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Efficacy of Ceftolozane/Tazobactam in Infections with Multidrug-Resistant Gram-Negative Bacteria: A Preliminary Clinical Experience in a Highly Endemic Hospital

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Abstract

Introduction: Ceftolozane/Tazobactam is a new cephalosporin/beta-lactams inhibitor combination proven to be a drug with efficacy against urinary tract infections, abdominal infections and nosocomial ventilator-associated pneumonia, supported by multi-resistant Gram-negative bacteria.

Methods: This retrospective study considerated a cohort of 85 patients (≥ 18 years), with a Gram-negative infection diagnosed between October 2017 and December 2020, treated with at least 72 hours of C/T therapy. The aim was to evaluate the efficacy, tolerability and to analyze any factors associated with a negative outcome.

Results: The clinical success achieved in patients treated with ceftolozane/tazobactam in this coorte was 59%. Risk factors independently associated with mortality were neutropenia (p=0.02) and ICU stay (p=0.009). High mortality in ICU is related to complexity of patients with multiple devices and concomitant infections that needed combination of antibiotic therapy.

Conclusion: Ceftolozano/tazobactam represents a therapy of choice in infections by Gram-MDR bacteria, also in that which multiple comorbidity and long hospital stay.

Keywords: Multi drug-resistant bacteria; Ceftolozano-tazobactam; *Pseudomonas*; ICU

Abbreviations: ICU: Intensive Care Units; IQR: Interquartile Range; MALDI-TOF/MS: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry; CCI: Charlson Comorbidity Index; HAP: Hospital Acquired Pneumonia; VAP: Ventilator Acquired Pneumonia

Introduction

In recent years, there has been a growing emergence of antibiotic resistance among common bacteria, mainly in the hospital setting. This phenomenon is linked to multiple factors: on the one hand, the inappropriate use of antibiotics in clinical, agricultural and industrial settings, on the other hand, the ability of microorganisms to acquire new resistances thanks to intrinsic mechanisms and external genetic contributions [1,2]. The multi-drug-resistance characterizes all bacterial species, but in particular GRAMs - which are developing resistance to the main classes of antibiotics that were effective in the past (including carbapenemics and some new molecules) [3-5]. In this scenario, dominated by an ever-narrower range of effective antibiotics, the advent of new drugs becomes extremely important for reaching the therapeutic target. All hospitalized patients are at risk of being infected by MDR bacteria, but ICU represents the setting at greatest risk and are those in which the use of new antibiotics is being most applied [6]. Ceftolozane/Tazobactam is a new cephalosporin/beta-lactams inhibitor combination proven to be a drug with efficacy against urinary tract infections, abdominal infections and nosocomial ventilator-associated pneumonia, supported by multi-resistant Gram-negative bacteria [7]. In this mind, the purpose of the study was to evaluate the efficacy of ceftolozane/tazobactam and risk factors related to 30-day mortality in subjects treated with this antibiotic.

Materials and Methods

The setting was a 980 beds Regional University Hospital in Ancona, Central Italy, including five Intensive Care Units (ICUs), 11 medical and 11 surgical wards. A cohort of 85 patients (≥ 18 years), with a Gram-negative infection diagnosed between October 2017 and December 2020, treated with at least 72 hours of C/T therapy, was considered. Patient variables included demographic data, presence of acute or chronic comorbidities, Charlson's Comorbidity Index [8], previous surgery (≤ 3 months), steroid and/or immunosuppressive therapy and invasive procedures (≤ 30 days and ≤ 72 h before infection onset, respectively). Sepsis or septic shock were evaluated according to criteria of International Consensus Definition for Sepsis and Septic shock [9]. Hospitalization variables included nosocomial or healthcare-related infection, days between admission and onset of infection, words submitting index culture. We considered the type of Gram-negative

