Available online on 15.02.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Check for updates

Research Article

Cephalosporin Utilization Pattern and Prescribing Trends in Gram-Negative Bacteria: Evidence for Facilitating Antimicrobial Stewardship

R. Bhavadharani *[1], K. Bhavadharini [1], Dr. S. Daniel Sundar Singh [2], Dr. K. Dhivya [2]

[1] Pharm. D Intern, Department of Clinical Pharmacy, C. L. Baid Metha College of Pharmacy, Chennai, India.

[2] Assistant Professor, Department of Clinical Pharmacy, C. L. Baid Metha College of Pharmacy, Chennai, India.

Article Info:

Article History:

Received 10 Nov 2024
Reviewed 27 Dec 2024
Accepted 20 Jan 2025
Published 15 Feb 2025

Cite this article as:

Bhavadharani R, Bhavadharini K, Singh SDS, Dhivya K, Cephalosporin Utilization Pattern and Prescribing Trends in Gram-Negative Bacteria: Evidence for Facilitating Antimicrobial Stewardship, Journal of Drug Delivery and Therapeutics. 2025; 15(2):34-39

DOI:

http://dx.doi.org/10.22270/jddt.v15i2.6987

*Address for Correspondence:

Bhavadharani R, Pharm D Intern, Department of Clinical Pharmacy, C. L. Baid Metha College of Pharmacy, Chennai, india

Abstract

Background: India faces a high burden of infectious diseases globally, with Gram-negative bacteria posing a major threat. Cephalosporins are commonly used to treat these infections, but focused data on their utilization for Gram-negative infections is scarce, hindering targeted treatment and antimicrobial stewardship efforts. Our study aims to address this by providing comprehensive data on cephalosporin use for Gram-negative infections, promoting rational drug use, and enhancing antimicrobial stewardship practices.

Methods: A prospective observational study was conducted in Chennai from July to October 2024, to evaluate cephalosporin use in Gram-negative infections. The study enrolled 126 patients aged 20-70 prescribed cephalosporins, either empirically or on definitive therapy based on culture results. Data on demographics, diagnoses, culture reports, and treatment were recorded, categorized as empirical or definitive, and analyzed using chi-square tests ($p < 0.05$).

Results: The analysis showed a significant preference for third-generation cephalosporins in empiric and definitive therapy, confirmed by substantial deviations from expected distributions ($p < 0.05$), with cefoperazone with sulbactam being the most frequently prescribed in empirical treatment.

Conclusion: The study reveals the predominant use of third-generation cephalosporins in treating Gram-negative infections, emphasizing the need for antimicrobial stewardship, stricter guidelines and treatment protocols to include definitive therapies, and promoting rational drug use by adhering to antibiotic policies to combat resistance.

Keywords: Cephalosporin, Gram-negative infection, Drug Utilization, Prescribing pattern, antimicrobial stewardship.

INTRODUCTION:

India, with its myriad of challenges, confronts a staggering reality: it harbors one of the highest rates of infectious disease worldwide.[1] In India, the crude death rate from infectious diseases is 417 per lakh people.[2] Specifically, Gram-negative infections stand as a menacing threat to health, particularly in people who have compromised immunity. Within medical settings, infections caused by these resilient bacteria, which defy conventional antibiotics, pose formidable challenges for healthcare providers.[3] Gram-negative bacteria are frequently implicated in serious conditions such as ventilator-associated pneumonia, catheter-related bloodstream infections, and sepsis acquired in intensive care units, including urinary tract infections. Among the primary culprits are Enterobacteriaceae and non-fermenting Gram-negative bacteria, including Pseudomonas aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia.[3,4] Gram-negative bacteria (GNB) are clinically critical in hospital settings, as they result in elevated morbidity and mortality rates.[4,5] According to the Global Antimicrobial Resistance and Use Surveillance System (Glass) annual report of 2022, there is a consistent global increase in gram-negative infections. Notably, Escherichia coli was identified as the predominant pathogen causing these infections. The report highlighted concerning levels of resistance in certain pathogens, particularly in Klebsiella pneumoniae and Acinetobacter spp. responsible for bloodstream infections raised significant concerns regarding antimicrobial resistance (AMR) trends.[6,7]

