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COMBINATION OF CEFTRIAXONE, SULBACTAM, AND DISODIUM EDETATE IN THE MANAGEMENT OF MULTI-DRUG RESISTANT GRAM-NEGATIVE PATHOGENS

Internal Medicine

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ABSTRACT

Background: Antimicrobial resistance (AMR) poses a global threat, contributing to millions of deaths annually. Disodium edetate (EDTA), a well-known chelating agent, acts as a potentiating and sensitizing agent when combined with antibiotics. Therefore, the present study aimed to conduct a comparative analysis of cefoperazone, sulbactam, and EDTA in combination with other antibiotics in terms of pathogen susceptibility. **Methods:** This retrospective study was conducted from January 2023 to July 2023. All patients (aged>25 years) admitted to the medical intensive care unit, surgical intensive care unit, and coronary care unit, with a duration of admission exceeding two days, were included. Gram-negative isolates were collected from the patients' blood, urine, and respiratory secretions. **Results:** Isolates were obtained from 40 urine, respiratory secretions, and blood samples, each. Ceftriaxone combined with sulbactam and EDTA showed the highest susceptibility among blood samples, particularly against K. pneumoniae, E. coli, Enterobacter spp, P. mirabilis (100%). In urine samples, K. pneumoniae displayed mixed susceptibility, with high efficacy observed for ceftriaxone, sulbactam, and EDTA. Escherichia coli showed high susceptibility across all antibiotics. Pseudomonas aeruginosa exhibited varied susceptibility, with the highest susceptibility seen with ceftriaxone combined with sulbactam and EDTA. Respiratory samples showed high susceptibility of A. baumannii to ceftriaxone with sulbactam and EDTA, contrasting with low susceptibility to other combinations, highlighting varied efficacy against different pathogens. **Conclusion:** Ceftriaxone combined with sulbactam and EDTA demonstrated high susceptibility against gram-negative pathogens, highlighting its potential as a valuable treatment option for antibiotic resistance.

KEYWORDS

Antimicrobial resistance, ceftriaxone, disodium edetate, gram-negative, sulbactam

INTRODUCTION

Antimicrobial resistance (AMR) poses a significant global threat, with bacterial resistance directly causing 1.27 million deaths in 2019 and contributing to an additional 4.95 million deaths [1]. The global challenge lies in reconciling antibiotic access with responsible use, prompting the World Health Organization (WHO) to introduce the Access, Watch, and Reserve (AWaRe) classification in the 2017 Essential Medicines List [2]. India tops the global list in human antibiotic consumption, with 12.9×109 units used in 2010, averaging 10.7 units per person, contributing significantly to AMR [3]. Factors contributing to India's challenge in reducing antibiotic use involve regulatory system shortcomings, non-prescription antibiotic sales, and the prevalence of unapproved fixed-dose combination antibiotics. Particularly worrisome are those with mismatched dosing regimens, sparking concerns about antimicrobial resistance, with scant data available in low- and middle-income countries [4].

As per India's 2017 report on antimicrobial resistance, over 70% of gram-negative bacteria, such as Escherichia coli and Klebsiella pneumoniae, and nearly half of Pseudomonas aeruginosa, displayed resistance to fluoroquinolones and third-generation cephalosporins [5].To overcome the issue of resistance, a combination of cefoperazone, sulbactam, and disodium edetate (EDTA)was formulated as an antibiotic adjuvant entity to confront the issue presented by multidrug-resistant (MDR) pathogens, including those producing extended-spectrum beta-lactamase (ESBL) or metallo-beta-lactamase (MBL). Disodium edetate, a well-known chelating agent, acts as a potentiating and sensitizing agent when combined with antibiotics [6, 7]. This innovative approach offers a promising strategy against resistant pathogens, utilizing EDTA's high affinity for metal ions and its unique molecular structure, binding to antibiotics through amino and carboxylate groups [8].

Therefore, this study aimed to conduct a comparative analysis of cefoperazone, sulbactam, and disodium edentate combination with other antibiotics, including ceftriaxone plus sulbactam, piperacillin plus tazobactam and meropenem in terms of pathogen susceptibility.

