Carbapenem versus Piperacillin-tazobactam for the treatment of ceftriaxone resistant gram negative bacteremia: matched cohorts by propensity score

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Background: Treatment of bacteremia caused by ESBL producing organisms remains controversial

Methods: Kaiser Permanente Northern California delivers care to 4 million members and is served by a centralized microbiological laboratory & an electronic medical record system. We identified patients hospitalized with a positive blood culture for ceftriaxone resistant *Escherichia coli*, Klebsiella and *Proteus mirabilis* between Jan 2008 and Dec 2015

Patients were grouped as:
Piperacillin-tazobactam (PTZ) group: received PTZ (and not carbapenem) OR initial therapy with PTZ followed by a switch to a carbapenem

Carbapenem group: received carbapenem (and not PTZ) OR initial therapy with carbapenem followed by a switch to PTZ

Patients could have received alternate antibiotics prior to a switch to PTZ or carbapenems. All isolates were resistant to ceftriaxone and susceptible to carbapenems and PTZ by in-vitro testing. Blood Stream Infection Mortality Risk Score (BSIMRS) was calculated for the 48 hour period of the positive blood culture.

Patients in the carbapenem group were matched 1:1 to patients in the PTZ group using a propensity score, which indicated the adjusted probability of being in the carbapenem group. Odds Ratio (OR) was calculated for 14 day mortality

Results: **Tables 1** & **2** depict the patient characteristics of the actual and propensity score matched cohorts, respectively

Table 1. Persons hospitalized with ceftriaxone-resistant PEK blood stream infection who were treated with either carbapenems or piperacillin-tazobactam, entire cohort, 2008-2014. Kaiser Permanente Northern California.[a]

	Initial antibiotic treatment[b]	
Characteristic	Piperacillin-Tazobactam (n=307)	Carbapenem (n=219)
Gender		
Female	138 (44.95)	113 (51.60)
Male	169 (55.05)	106 (48.40)
Age, mean (median) in years	70.84 (73.60)	72.22 (74.40)
Bacteria type		
Escherichia coli	251 (81.76)	196 (89.50)
Klebsiella	25 (8.14)	15 (6.85)
Proteus mirabilis	31 (10.10)	8 (3.65)
Charlson comorbidity score		
0	55 (17.92)	40 (18.26)
1	36 (11.73)	19 (8.68)
2	36 (11.73)	30 (13.70)
3+	180 (58.63)	130 (59.36)
Blood stream infection mortality risk score > 5	110 (35.83)	31 (14.16)
Source of infection		
Urine/line	195 (63.52)	183 (83.56)
Abdomen	63 (20.52)	19 (8.68)
Other	14 (4.56)	5 (2.28)
Unknown	35 (11.40)	12 (5.48)
Hours from index culture to initiation of carbapenem or PTZ, mean (median)	7.58 (2.85)	16.40 (9.15)
PEK bloodstream relapse infection, 5 to 30 days after index date	8 (2.61)	1 (0.46)
Clostridium difficile infection within 90 days after index date	23 (7.49)	19 (8.68)
Death within 14 days of index date	41 (13.36)	11 (5.02)
Death within 30 days of index date	51 (16.61)	23 (10.50)

[a] Study cohort consisted of all persons hospitalized within 48 hours of having a blood specimen positive for ceftriaxone-resistant PEK who were treated with either carbapenems or piperacillin-tazobactam within 48 hours the time the specimen was obtained. The index date was the order date of the positive PEK specimen. Unless otherwise indicated, all cells indicate number (percent) of infections.

[b] Indicates which of these two antibiotics - piperacillin-tazobactam (PTZ) or carbapenem - was first administered to the patient in the 24 hours prior, to 48 hours after, the index date. Patients could have received other antibiotics prior to the initiation of PTZ or carbapenem. Of the 307 patients who initiated with PTZ, 226 were subsequently given carbapenem, and of the 219 who initiated carbapenem, 9 were subsequently given PTZ.

