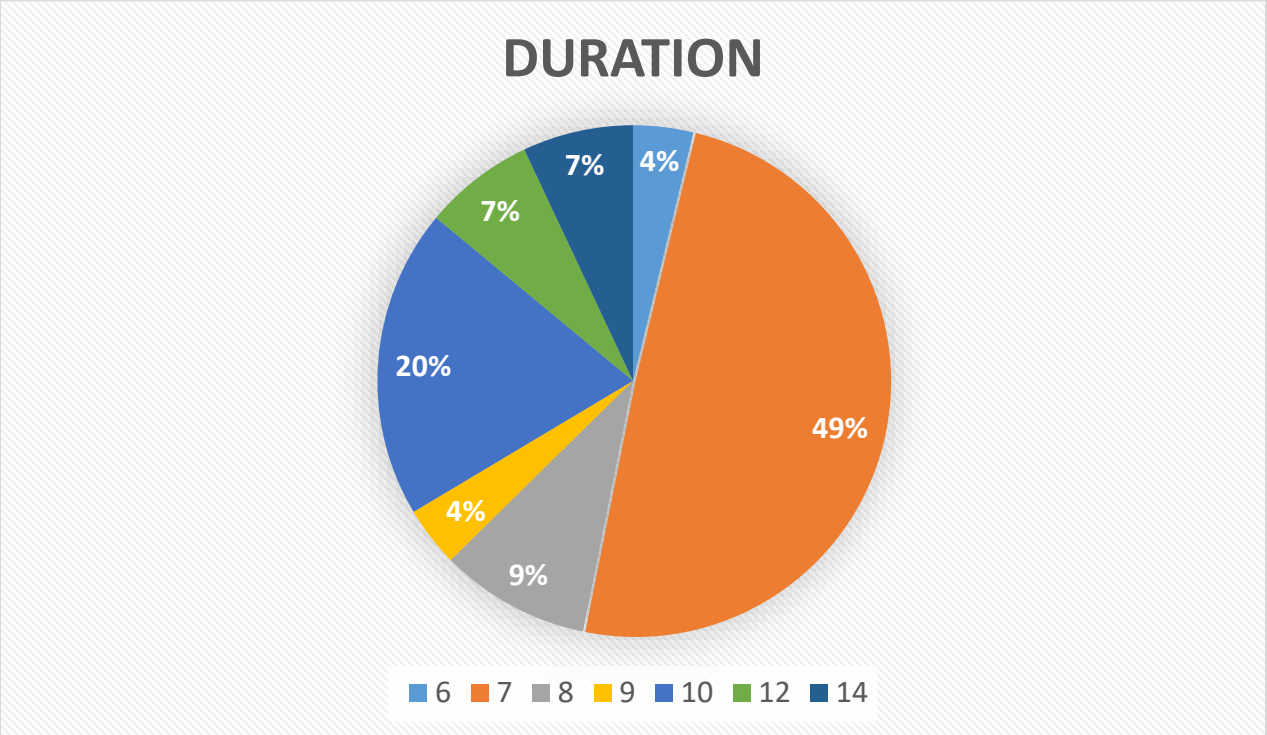

Chart 02: Duration

Culture and sensitivity test:

Culture and sensitivity test was not done in most of the patients (85.4 %) only in 23 case's culture and sensitivity was done. Of the 23 cases in which test was done, growth was observed in most of the cases, but among them 3 patients (13.04) were resistant to ceftriaxone antibiotic which is given in below (Table 07).

Culture and Sensitivity Test	Frequency	Percent
NO	135	85.4
YES	23	14.6
RESISTANT	03	13.04
TOTAL	158	100.0

TABLE 07: The culture and sensitivity test for the study participants.

CEFTRIAXONE PRESCRIPTION PATTERN:

The utilization rate of ceftriaxone was found 45.01% prevalence at the medical and pulmonology wards of the Hayatabad Medical Complex and Khyber Teaching Hospital during the study period. It was prescribed empirically for most of the cases (77.8 %) and non-empiric for 22.2 % of cases. The top indications for ceftriaxone use were fever workup (14.6 %), chronic obstructive pulmonary disease (5.1 %), enteric fever (5.1 %), and decompensated chronic liver disease (3.2 %) (Table 8 and table 09).

