REVIEW

Appropriate Use of Ceftriaxone in Sub-Saharan Africa: A Systematic Review

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Introduction: Ceftriaxone is the most frequently used antibiotic for the treatment of various bacterial infections in hospitalized and ambulatory patients. Despite this, inappropriate ceftriaxone use is common.

Objective: The aim of this review is to assess the appropriate use of ceftriaxone in sub-Saharan African countries.

Methods: A systematic search was done on PubMed, EMBASE, Cochrane Libraries and Google Scholar for papers published addressing the prescribing pattern and use of ceftriaxone in sub-Saharan Africa. The findings were reported in medians and quartiles.

Results: A total of 15 articles met the inclusion criteria. Pneumonia and sepsis were the most frequently diagnosed infections in the included studies. The overall median prevalence of appropriate ceftriaxone use is 39.2% (IQR: 29.9–60.9), showing that most of the included studies reported a higher prevalence of inappropriate ceftriaxone use. Although there are a higher number of patients with inappropriate use of ceftriaxone, a relatively higher number of patients got appropriate daily dose (79.8%, IQR: 45.7–89.4) of ceftriaxone than appropriate duration of ceftriaxone (55%, IQR: 52.2–80).

Conclusion: The review revealed that three in five patients with ceftriaxone got inappropriate ceftriaxone's dose, frequency or duration. A relatively higher number of patients got appropriate daily dose of ceftriaxone. On the other hand, approximately more than half of the patients got inappropriate duration, too short or too long, of ceftriaxone. Hence, prescribers are recommended to adhere to their country-specific treatment guideline. Moreover, it is highly recommended to either commence or strengthen antimicrobial stewardship program effectively in their healthcare settings.

Keywords: ceftriaxone, ceftriaxone use evaluation, prescribing pattern, sub-Saharan Africa

Introduction

The quality of health and medical care is determined by the rational prescribing and appropriate use of drugs.[1] The introduction of antibiotics during mid-20th century significantly reduces patients' morbidity and mortality, and associated healthcare costs. Antibiotics are highly prescribed medications in low- and middle-income countries.[2] However, they are also inappropriately used medications.[3–5] Appropriate antibiotic use is associated with a higher proportion of unsuccessful patient outcomes (including death, re-operation, re-hospitalization or additional parental antibiotic therapies), increased length of hospital stay and treatment,[6] increased 30-day and in-hospital mortality,[7] treatment failure, and increased cost of treatment.[8] The problem also contributes to high rates of antibiotic resistance,[9–11] one of the top ten global public health threats facing humanity.[12]

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Due to its cost-effective and safety profile, ceftriaxone is one of the most widely used antibiotics in sub-Saharan Africa (SSA)[13,14] to treat different types of infections including lung infections, central nervous system infections, bone infections, abdominal infections, skin and soft tissue infections, and urinary tract infections. However, a higher rate of inappropriate use was reported in different studies.[15,16] In addition, bacterial resistance is increasingly common among ceftriaxone users, raising concern that it may be no longer effective for infection treatment in East Africa.[17,18] Inappropriate use is the main driving force for the development of antimicrobial resistance. Because bacteria will eventually develop means to avoid being killed by antibiotics, judicious use of antibiotics by all stakeholders is imperative.[19] However, there are no organized data showing the extent of appropriate ceftriaxone use in SSA countries. The review is, therefore, aimed at summarizing the proper use of ceftriaxone in this region.

Methods

This systematic review was performed based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 guidance.[20]

Data Source and Eligibility Criteria

A systematic search was conducted on PubMed, Google Scholar, EMBASE and Cochrane Libraries. Boolean operators ("OR," "AND") and truncation were used to identify relevant articles that meet the research question. The search was conducted with the aid of carefully selected keywords and indexing terms. In addition, a reference list of included articles was evaluated for inclusion. A systematic search of the literature was conducted among studies published from 1st January 2010 to 30th February 2020.

All studies that focused on ceftriaxone prescribing pattern and rational use in SSA countries were included. In addition, studies must use appropriate antibiotic use guideline (eg IDSA) to evaluate indication, dose, dosage, frequency and duration of ceftriaxone.

Inclusion and Exclusion Criteria

All observational studies published in English language that address ceftriaxone use pattern and rational use in SSA countries were included. However, conference abstracts, editorial reports, or letters to the editors, case reports, case series and studies with limited information were excluded.