In India, the data from the Antimicrobial Resistance Research & Surveillance Network (AMRSN) annual report of 2021 highlights a notable increase in the prevalence of gram-negative infections specifically, Enterobacterales accounted for 49.5% of the isolates, indicating their significant presence in the surveillance data.[8]

Three classes of antibiotics are predominantly used to treat infectious diseases in India, which are cephalosporins, broad-spectrum penicillin, and fluoro-quinolones.[9] Cephalosporins, a class of beta-lactam antibiotics, are employed to treat various infections caused by both gram-positive and gram-negative bacteria. Based on their history of discovery and their spectrum against the bacterium, the Cephalosporin class has 5 generations. First-generation cephalosporins demonstrate efficacy against a wide spectrum of both gram-positive and limited activity against gram-negative bacteria, covering pathogens like Proteus mirabilis, Klebsiella pneumoniae, and Escherichia coli. Second-generation cephalosporins extend their susceptibility to Moraxella catarrhalis, Bacteroides spp., and Haemophilus influenzae.[3] However, third-generation cephalosporins exhibit reduced activity against Gram-positive bacteria compared to earlier generations but demonstrate enhanced effectiveness against a broader range of Gram-negative bacteria, including Haemophilus influenzae, Neisseria species, and members of the Enterobacteriaceae family. Comparable to third-generation counterparts, fourth-generation cephalon-sporins offer heightened protection against gram-negative bacteria, particularly those harboring antibiotic resistance mechanisms such as beta-lactamase. Finally, fifth-generation cephalosporins target pneumococci and methicillin-resistant staphylococci, providing tailored efficacy against these resistant strains. Thus, the gram-negative coverage of cephalosporins increases from the first to the fourth generation, with the fifth generation offering effectiveness against many resistant strains.[3]

Numerous studies have investigated the utilization of cephalosporins. One study investigates the use of third- and fourth-generation cephalosporins for treating Gram-negative bacterial infections in hospital settings. Other studies explore cephalosporin usage patterns within specific departments such as general medicine, pediatrics, and others.[11,12] While existing research often delves into the broader patterns of cephalosporin usage across various medical departments or specific infections, there is a lack of comprehensive data particularly addressing the use of cephalosporins for gram-negative infections.

Our study aims to bridge this gap and thus significantly improve patient outcomes and contribute to the advancement of antimicrobial stewardship initiatives in healthcare settings. This can further help in assessing instances of treatment failure to inform future prevention strategies and empower clinicians to provide tailored treatments rather than empirical ones and prevent the emergence of resistance.[13]

METHODS:

A prospective observational study was conducted in Chennai over three months from July 10, 2024, to October 10, 2024, aiming to evaluate the utilization pattern of cephalosporins in gram-negative bacterial infections. The study enrolled 126 patients aged between 20-70 who were prescribed cephalosporins, either alone or in combination with other antibiotics. The patient was included based on culture which shows gram-negative microorganisms or suspected gram-negative organisms and prescribed cephalosporins, either alone or in combination with other antibiotics. Patients not receiving cephalosporin therapy, or admitted for prophylaxis, not in-between 20-70, and gram-positive microorganism culture reports were excluded. The information about diagnoses, culture reports, treatment types, and cephalosporin data such as indication, dosage, frequency, and duration of therapy, were recorded in a predefined pro forma. Patient consent was secured for documentation. Cephalosporin usage was categorized as empirical (based on clinical evidence of infection without isolated organisms) and definitive (based on culture reports). The collected data were meticulously processed to examine the distribution of cephalosporin in empirical and definitive therapy, as well as the drug utilization pattern. The collected data underwent analysis through the chi-square test goodness of fit and were also presented in terms of mean, median, standard deviation (SD), and percentage, and further analysis was done by calculating for standardized residuals. A significance level of chi-square goodness of fit test of $p < 0.05$ was found to be statistically significant.

RESULTS:

During the study period, a total of 126 participants were included in the study. The baseline characteristics of the study population are summarized in Table 1.

