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Is ceftriaxone Sulbactam EDTA the answer to the rising trends of antibiotic resistance in respiratory infections?

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I. Introduction

Patients with respiratory infections in the intensive care unit pose a challenge due to the presence of animmunocompromised state,hyperglycemia, and the presence of nosocomial pathogens that are resistant to common antibiotics.[1,2]. Patients withcommunity-acquired pneumonia who are hospitalized also pose a challenge since their arrival at the hospital are preceded by the use of several antibiotics contributingto the development of high antimicrobial resistance.[3] Hence it is imperative to choose the antibiotics with care when treating patients with respiratory infections in the hospital or intensive care unit (ICU.)The choice of drug for empirical antibiotic therapy has to be made based on knowledge about the current isolates in the hospital and community and the local trends of susceptibility and resistance patterns of common pathogens.

Gram-negative isolates such as *Klebsiella pneumonaie, Pseudomonas aeruginosa,*and multi-drug resistant *Proteus* are challenging pathogens implicated in difficult-to-treat respiratory infections. Another challenging pathogen in the hospital and ICU setting is *Acinetobacter baumanii.*[4]This organism has the tremendous potential to accumulate antibiotic-resistant determinants after exposure to inappropriateantibiotic useand can resist adverse conditions.[5,6]The genus *Achromobacter* is an obligately aerobic, non-fermentative; oxidase- and catalase-positive bacterium.[7]. Due to biochemical similarities,*Achromobacter* spp. are frequently misidentified as other common (i.e., *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Burkholderiacepacia* complex, *Acinetobacter* spp nonfermenting Gram-negative bacilli with conventional methods[7,8,9,10]

In the era of antibiotic resistance, the choice for an empiric antibiotic therapy needs to be made prudently with a rationale of offering a broadspectrum of activity against pathogens including beta-lactamase-producing pathogens. It is important to consider the side effects of antibiotics and institutional antibiograms.As the numbers of antibiotic-resistant bacterial strains continue to grow, there is an increased risk of superinfection in severely ill patients, especially in intensive care units (ICUs).[11]

Salts of Ethylenediamine tetraacetic acid (EDTA) have long been used as antimicrobial agents, particularly against bacteria. They have also been used as enhancers of other agents, such as the removal or destruction of covalently bound lipid component.[12].Ceftriaxone+Sulbactam+Disodium EDTA was one of the antibiotics used to prevent secondary infections.

II. Material And Methods

The study was a single-center, retrospectiveanalysis of data from tertiary carehospital patients treated in the ICU or wards.Patients admitted toICU who received empirical antibiotic therapyincluding Ceftriaxone+Sulbactam+Disodium EDTA were included in the study. The Kirby Bauer disc diffusion method was used to test the susceptibilities of the antibiotics according to CLSI criteria. The antibiotics tested included Ceftriaxone+Sulbactam+Disodium EDTA, meropenem, andpiperacillin-tazobactam.Theisolates wereanalyzed with the following discs, namely, for non-fermenters like *Acinetobacter* and *Pseudomonas* (100μg), piperacillin/tazobactam (100/10 μg), ceftriaxone sulbactam EDTA (30 /30μg), and meropenem (10 μg),

Study Design:single-centre, retrospective analysisof antibiotic susceptibility data from tertiary care hospital

Study Location: Super Specialty tertiary carecentres, Pune in India
Study Duration:- June 2018 to March 2021

Sample size: 922 samples from patients admitted to the ICU
Subjects & selection method: Patients admitted to the ICU from a tertiary care hospital
E**T**

Inclusion criteria:

Respiratory samples such as Bronchoalveolar lavage (BAL), Endotracheal tube secretion (ETT , tracheal tube (TT)secretion & Sputum from a patient admitted to the ICU & Wards from Tertiary care Hospitals.

Exclusion criteria
Respiratory samples collected in OPD (Outpatient Department) of Tertiary care Hospitals.

