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Epidemiology, Risk Factors, and Outcomes of a Novel Piperacillin/Tazobactam-Non-Susceptible, β-lactam-Pan-Susceptible (TZP-NS/BL-PS) Phenotype in Enterobacteriaceae

Abrar K. Thabit[1,2], Sean M. Stainton[1], Joseph L. Kuti[1], Jaber Aslanzadeh[3], David P. Nicolau[1, 4]

[1]Center for Anti-infective Research and Development, Hartford Hospital, Hartford, CT, USA; [2] Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia;
[3] Department of Pathology and Laboratory Medicine, Hartford Hospital, Hartford, CT, USA; [4] Division of Infectious Diseases, Hartford Hospital, Hartford, CT, USA

Correspondence:
David P. Nicolau, PharmD, FCCP, FIDSA
Center for Anti-infective Research and Development
Hartford Hospital
80 Seymour Street
Hartford, CT 06102
Tel: 860-972-3941
Fax: 860-545-3992
Email: david.nicolau@hhchealth.org

ABSTRACT (revised)

Background: Our group has recently identified a novel phenotypic profile among *Escherichia coli* and *Klebsiella pneumoniae* portraying TZP MICs ≥ 32 µg/mL while retaining susceptibility to other β-lactams. This phenotype could have implications for TZP, which is often prescribed empirically and cascaded with selective reporting (i.e., hidden) by the lab.

Methods: A retrospective study was conducted for patients presenting to Hartford Hospital between Jan 2012 and Dec 2015. Patient characteristics, established risk factors for resistance, and course of infection are reported.

Results: Of 7508 patients with *E. coli* and *K. pneumoniae* isolated, 101 (1.3%) had TZP-NS/BL-PS isolated. Eighty-five (83%) were admitted to the hospital; the other 16 had the organism isolated in the ED but were discharged directly or in outpatient clinics. Of the 85 isolates from admitted patients, 68 (80%) were *E. coli*, 34 (40%) were community-acquired, 31 (36.5%) healthcare-associated, and 20 (23.5%) hospital-acquired. TZP-NS/BL-PS strains were predominately isolated from urine [67 (78%)], followed by blood. Patients mean age was 65 ± 19 years, and 72 (84%) had at least one risk factor for resistance. The most common risk factors were previous admission within 6 months (47%), infection within 6 months (44%), and prior stay at skilled nursing facility (32%). Twenty-six (31%) patients previously received a β-lactam; 10 (12%) received TZP. Fifty-five (65%) of these isolates caused symptomatic infection; most [42 (76%)] were successfully treated with a β-lactam, a fluoroquinolone, TMP/SMX, or an aminoglycoside. Four patients were treated with TZP.

Conclusions: The prevalence of TZP-NS/BL-PS *E. coli* and *K. pneumoniae* at our hospital was very low. Most infected patients were successfully treated with available antibiotics reported by our lab. Most patients with TZP-NS/BL-PS isolates had established risk factors for resistance, but few received TZP previously. Antibiotic susceptibility cascading and selective reporting is a common stewardship method to limit the use of broad spectrum antibiotics. Labs should reconsider resistance reporting until more data regarding TZP outcomes for such organisms become available.

INTRODUCTION

- Antimicrobial resistance among Gram-negative bacteria, particularly Enterobacteriaceae, has become a global threat (1).
- Piperacillin/tazobactam (TZP) is a potent broad spectrum antibiotic commonly initiated as empiric therapy to treat infections presumably caused by antimicrobial resistant organisms (2).
- The susceptibility minimum inhibitory concentration (MIC) breakpoint of TZP against Enterobacteriaceae is ≤ 16 µg/mL (3).
- A recent surveillance study (4) in 30 hospitals across the US by our group identified a novel phenotypic profile among *Escherichia coli* and *Klebsiella pneumoniae* comprised of TZP MICs ≥ 32 µg/mL (i.e., non-susceptible due to porin mutation) while maintaining susceptibility to most other β-lactams (TZP-non-susceptible, β-lactam-pan-susceptible, TZP-NS/BL-PS).
- This phenotype was observed within approximately 5% of the Enterobacteriaceae isolated (4).
- TZP susceptibility results are often cascaded and selectively reported (if at all) by the microbiology lab to limit TZP use against Enterobacteriaceae.