Table 1: Characteristics of Study Population (n=126)

Characteristics	N(%)
Gender	
Male	60 (47.6)
Female	66 (52.4)
Age (Mean ± SD)	59.45 ± 11.06 years
Infection Classification	
UTI	42 (33.3)
Bacteremia	4 (3.1)
Sepsis	33 (26.2)
Pneumonia	15 (11.9)
Cellulitis	23 (18.3)
Meningitis	5 (4)
Others	4 (3.2)
Bacteriological Investigation	
Done	119 (94.5)
Not Done	7 (5.5)
Type of Treatment with Cephalosporins	
Empiric	84 (49.7)
Definitive	85 (50.3)

The study population comprised both males and females with a mean age of 59.45 years. Among the diagnoses, urinary tract infections (UTI) were the most frequently observed condition (33.3%), whereas other infections accounted for the lowest proportion (3.2%). Bacterio-logical examinations were conducted for the majority of patients, while a small subset did not undergo culture testing. Cephalosporins were utilized either empirically or as definitive therapy, with some patients receiving both treatment approaches.

Table 2: Distribution of Cephalosporins Prescribed Based on Their Generation

Cephalosporin Generation	Drugs	Empiric N (%)	Drugs	Definitive N (%)
First generation	Cefazolin	3(3.6)	-	-
Second generation	Cefuroxime	20(23.8)	Cefuroxime	10(11.8)
			Cefuroxime axetil	9(10.7)
Third generation	Ceftriaxone	21(25)	Ceftriaxone	11(12.9)
	Ceftazidime	6(7.1)	Ceftazidime	11(12.9)
	Cefotaxime	4(4.8)	Cefotaxime	6(7)
	Cefoperazone with sulbactam	30(35.7)	Cefoperazone with sulbactam	17(20)
			Cefixime	5(5.9)
			Ceftazidime avibactam	10(11.8)
Fourth generation	-	-	-	-
Fifth generation	-	-	Ceftaroline	6(7)

The data were arranged, and the cephalosporins were listed in Table 2 by their respective generations. In empirical therapy, 84 patients were provided with cephalosporins based on suspected gram-negative bacterial causation. Among these, third-generation cephalosporins, particularly cefoperazone with sulbactam (35.7%), were the most frequently prescribed. Notably, no patients received fourth or fifth-generation cephalosporins empirically. At the same time, 85 patients received cephalosporins as definitive therapy, third-generation cephalosporins, especially cefoperazone with sulbactam, a third-generation cephalosporin was again prevalent (20%). No patients received first or fourth-generation cephalosporins in definitive therapy.

The results have been discussed separately as empiric and definitive treatments. Figure 1 presents a comparison of empiric versus definitive cephalosporin usage, comparing the utilization patterns of cephalosporins in empiric and definitive therapies for Gram-negative infections. In empiric therapy, third-generation cephalosporins dominate, with cefoperazone (35.7%) being the most frequently used, followed by ceftriaxone (25%) and cefuroxime (23.8%). These findings reflect their preference for initiating treatment when culture results are unavailable. In contrast, definitive therapy shows a more balanced distribution, with cefoperazone still leading (20%) but with reduced usage compared to empiric therapy. Additionally, ceftazidime (11.8%) and cefuroxime axetil (10.7%) are more prominently used in definitive therapy, reflecting tailored treatment based on culture and sensitivity results. Certain cephalosporins, such as ceftaroline and cefixime, are absent in both empiric and definitive therapies, suggesting limited application in this context. Overall, empiric therapy demonstrates a stronger reliance on third-generation cephalosporins, while definitive therapy incorporates a wider range of options to address specific microbial profiles.