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bacteria isolated, if available, the site of isolation (urinary tract, bronchial/pleural fluid, abdominal fluid, wounds, blood), previous (≤ 30 days) or concomitant infections. Treatment variables included antibiotic therapy with Ceftolozane /tazobactam in monotherapy or combination therapy. Dosages used was equal to 1.5 g tid equal to 3 g tid for nosocomial pneumonia. The outcome measured was death, relapse, or persistence of infection within 30 days from the first positive culture. Strains were identified by Matrix-Assisted Laser Desorption/ Ionization Time-Of Flight Mass Spectrometry (MALDI-TOF/MS). Susceptibility testing were performed by Vitek 2 system 202 (bio-Merieux, Marcy l'Etoile, France) and interpreted according to the EUCAST 2022 definition [10]. Categorical variables were expressed as absolute numbers and their relative frequencies and compared by the $\chi 2$ or Fisher exact test; continuous variables were expressed as median and Interquartile Range (IQR) and evaluated by the Wilcoxon test and the Mann Whitney U test (for no normally distributed variables). Variables that reached a statistical significance ($p<0.05$) at univariate analysis were analyzed by multivariate logistic regression analysis to identify independent risk factors for mortality. The results obtained were analyzed using the software package SPSS 20.0 (IBM, Armonk, NY, USA).

