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Piperacillin/Tazobactam- and Cefepime-Based Therapy in Hospitalized Patients and the Risk of Subsequent Isolation of Multidrug-Resistant Organisms

Krystina Woods, MD, Tomasz Jodlowski, PharmD, Manuel Revuelta, MD, Donna Mildvan, MD, David C. Perlman, MD, Jörg Ruhe, MD, MPH

Division of Infectious Diseases, Beth Israel Medical Center, Albert Einstein College of Medicine, New York, NY

Jörg Ruhe, MD MPH
Division of Infectious Diseases
Beth Israel Medical Center
First Avenue at 16th Street
New York, NY 10003
Phone: (212) 420-4005
Fax : (212) 420-4498
Email: jruhe@chpnet.org

Abstract

Introduction: Piperacillin/tazobactam (PT) and Cefepime (CEF) are both frequently used and effective broad-spectrum agents for the treatment of healthcare-associated infections. Few comparative data exist on the rates of subsequent isolation of multidrug-resistant organisms (MDRO) from clinical specimens in PT- and CEF-treated patients (pts).

Methods: A retrospective cohort study was performed on all adult hospitalized pts who received PT or CEF (=target agents) for at least five days at a tertiary care medical center before, during, and after a hospital-wide replacement of PT with CEF as the preferred broad-spectrum ß-lactam. Zero time (ZT) was defined as the day therapy was started. Pts treated with PT were compared to pts treated with CEF with regard to a variety of characteristics. The primary outcome was the subsequent colonization or infection with MDRO.

Results: A total of 236 pts were included. The median age was 67 years, 145 (61%) were male. The median Charlson comorbidity score was 2. 132 (56%) pts were treated with PT, and 104 (44%) pts were treated with CEF. Both cohorts were very similar with regard to a variety of demographic and clinical characteristics (P>0.2). MDRO (MRSA:n=18; VRE:n=6; GNR:n=21; *Cdiff*:n=13) were isolated from 27 (21%) PT-treated pts and 24 (23%) CEF-treated pts at a median of 11 days after ZT (P=0.63). Metronidazole use was more common in CEF pts, but not associated with MDRO including *Cdiff* (P>0.20). On logistic regression analyses, independent predictors of subsequent isolation of MDRO were: Length of stay between ZT and 90 days, previous stay in long-term care facility, and surgery between ZT and 90 days (P<0.05).

Conclusions: Treatment with PT and CEF resulted in similar risk of subsequent MDRO isolation.

Introduction

Selective pressure exerted by the administration of broad-spectrum antimicrobials has been associated with the emergence of multidrug-resistant organisms such as MRSA, VRE, ESBL- and carbapenemase-producing gram-negatives, and *C. difficile* in multiple studies[1-5].

Piperacillin/tazobactam (PT) and Cefepime (CEF) are both frequently used and effective broad-spectrum agents for the treatment of healthcare-associated infections. Few comparative data exist on the rates of subsequent isolation of multidrug-resistant organisms (MDRO) from clinical specimens in PT- and CEF-treated patients.

Methods

A retrospective cohort study was performed on all hospitalized adult patients who received PT or CEF (=target agents) for at least five days at a tertiary care medical center before (6/2010 and 7/2010), during (8/2010 and 9/2010), and after (10/2010 and 11/2010) a hospital-wide replacement of PT with CEF as the preferred broad-spectrum ß-lactam.

Zero time (ZT) was defined as the day therapy with a target agent was started. Patients treated with PT were compared to patients treated with CEF with regard to a variety of demographic and clinical characteristics.

Methods (continued)

The **primary outcome** was the subsequent colonization or infection with MDRO including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), gram-negatives resistant to >3 drug classes (GNR), or *Clostridium difficile* (*Cdiff*) within the next 90 days.

Exclusion criteria: Patients with MDRO isolated prior to or at ZT, patients treated with <5 days of target agent, patients on additional broad-spectrum agents administered during target agent therapy, patients with sequential therapy (i.e., switch from one target agent to the other), and incomplete medical records. Concomitant vancomycin (VAN) or metronidazole (MET) therapy was permitted.

Bivariate analyses using the Pearson's χ^2 test, the Fisher's exact test, and the Mann-Whitney U test were performed to compare categorical and continuous variables, respectively. Logistic regression models were used to determine independent predictors of subsequent isolation of MDRO (P<0.05); variables with a P<0.2 on bivariate analyses and plausible interaction terms were entered into the model.

Results

A total of 959 hospitalized adult patients were treated with either PT or CEF during the observation period. 723 patients were excluded due to: Prior MDRO (n=131), less than 5 days of target agent therapy (n=324), use of additional concurrent antibiotics (n=188), sequential therapy (n=66), and incomplete medical records (n=14).