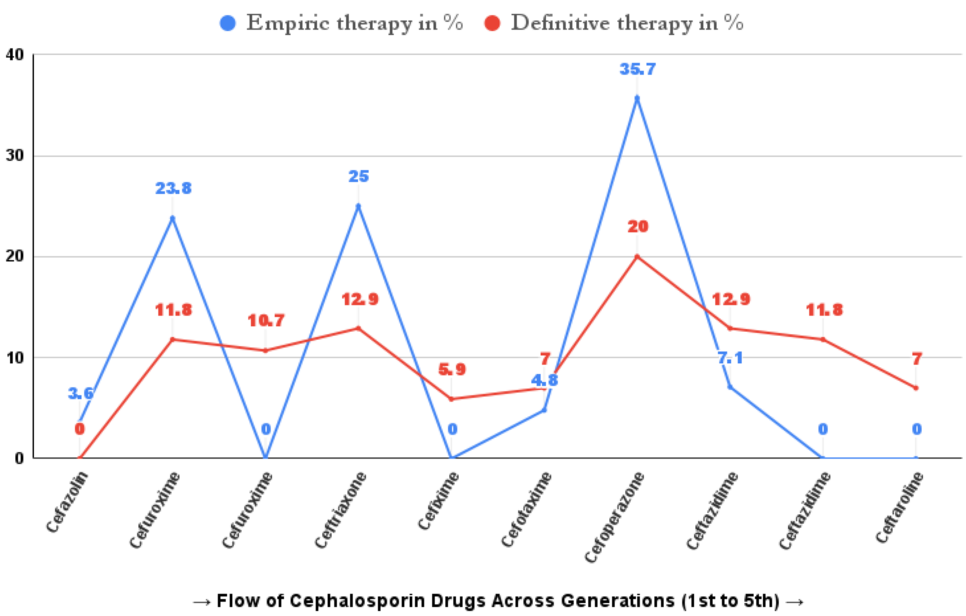

Figure 1: Cephalosporin utilization pattern in Empiric vs definitive therapy

Table 3: Chi-Square Goodness of Fit Test Applied for Empiric Therapy

S. No	Test description	Significance level (p-value should be <0.05)
1	Distribution of Cephalosporin based on their generation in Empiric therapy	0.004*
2	Distribution of Cephalosporin drugs irrespective of generation in Empiric therapy	0.026*
(*) indicate statistical significance at p < 0.05.		

Table 4: Chi-Square Goodness of Fit Test Applied for Definitive Therapy

S. No	Test description	Significance level (p-value should be <0.05)
1	Distribution of Cephalosporin based on their generation in Definitive therapy	0.034*
2	Distribution of Cephalosporin drugs irrespective of generation in Definitive therapy	0.042*
(*) indicate statistical significance at p < 0.05.		

All the results were subjected to rigorous statistical analysis, and proven significant. The statistical p-values for empiric therapy are provided in Table 3, while those for definitive therapy are presented in Table 4. For empiric treatment, the distribution of cephalosporin across generations showed a significant deviation from the expected distribution (p-value = 0.004), with third-generation cephalosporins having a standardized residual of +5.26, indicating third-generation cephalosporins are used significantly more frequently than expected. Similarly, the distribution of cephalosporin drugs irrespective of their generation in empiric treatment also showed a significant deviation (p-value = 0.026), with cefoperazone with sulbactam having a standardized residual of +2.83, proving its higher-than-expected usage.

For definitive treatment, the distribution of cephalosporin generations again showed a significant deviation from the expected distribution (p-value = 0.034), with third-generation cephalosporins having a standardized residual of +5.08, indicating a significantly higher usage. The distribution of cephalosporin drugs irrespective of generation in definitive treatment also showed a significant deviation (p-value = 0.042). However, the standardized residual for cefoperazone with sulbactam was +1.24, suggesting a slight but not significant increase in its usage. These findings confirm that third-generation cephalosporins are more frequently used in both empiric and definitive treatments, with cefoperazone sulbactam being notably used more in empiric treatments.

DISCUSSION:

Our study focuses on examining the utilization patterns and prescribing trends of cephalosporins in the treatment of Gram-negative bacterial infections. It aims to offer insights into antibiotic stewardship and clinical decision-making within hospital environments. The appropriate choice and utilization of cephalosporins are essential to provide safe and effective therapy for successful conditions.[13] The demographic analysis showed a higher proportion of females (52.4%) compared to males (47.6%) in our study which is in contrast with the study by Dominic KS *et al.*,[11] Our study revealed an average patient age of 59.45 years (SD ±11.06 years), differing from the average age of 47 years reported by Shetty YC *et al.,*[14]. Despite these differences in demographics, they are unlikely to affect our study outcomes.

The primary finding in our study highlights the predominant use of third-generation cephalosporins in both empiric and definitive treatments. These findings are consistent with observations reported by Protic D *et al.*,[10] Among these, cefoperazone with sulbactam emerged as the most frequently prescribed agent in empiric therapy, while no drug was significantly used more in definitive therapy. This preference underscores the broad-spectrum activity of cefoperazone with sulbactam, making it a reliable choice for initial treatment when culture results are unavailable. However, these results differ from those reported by Gururaja MP *et al.*,[15], who identified ceftriaxone as the most commonly prescribed third-generation cephalosporin. Moreover, several studies have consistently highlighted a strong preference for ceftriaxone in clinical practice.[14,16] These differences highlight variability in antibiotic choice across different healthcare settings and underscore the importance of regional guidelines and local resistance patterns in guiding treatment decisions.