Search Strategy

The following search terms were used: "ceftriaxone use evaluation*", "ceftriaxone prescribing pattern", "cephalosporin use", "antibiotic use pattern", and "sub-Saharan". All search results from each database were saved, and exported into covidence. Duplicate studies were removed. The initial title and abstract screening were done by ABB and BMB. Three categories (yes, no, maybe) were used during the selection process. The full text of studies judged as 'yes' or "maybe" during initial screening was assessed based on the eligibility criteria by ABB and BMB. In both initial and full-text assessments, the third author (GTT) resolved any discrepancies arising between the two authors (ABB and BMB) (Figure 1).

Data Extraction

ABB and BMB independently extract relevant data using a standardized data abstraction format. These include study characteristics (study setting, and design, and sample size) and the result of studies (ceftriaxone use pattern, inappropriate of prescribing pattern and use of ceftriaxone). All disagreements were resolved by the third author (GTT).

Study Quality Assessment

The methodological quality and risk of bias of the included studies were independently assessed by two authors (ABB and BMB) using the Newcastle-Ottawa scale.[21] The scale rates study quality out of 10 points (stars). For ease of evaluation, the tool included important indicators categorized into three major domains. The first section assesses the methodological quality of a study, which has a maximum of 5 stars. The second section considers the comparability of the study and takes 2 stars, and the remaining section assesses the outcomes of studies related to the statistical analysis. The mean score of these two authors was taken for the final decision, and studies with a score of five and above points/stars were considered as good quality (Table 1).

Data Analysis

The extracted data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0 software. The prevalence of appropriate ceftriaxone indication, dose, frequency and duration of was summarized in medians and interquartile ranges.
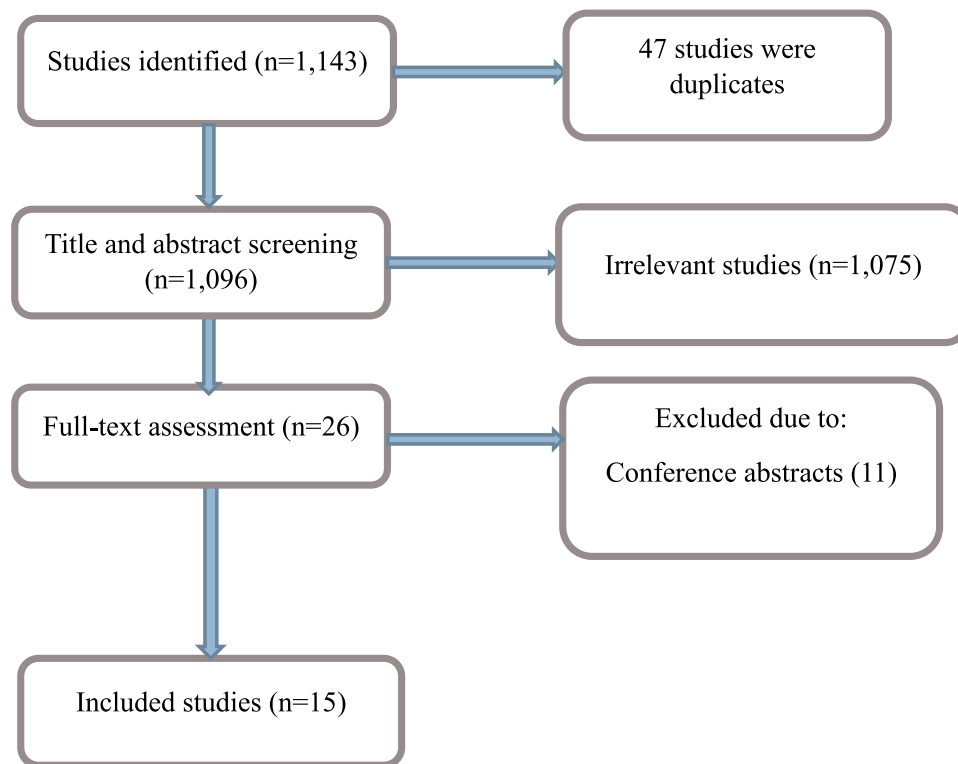
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Infection and Drug Resistance 2021:14

Figure 1 Article screening process.

Definition of Terms

Sub-Saharan Africa: Is geographically and ethno-culturally the area of the continents of Africa that lies south of the Sahara.

Appropriate use of ceftriaxone: It refers to the use of ceftriaxone to the right indication at the right dose, frequency, route and duration, and its value was taken directly from the included studies.