METHODS

This retrospective study was conducted from January 2023 to July 2023. All patients (aged >25 years) admitted to the medical intensive care unit, surgical intensive care unit, and coronary care unit, with a duration of admission exceeding two days, were included in the study. Patients attending the outpatient department were excluded from the study. Gram-negative isolates were collected from the patients' blood, urine, and respiratory secretions. Samples other than blood, urine and respiratory secretions were excluded. The sample size was calculated by using the estimated prevalence of resistance rates. Isolates were obtained from 40 urine, respiratory secretions, and blood samples, each. Antibiotic susceptibility results were interpreted as per the Clinical & Laboratory Standards Institute (CLSI) guidelines (2020) [9].

RESULTS

Table 1 represents the susceptibility scores of the blood samples. Ceftriaxone combined with sulbactam and disodium edentate demonstrated the highest susceptibility, with all strains of K. pneumonia (100%) being susceptible. However, a significant proportion of K. pneumonia strains exhibited resistance to cefoperazone plus sulbactam (94.2%) and piperacillin plus tazobactam (84.2%) (Fig 1). Acinetobacter baumannii displayed alarming levels of resistance across all antibiotics tested, with all strains being resistant (100%). Escherichia coli showed good susceptibility to all antibiotics, with susceptibility ranging from 40.0% to 100%. Enterobacter strains exhibited susceptibility to ceftriaxone plus sulbactam and meropenem (100%), but resistance to other combinations. Pseudomonas aeruginosa demonstrated moderate susceptibility to ceftriaxone in combination with sulbactam and disodium edentate (80.0%) and meropenem (50.0%), but high resistance to other combinations. Proteus strains were universally susceptible to all antibiotics tested (100%). Overall, the data underscores the critical importance of understanding bacterial susceptibility patterns to guide effective antibiotic therapy and combat the rising issue of antibiotic resistance (Table 1).

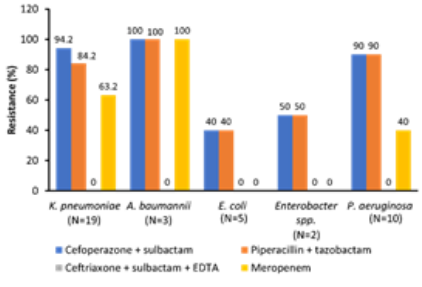

Figure 1: Resistance patterns of gram-negative bacterial isolates in blood culture EDTA, disodium edetate.

Table 2 presents the susceptibility scores for various bacteria to

different antibiotic combinations in urine samples. Klebsiella pneumoniae exhibited mixed susceptibility, with higher susceptibility to ceftriaxone in combination with sulbactam and disodium edetate (87.5%) (Fig 2). Escherichia coli displayed high susceptibility across all antibiotics, with ceftriaxone in combination with sulbactam and disodium edetate showing complete efficacy (100%). Enterobacter spp. showed excellent susceptibility to all antibiotics. Pseudomonas aeruginosa had moderate susceptibility to cefoperazone+ sulbactam (32.3%) and piperacillin + tazobactam (55.6%), while ceftriaxone + sulbactam + disodium edetate exhibited the highest efficacy (100%). Proteus mirabilis exhibited complete susceptibility to all antibiotics.

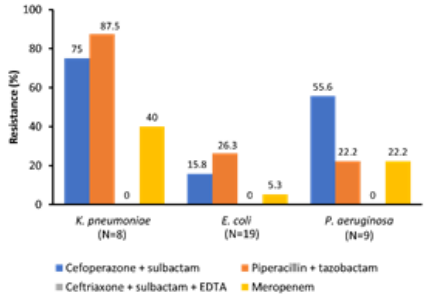

Figure 2: Resistance patterns of gram-negative bacterial isolates in urine culture EDTA, disodium edetate

Furthermore, table 3 represents the results of susceptibility scores of the respiratory secretions. Klebsiella pneumoniae was highly susceptible to ceftriaxone + sulbactam + disodium edetate (81.2%), whereas its susceptibility to cefoperazone+ sulbactam and piperacillin + tazobactam was low (6.2%) (Fig 3). Acinetobacter baumannii displayed high susceptibility to ceftriaxone in combination with sulbactam and disodium edetate (91.7%), whereas it was uniformly resistant to cefoperazone+ sulbactam and piperacillin + tazobactam. Escherichia coli exhibited high susceptibility to all tested antibiotics, with ceftriaxone in combination with sulbactam and disodium edetate demonstrating complete efficacy (100%). Enterobacter spp. showed complete susceptibility to ceftriaxone in combination with sulbactam and disodium edetate, albeit limited data availability. Pseudomonas aeruginosa displayed high susceptibility to ceftriaxone in combination with sulbactam and disodium edentate (100%).