The preference for cefoperazone-sulbactam in empiric therapy in our study has been attributed to its broader spectrum of activity against β-lactamase-producing gram-negative organisms, including Pseudomonas aeruginosa, which is likely prevalent in our study setting.[17] Cefoperazone with sulbactam combination's ability to target resistant pathogens, particularly in hospital-acquired infections, has made it an ideal choice for empiric treatment. The addition of sulbactam has enhanced the efficacy of cefoperazone by inhibiting β-lactamase, further extending its activity against resistant strains.[18] These factors have contributed to its higher usage over ceftriaxone in empiric therapy.

Although cefoperazone with sulbactam was preferred for empiric therapy due to its broad-spectrum activity against gram-negative organisms, it was not always the most effective choice for all infections. More targeted antibiotics, such as ceftazidime or ceftriaxone, have been shown to offer better efficacy against specific pathogens like Enterobacteriaceae or Neisseria spp., with fewer potential broad-spectrum side effects.[19,20] Therefore, when a more effective option was available, using the more targeted antibiotic was preferable.

While broad-spectrum agents like cefoperazone-sulbactam are useful in empiric therapy, their overuse may increase resistance. Therefore, a balanced approach, incorporating more targeted therapies when appropriate, is essential to minimize resistance development and optimize patient outcomes in both empiric and definitive treatments.

The study's limitations include its single-center design, which may affect the generalizability of the findings to other healthcare settings with different patient populations or antibiotic resistance patterns. Additionally, limited information on pathogen identification, such as resistance profiles and sensitivity results, may have hindered a deeper understanding of how resistance patterns influenced antibiotic choices. Furthermore, variations in clinical practices specific to the study institution could limit the broader applicability of the results, as they may not align with national or global guidelines. These factors should be taken into account when interpreting the study's conclusions and the study is open for more future investigations.

CONCLUSION:

In conclusion, the significance of cephalosporins in combating Gram-negative infections cannot be overstated. It highlights the necessity for ongoing research and vigilant surveillance to prevent resistance and minimize adverse effects. This is particularly pertinent with third-generation cephalosporins, whose broad spectrum of activity makes them indispensable in clinical practice. However, their excessive use has contributed to the emergence of resistant strains, emphasizing the importance of judicious prescribing practices and antimicrobial stewardship initiatives.

Navigating the complex antimicrobial therapy landscape requires striking a balance between efficacy and stewardship, achieved through rational prescribing practices, promoting stewardship, and fostering ongoing research to safeguard cephalosporin efficacy against Gram-negative infections for future generations.

Conflict of Interest: The authors have no conflicts of interest regarding this investigation.

Acknowledgments: Not-applicable

Author Contributions: All authors have equal contribution in the preparation of manuscript and compilation.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Ethical approval: Not applicable.

REFERENCES:

1. Ganguly NK. Situation Analysis: Antibiotic Use and Resistance in India [Internet]. Global Antibiotic Resistance Partnership-India (GARP-India) and National Working Group (NWG). 2011 Mar. [cited 2024 May 24]. Available from: https://onehealthtrust.org/wp-content/uploads/2017/06/india-report-web_8.pdf .

2. Laxminarayan R, Chaudhury RR. Antibiotic Resistance in India: Drivers and Opportunities for Action. PLoS Med. 2016 Mar 2;13(3):e1001974. https://doi.org/10.1371/journal.pmed.1001974 PMid:26934098 PMCid:PMC4775002

3. Bui T, Patel P, Preuss CV. Cephalosporins. [Updated 2024 Feb 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing

2024 Jan. [cited 2024 May 24]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551517/

4. Ak O, Batirel A, Ozer S, Çolakoğlu S. Nosocomial infections and risk factors in the intensive care unit of a teaching and research hospital: a prospective cohort study. Med Sci Monit. 2011 May;17(5):PH29-34. https://doi.org/10.12659/MSM.881750 PMid:21525819 PMCid:PMC3539590

