Treatment Outcomes in Piperacillin-tazobactam Non-susceptible (TZP-NS)/Ceftriaxone Susceptible (CRO-S) Infections

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BACKGROUND

- Approximately 30% of healthcare-associated infections are caused by Enterobacterales, for which ceftriaxone (CRO) and piperacillin-tazobactam (TZP) are common empiric treatment options
- The emergence of TZP-NS/CRO-S *Escherichia coli* (*Ec*) and *Klebsiella pneumoniae* (*Kp*), has been described in recent epidemiologic studies (4.2%) with limited data comparing carbapenem vs carbapenem-sparing therapies
- *In vitro* studies have hypothesized the mechanism of resistance to result from hyperproduction of Ambler class A (TEM-1/2 and SHV-1) penicillinases, overcoming the inhibitory effect of tazobactam via saturation
- Given the unique resistance pattern and lack of clinical data for carbapenem-sparing treatment options, this may lead to unnecessary carbapenem use
- Overuse of carbapenems may result in an increased risk for drug resistance and *Clostridioides difficile* infection (CDI)

OBJECTIVE

To compare treatment outcomes for patients with TZP-NS/CRO-S *Ec* and *Kp* infections when using carbapenem vs carbapenem-sparing regimens

METHODS

- **Study Design**
  - Multicenter, IRB approved, retrospective chart review (NYULH – Tisch, Brooklyn, and Orthopedic hospitals)
  - Microbiology lab culture data with *Ec* and/or *Kp* isolates with TZP-NS/CRO-S phenotype
- **Inclusion Criteria**
  - Age ≥ 21 years old
  - Infection with TZP-NS/CRO-S phenotype
  - Received at least 48h of inpatient carbapenem vs non-carbapenem agents as targeted therapy
- **Exclusion Criteria**
  - Emergency department and/or observational unit stay only
  - Admitted for < 48 hours
  - Admitted to the intensive care unit (ICU) within 72 hours of culture collection
  - Concomitant infection with multidrug-resistant gram-negative organisms
- **Data Collection**
  - Baseline demographics, past medical history, clinical characteristics, microbiology data, details of the treatment course including antimicrobials, dose, frequency, and duration
- **Outcomes**
  - **Primary:** composite of in-hospital mortality, need for escalation to ICU, infection- or treatment-related readmission, and infection recurrence
  - **Secondary:** evaluated individual components of the primary endpoint, intravenous (IV) to oral (PO) switch, infection-related length of stay (LOS), and CDI within 30 days

Table 1. Definitions

Definitions	
Empiric therapy	Antimicrobial agent with potential activity against Enterobacterales that was administered for the greatest portion of the first 48 hours form date of culture collection
Targeted therapy	Antimicrobial agent with *in vitro* activity against the *Ec* and *Kp* isolate that was administered for the greatest portion of time between 48 hours after culture collection and the end of the inpatient index treatment course
Infection-related readmission*	Hospitalization within 30 days of discharge relate to previous or new infection
Treatment-related readmission*	Hospitalization within 30 days of discharge related to complications of the antimicrobial treatment course, including antibiotic toxicity, antibiotic non-adherence, or hardware complications
Infection-related LOS	Calculated from date of culture collection to discharge date

*both readmission variables excluded admissions to hospice or rehabilitation

RESULTS

Table 2. Baseline Characteristics

Variables	Total N=200	Carbapenem n=51	Carbapenem-sparing n=149	P-value
Age, years, median (IQR)	69 (52-82)	65 (52-74)	72 (56-82)	0.059
Male	101 (51)	29 (57)	72 (48)	0.292
Actual weight, kg, median (IQR)	71 (59-91)	72 (60-91)	71 (59-85)	0.402
BMI, median (IQR)	26 (22-30)	26 (22-30)	26 (22-30)	0.820
Comorbidities & Hospital Exposures				
Diabetes mellitus	83 (42)	18 (35)	65 (44)	0.297
Moderate to severe chronic kidney disease	54 (27)	17 (33)	37 (25)	0.238
Chronic obstructive pulmonary disease	41 (21)	14 (28)	27 (18)	0.154
Immunocompromised	**31 (16)**	**15 (29)**	**16 (11)**	**0.001**
Charlson comorbidity index, median (IQR)	6 (3-10)	6 (3-10)	6 (4-9)	0.640
COVID-19 infection during admission	6 (3)	1 (2)	5 (3)	1.000
Time to culture from admission, days, median (IQR)	**1 (0-9)**	**2 (2-9)**	**1 (0-4)**	**0.006**
Hospitalization in last 90 days	65 (33)	19 (37)	46 (31)	0.401
Hospital length of stay, days, median (IQR)	**11 (6-26)**	**14 (8-26)**	**10 (6-18)**	**0.006**

All data presented as n (%) unless otherwise specified; IQR interquartile range; Immunocompromised is defined as having leukemia, lymphoma, AIDs, solid organ transplant, or hematopoietic stem cell transplant