Results
General Characteristics of the Included Studies

Of the 1143 studies, 15 fulfilled the inclusion criteria. Out of 15 studies, eight in Ethiopia, three in Tanzania, one in Uganda, one in Ghana, one in Sudan, and one in Eritrea. Only two studies were conducted at both public and private hospitals, while the remaining were done at public hospitals. In addition, nine studies used retrospective cross-sectional study design, and the rest of studies employed prospective cross-sectional study design. A total of 4706 patients were involved in the review, and 90–601 patients were also targeted in the individual study. The highest appropriate ceftriaxone use (93%) was

reported in Ghana[22] got appropriate ceftriaxone, whereas the lowest (6.7%) was seen in Sudan[23] (Table 2).

Ceftriaxone Use Pattern and Appropriateness

Ceftriaxone is used for the treatment of various infections. The frequent diagnosed infections are; pneumonia (a median of 24.8%, (IQR: 16.2 −31.1)), sepsis (a median of 9.2%, (IQR: 3.7–16.1)), for surgical prophylaxis (a median of 7.7%, (IQR: 0–20.7)), meningitis (a median of 7.5%, (IQR: 3–20.9)), and urinary tract infection (a median 7.2%, (IQR: 4.5 13.1)). Ceftriaxone is appropriately used for a median of 39.2% (IQR: 29.9–60.9) of surgical patients. The highest median percentage of patients (51.2%, IQR; 33.1–73.4) got 2–7 days of ceftriaxone, while the lowest median percentage of patients (2.2%, IQR: 0.6–3.85) got ceftriaxone for more than two weeks. In addition, a higher median of 73.3% (IQR: 51.5–77.8) ceftriaxone users used 2gm daily dose, while the lowest percentage of ceftriaxone users (0.8%, IQR: 0.3–1.5) used 3gm daily. Afriyie et al[22] reported that the daily dose of ceftriaxone was administered appropriately to all patients; on the contrary, lowest percentage of patients (18.0%) got appropriate daily dose in Manirakiza et al. study.[28] The

Table 1 Study Quality Assessment Using Newcastle-Ottawa Quality Assessment Scale

S.n	Author Yr (Ref)	Methodological Quality (4pts)	Comparability (2)	Outcome Measurement and Analysis (2)	Total (8)
1	Abebe FA et al. 2012[24]	3	1	1.5	5.5
2	Afriyie DK et al. 2017[22]	3	1	1.5	5.5
3	Ayele AA et al. 2018[16]	3.5	1	1.5	6
4	Ayinalem GA et al. 2013[25]	3	1	1.5	5.5
5	Bantie et al. 2014[26]	3	1	1.5	5.5
6	Berhe YH et al. 2019[15]	3	1.5	1.5	6
7	Eulambius M et al. 2019[27]	3	0.5	2	5.5
8	Manirakiza L et al. 2019[28]	3.5	0.5	2	6
9	Sasi P et al. 2019[29]	3.5	2	2	7.5
10	Hussien LA. 2019[23]	3.5	1.5	2	7
11	Negese S et al. 2017[30]	3.5	1.5	2	7
12	Shimels T et al. 2015[31]	3.5	1	1.5	6
13	Sonda TB et al. 2019[14]	3.5	1	1.5	6
14	Geresu G et al. 2018[32]	2.5	1	1.5	5
15	Muhammed OS et al. 2020[33]	3	1	1.5	5.5

median prevalence of patients with appropriate daily dose of ceftriaxone was 79.8% (IQR: 40.9–91.0%). Shimels et al[31] reported the highest percentage of patients with appropriate duration of ceftriaxone (91.5%), while the lowest prevalence (18.0%) was reported by Negese et al. study.[30] The overall median percentage of (55%, IQR: 52.2–80) patients got an appropriate duration of ceftriaxone (Table 3).

Discussion

Dramatic increase in antibiotic utilization in the healthcare system contributes to inappropriate antibiotic use, and continues to drive antibiotic resistant microbes. This will return disease management back to the pre-antibiotic era whereby people were dying due to minor infections. Hence, judicious use of these precious substances is very essential. However, empiric prescription of broad-spectrum antibiotic for various diseases for very short or prolonged duration becomes a common practice in developing countries. This review was designed to systematically assess the appropriateness of ceftriaxone use in SSA countries. Our review showed that ceftriaxone was frequently used for pneumonia (a median of 24.8%), sepsis

(a median of 9.2%), for surgical prophylaxis (a median of 7.7%), meningitis (a median of 7.5%), and urinary tract infections (a median 7.2%). Ceftriaxone is a drug of choice for various bacterial infections, ranging from mild to life threatening conditions, in both hospitalized and ambulatory patients due to its higher antibacterial potency and low potential toxicity.[34] In addition, it is easily available, cost-effective, broad-spectrum antibiotic, and usually prescribed empirically without supported by microbiological testing.