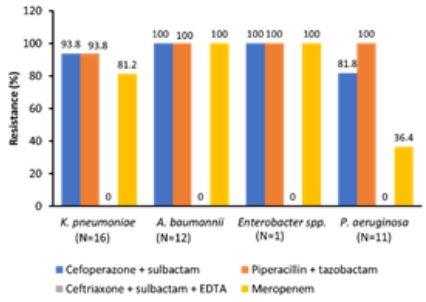

Figure 3: Resistance patterns of gram-negative bacterial isolates in blood culture EDTA, disodium edetate.

DISCUSSION

Bacterial AMR has become a significant public health issue, marked by bacteria evolving to diminish the efficacy of infection-treating drugs [10]. Over the past 15 to 20 years, the incidence of infections caused by gram-negative bacteria in intensive care units has risen and these are associated with high morbidity and mortality [11]. Therefore, understanding the comparative efficacy of different antibiotic combinations is crucial for informing strategies to mitigate the rise of AMR.

The combination of ceftriaxone, sulbactam, and EDTA has been developed to target a wide range of bacterial infections. In this study, samples were obtained from the urine, respiratory secretions, and blood, with gram-negative bacteria being the predominant pathogens in all cases. According to the National Health Service report of 2017, E. coli, P.aeruginosa and Klebsiella spp. contributed to 72% of all gram-negative bloodstream infections. Among them E. coli represented 59% of total infections [12]. A recent comparative in vitro study of gram-negative bacterial isolates demonstrated that ceftriaxone, sulbactam, and EDTA exhibited notable sensitivity rates, demonstrating 94% effectiveness against Enterobacteriaceae and 97% against Acinetobacter and Pseudomonas spp. followed by colistin [13].Another study performed by Satras et al. revealed that ceftriaxone, sulbactam, and EDTA exhibited superior antibacterial activity (87.80%) compared to carbapenem drugs such as meropenem and imipenem, and it significantly better performed to piperacillin plus tazobactam against clinical pathogens [14]. However, the current study revealed that ceftriaxone, sulbactam, and EDTA had highest susceptibility, particularly against Enterobacter spp.(100%). Acinetobacter baumannii displayed complete resistance to all antibiotics tested. Escherichia coli exhibited good susceptibility across all antibiotics, highlighting the importance of antibiotic therapy based on bacterial susceptibility patterns to combat antibiotic resistance.

According to a retrospective analysis, ceftriaxone combined with sulbactam and EDTA exhibited the highest susceptibility (100%) against A. baumannii, P. aeruginosa, and K. pneumoniae compared to other antibiotics. While meropenem also showed similar susceptibility against P. aeruginosa (100%), it faced significant resistance in K. pneumoniae and A. baumannii strains [15,16]. However, the present study demonstrated that E. coli and Enterobacter spp. displayed high susceptibility across all antibiotics tested, while K. pneumoniae and P. aeruginosa showed high susceptible to ceftriaxone combined with sulbactam and EDTA.

Previous study reported that A. baumannii was predominantly isolated from pus samples, indicating its significant role in skin and soft tissue infections. Additionally, respiratory samples demonstrated a presence of A. baumannii, suggesting its involvement in respiratory infections. This shows the diverse clinical manifestations associated with A. baumannii infections [16]. The current study has demonstrated superior activity of ceftriaxone, sulbactam, and EDTA against isolates from respiratory secretions such as A. baumanii, P. aeruginosa, as compared to other antibiotic combinations [17].

CONCLUSION

The rise of AMR represents a major global health concern, underscoring the necessity for efficient treatment approaches. Ceftriaxone, sulbactam, and EDTA has shown promising efficacy against a wide range of pathogens, including high susceptibility rates against Enterobacter spp., K. pneumoniae and P. aeruginosa. This study indicates the favorable bacteriological eradication with this combination, suggesting its potential as a valuable tool in combating AMR. Tailored antibiotic therapy based on susceptibility patterns is crucial in combating AMR and improving patient outcomes.