OBJECTIVES

- To determine the frequency of TZP-NS/BL-PS Enterobacteriaceae isolates over a 4-year period at Hartford Hospital
- To describe characteristics of patients harboring TZP-NS/BL-PS Enterobacteriaceae at Hartford Hospital and the presence of established risk factors for antibiotic resistance
- To determine the impact of infection with TZP-NS/BL-PS Enterobacteriaceae on TZP treatment outcomes compared with TZP-susceptible isolates

MATERIALS & METHODS

Study Design

- Retrospective, descriptive study to assess the epidemiology, characteristics, and outcomes of TZP-NS/BL-PS Enterobacteriaceae
- The study was approved by the Institutional Review Board at Hartford Hospital, Hartford, CT, USA.

Patients

- Male and female patients aged ≥ 18 years at the time of admission during the period from January 2012 to December 2015 with a positive culture from any source for TZP-NS/BL-PS *E. coli* or *K. pneumoniae* were included.
- Patients discharged directly from the Emergency Department were excluded from the analysis reporting patient characteristics. Patients without signs and symptoms of infection were excluded from the analysis reporting outcomes.

Definitions

- **Acquisition:**
  - **Hospital-acquired:** Organism isolated after day 1 of current hospital stay (i.e. signs and symptoms absent at the time of admission)
  - **Healthcare-associated:** Organism isolated within 1 day of hospital admission in a patient with a previous hospital admission or stay in a skilled-nursing facility within 6 months
  - **Community-acquired:** Organism isolated within 1 day of hospital admission in a patient with no previous hospital admission or skilled nursing facility stay within 6 months
- **Fever:** oral temperature of > 38℃
- **Elevated White Blood Cell (WBC) count:** > 11 x 10^3 cells/mm^3
- **Clinical outcomes:**
  - **Clinical success:** Resolution of signs and symptoms of infection with the return to baseline status without evidence of active infection
  - **Clinical failure:** Death due to infection or readmission to hospital due to infection within 30 days of discharge
- **Microbiological outcomes:**
  - **Eradication:** Elimination of the infecting organism from the infection site (or sites) during or upon completion of TZP therapy as evidenced by a repeat culture
  - **Presumed eradication:** Improved clinical response without a repeat culture
  - **Persistence:** Presence of TZP-NS/BL-PS pathogen from infection site (or sites) during or upon completion of TZP therapy as evidenced by a repeat culture
  - **Presumed persistence:** Lack of clinical response without a repeat culture
- **Resistance risk factors**
  - Number of patients previously admitted within 6 months, number of previous admissions, prior stay at SNF, immunosuppressed, surgery in last 6 months, dialysis, mechanical ventilation, enteral/parenteral nutrition, indwelling catheter, TZP use in last 6 months, time in weeks from TZP treatment to infection, infection in last 6 months, β-lactam therapy in the last 6 months

RESULTS

Patients Demographics and Characteristics

- Of 7508 non-duplicate patients with positive cultures for *E. coli* and *K. pneumoniae* between January 2012 and December 2015, 101 (1.3%) were observed to have the TZP-NS/BL-PS phenotype. Eighty-five patients were admitted and included in the reporting below.
- Table 1 lists patients' demographics and characteristics for the 85 admitted patients harboring the TZP-NS/BL-PS phenotype.
- The most common infection type was a UTI, the most commonly isolated bacteria was *E. coli*, and most infections were community-acquired.