The final cohort consisted of 236 patients. The median age of the cohort was 67 years, 145 (61%) were male. The median Charlson comorbidity score was 2. 132 (56%) patients were treated with PT, and 104 (44%) patients were treated with CEF. Both cohorts were very similar with regard to a variety of characteristics including age, length of stay (LOS), type of service, ICU stay, comorbidities, indication for and duration of target therapy, VAN use, and mortality (P>0.2; Table 1). Concurrent MET use was more common in CEF pts (P<0.001). **MDRO** (MRSA: n=18; VRE: n=6; GNR: n=21; *Cdiff*: n=13) **were isolated from 27 (21%) PT-treated patients and 24 (23%) CEF-treated patients** at a median of 11 days after ZT **(P=0.63)**. In a subgroup analysis that compared patients treated with PT to patients treated with both CEF and MET, rates of subsequent isolation of any MDRO and *Cdiff* specifically did not differ (P>0.2).

Results (continued)

Table 1. Comparison of demographic and clinical characteristics between hospitalized patients treated with piperacillin/tazobactam and hospitalized patients treated with cefepime (N=236)

Characteristics	Piperacillin/ tazobactam (N=132); n (%)	Cefepime (N=104) n (%)	Odds ratio (95% CI)	P
Age, median	68	65	---	>0.20
Male sex	79 (60)	66 (63)	0.86 (0.51-1.46)	>0.20
Medical ward (vs. surgical ward) at ZT	90 (68)	79 (76)	0.68 (0.38-1.21)	0.19
ICU stay (current admission)	44 (33)	41 (39)	0.77 (0.45-1.31)	>0.20
LOS current admission, median days	12	12	---	>0.20
LOS ZT to 90d, median days	16	14	---	>0.20
Hospitalization during previous 90 days	45 (34)	42 (40)	0.76 (0.45-1.30)	> 0.20
LTCF during previous 90 days	11 (8)	8 (8)	1.09 (0.42-2.82)	>0.20
Underlying comorbidities				
Charlson score, median	2	2	---	>0.20
COPD or asthma	22 (17)	20 (19)	0.84 (0.43-1.64)	>0.20
HIV	10 (8)	14 (14)	0.53 (0.22-1.24)	0.14
Diabetes mellitus	33 (25)	32 (31)	0.75 (0.42-1.33)	>0.20
ESRD	7 (5)	2 (2)	2.86 (0.58-14.05)	0.18
ESLD	3 (2)	3 (3)	0.78 (0.16-3.96)	>0.20
Leukemia/lymphoma	5 (4)	7 (7)	0.55 (0.17-1.77)	>0.20
Current solid malignancy	36 (27)	20 (19)	1.58 (0.85-2.93)	0.15
Peripheral vascular disease	13 (10)	17 (16)	0.56 (0.26-1.21)	0.14
Chronic neurological disease	15 (11)	12 (12)	0.98 (0.44-2.20)	>0.20
Indications for antibiotics				
Pneumonia	48 (36)	36 (35)	1.09 (0.64-1.87)	>0.20
Skin and soft tissue infections/bone	26 (20)	20 (19)	1.04 (0.54-1.99)	>0.20
Intra-abdominal infection	26 (20)	9 (9)	2.61 (1.12-5.86)	**0.02**
Empiric	27 (21)	23 (22)	0.91 (0.49-1.71)	>0.20
Microbiological data				
Median nr. of cultures done (ZT to 90 days)	6	6	---	>0.20
Susceptible organism isolated (ZT to 90 days)	40 (30)	23 (22)	1.53 (0.85-2.77)	0.16
MDRO isolated (ZT to 90 days)	**27 (21)**	**24 (23)**	**0.86 (0.46-1.60)**	**0.63**
Median number of days to isolation of MDRO (range)	11 (2 – 61)	11 (2-63)	---	>0.20
MRSA	12 (9)	6 (6)	1.63 (0.59-4.51)	>0.20
VRE	3 (2)	3 (3)	0.78 (0.16-3.96)	>0.20
MDR gram-negative	10 (8)	11 (11)	0.42 (0.28-1.70)	>0.20
Clostridium difficile	6 (5)	7 (7)	0.66 (0.22-2.03)	>0.20
Therapy and outcome				
Median duration of therapy, days (range)	7 (5-36)	8 (5-34)	---	>0.20
Concomitant metronidazole use for ≥5 days	16 (12)	43 (41)	0.20 (0.10-0.38)	**<0.001**
Concomitant vancomycin use for ≥5 days	75 (57)	70 (67)	0.64 (0.37-1.09)	0.10
Surgery between ZT and 90d	32 (24)	21 (20)	1.27 (0.68-2.36)	>0.20
Mortality	18 (14)	14 (14)	1.02 (0.48-2.15)	>0.20

ZT, zero time; LTCF, long-term care facility; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; ESLD, end-stage liver disease; MDRO, multidrug-resistant organism

Patients from whom MDRO were subsequently isolated were then compared to patients from whom no MDRO was isolated (Table 2). Concurrent MET use was not associated with the subsequent isolation of MDRO including *Cdiff* (P=0.36).