Results

During the study period, therapy with Ceftolozano/Tazobactam was set up in 85 patients: 56 (66%) male, 29 (34%) female, with a median age of 61 years (Table 1). Sixty-nine patients had at least one comorbidity. Among the chronic pathologies, the most frequents were cardiovascular diseases (41%), followed by neurological diseases (22%), diabetes (21%), hematological malignancies (15%), gastrointestinal diseases (14%), COPD (13%), chronic hepatitis (13%), chronic renal failure (12%), solid tumors (9%), neutropenia (7%), solid organ transplantation (2%) and HIV (1%). Of the 8 patients with solid organ tumors, 2 patients had pancreatic cancer, 2 patients tumor from gastrointestinal tract's origin, 1 renal cancer, 1 breast and 1 liver cancer. The Charlson Comorbidity Index (CCI) was greater than 3 in 49 patients, with a median value of 3. The acute comorbidities, which affected patients most frequently, were pneumonia, diagnosed in 46 patients (54%) and septic shock, which affected 10 patients (12%). Acute renal failure was present in two patients. Thirty-nine percent of patients were in an intensive care unit at the time of infection, 20% in a medical ward and 7% in a surgical ward. 30% were at home, three in a rehabilitation facility. As regards pre-infection variables: CVC was present in 60% of the patients, bladder catheter was present in 60% of the patients. Forty-eight percent of patients had undergone steroid therapy in the month preceding the infection. Thirty-eight percent had SNG, 34% required mechanical ventilation, 28% underwent surgical drainage placement, 17% were on immunosuppressive therapy in the month prior to infection, 16% underwent endoscopic maneuvers and 5% had undergone dialysis in the days preceding the infection. There were 26 patients with a positive history of surgery in the three months preceding the infection, i.e. 31%. Of these, 13 underwent gastrointestinal surgery, 5 cardiovascular surgery, 4 neurosurgery, 4 orthopedic surgery, 3 thoracic surgery and 1 plastic surgery. According to the prescription criteria, 34 patients were treated for HAP/VAP (of which 12 had cystic fibrosis), 29 for urinary tract infection, 10 for intra-abdominal infection, 12 patients were treated with the drug in the absence of the indications specified in the prescription form (1 for *P. aeruginosa* endocarditis, 8 for febrile state, 2 for sepsis and 2 for skin infections). Sites of isolation were, in order of frequency: bronchial secretions or pleural fluid (50%), urinary tract (26%), blood (12%), wounds (7%) and peritoneal fluid or abdomen (6%). The isolated bacteria are: *P. aeruginosa* in 61 isolates (72%), *E. coli* ESBL in 10 isolates (12%), *Klebsiella spp* in 5 isolates (6%), no cultures were required in 5 patients (6%) and in 4 patients other bacteria were isolated (5%). Observing the isolates, it is evident that in most cases the infection is due to *P. aeruginosa*, both in males (70%) and in females (74%). Of the total 85 patients, 12 were positive for SARS-CoV-2 (COVID-19), all hospitalized in the ICU, of these 8 were suffering from pneumonia, 3 from urinary tract and only in one case Ceftolozano/Tazobactam was used empirically. Antibiotic therapy had a median duration of 10 days with an IQR ranging from 7 to 13. Ceftolozane/tazobactam monotherapy (72%) was administered in 61 patients, while combination therapy with other antibiotics was set in the remaining patients. In 66% of cases, the infections had nosocomial origin, in 33%, they were polymicrobial and in 40%, there was the detection of other infections in the previous 30 days. Of the 85 ceftolozane/tazobactam-treated patients, 35 experienced clinical treatment failure (41% treatment failure rate), defined as death at 30 days and/or recurrence or persistence of infection. Of these, 18 experienced relapse of infection and 18 died within 30 days of the onset of infection. The median age of this subpopulation is 66 years, higher than the median age of 61 years for the general study population. Nineteen of patients underwent relapse, which is equivalent to 22% of the population under examination. The variable referred to the patient's gender was statistically significant (p 0.034). Among chronic comorbidities, the presence of hematological malignancies and neutropenia were statistically significant, in fact these variables were more frequent in patients who experienced clinical failure, 10 out of 31 patients for hematological malignancies (p 0.011) and 5 of 31 patients for neutropenia (p 0.038). Even chronic hepatitis (p 0.023) was associated with greater clinical success (10 out of 50 patients) and the result is statistically significant. There are no statistically significant difference in the two groups on the other comorbidities. In 68% of subjects with treatment failure, the Charlson Comorbidity Index was greater than 3, while in the population with treatment success it was greater than 3 in 52% of cases, but the p value is not statistically significant. With regard to the response to therapy based on the hospitalization department, surgical patients were those with the best outcome, in fact no surgical patient experienced therapeutic failure, with 12% of successes (p 0.04). Conversely, patients admitted to an intensive care unit had the worst outcome with 57% of treatment failures versus 26% successes (p 0.003). None of the pre-infection variables showed a statistically significant difference. The most frequent acute comorbidities in patients enrolled in the study were pneumonia and septic shock. It is interesting to note that 63% of patients with clinical failure of therapy had pneumonia, versus 48% of patients who were clinically successful. Septic shock was detected in 20% of treatment failures and 6% of treatment successes; therefore, it is more frequent in patients with clinical failure even if it has not reached statistical significance (p 0.084). Finally, acute renal failure was found in 6% of patients with treatment failure. Among the sites of infection, only the variable of bronchial sputum and pleural fluid was statistically significant (p 0.045), in fact 62% of the patients, in whom there was an isolation of pulmonary origin, had clinical failure of the therapy. The other variable that tends towards significance, without however reaching it with a p value of 0.076, is isolation from the urinary tract which in 34% of patients was associated with therapeutic success. The variable referring to the presence of concomitant infections was statistically significant (p 0.036), in fact 46% of the patients who experienced clinical failure of the therapy had a concomitant infection, against 24% of the patients who, on the other hand, had had therapeutic success. The variable of previous infections was not statistically significant with 38% of subjects having therapeutic success versus 3% undergoing clinical failure. In the multivariate analysis, the variables independently associated with the negative outcome were neutropenia