5. Hormozi SF, Vasei N, Aminianfar M, Darvishi M, Saeedi AA. Antibiotic resistance in patients suffering from nosocomial infections in Besat Hospital. Eur J Transl Myol. 2018 Jul 16;28(3):7594. https://doi.org/10.4081/ejtm.2018.7594 PMid:30344978 PMCid:PMC6176389

6. Global antimicrobial resistance and use surveillance system (GLASS) report 2022 [Internet]. Geneva: World Health Organization. 2022. [cited 2024 May 24]. Available from: https://www.who.int/publications/i/item/9789240062702

7. Ajulo S, Awosile B. Global antimicrobial resistance and use surveillance system (GLASS 2022): Investigating the relationship between antimicrobial resistance and antimicrobial consumption data across the participating countries. PLoS One. 2024 Feb 5;19(2):e0297921. https://doi.org/10.1371/journal.pone.0297921 PMid:38315668 PMCid:PMC10843100

8. Annual Report 2021: Antimicrobial Resistance Research and Surveillance Network [Internet]. 2022 [cited 2024 May 24]. Available from: https://main.icmr.nic.in/sites/default/files/upload_documents/AMR_Annual_Report_2021.pdf

9. Plump W. Study Shows Significant Increase in Antibiotic Use Across the World [Internet]. Princeton Environmental Institute. 2014 Jul 10. [cited 2024 May 24]. Available from: https://www.princeton.edu/news/2014/07/10/study-shows-significant-increase-antibiotic-use-across-world

10. Protic D, Pejovic A, Djukanovic N, Toskovic B, Zdravkovic M, Todorovic Z. Analysis of the third- and fourth-generation cephalosporin use for the treatment of infections caused by gram-negative bacteria in hospital settings. International Journal of Clinical Practice. 2016 Dec;70(12):1033-40. https://doi.org/10.1111/ijcp.12911 PMid:28032422

11. Dominic KS, Nandakumar UP, Chand S. A retrospective study on drug usage pattern of cephalosporins in a general medicine department. Plant Archives. 2020;20(2):2383-7.

12. Juno AA, Baig MT, Khan RA. A prospective study on cephalosporin utilization by pattern in pediatric patients. Journal of Hunan University Natural Sciences. 2022;49(2). https://doi.org/10.55463/issn.1674-2974.49.2.3

13. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2014. Available at http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html .

14. Shetty YC, Manjesh PS, Churiwala W, Jain SM, Singh VK. Drug use evaluation of cephalosporins in a tertiary care hospital. Perspectives in Clinical Research. 2022 Jan 1;13(1):38-42. https://doi.org/10.4103/picr.PICR_29_20 PMid:35198427 PMCid:PMC8815671

15. Gururaja MP. Cephalosporin utilization evaluation in a University Teaching Hospital: a prospective study. Journal of Drug Delivery and Therapeutics. 2013 Mar 15;3(2). https://doi.org/10.22270/jddt.v3i2.399

16. Joel JJ, Bhat VS, ER AR. Study on drug utilization pattern of antibiotics in respiratory tract infections. Research Journal of Pharmacy and Technology. 2019;12(3):1189-92. https://doi.org/10.5958/0974-360X.2019.00197.5

17. Xin X, Jian L, Xia X, Jia B, Huang W, Li C, et.al. multicentre clinical study on the injection of ceftriaxone/sulbactam compared with cefoperazone/sulbactam in the treatment of respiratory and urinary tract infections. Annals of clinical microbiology and antimicrobials. 2013 Dec;12:1-8. https://doi.org/10.1186/1476-0711-12-38 PMid:24321187 PMCid:PMC4029302

18. Williams JD. β-Lactamase inhibition and in vitro activity of sulbactam and sulbactam/cefoperazone. Clinical infectious diseases. 1997 Mar 1;24(3):494-7. https://doi.org/10.1093/clinids/24.3.494 PMid:9114205

19. Richards DM, Brogden RN. Ceftazidime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs. 1985 Feb;29(2):105-61. https://doi.org/10.2165/00003495-198529020-00002 PMid:3884319

20. Congeni BL. Comparison of ceftriaxone and traditional therapy of bacterial meningitis. Antimicrobial agents and chemotherapy. 1984 Jan;25(1):40-4. https://doi.org/10.1128/AAC.25.1.40 PMid:6322681 PMCid:PMC185431