Treatment type	Frequency	Percent
NON-EMPIRIC	35	22.2
EMPIRIC	123	77.8
Total	158	100.0

TABLE 08: Ceftriaxone prescription pattern for the study participants.

In Non-empiric the Culture and sensitivity test performed or C-reactive protein test result greater than 30 mg/L while in Empiric the Culture and sensitivity test not performed or C-reactive protein test result less than 30 mg/L [25].

Indication for use	Frequency	Percent
Chronic Obstructive Pulmonary Disease	8	5.1
Decompensated Chronic Liver Disease	5	3.2
Enteric Fever	8	5.1
Fever Workup	23	14.6
Hepatocellular Carcinoma	3	1.9
Ischemic CVA	5	3.2
Post TB Bronchhiectasis	4	2.5
Urinary Tract Infection	5	3.2

TABLE 09: Indication for use of ceftriaxone in the study participants.

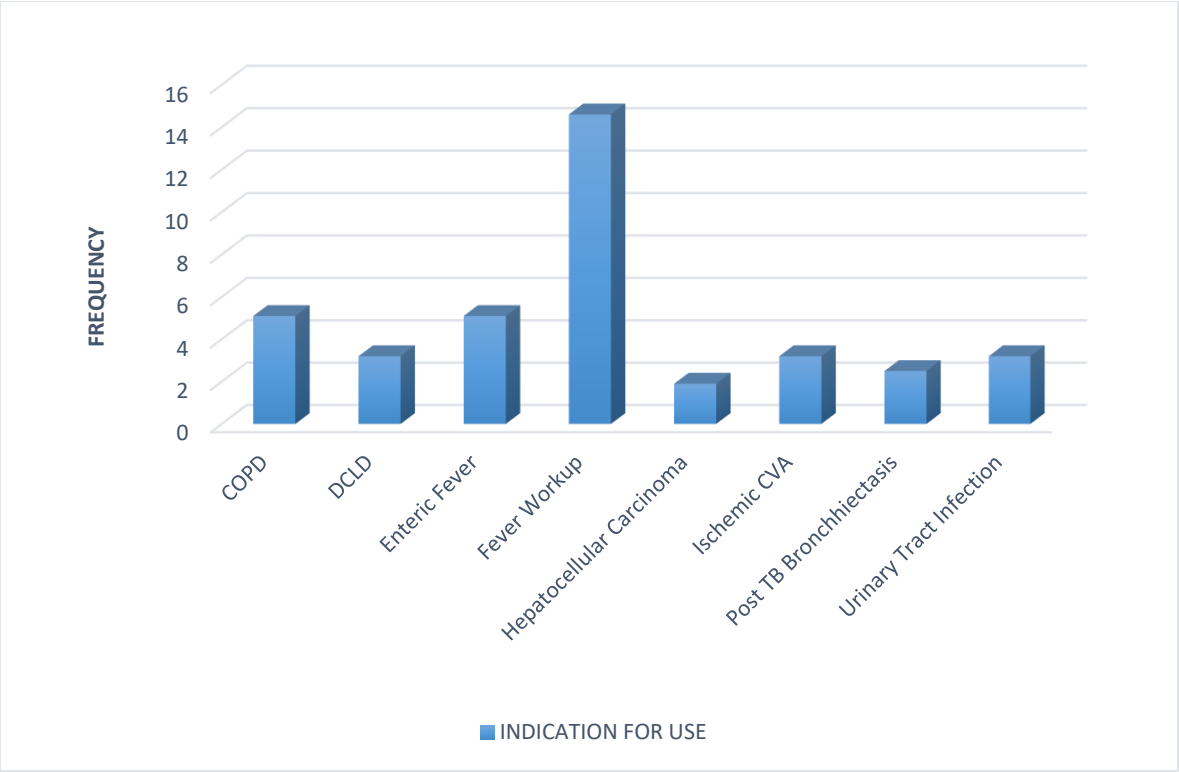

CHART 03: Indication for use.