(p 0.020) and ICU stay (p 0.009). To investigate the reason for the higher mortality of patients admitted to the ICU, a second analysis was conducted comparing patients in intensive care and non-intensive care. (Table 2). There were no differences in gender and age between two groups. ICU patients were characterized by multiple serious comorbidities. Cardiovascular diseases, chronic renal failure, neutropenia and GI tract diseases were significantly more present in the group of patients in ICU (with p 0.046, p 0.031, p 0.041 and p 0.019, respectively). Even acute comorbidities with a strong impact on mortality, such as septic shock, were statistically more present in patients admitted to the ICU (p 0.031). As regards factors predisposing infection, patients in intensive care were more often carriers of devices such as CVC (p<0.001), SNG (P<0.001), CV (p<0.001), surgical drainage (p<0.001). Moreover, as can be imagined, patients in the ICU were subjected to mechanical ventilation with a statistically significant difference compared to the others (p<0.001). In addition, CVVH was more frequently used in ICU (p 0.01) and patients in intensive care department were more frequently post-surgery patients (p 0.004). Finally, a comparison of the two groups' shows that in ICU bacteria were isolated more frequently from BAL (p 0.046) and Ceftolozano/ tazobactam was used less frequently in monotherapy (p 0.005). Significantly variables confirmed ad multivariate analysis were the presence of CVC (p 0.021), SNG (p 0.030), concomitant infections (p 0.043) and monotherapy (p 0.047).

Variables	Total (85)	Succesfull clinical outcome (50)	Clinical failure (35)	p univariate	p multivariate
Patients variables					
Male, n° (%)	56 (66)	38 (76)	18 (51)	0.034	
Age (years), (median-IQR)	61(49-73)	61 (47.5-73)	61 (49-73)	0.06	
Charlsons CI >3, n° (%)	49 (58)	26 (52)	23 (68)	0.229	
Comorbidities, n° (%)					
Diabetes	18 (21)	10 (20)	8 (23)	0.962	
COPD	11 (13)	6 (12)	5 (14)	1	
Ematological diseases	13 (15)	3 (6)	10 (29)	0.011	
Solid tumors	8 (9)	7 (14)	1 (3)	0.133	
Chronic hepatitis	11 (13)	10 (20)	1 (3)	0.023	
Cardio-vascular diseases	35 (41)	17 (34)	18 (51)	0.167	
Neurological diseases	19 (22)	11 (22)	8 (23)	1	
Cronic kidney failure	10 (12)	4 (8)	6 (17)	0.305	
HIV	1 (1)	1 (2)	0 (0)	1	
Neutropenia	6 (7)	1 (2)	5 (15)	0.038	0.02
Gastro-intestinal disease	12 (14)	10 (20)	2 (6)	0.111	
Solid organ transplant	2 (2)	1 (2)	1 (3)	1	
Acute comorbidities, n° (%)					
Septic shock	10 (12)	3 (6)	7 (20)	0.084	
Pneumonia	46 (54)	24 (48)	22 (63)	0.176	
Acute kidney failure	2 (2)	0 (0)	2 (6)	0.167	
Hospitalization variables					
Nosocomial infection, n° (%)	56 (66)	30 (60)	26 (74)	0.245	
Wards submitting index culture, n° (%)					
ICU	33 (39)	13 (26)	20 (57)	0.003	0.009
Surgery	6 (7)	6 (12)	0 (0)	0.04	
Medicine	17 (20)	11 (22)	6 (17)	0.783	
Pre-infection variables					
CVC, n° (%)	51 (60)	26 (52)	25 (71)	0.115	
SNG, n° (%)	32 (38)	15 (30)	17 (49)	0.131	
Surgical drainage, n° (%)	24 (28)	14 (28)	10 (29)	1	
Urinary catheter, n° (%)	51 (60)	28 (56)	23 (66)	0.288	
Endoscopy, n° (%) a	13 (16)	9 (18)	4 (12)	0.64	
Mechanical ventilation, n° (%)a	29 (34)	13 (26)	16 (46)	0.098	
CVVH, n° (%)	4 (5)	1 (2)	3 (9)	0.301	
Steroid therapy, n° (%)b	41 (48)	22 (44)	19 (54)	0.476	
Immunosuppressive therapy, n° (%)b,c	14 (17)	5 (10)	9 (26)	0.104	
Previous Surgery, n° (%)d	26 (31)	17 (34)	9 (26)	0.564	
Gastro-intestinal surgery	13 (15)	10 (20)	3 (9)	0.257	
Cardio-vascular surgery	5 (6)	2 (4)	3 (9)	0.399	