Table 2. Comparison of demographic and clinical characteristics between hospitalized patients with subsequent colonization or infection with MDRO and hospitalized patients without subsequent colonization or infection with MDRO (N=236)

Characteristics	MDRO (N=51); n (%)	No MDRO (N=185) n (%)	Odds ratio (95% CI)	P
Age, median	67	66	---	>0.20
Medical ward (vs. surgical ward) at ZT	33 (65)	136 (74)	0.66 (0.34-1.28)	>0.20
ICU stay (current admission)	21 (41)	64 (35)	1.32 (0.70-2.50)	>0.20
LOS ZT to 90d, median days	27	13	---	**<0.0001**
Hospitalization during previous 90 days	14 (28)	73 (40)	0.58 (0.29-1.15)	0.12
LTCF during previous 90 days	8 (16)	11 (6)	2.94 (1.12-7.76)	**0.02**
Underlying comorbidities				
Charlson score, median	2	2	---	>0.20
COPD or asthma	10 (20)	32 (17)	1.17 (0.53-2.57)	>0.20
HIV	6 (12)	18 (10)	1.24 (0.46-3.30)	>0.20
Diabetes mellitus	20 (39)	45 (24)	2.00 (1.04-3.86)	**0.04**
ESRD	5 (10)	4 (2)	4.92 (1.27-19.05)	**0.01**
ESLD	1 (2)	5 (3)	0.72 (0.08-6.31)	>0.20
Leukemia/lymphoma	3 (6)	9 (5)	1.22 (0.32-4.69)	>0.20
Current solid malignancy	13 (26)	43 (23)	1.13 (0.55-2.31)	>0.20
Peripheral vascular disease	8 (16)	22 (12)	1.38 (0.57-3.31)	>0.20
Chronic neurological disease	9 (18)	18 (10)	1.99 (0.83-4.74)	0.12
Indications for antibiotics				
Pneumonia	20 (39)	64 (35)	1.21 (0.64-2.29)	>0.20
Skin and soft tissue infections/bone	13 (26)	33 (18)	1.57 (0.75-3.26)	>0.20
Intra-abdominal infection	6 (12)	29 (16)	0.71 (0.28-1.82)	>0.20
Empiric	7 (14)	43 (23)	0.52 (0.22-1.24)	0.14
Therapy and outcome				
Median duration of therapy, days (range)	9 (5-34)	7 (5-36)	---	**0.02**
Concomitant metronidazole use for ≥5 days	15 (29)	44 (24)	1.34 (0.67-2.66)	>0.20
Concomitant vancomycin use for ≥5 days	36 (71)	109 (59)	1.67 (0.86-3.27)	0.13
Surgery between ZT and 90d	21 (41)	32 (17)	3.35 (1.70-6.58)	**<0.001**
Piperacillin/tazobactam use	27 (53)	105 (57)	0.86 (0.46-1.60)	**0.63**
Mortality	9 (18)	23 (12)	1.51 (0.65-3.50)	>0.20

MDRO, multidrug-resistant organism; ZT, zero time; LTCF, long-term care facility; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; ESLD, end-stage liver disease;

On logistic regression analyses (Table 3), **independent predictors of subsequent isolation of MDRO** were: Length of stay between ZT and 90 days, previous stay in long-term care facility, and surgery between ZT and 90 days (P<0.05)

Table 3. Independent predictors of subsequent isolation of MDRO on logistic regression analysis (N=236)

Risk Factor	Adjusted Odds Ratio (95% CI)	P
Length of stay (ZT to 90 days)	1.06 (1.03-1.08)	**<0.001**
Previous stay in LTCF	3.49 (1.21-10.12)	**0.02**
Surgery (ZT to 90 days)	2.31 (1.07-4.99)	**0.03**

MDRO, multidrug-resistant organism; LTCF, long-term care facility

Conclusion

Hospitalized patients treated with PT and CEF did not differ significantly with regard to a variety of important clinical characteristics in our study; the use of PT and CEF resulted in similar risk of subsequent MDRO isolation.

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