COMPLIANCE OF PATIENT TO TREATMENT REGIMEN:

Most of the patients were compliant to the treatment regimen prescribed by prescriber (80.4 %) and (19.6 %) patients does not show compliance most of them due to mental issues. The number shown in below (Table 10).

Compliance	Frequency	Percent
NO	31	19.6
YES	127	80.4
Total	158	100.0

Table 10: Compliance of the study participants to treatment regimen.

4 DISCUSSION:

This study was carried out to investigate ceftriaxone use among inpatients in a tertiary care hospital in Peshawar, Pakistan, aimed to investigate the utilization of ceftriaxone among inpatients. The

findings indicated that ceftriaxone was the most commonly prescribed antibiotic upon admission. Ceftriaxone's popularity as a choice antibiotic is attributed to several factors, including its high potency, broad spectrum of activity, and a relatively low risk of toxicity. In clinical practice, ceftriaxone is used as a first-line treatment for various infections, including: Acute bacterial meningitis, Severe cases of community-acquired pneumonia, Complicated intra-abdominal infections (both mild to moderate and severe cases), Hospital-acquired pneumonia, Infections caused by Neisseria gonorrhoeae, Severe cases of pyelonephritis or prostatitis. Additionally, ceftriaxone serves as a second-line treatment option for: acute invasive bacterial diarrhea/dysentery, bone and joint infections, mild to moderate cases of pyelonephritis or prostatitis, sepsis in neonates and children [26].The prescription of ceftriaxone as an empirical antibiotic in 77.8% of cases, is consistent with similar findings from studies conducted at Ethiopian and Port of Spain tertiary hospitals. In those studies, the use of ceftriaxone was reported at 87.3% and 79.5%, respectively [27] while the other drugs have not yet reported [32-40]. The high use of Ceftriaxone points toward its easy availability, economic value and its coverage of the most common gram-positive and gram-negative pathogens and its suitability to the local epidemiology. One of the most common reason for high empirical use of ceftriaxone was its use as empirical therapy for presumed infections [28].Ceftriaxone was commonly used in cases of pneumonia and fever work up.

The prescription having ceftriaxone of dose 2g as the most common dosage (78.5%), is consistent with findings from a study conducted at Korean hospitals, where the 2g dose was found to be the most commonly prescribed dose, with a reported prevalence of 85.3%. This indicates a common practice in both settings, where the 2g dose of ceftriaxone is widely utilized for the treatment of various infections [29].The frequency of ceftriaxone administration, with a frequency of "BD" (which typically stands for "twice daily"), was reported as 71.5%. Whereas a study conducted in Ambessa showed that the daily administration was inappropriate with 98.4% and where it was more a tradition of practice [30]. Culture sensitivity test was not performed for 85.4% patients and for 14.6 percent patients it was performed but after starting administration of ceftriaxone.

The situation here can be compared with Ethiopia that their patients did not have culture sensitivity test despite being on ceftriaxone [31].

5 CONCLUSION:

This study revealed that the use of ceftriaxone was inappropriate. The reasons for inappropriate use of ceftriaxone was regarding to indication for use, continued empiric use for suspected infections, and empiric fever therapy. This could be due to the practice of giving empiric antibiotics for fever despite no clinical, biochemical, radiological or microbiological evidence of bacterial infection. Most patients may have viral illnesses only and the use of empiric antimicrobials in these cases has resulted in additional medical care costs on patient and increased financial burdens on hospital. But the dose, frequency and duration were appropriate.

Hence we recommend the following:

- The clinical pharmacists in all wards should monitor & ensure the judicial use of ceftriaxone and other antibiotics.
- Setting antibiotic control system.
- Intensification of education and training programs.
- Easy access of the national STG to all health professionals.
- Setting continuous drug use evaluation programs.
- Hospital should have Drug therapeutic Committee (DTC) that can evaluate in correct prescription.