Neuro surgery	4 (5)	3 (6)	1 (3)	0.64	
Ortopedic surgery	4 (5)	2 (4)	2 (6)	1	
Plastic surgery	1 (1)	1 (2)	0 (0)	1	
Thoracic surgery	3 (4)	2 (4)	1 (3)	1	
Microbiologic variables					
Pseudomonas aeruginosa	61 (72)	35 (70)	26 (74)	0.665	
Escherichia coli ESBL	10 (12)	6 (12)	4 (11)	1	
Klebsiella spp	5 (6)	2 (4)	3 (9)	0.645	
Empirical use	5 (6)	5 (10)	0 (0)	0.074	
Othere	4 (5)	2 (4)	2 (6)	1	
Sites of isolation, n° (%)					
Urinary tract	21 (26)	16 (34)	5 (15)	0.076	
Bronchial / pleural fluid	40 (50)	19 (40)	21 (62)	0.045	
abdominal fluid	4 (5)	3 (6)	1 (3)	0.64	
wounds	6 (7)	5 (11)	1 (3)	0.393	
blood	10 (12)	4 (9)	6 (17)	0.305	
Other infections, n° (%)					
Previous infections	34 (40)	19 (38)	15 (3)	0.822	
Concomitant infections	28 (33)	12 (24)	16 (46)	0.036	
Days of antibiotic therapy, (median-IQR)	10 (7-13)	10 (7-13)	10 (7-13)	0.515	
Monotherapy, n° (%)	61 (72)	37 (74)	24 (69)	0.39	
Note: IQR: Interquartile range; COPD: Chronic obstructive pulmonary disease; SOT: Solid organ transplantation, CVVH Continuous Veno-Venous Hemofiltration. aDuring the 72-h preceding BSI onset; bDuring the 30 days preceding BSI onset; cExcluding therapy with steroids; dDuring the 3 months preceding BSI onset; eOthers 3 Stenotrophomonas maltophilia and 1 Haemophilus paraeinfluenzae; n° (%): Mean percentage					

Table 1: Comparison of patients based on days of RDV therapy.

Variables	Total (85)	ICU (33)	Non-ICU (52)	p univariate	p multivariate
Patients variables					
Male, n°(%)	56 (66)	22 (66)	34 (65)	0.903	
Age (years), (median-IQR)	61(49-73)	61(47-73)	61(49-73)	0.371	
Charlsons CI >3, n° (%)	49 (58)	20 (60)	29 (55)	0.543	
Comorbidities , n° (%)					
Diabetes	18 (21)	6 (18)	12 (23)	0.59	
COPD	11 (13)	5 (15)	6 (11)	0.629	
Ematological diseases	13 (15)	5 (15)	8 (15)	0.59	
Solid tumors	8 (9)	2 (6)	6 (11)	0.399	
Chronic Hepatitis	11 (13)	2 (6)	9 (17)	0.132	
Cardio-vascular Diseases	35 (41)	18 (54)	17 (32)	0.046	
Neurological diseases	19 (22)	5 (15)	14 (27)	0.204	
Cronic kidney failure	10 (12)	7 (21)	3 (6)	0.031	
HIV	1 (1)	0 (0)	1 (2)	1	
Neutropenia	6 (7)	0 (0)	6 (11)	0.041	
Gastro-intestinal diseases	12 (14)	1 (3)	11(21)	0.019	
Solid organ transplant	2 (2)	0 (0)	2 (4)	0.254	
Acute comorbidities, n° (%)					
Septic shock	10 (12)	6 (18)	2 (4)	0.031	
Pneumonia	46 (54)	22 (66)	15 (28)	0.64	
Acute kidney failure	2 (2)	1 (3)	1 (2)	0.743	
Hospitalization variables					
Nosocomial infection, n° (%)	56 (66)	33 (100)	23 (44)	0.123	
Pre-infection variables					
CVC, n° (%)	51 (60)	32 (97)	19 (36)	<0.001	0.021
SNG, n° (%)	32 (38)	25 (75)	7 (13)	<0.001	0.03
Surgical drainage, n° (%)	24 (28)	17 (51)	7 (13)	<0.001	
Urinary catheter, n° (%)	51 (60)	32 (97)	20 (38)	<0.001	
Endoscopy, n° (%)	13 (16)	3 (9)	10 (19)	0.193	