Table 1. Baseline demographics and infection characteristics for patients with TZP-NS/BL-PS *E. coli* or *K. pneumoniae* isolated

Characteristic	All Patients[a] (n=85)	Patients with confirmed infection due TZP-NS/BL-PS organism[b] (n=55)
Baseline demographics		
Age, years (mean ± SD)	65.4 ± 19.2	64.2 ± 21.4
Sex, female, n (%)	53 (62.4)	32 (58.2)
Ethnicity, n (%)		
Hispanic	21 (24.7)	17 (30.9)
Non-Hispanic	64 (75.3)	38 (69.1)
Race, n (%)		
White	78 (91.8)	49 (89.1)
Black	7 (8.2)	6 (10.9)
Length of stay, days (median [IQR])	6 [4-11]	5 [4-9]
Patients with at least one day spent in ICU, n (%)	18 (21.2)	10 (18.2)
Established resistance risk factors		
Number of patients previously admitted within 6 months, n (%)	40 (47.1)	25 (45.5)
Number of previous admissions, median [IQR]	1 [1-2]	2 [1-2]
Prior stay at SNF, n (%)	27 (31.8)	17 (30.9)
Immunosuppressed[c], n (%)	14 (16.5)	7 (12.7)
Surgery in last 6 months, % n (%)	24 (28.2)	13 (23.6)
Dialysis, n (%)	2 (2.4)	1 (1.8)
Mechanical ventilation, n (%)	4 (4.7)	3 (5.5)
Enteral/parenteral nutrition, n (%)	8 (9.4)	5 (9.1)
Indwelling catheter, n (%)	21 (24.7)	17 (30.9)
TZP use in last 6 months, n (%)	10 (11.8)	4 (7.3)
TZP treatment to infection, weeks (mean±SD)	9.9 ± 7.1	11 ± 7.5
Infection in last 6 months, n (%)	37 (43.5)	27 (49.1)
β-lactam therapy in the last 6 months, n (%)	26 (30.6)	21 (38.2)
Number of patients with at least one risk factor, n (%)	72 (84.7)	46 (83.6)
Infection characteristics		
Number of patients with concurrent infection, n (%)	25 (29.4)	14 (25.5)
Polymicrobial with TZP-NS/ BL-PS organism, n (%)	13 (17.8)	11 (20)
Charlson co-morbidity score, median [IQR]	5 [3-6]	5 [3-6]
Sepsis based on SOFA score, n (%)	22 (25.9)	17 (30.9)
Unit during isolation, n (%)		
Emergency department	48 (56.5)	35 (63.6)
Medicine	34 (40)	18 (32.7)
ICU	3 (3.5)	2 (3.6)
Bacteria, n (%)		
Escherichia coli	68 (80)	43 (78.2)
Klebsiella pneumoniae	17 (20)	12 (21.8)
TZP-resistant[d]	39 (45.3)	24 (43.6)
Acquisition, n (%)		
Community-acquired	34 (40)	21 (40)
Healthcare-associated	31 (36.5)	22 (38.2)
Hospital-acquired	20 (23.5)	12 (21.8)
Culture source, n (%)[e]		
Urine	67 (77.9)	43 (78.2)
Blood	8 (9.3)	8 (14.5)
Skin	5 (5.8)	4 (7.3)
Respiratory	2 (2.3)	2 (3.6)
Other	7 (8.1)	1 (1.8)

ICU, intensive care unit; IQR, inter-quartile range; SNF, skilled nursing facility; SOFA, Sequential Organ Failure Assessment; TZP, piperacillin/tazobactam; TZP-NS/BL-PS, piperacillin/tazobactam-non-susceptible, β-lactam-pan-susceptible
[a] Including all patients from whom a TZP-NS/BL-PS organism was isolated [b] Including patients with signs and symptoms of infection due to a TZP-NS/BL-PS organism only [c] Presence of immunosuppressive disease (e.g., HIV infection, solid organ transplant, or cancer) and/or therapy (e.g., receipt of > 20mg of prednisone per day or of an equivalent corticosteroid for ≥ 14 days before admission) [d] Does not include isolates with intermediate resistance to piperacillin/tazobactam [e] Percentages add to >100% as some patients had the organisms isolated from more than one site

Hospital Course and Outcomes of Patients Infected with TZP-NS/BL-PS Organisms

- A total of 55 patients showed signs and symptoms of infection presumed to be caused by the TZP-NS/BL-PS pathogen.
- Hospital course and outcomes of these patients are presented in Table 2.