6 LIMITATIONS OF THE STUDY:

The present study focused only on internal medicine and pulmonology departments. But, a more representative result would be obtained if other departments (for example, surgical and orthopedic) were included. Despite the large sample size in most departments, it was a retrospective study that may under estimate the rate of inappropriate use of ceftriaxone. In addition, the evaluation was relied merely on the patient's medical records for which practices might have actually been different.

7 REFFERENCES:

1- Durham SH, Wingler MJ, Eiland LS. Appropriate Use of Ceftriaxone in the Emergency Department of a Veteran's Health Care System. J Pharm Technol. 2017 Dec;33(6):215–8. doi: 10.1177/8755122517720293. Epub 2017 Jul 13. PMCID: PMC5998470.

2- : Sonda TB, Horumpende PG, Kumburu HH, van Zwetselaar M, Mshana SE, Alifrangis M, et al. (2019) Ceftriaxone use in a tertiary care hospital in Kilimanjaro, Tanzania: A need for a hospital antibiotic stewardship programme. PLoS ONE 14 (8): e0220261. https://doi.org/10.1371/journal.pone.0220261

3-https://www.ncbi.nlm.nih.gov/books/NBK545311/#_ncbi_dlg_citbx_NBK545311. Accessed on 05-October-2023.

4- Very Well Health; https://www.verywellhealth.com/. Accessed on October-2023.

5- Li X, Li H, Li S, Zhu F, Kim DJ, Xie H, Li Y, Nadas J, Oi N, Zykova TA, Yu DH, Lee MH, Kim MO, Wang L, Ma W, Lubet RA, Bode AM, Dong Z, Dong Z. Ceftriaxone, an FDA-approved cephalosporin antibiotic, suppresses lung cancer growth by targeting Aurora B. Carcinogenesis. 2012 Dec;33(12):2548-57. doi: 10.1093/carcin/bgs283. Epub 2012 Sep 7. PMID: 22962305; PMCID: PMC3510736.

6- https://www.verywellhealth.com/. Accessed on 12-October-2023.

7- Squires E, Cleeland R, Christenson J, Boehni E. Interpretation of susceptibility testing of ceftriaxone. Am J Med. 1984 Oct 19;77(4C):12-6. PMID: 6093512.

8- Berhe, Y.H., Amaha, N.D. & Ghebrenegus, A.S. Evaluation of ceftriaxone use in the medical ward of Halibet National Referral and teaching hospital in 2017 in Asmara, Eritrea: a cross sectional retrospective study. *BMC Infect Dis* **19**, 465 (2019). https://doi.org/10.1186/s12879-019-4087-z.

9- Muhammad J, Shamsur R, Majed A, Abdul W, Abdul R,Elhassan H, et al.(2019) Ceftriaxone Drug Utilization Evaluation (DUE) at Prince Abdulaziz Bin Moussae'ed Hospital, Arar, Kingdom of Saudi Arabia. 10.18502/sjms.v14i4.5905.

10- Wakuma W, Debisa A, et al. Retrospective drug use evaluation of ceftriaxone in resource limited setting in case of bedele general hospital, Ethiopia.(Nov 28th, 2022) https://doi.org/10.21203/rs.3.rs-2315263/v1.

11-Leonard Manirakiza, Victoria Nambasa, Stella Nanyonga, Allan Serwanga, Matovu Alphonsus, Nankola Denis, Helen Ndagije. Drug Use Evaluation (DUE) of Ceftriaxone in Mubende Regional Referral Hospital, Uganda: A Cross-Sectional Survey. J Pharm Pharmacol Res 3 (2019): 105-115.

12- Saleem Z, Saeed H, Hassali MA, Godman B, Asif U, Yousaf M, Ahmed Z, Riaz H, Raza SA. Pattern of inappropriate antibiotic use among hospitalized patients in Pakistan: a longitudinal surveillance and implications. Antimicrob Resist Infect Control. 2019 Nov 21;8:188. doi: 10.1186/s13756-019-0649-5. PMID: 31768252; PMCID: PMC6873729.