Mechanical ventilation, n° (%)	29 (34)	26 (79)	3 (6)	<0.001	
CVVH, n° (%)	4 (5)	4 (12)	0 (0)	0.01	
Steroid therapy, n° (%)	41 (48)	20 (60)	21 (40)	0.069	
Immunosuppressive therapy, n° (%)	14 (17)	4 (12)	10 (19)	0.389	
Previous Surgery, n° (%)	26 (31)	16 (48)	10 (19)	0.004	
Gastro-intestinal surgery	13 (15)	6 (18)	7 (13)	0.556	
Cardio-vascular surgery	5 (6)	4 (12)	1 (2)	0.051	
Neuro surgery	4 (5)	2 (6)	2 (4)	0.638	
Ortopedic surgery	4 (5)	4 (12)	0 (0)	0.01	
Plastic surgery	1 (1)	0 (0)	1 (2)	0.423	
Thoracic surgery	3 (4)	2 (6)	1 (2)	0.314	
Microbiologic variables					
Pseudomonas aeruginosa	61 (72)	26 (78)	35 (67)	1.936	
Escherichia coli ESBL	10 (12)	4 (12)	6 (11)	0.935	
Klebsiella pneumoniae KPC	5 (6)	0 (0)	5 (10)	0.075	
Empirical use	5 (6)	2 (6)	3 (6)	0.955	
other	4 (5)	1 (3)	3 (6)	0.561	
Sites of isolation					
Urinary tract	21 (26)	9 (27)	14 (27)	0.904	
Bronchial/pleural fluid	40 (50)	20 (60)	20 (38)	0.046	
abdominal fluid	4 (5)	1 (3)	3 (6)	0.561	
wounds	6 (7)	0 (0)	6 (11)	0.847	
blood	10 (12)	3 (10)	7 (13)	0.574	
Other infections, n° (%)					
Previous infections	34 (40)	17 (51)	17 (32)	0.084	
Concomitant infections	28 (33)	18 (54)	9 (17)	0.084	0.043
Days of antibiotic therapy, (median-IQR)	10 (7-13)	10 (7-13)	10 (7-13)	0.351	
Monotherapy, n° (%)	61 (72)	15 (45)	46 (88)	0.005	0.047

Note: IQR: Interquartile range; COPD: Chronic obstructive pulmonary disease; SOT: Solid organ transplantation, CVVH: Continuous Veno-Venous Hemofiltration; aDuring the 72-h preceding BSI onset; bDuring the 30 days preceding BSI onset; cExcluding therapy with steroids; dDuring the 3 months preceding BSI onset; eOthers: 3 Stenotrophomonas maltophilia and 1 Haemophilus paraeinfluenzae; n° (%): Mean percentage

Table 2: Demographic and clinical characteristics of ICU patients.