Table 2. Hospital course and outcomes of 55 patients infected with TZP-NS/BL-PS Enterobacteriaceae

Characteristic	Number (%), unless otherwise indicated (n=55)
Type of infection	
Bacteremia	4 (7.3)
Intra-abdominal	1 (1.8)
Intra-abdominal with bacteremia	1 (1.8)
ABSSSI	4 (7.3)
UTI	39 (70.9)
UTI with bacteremia	4 (7.3)
Pneumonia	2 (3.6)
Infection course	
Signs and symptoms started from ED	39 (70.9)
Baseline temperature, °C (mean ± SD)	38.2 ± 8.2
Baseline WBC, × 10^3 cells/mm^3 (mean ± SD)	12.7 ± 6.4
Treatment, n (%)	
Piperacillin/tazobactam	4 (7.3)
Cephalosporins	46 (83.6)
Carbapenems	10 (18.2)
Fluoroquinolones	18 (32.7)
Sulfamethoxazole/trimethoprim	5 (9.1)
Aminoglycosides	1 (1.8)
Clinical outcome, n (%)	
Success	42 (76.4)
Failure	12 (21.8)
Undetermined	1 (1.8)
Microbiological outcome	
Eradication	2 (3.6)
Presumed eradication	45 (81.8)
Persistence	2 (3.6)
Presumed persistence	6 (10.9)
Days to normalization of temperature, days (mean ± SD) (n=55)	1.6 ± 2.8
Days to normalization of temperature in patients with baseline fever only (n=13), days (mean ± SD)	2.4 ± 1.4
Days to normalization of WBC, days (mean ± SD) (n=55)	0.1 ± 0.2
Days to normalization of WBC in patients with elevated baseline WBC only (n=24), days (mean ± SD)	2.7 ± 2.5
Death, n (%)	3 (5.5)
Death while on antibiotic therapy, n (%)	1 (1.8)
Infectious Diseases consult obtained, n (%)	16 (29.1)
Disposition	
Home	28 (50.9)
Skilled nursing facility	24 (43.6)
Other	3 (5.5)
Re-admitted within 30 days of discharge, n (%)	12 (21.8)
Re-admission due to infection, n (%)	6 (10.9)

ABSSSI, acute bacterial skin and skin structure infection; ED, emergency department; UTI, urinary tract infection; WBC, white blood cells count

Outcomes of Patients Infected with TZP-NS/BL-PS Organisms and Treated with TZP

- Of the 55 patients infected with TZP-NS/BL-PS pathogens, only 4 received TZP therapy.
- Three of these patients had at least one established risk factor for antibiotic resistance.
- Length of hospital stay ranged 2-9 days.
- 2 of 4 patients (one each with a complicated intra-abdominal infection (cIAI) and acute bacterial skin and skin structure infection) were successfully treated with TZP. One patient died while receiving TZP for a cIAI. The final patient with urosepsis was made CMO on hospital day 2 and outcome of TZP treatment could not be determined.
- Both patients with successful responses also received ceftriaxone, ertapenem, or cefepime as part of their treatment regimen.

CONCLUSIONS

- The TZP-NS/BL-PS phenotype was identified in our hospital over the last 4 years, albeit frequency was rare at 1.3% of all non-duplicate cultures.
- Although most patients had at least one established risk factor for resistance, community-acquired infections due to this phenotype without any identifiable risk factors were still observed.
- The majority of patients were successfully treated with a microbiologically active antibiotic based on the antimicrobial susceptibility profile; however, a few patients did receive TZP with mixed results.
- Antibiotic susceptibility cascading and selective reporting is a common stewardship strategy to limit the use of broad spectrum antibiotics, which was certainly the case at our institution where TZP non-susceptibility was never reported to the providers. In lieu of limited data with TZP for the treatment of this phenotype and the high prevalence of TZP empiric use in US hospitals, microbiology labs should reconsider cascading resistance reporting automatically until more data regarding TZP outcomes for such organisms become available.

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