13- Meresa Bishaw B, Tegegne GT, Berha AB. Appropriate Use of Ceftriaxone in Sub-Saharan Africa: A Systematic Review. *Infect Drug Resist*. 2021;14:3477-3484 https://doi.org/10.2147/IDR.S329996

14- Kutyabami P, Munanura EI, Kalidi R, Balikuna S, Ndagire M, Kaggwa B, Nambatya W, Kamba PF, Musiimenta A, Kesi DN, Nambasa V, Serwanga A, Ndagije HB. Evaluation of the Clinical Use of Ceftriaxone among In-Patients in Selected Health Facilities in Uganda. Antibiotics (Basel). 2021 Jun 25;10(7):779. doi: 10.3390/antibiotics10070779. PMID: 34202391; PMCID: PMC8300672.

15- Ashagrachew T, Tesfa , Gebremariam B. The contribution of nano-based strategies in overcoming ceftriaxone resistance: a literature review.PRP, 30 july 2021. https://doi.org/10.1002/prp2.849

16- Lee C-R, Cho IH, Jeong BC, Lee SH. Strategies to Minimize Antibiotic Resistance. *International Journal of Environmental Research and Public Health*. 2013; 10(9):4274-4305. https://doi.org/10.3390/ijerph10094274

17- Sharma, V.D., Singla, A., Chaudhary, M. *et al.* Population Pharmacokinetics of Fixed Dose Combination of Ceftriaxone and Sulbactam in Healthy and Infected Subjects. *AAPS PharmSciTech* 17, 1192–1203 (2016). https://doi.org/10.1208/s12249-015-0454-2

18- Sileshi, A., Tenna, A., Feyissa, M. *et al.* Evaluation of ceftriaxone utilization in medical and emergency wards of Tikur Anbessa specialized hospital: a prospective cross-sectional study. *BMC Pharmacol Toxicol* 17, 7 (2016). https://doi.org/10.1186/s40360-016-0057-x

19- Kaur I, Singh J. Cutaneous drug reaction with intravenous ceftriaxone. Indian J Pharmacol. 2009 Dec;41(6):284-5. doi: 10.4103/0253-7613.59933. PMID: 20407561; PMCID: PMC2846504.

20- https://www.verywellhealth.com/. Accessed on 12-October-2023.

21- Lacroix C, Bera-Jonville AP, Montastruc F, Velly L, Micallef J, Guilhaumou R. Serious Neurological Adverse Events of Ceftriaxone. Antibiotics (Basel). 2021 May 6;10(5):540. doi: 10.3390/antibiotics10050540. PMID: 34066591; PMCID: PMC8148437.

22- Very Well Health; https://www.verywellhealth.com/. Accessed on October-2023.

23- https://www.verywellhealth.com/. Accessed on 12-October-2023.

24- Xu W, Zhou Q, Liu J, Zhang Y, Zhu X, Zhu B, Yin Y. In Vitro Study of the Interaction of Gentamicin with Ceftriaxone and Azithromycin against *Neisseria gonorrhoeae* Using Agar Dilution Method. Antibiotics (Basel). 2022 Aug 10;11(8):1083. doi: 10.3390/antibiotics11081083. PMID: 36009953; PMCID: PMC9405204.

25 Cals JW, Ebell MH. C-reactive protein: guiding antibiotic prescribing decisions at the point of care. Br J Gen Pract. 2018 Mar;68(668):112-113.
doi: 10.3399/bjgp18X694901. PMID: 29472204; PMCID: PMC5819954.

26- Sonda TB, Horumpende PG, Kumburu HH, van Zwetselaar M, Mshana SE, Alifrangis M, Lund O, Aarestrup FM, Chilongola JO, Mmbaga BT, Kibiki GS. Ceftriaxone use in a tertiary care hospital in Kilimanjaro, Tanzania: A need for a hospital antibiotic stewardship programme. PLoS One. 2019 Aug 5;14(8):e0220261. doi: 10.1371/journal.pone.0220261. PMID: 31381579; PMCID: PMC6681960.