Procedure methodology
Different Respiratory samples such as bronchoalveolar lavage (BAL) , ETT secretion (Endotracheal tube) , TT secretion (Tracheostomy tube) and sputum specimen were collected from patients in a period of three years (June , 2018 to March , 2021), from tertiary care centres in Pune.All the samples were collected aseptically in sterile containers in sufficient amount andinoculated on th e different selective and non- selective culture media as per the standard microbiological techniques. The collection and processing of the samples weredone as per a common Standard Operating Proce dures.Antimicrobial susceptibility testing was performed by the Kirby–Bauer disk diffusion method as recommended by the Clinical Laboratory Standards Institute (CLSI) guidelines . Antibiotics sensitivity disc of Elores (45 µg) were obtained from Abtek while rest of the antibiotic discs such as piperacillin-tazobactam (110 µg), meropenem (10 µg) and imipenem (10 µg) were obtained from HiMedia, India. The zone diameters of each drug are interpreted using the criteria publishedby the Clinical and Laboratory Standards Institute (CLSI) as well as in-house criteria given for Elores.

Statistical analysis
Data was analysed calculating percentages of samples that were sensitive , intermediate or resistant to the antibiotics tested.

III. Result

Table 2: Susceptibility trends of Ceftriaxone+Sulbactam+Disodium EDTA(ELORES)

Ceftriaxone+Sulbactam+Disodium EDTA **(Elores)**							
BAL, ET , Sputum, TT							
Pathogen	**Total No.**	**Sensitive**		**Intermediate**		**Resistant**	
		No.	**%**	**No.**	**%**	**No.**	**%**
A baumanii	115	102	88.70%	7	6.09%	6	5.22%
Achromobacter	4	4	100.00%	0	0.00%	0	0.00%
Citrobacter	13	13	100.00%	0	0.00%	0	0.00%
E.Coli	251	235	93.63%	6	2.39%	10	3.98%
Enterobacter	74	56	75.68%	10	13.51%	8	10.81%
Klebsiella Pneumoniae	174	150	86.21%	11	6.32%	13	7.47%
Morganella	5	4	80.00%	1	20.00%	0	0.00%
Pseudomonas Aeroginosa	240	77	32.08%	66	27.5%	97	40.4%
Proteus	42	37	88.10%	3	7.14%	2	4.76%
Providencia	4	4	100.00%	0	0.00%	0	0.00%

Table 2: Susceptibility trends of meropenem

Meropenam							
BAL, ET , Sputum, TT							
Pathogen	**Total No.**	**Sensitive**		**Intermediate**		**Resistant**	
		No.	**%**	**No.**	**%**	**No.**	**%**
A baumanii	115	25	21.74%	1	0.87%	89	77.39%
Achromobacter	4	4	100.00%	0	0.00%	0	0.00%

Citrobacter	13	12	92.31%	1	7.69%	0	0.00%
Coli	250	165	66.00%	25	10.00%	60	24.00%
Enterobacter	74	37	50.00%	10	13.51%	27	36.49%
Klebsiella pneumoniae	174	79	45.40%	24	13.79%	71	40.80%
Morganella	5	4	80.00%	1	20.00%	0	0.00%
Pseudomonas aeroginosa	241	178	78.3%	4	1.6%	59	24.4%
Proteus	42	33	78.57%	2	4.76%	7	16.67%
Providencia	4	2	50.00%	0	0.00%	2	0.00%

Table 2: Susceptibility trends of Piperacillin taozbactam

Piperacillin + Tazobactum							
BAL, ET , Sputum, TT							
Pathogen	**Total No.**	**Sensitive**		**Intermediate**		**Resistant**	
		No.	**%**	**No.**	**%**	**No.**	**%**
A baumanii	114	24	21.05%	3	2.63%	87	76.32%
Achromobacter	4	3	75.00%	0	0.00%	1	0.00%
Citrobacter	13	7	53.85%	2	15.38%	4	30.77%
Coli	251	110	43.82%	47	18.73%	94	37.45%
Enterobacter	74	38	51.35%	13	17.57%	23	31.08%
Klebsiella pneumoniae	174	67	38.51%	24	13.79%	83	47.70%
Morganella	5	4	80.00%	1	20.00%	0	0.00%
Pseudomonas aeroginosa	241	171	70.9%	31	12.8%	39	16.1%
Proteus	42	31	73.81%	5	11.90%	6	14.29%
Providencia	4	2	50.00%	0	0.00%	2	0.00%