Despite inconsistencies among studies regarding study design and study population, the review found that a median of 39.2% (IQR: 29.9–60.9) of patients got appropriate ceftriaxone use. Ceftriaxone was inappropriately prescribed for more than half of the patients. This may be due to inappropriate use of ceftriaxone during perioperative period as prophylaxis, and wrong indication, dose, frequency and duration. In addition, unavailability of alternative antibiotics and inconsistency of drug supply may contribute to the inappropriate use of ceftriaxone. Although there is no review conducted particularly in ceftriaxone use, a relatively higher percentage of appropriate antibiotic use (51.8%, 95% CI: 32.2–66.2) was

Table 2 General Characteristics of the Included Studies

S.n	Author Yr (Ref)	Study Country	Study Setting (Private or Public)	Sample Size (n)	Appropriate Prescribing Practice (%)	Common Indications				Prophylaxis (%)	No Indication (%)	Others[a] (%)
						Pneumonia/ RTI (%)	Sepsis (%)	Meningitis (%)	UTI (%)			
1	Abebe FA et al. 2012[24]	Ethiopia	Public	296	35.8	21.4	19.4	4.9	14.5	33	NR	6.8
2	Afriyie DK et al. 2017[22]	Ghana	Public	251	93	5.6	9.6	19.9	11.6	2.4	4.4 *	46.5
3	Ayele AA et al. 2018[16]	Ethiopia	Public	390	19.8	29.3	1.5	24.1	8.5	16.4	3.1	17.1
4	Ayinalem GA et al. 2013[25]	Ethiopia	Public	316	54	36.4	4.7	30.4	20.9	0	0	7.6
5	Bantie et al. 2014[26]	Ethiopia	Public	264	61	27.7	5.7	12.1	3.8	25	8.71	7.9
6	Berhe YH et al. 2019[15]	Eritrea	Public	109	27.5	36.7	21.8	2.8	5.5	0	2.3	30.9
7	Eulambius M et al. 2019[27]	Tanzania	Public and Private	600	33.9	13.4	9.2	2.5	7.2	55	NR	12.5
8	Manirakiza L et al. 2019[28]	Uganda	Public	100	53	19	19	22	9	2	1	28
9	Sasi P et al. 2019[29]	Tanzania	Public	360	30	29.4	0	7.5	1.7	0	0	60
10	Hussien LA. 2019[23]	Sudan	Public	90	6.7	3.3	31	2.2	31	0	NR	32.4
11	Negese S et al. 2017[30]	Ethiopia	Public	127	29.9	22	12.6	7.1	3.9	15	NR	39.4
12	Shimels T et al. 2015[31]	Ethiopia	Public and Private	477	61.7	32.7	13.1	14.7	6.1	7.7	NR	25.8
13	Sonda TB et al. 2019[14]	Tanzania	Public	322	48.9	11.2	8.7	1.6	0	13.6	6.9	58
14	Geresu G et al. 2018[32]	Ethiopia	Public	403	39.2	46.2	2.2	21.8	15.9	0	NR	13.8
15	Muhammed OS et al. 2020[33]	Ethiopia	Public	601	60.6	24.8	2.7	3.2	5	39.8	NR	24.5

Notes: *Indication for suspecting of malaria with bacterial infection [a]Others include; typhoid fever, acute febrile illness, cellulitis, sexually transmitted diseases, acute gastroenteritis, tuberculosis, PUD, cough, osteomyelitis and others.
Abbreviations: NR, not reported; ref, reference; LRTI, Lower respiratory tract infection; UTI, Urinary tract infection.