27- Evaluation of ceftriaxone use in the medical wards of Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and its outcome
Azlina Ibrahim1*, Isa Naina Mohamed2, Najma Kori1, Chee Lan Lau3, Azmi Mohd Tamil4, Ramliza Ramli5 and Petrick Periayasamy1.

28- Lee, Hyuck, Dongsik Jung, Joon Sup Yeom and Jun Seong Son, et al. "Evaluation of ceftriaxone utilization at multicenter study." *Korean J Intern Med* 24(2009):374-380.

29- Lee, Hyuck, Dongsik Jung, Joon Sup Yeom and Jun Seong Son, et al. "Evaluation of ceftriaxone utilization at multicenter study." *Korean J Intern Med* 24(2009):374-380.

30- Sileshi, Alemayehu, Admasu Tenna, Mamo Feyissa and Workineh Shibeshi, et al. "Evaluation of ceftriaxone utilization in medical and emergency wards of Tikur Anbessa specialized hospital: a prospective cross-sectional study". *BMC Pharmacol Toxicol* 17(2016):7.

31- Sewagegn Negese."Evaluation of Ceftriaxone Use for Hospitalized Patients in Ethiopia: The Case of a Referral Hospital". *Int J Pharm Sci &Scient Res* 3(2017):26-31.

32- Ilyas N, Nawaz H, Gamaryani A et al., Epilepsy; An Insight into Epileptogenic Potential of Infections and Antibiotics. Biomed J Sci & Tech Res 53(2)-2023. BJSTR. MS.ID.008376.

33- Hasnain M, Raziq M, Ashfaq M et al., Cardiovascular Complications of anticancer therapy in Pashtun Ethnicity ; Xi'an Shiyou Xueyuan Xuebao/Journal of Xi'an Petroleum Institute (Natural Science Edition) ; December 2023

34- Khan S, Ullah S, Bilal M, et al., A Systematic and Comprehensive Review on Recent Trends in Helicobacter Pylori Eradication: Current Opinion and Future Perspective. Biomed J Sci & Tech Res 44(3)-2022. BJSTR. MS.ID.007069.

35- Faisal S, Khan S, Shah AS et al., Biochemical identification, antibiotic sensitivity and resistance pattern for salmonella typhi and salmonella paratyphi; Journal by Innovative Scientific Information & Services Network; Bioscience Research, 2021 18(3): 2284-2291

36- Hasnain M, jan A, Khan S, et al., Level of Knowledge and Attitude of Undergraduate Students of University of Peshawar about HIV/AIDS and its Patients. RADS J Pharm Pharm Sci. 2021; 9(3):151- 159.

37- Hadi I, Hasnain M, Idrees A, et al., Nutritional Assessment by Anthropometric Methods under Five Years of
Children's in Tertiary Care Hospital in Peshawar, Khyber Pukhtunkhwa, Pakistan. J Nutr Food Sci. 12:866, 2022.

38- Khan S, Faisal S, Shah SA, et al., Irrational use of antibiotics as major cause of drug resistance in developing and developed countries; Journal by Innovative Scientific Information & Services Network Bioscience Research, 2021 18(3): 2292-2300.

39- Begum S, Shah AS, Hasnain M, et al., Detection of Helicobacter Phylori Virulence genes by Polymerase Chain Reaction in gastric biopsies among Dyspepsia patients; Xi'an Shiyou Xueyuan Xuebao/Journal of Xi'an Petroleum Institute (Natural Science Edition) ; December 2022

40- Karim M, Khan S, Ullah I et al., Etiology and Antibiotic Resistant Pattern of Urinary Tract Bacterial Pathogen in District Mardan. Biomed J Sci & Tech Res 52(5)- 2023. BJSTR. MS.ID.008330.