IV. Discussion

The incidence of infections in the ICU usually ranges from 2.3% to 49.2%.[13]The rising trends of antibiotic resistanceespecially for pathogens such as *Acinetobacter* spp., Pseudomonas spp,*Klebsiella*, and *Achromobacter*globally, especially in the hospitalsetup hasgiven cause for concern to clinicians and microbiologists. For *Acinetobacter* spp., the majority of the antibiotics have been reported to beineffective with resistance rates varying from 76.99% to 92.01%.[2]

In ICUs in Indian Tertiary care hospitals, the rates ofnosocomial infections have ranged from 11.97% and 17.7% .[13,14]The incidence rates of nosocomial infections vary based on the local epidemiology and hospital conditions. A diverse spectrum of pathogens is observed which varies from region to region. Gram-negative organisms are the most common cause of infections in developing countries.[15] The inappropriate use of antibiotics has been implicated in the development of drug resistance in developing countries. [15]

Given the rising trends of resistance to the current antibiotics,clinicians and intensivists are faced with the dual challenge of choosing an effective empiric antibiotic that would also be safeand would result in improved outcomes of both hospital-acquired and severe community-acquired respiratory infections.

The solution to the problem of antibiotic resistance is to use new antibiotics or combinations of antibiotics. Anotherapproach to the dilemma of resistant pathogens is to combine antibiotics with potentiating and sensitizing agents such as ethylenediaminetetraacetic acid (EDTA) . EDTA is a chelating agentwith a high affinity for metal ions and a high density of ligands. EDTA bindsthrough its two amino and four carboxylate groups.[16]*(Finnegan S).* EDTA can "sequester" metal ions such as Ca^{2+} and Fe^{3+}. After the metal ions bind to EDTA, the resulting complex helps the metal ions to remain in solution but the ions have a reducedreactivity. EDTA has been extensively used for the managementof patients with poisoning due to heavy metal ions such as

lead and mercury.[16] EDTA, by itselfdoes not have potent antimicrobial activity. But, EDTA is considered to be a 'potentiator' of the activity of other antimicrobial agents.[17,18]

An antibiotic adjuvant entity (AAE) of ceftriaxone, sulbactam and disodium edetate was developed for the MDR ESBL and MBL producing pathogens. The combination was expected to give multiple mechanisms of antibacterial actions. Sulbactam is a beta-lactamase inhibitor while EDTA exerts its antibacterial action through antibiofilm and metal chelating properties. EDTA is also considered to be penetration enhancer for the by increasing the membrane porosity. This will result in decreased minimum inhibitory concentration (MIC) values of drugs.[15]. This combination of ceftriaxone, sulbactam and disodium edetate has been approved by the Indian regulatory authority for the treatment of MDR ESBL/MBL associated infections.[19]

The findings of the current in vitro study have demonstrated that Ceftriaxone Sulbactam EDTA has retained sensitivity against pathogens that are resistant to carbapenems and Piperacillin tazobactam. Ceftriaxone Sulbactam EDTA is effective against difficult to treat pathogens such as *Acinetobacter baumanii, Pseudomonas aeruginosa, Klebsiella pneumonia,* proteus spp and *Achromobacter.*

V. Conclusion

Ceftriaxone Sulbactam EDTA can be an effective and safe empiric antibiotic to treat severe community acquired respiratory tract infections and nosocomialpneumonia..EDTA improves antibiotic penetration and makes Ceftriaxone Sulbactam effective even against pathogens resistant to meropenem and piperacillin tazobactam.

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