Table 2. Persons hospitalized with ceftriaxone-resistant PEK blood stream infection who were treated with either carbapenems or piperacillin-tazobactam, propensity-score matched cohort, 2008-2014. Kaiser Permanente Northern California.[a]

	Initial antibiotic treatment[b]	
Characteristic	Piperacillin-Tazobactam (n=149)	Carbapenem (n=149)
Gender		
Female	74 (49.66)	66 (44.30)
Male	75 (50.34)	83 (55.70)
Age, mean (median) in years	72.90 (75.04)	72.43(74.40)
Bacteria type		
Escherichia coli	132 (88.59)	130 (87.25)
Klebsiella	12 (8.05)	11 (7.38)
Proteus mirabilis	5 (3.36)	8 (5.37)
Charlson comorbidity score		
0	29 (19.46)	25 (16.78)
1	15 (10.07)	14 (9.40)
2	18 (12.08)	18(12.08)
3+	87 (58.39)	92 (61.74)
Blood stream infection mortality risk score > 5	30 (20.13)	28 (18.79)
Immunocompromised [c]	35 (23.49)	37(24.83)
Source of infection		
Urine/line	121 (81.21)	120 (80.54)
Abdomen	15 (10.07)	17 (11.41)
Other	1 (0.67)	4 (2.68)
Unknown	12 (8.05)	8 (5.37)
Hours from index culture to initiation of carbapenem or PTZ, mean (median)	11. 42 (3.92)	11.93 (4.25)
PEK bloodstream relapse infection, 5 to 30 days after index date	3 (2.01)	0 (0.00)
Clostridium difficile infection within 90 days after index date	12 (8.05)	10 (6.71)
Death within 14 days of index date	12 (8.05)	10 (6.71)
Death within 30 days of index date	17 (11.41)	20 (13.42)

[a] Study cohort consisted of all persons hospitalized within 48 hours of having a blood specimen positive for ceftriaxone-resistant PEK who were treated with either carbapenems or piperacillin-tazobactam within 48 hours the time the specimen was obtained. The index date was the order date of the positive PEK specimen. Unless otherwise indicated, all cells indicate number (percent) of infections. Propensity score methods were used to match PTZ initiators with carbapenem initiators 1:1.

[b] Indicates which of these two antibiotics - piperacillin-tazobactam (PTZ) or carbapenem - was first administered to the patient in the 24 hours prior, to 48 hours after, the index date. Patients could have received other antibiotics prior to the initiation of PTZ or carbapenem. Of the 168 patients who initiated with PTZ, 131 were subsequently given carbapenem, and of the 168 who initiated carbapenem, 6 were subsequently given PTZ.

[c] Patients who were diagnosed with cancer (excluding non-melanoma skin cancer), had an organ or tissue transplant, or were prescribed steroids, methotrexate, cyclosporine, monoclonal antibodies, mycophenolate mofetil, tumor necrosis factor-α (TNF) blockers, abatacept, anakinra, rituximab, or tocilizumab in the year before their index date were classified as being immunocompromised

Results: Table **3**: Odds Ratio* for adverse outcomes in PTZ group compared to carbapenem group in propensity scored matched cohort

Outcome	Odds Ratio with 95% Confidence Interval	P value
Death in 14 days from index date	1.22 (0.46, 3.34)	0.66
Death in 30 days from index date	0.81 (0.36, 1.80)	0.58
Clostridium difficile infection within 90 days of index date	1.20 (0.48, 3.10)	0.67

*Odds Ratio calculated using conditional logistic regression modeling with hospital facility and hours from draw of blood culture to imitation of PTZ or carbapenem included as variables

Conclusions:

- There was no significant difference in the 14 day and 30 day mortality rates between PTZ and carbapenems in the propensity score matched cohort
- Clostridium difficile infection rates were similar between PTZ and carbapenem groups within 90 days of index blood stream infection