Table 3 Pattern of Ceftriaxone Use in the Included Studies

S.n	Author Yr (Ref)	% of Patients Who Used the Specified Dose of Ceftriaxone Daily				% of Patients with Appropriate Daily Ceftriaxone Dose (%)	% of Patients Who Used the Specified Duration of Ceftriaxone					% of Patients with Appropriate Ceftriaxone Duration (%)
		< 2gm	2gm	3gm	4gm		Stat	1 d	2–7 d	8–14 d	>14 d	
1	Abebe FA et al. 2012[24]	16.6	79.4	5.3	3.7	79.4	1.69	10.47	51.69	28.04	8.11	51.7
2	Afriyie DK et al. 2017[22]	57.6	39.4	1.5	1.5	100	12	43.4	48.6	0	0	85.7
3	Ayele AA et al. 2018[16]	1.5	76.9	1.5	20	80.1	0	5.1	25.9	37.2	31.8	53
4	Ayinalem GA et al. 2013[25]	9.5	63.6	0.9	25.9	77.4	8.5	13.3	76.6	2.8	1.3	52.6
5	Bantie et al. 2014[26]	–	–	–	–	86	–	–	–	–	–	82
6	Berhe YH et al. 2019[15]	5.5	94.5	0	0	50.5	11.4	20	28.4	35.5	4.7	26.6
7	Eulambius M et al. 2019[27]	19	74	0	1	18	0	7	88	5	0	78
8	Manirakiza L et al. 2019[28]	72.9	22.9	6	3.6	31.2	15.6	50	32.2	2.2	0	55
9	Sasi P et al. 2019[29]	87.7	11.1	0.5	0.5	0	0	15.6	33.9	48.3	2.2	
10	Hussien LA. 2019[23]	23.6	71.7	0.8	3.9	94.2	4.7	5.5	70.1	17.3	2.4	71.7
11	Negese S et al. 2017[30]	0	73.5	0	26.5	87.8	0	1.2	83.9	13.6	1.2	18
12	Shimels T et al. 2015[31]	0	78.6	18.6	2.8	95.8	5.1	14.5	68.1	9.3	3	91.6

Note: NB, some of the included studies did not report information on the appropriateness of daily dose, frequency and duration of ceftriaxone.
Abbreviations: Stat, the first single dose; ref, reference.

reported in a recent review of Ethiopian studies.[35] This difference may be due to the different local antimicrobial resistance pattern, drug availability and study population. This review targeted ceftriaxone use only, while the latter considered all types of antimicrobials. In addition, the extent of appropriate ceftriaxone use is lower than the study done in the USA ambulatory patients, reported a -69.8%.[36] This may be due to organized healthcare system, adequate drug supply system and availability of blood culture in the USA.

Our review also revealed that a median of 48.5% of patients used ≤2gm of ceftriaxone daily, while the majority of patients (88.0%) got ≤2gm of ceftriaxone in Lee h et al. study.[37] The different diagnoses and severity of infections between the two studies may be responsible for this gap. The median prevalence of patients with appropriate ceftriaxone daily dose was 79.8% (IQR: 40.9–91.0%). On the contrary, a lower median of (55%, IQR: 52.2–80) patients got an appropriate duration of ceftriaxone. The availability of a simplified once-daily dose of ceftriaxone has given an opportunity for healthcare workers to prescribe or administer an appropriate daily dose of ceftriaxone. In addition, the empiric use of ceftriaxone as first line for various infections, and then changed to other alternative

medications due to poor prognosis, inadequate supply, toxicities or the change of provisional diagnosis may contribute to inappropriate duration of ceftriaxone.

The review has the following strengths: It is the first systematic review focusing on a single antibiotic, and comprehensively involving studies from every corner of the SSA. On the other hand, as studies are heterogeneous in terms of study population and design, it is problematic to perform a pooled prevalence. In addition, some studies did not report specific information on the appropriateness of daily dose, frequency and duration of ceftriaxone, which could alter the analysis.

Conclusion

The review revealed that ceftriaxone was inappropriately prescribed to more than half of the patients. Of which, approximately half the patients took wrong duration of ceftriaxone. In contrast, due to ease of administration and availability in a single dose, more than three-fourths of the patients got appropriate daily dose. Ceftriaxone is one of the cost-effective broad-spectrum and safe antibiotics used to manage mild to life threatening infections, particularly in low-income countries. Hence, it should be reserved, and used appropriately. Therefore, prescribers should take this into

consideration, while they are prescribing, and stick to the updated treatment guideline. In addition, initiating or strengthening antimicrobial stewardship program is of paramount importance for the rational use of ceftriaxone. Further, researchers have to investigate reasons and associated information for inappropriate use of ceftriaxone to design customized relevant prevention strategies.

Abbreviations

IQR, Interquartile Range; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SAP, Surgical Antibiotic Prophylaxis; SSA, Sub-Saharan Africa; SSI, Surgical Site Infection.

Data Sharing Statement

The datasets used during the current study are available from the corresponding author on a reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, in the conception, study design, execution, acquisition of data, analysis, and interpretation; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Disclosure

The authors declared that they have no conflicts of interest in this work.

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