Discussion

The clinical success achieved in patients treated with ceftolozane/ tazobactam in this coorte is 59%. In literature, the success rate of clinical treatment is between 58% and 77% [11-13]. The variability is linked to the different populations enrolled in the studies, but also to the type of isolate, the site of the infection and also to the criteria used. In our study, the clinical isolate most frequently treated with Ceftolozane/ Tazobactam is *P. aeruginosa*, used also against *E. coli* ESBL, *Klebsiella spp*. and other clinical isolates in 5%. The technical data sheet of the drug and numerous scientific evidences confirm the effectiveness of the molecules against these agents [14,15]. An empirical use of Ceftolozane/ Tazobactam was also made in a consistent percentage of cases. This is also a common and approved use of this drug, in particular in a high settings or departments known to be endemic [16]. In univariate analysis, male gender was found to be a positive prognostic factor. This result probably depends on the preponderance of males in the study population. Hospitalization in ICU, represents a negative prognostic factor in this study, on the contrary, permanence in the surgical ward was a protective factor, both reaching statistical significance. These data can be explained by the surgeons' habit of promptly referring to the infectious disease specialist for both empirical and targeted antibiotic therapies during an infection, reducing the patient's exposure to ineffective therapies. Patients admitted to intensive care are often affected by polymicrobial infections, which contribute to aggravating a clinical picture that is already compromised from the start [17]. Patients with hematological malignancy and neutropenia were statistically related with a worst outcome. These correlations can be explained by a general state of immunosuppression, which does not allow the patient's immune system to guarantee a synergistic action with the antibiotic against the bacterial infection [18,19] . However, as confirmed by the study by Coppola et al. in patients with hematological malignancies, including neutropenic patients, ceftolozane/tazobactam was more effective and well tolerated than alternative therapies for *P. aeruginosa* infection [20]. Bronchial and pleural fluid were the isolation sites significantly related to a negative prognostic factor. This can be explained by the difficulty of the antibiotic to reach the pulmonary epithelium, as found in the study by Boisson, et al. [21]. Having multiple concurrent infections has a statistically significant correlation with a negative outcome. Again, patients with multiple infections were severely compromised, and clinical isolates revealed different bacteria at multiple sites of infection (eg, complicated urinary tract infection associated with nosocomial pneumonia) [22,23]. A high rate of relapse (21%) was observed in this study. Observing the characteristics of this subpopulation, a median age of 55 years and a Charlson Comorbidity Index >3 are found in 50% of cases. This result could depend on the heterogeneity of the population or on the delay in starting therapy. In fact, in 66% of the patients with relapse, another empiric therapy had already been set up previously and it may have lengthened the prescribing time for ceftolozane/tazobactam. The median time between positive culture and prescription was 9 days

in the general population, whereas in patients who experienced relapse it was 11 days. The comparative analysis between patients treated with Ceftoloxano/Tazobactam in ICU to other wards shows that probably the higher mortality of patients referred to an intensive care unit is linked to the characteristics of the patients. In fact, these are patients with multiple and serious comorbidities that are highly lethal in themselves. Moreover, the fact of being recovering from surgery, being carriers of devices (CV, CVC, SNG, drainage) makes them more susceptible to colonization which, following immunosuppression or prolonged hospitalization, can become real infections [24,25]. There are instead no differences in the type of isolated bacteria or in the management of the antibiotic therapy. An exception is the use of Ceftolozano/Tazobactam in monotherapy, which is not widespread in the ICU. The data can be explained by a habit of managing patients that are more complex and with co-infections and preferring a broad-spectrum therapy. It is important to consider that in the period under review, many of the patients were COVID positive and this made their management even more difficult and the access to the intensive care unit of patients with cystic fibrosis that are often colonized by MDR bacteria.

Conclusion

Ceftolozano/tazobactam represents a therapy of choice in infections by Gram-MDR bacteria, also in witch with multiple comorbidity and long hospital stay. From the results, emerges the importance of implement antimicrobial stewardship practices. Particularly in medical wards and endemic ICUs, the early initiation of an anti-MDR therapy could provide an advantage in preventing relapse. Patients with pneumonia deserve particular attention, in which the choice of Ceftalozane/Tazobactam and in particular of antibiotics with good alveolar penetration should be started early. This study has several limitations. The first limitation is that it is a retrospective study, so for example patients that had continued their hospitalization in extra-hospital facilities, collection data could be challenging and inaccurate. Furthermore, it is a single-center study, conducted on a limited number of patients, so more studies are needed to confirm this data results. This study could be considered as a starting point for further prospective studies.

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