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Table 1: Susceptibility results of blood culture

Microorganisms	Susceptibility score	Cefoperazone + sulbactam	Piperacillin+tazobactam	Ceftriaxone+ sulbactam + EDTA	Meropenem
Klebsiella pneumoniae **(N=19)**	**S**	1 (5.3)	3 (15.8)	19 (100)	6 (31.6)
	I	2 (10.5)	0	0	1 (5.3)
	R	16 (94.2)	16 (84.2)	0	12 (63.2)
Acinetobacter baumannii **(N=3)**	**S**	0	0	2 (66.7)	0
	I	0	0	1 (33.3)	0
	R	3 (100)	3 (100)	0	3 (100)
Escherichia coli **(N=5)**	**S**	3 (60.0)	2 (40.0)	5 (100)	5 (100)
	I	0	1 (20.0)	0	0
	R	2 (40.0)	2 (40.0)	0	0
Enterobacter spp. **(N=2)**	**S**	0	0	2 (100)	2 (100)
	I	1 (50.0)	1 (50.0)	0	0
	R	1 (50.0)	1 (50.0)	0	0
Pseudomonas aeruginosa **(N=10)**	**S**	0	0	8 (80.0)	5 (50.0)
	I	1 (10.0)	1 (10.0)	2 (20.0)	1 (10.0)
	R	9 (90.0)	9 (90.0)	0	4 (40.0)
Proteus mirabilis **(N=1)**	**S**	1 (100)	1 (100)	1 (100)	1 (100)
	I	0	0	0	0
	R	0	0	0	0

Data presented as n (%).
EDTA, disodium edetate;I, intermittent; R, resistant; S, susceptible.

Table 2:Susceptibility results of urine cultures

Microorganisms	Susceptibility score	Cefoperazone + sulbactam	Piperacillin + tazobactam	Ceftriaxone+ sulbactam + EDTA	Meropenem
***Klebsiella pneumoniae* (N=8)**	**S**	1 (12.5)	0	7 (87.5)	3 (37.5)
	I	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)
	R	6 (75.0)	7 (87.5)	0	4 (40.0)
***Escherichia coli* (N=19)**	**S**	14 (73.7)	12 (63.2)	19 (100)	18 (94.7)
	I	2 (10.5)	2 (10.5)	0	0
	R	3 (15.8)	5 (26.3)	0	1 (5.3)
***Enterobacter spp.* (N=2)**	**S**	2 (100)	1 (50.0)	2 (100)	2 (100)
	I	0	1 (50.0)	0	0
	R	0		0	0
***Pseudomonas aeruginosa* (N=9)**	**S**	3 (33.3)	5 (55.6)	9 (100)	7 (77.8)
	I	1 (11.1)	2 (22.2)	0	0
	R	5 (55.6)	2 (22.2)	0	2 (22.2)
***Proteus mirabilis* (N=1)**	**S**	1 (100)	1 (100)	1 (100)	1 (100)
	I	0	0	0	0
	R	0	0	0	0
***Providencia rettgeri* (N=1)**	**S**	0	0	0	0
	I	1 (100)	1 (100)	1 (100)	1 (100)
	R	0	0	0	0

Data presented as n (%).
EDTA, disodium edetate; I, intermittent; R, resistant; S, susceptible.

Table 3: Susceptibility results of respiratory cultures

Microorganisms	Susceptibility score	Cefoperazone + sulbactam	Piperacillin + tazobactam	Ceftriaxone+ sulbactam + EDTA	Meropenem
***Klebsiella pneumoniae* (N=16)**	**S**	1 (6.2)	1 (6.2)	13 (81.2)	3 (18.8)
	I	0	0	3 (18.8)	0
	R	15 (93.8)	15 (93.8)	0	13 (81.2)
***Acinetobacter baumannii*(N=12)**	**S**	0	0	11 (91.7)	0
	I	0	0	1 (8.3)	0
	R	12 (100)	12 (100)	0	12 (100)
***Enterobacter spp.* (N=1)**	**S**	0	0	1 (100)	0
	I	0	0	0	0
	R	1 (100)	1 (100)	0	1 (100)
***Pseudomonas aeruginosa* (N=11)**	**S**	2 (18.2)	0	11 (100)	4 (36.4)
	I	0	0	0	3 (27.3)
	R	9 (81.8)	11 (100)	0	4 (36.4)

Data presented as n (%).
EDTA, disodium edetate; I, intermittent; R, resistant; S, susceptible.

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