Figure 1. Microbiology

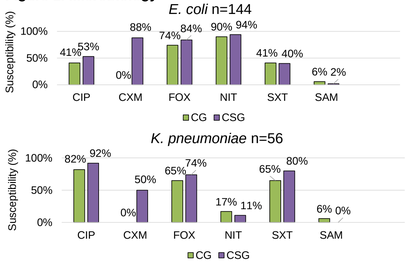
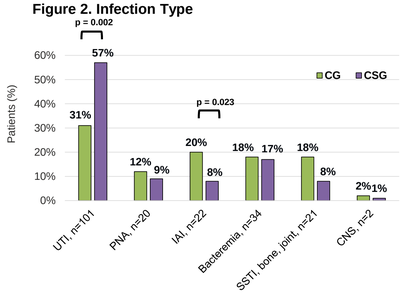


Figure 2. Infection Type



All data presented as (%) susceptible; CIP: ciprofloxacin; CXM: cefuroxime; FOX: cefoxitin; NIT: nitrofurantoin; SXT: sulfamethoxazole-trimethoprim; SAM: ampicillin-sulbactam; CG: carbapenem group; CGS: carbapenem-sparing group; UTI: urinary tract infection; PNA: pneumonia; IAI: intra-abdominal infection; SSTI: skin and soft tissue infection; CNS: central nervous system infection

Table 3. Empiric and Targeted Therapies

	Carbapenem, n=51	Carbapenem-sparing, n=149	P-value
Empiric therapy			
Piperacillin-tazobactam	35 (69)	56 (38)	<0.001
Ceftriaxone	3 (6)	53 (36)	<0.001
Inpatient targeted therapy			
Meropenem	45 (88)	-	-
Ertapenem	6 (12)	-	-
Ceftriaxone	-	87 (58)	-
Cefepime	-	36 (24)	-

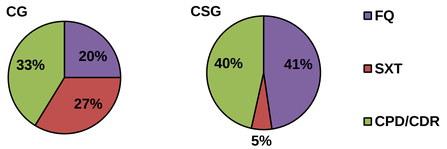
All data presented as n(%) unless otherwise specified; Other carbapenem-sparing inpatient targeted therapy: Fluoroquinolone 20 (13); Aztreonam 4 (3); SXT 1 (1)

Table 4. Primary and Secondary Outcomes

Variables	Carbapenem n=51	Carbapenem-sparing n=149	P-value
Primary composite outcome[1]	14(28)	26 (17)	0.123
In-hospital mortality	7 (14)	11 (7)	0.254
Escalation to ICU	4 (8)	3 (2)	0.072
Infection-related readmission	3 (6)	11 (7)	1
Treatment-related readmission	1 (2)	1 (0.7)	0.446
Infection recurrence within 30 days	2 (4)	5 (3)	1
LOS after positive culture, days, median (IQR)[2]	9 (6-17)	8 (6-13)	0.207
CDI rate	0	0	-
IV to PO switch[3]	**15 (29)**	**100 (67)**	**<0.001**
UTI	8/16 (50)	59/85 (69)	0.132
Bacteremia	4/9 (44)	19/25 (76)	0.111
IAI	**0/10 (0)**	**8/12 (67)**	**0.002**
SSTI, Bone, Joint	**2/9 (22)**	**9/12 (75)**	**0.030**
PNA	1/6 (17)	5/14 (36)	0.613
IV during admission and discharge[4]	**21 (41)**	**8 (5)**	**<0.001**
Time to PO switch, days, median (IQR)[5]	6 (3-9)	4 (3-7)	0.196
Readmission within 30 days	5/44 (11)	20/138 (14)	0.600
Infection recurrence within 30 days	2 (4)	6 (4)	1

All data presented as n(%) unless otherwise stated
1. No difference in primary composite outcome was shown when broken down by individual components or infection type
2. Pneumonia LOS in the CG compared to CSG: 21 days vs 14 days, p=0.020, respectively
3. No IV to PO switch for CNS infections
4. UTI IV during admission and discharge in CG vs CSG: 38% vs 1%, p<0.001 and IAI in CS vs CSG: 70% vs 0%, p=0.001, respectively
5. No difference in Time to PO switch by infection type

Figure 3. Top Three Oral Antibiotics Switched



FQ: fluoroquinolone; SXT: sulfamethoxazole-trimethoprim; CPD: cefpodoxime; CDR: cedfinir

CONCLUSION

- Treatment with carbapenem-sparing agents compared to carbapenems did not lead to worse patient-related outcomes
- Patients treated with carbapenem-sparing therapy were more frequently switched to oral antibiotics during their inpatient stay, and were switched two days earlier than those on carbapenem therapy
- Non-carbapenem agents, including cephalosporins, may be utilized for TZP-NS/CRO-S infections in non-critically ill patients to spare carbapenem therapy without adversely affecting patient outcomes
- Further studies are warranted to compare clinical outcomes between carbapenem and carbapenem-sparing therapies in critically ill patients with TZP-NS/CRO-S infections

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