Clinical and demographic features associated with β-lactamase producing Enterobacterales in an academic medical center in Loma Linda, CA

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Abstract

Background

Emergence of antibiotic resistant bacteria is a threat to public health. The aim of this study is to identify clinical and demographic features associated with β-lactamase producing Enterobacterales, specifically carbapenemase producing (CPE) and extended spectrum β-lactamase producing (ESBL) Enterobacterales in patients at Loma Linda University Health, an academic medical center in Loma Linda, California.

Methods

This retrospective case control study compared patients with/without β-lactamase producing Enterobacterales. Cases and controls were identified from microbiology records with Enterobacterales isolated between January 1, 2020, and December 31, 2021. Case subjects were individuals with ≥1 CPE isolate (confirmed by sendout testing) and control subjects were those with ≥1 isolate that were all non-CPE. We identified isolates of interest, defined as the first CPE isolate in cases and the first non-CPE isolate for controls. For each isolate of interest and corresponding specimen collection date, we extracted electronic medical record data including inpatient antibiotics received in the preceding 6 months, organism (genus level), patient sex and age. We performed similar analysis with ESBL-producing Enterobacterales.

Results

On multiple logistic regression, age (OR, 1.03; 95%CI, 1.01-1.05), receipt of non-carbapenem β-lactams (1.09; 1.06-1.12), carbapenems (1.15; 1.07-1.23), doxycycline (1.32; 1.10-1.58), and tetracycline (1.65; 1.03-2.63), were independently associated with increased odds of CPE infection. Similarly, gender (2.48; 1.86-3.30), age (1.01; 1.01-1.02), receipt of non-carbapenem β-lactams (1.06; 1.04-1.09), carbapenems (1.09; 1.02-1.16), and vancomycin (1.05; 1.00-1.09) were associated with increased odds of infection with ESBL-producing Enterobacterales.

Conclusion

Age and receipt of β-lactams (including carbapenems) were associated with increased odds of infection with both CPE and ESBL-producing Enterobacterales in an academic medical center in Southern California, highlighting the importance of antibiotic stewardship.

Background

Emergence of antibiotic resistant bacteria is a significant threat to public health with >35,000 deaths/year from resistant infections in the US (1). Bacteria can develop resistance through resistance genes such as those expressing β-lactamases, including extended-spectrum β-lactamase (ESBL) and carbapenemase produced by Enterobacterales (CPE). Prior studies provide some insight into how these genes are emerging. In US hospitals in 2017, ESBLs accounted for 32% of multi-drug resistant (MDR) infections and increased in incidence 2012-2017. In contrast, carbapenem resistant enterobacterales (CRE) accounted for 2.1% of MDR infections with no change in incidence (2). ESBL bacteremia was associated with a history of carbapenem-resistant colonization/infection, recent international hospitalization in a high-burden region (3), presence of a urinary catheter, diabetes, and hospitalization (4). Isolation of ESBL-producing E. coli is associated with receipt of β-lactams and age (5). Risk factors for CRE infection include prior use of antibiotics (6, 7), although associated antibiotic classes vary (7-9); poor functional status; ICU stay (7); residence in a skilled nursing facility with ventilator care and in a long-term care facility (10, 11); mechanical ventilation (11); and prior CRE colonization (12).

There is a critical public health need to understand of the burden of antimicrobial resistance and factors contributing to this burden. Evidence of horizontal transfer of β-lactamase genes amongst hospitalized patients would also inform the relevance of infection control measures that place significant burdens on hospital resources, staff, and patients (13) but can be effective against emerging organisms (14). Here we seek to understand the emergence of β-lactamases in an academic medical center using retrospective analysis to identify independent risk factors for isolation of ESBLs and CPE.

Methods

- Case control study comparing patients with/without β-lactamase producing Enterobacterales. Case subjects and controls were identified from LLUH microbiology records with Enterobacterales isolated in 2020 -2021 with the following criteria:

	Cases	**Controls**
definition	38/214 patients with ≥1 CPE/ESBL isolate	9922/9708 patients with ≥1 isolate all non-CPE/non-ESBL
isolate of interest	first CPE/ESBL isolate of each patient	first non-CPE/non-ESBL isolate of each patient

- For each isolate of interest and corresponding specimen collection date, we extracted electronic medical record data including number of days of inpatient antibiotics received in the preceding 6 months, organism (genus level), patient sex and age.
- For each factor, simple logistic regression was performed. Factors with significant odds ratios on simple logistic regression were used in multiple logistic regression with bidirectional stepwise variable selection by the Akaike Information Criterion to identify independent risk factors.

Results

Associations Between Inpatient Antibiotics Received 180 days Prior to Culture Collection with CPE Enterobacteria Estimated with Simple Logistic Regression Models—2020-2021

			(# of days of antibiotic) in (# of patients)	
Factor	OR	p	cases	controls
β-lactam	**1.08 (1.05-1.10)**	**<0.001*** **	**319 in 38**	**15170 in 9922**
β-lactam no carbapenems	**1.07 (1.05-1.10)**	**<0.001*** **	**273 in 38**	**14684 in 9922**
penicillins	**1.10 (1.05-1.16)**	**<0.001*** **	**98 in 38**	**7178 in 9922**
penicillin	NA	0.99	0 in 38	134 in 9922
ampicillin	1.06 (0.87-1.30)	0.56	6 in 38	745 in 9922
ampicillin/sulbactam	**1.34 (1.18-1.53)**	**<0.001*** **	**24 in 38**	**419 in 9922**
amoxicillin	NA	0.99	0 in 38	159 in 9922
amoxicillin/clavulanate	1.13 (0.90-1.42)	0.31	4 in 38	232 in 9922
nafcillin	1.03 (0.85-1.25)	0.73	4 in 38	485 in 9922
piperacillin/tazobactam	**1.15 (1.09-1.23)**	**<0.001*** **	**90 in 38**	**6302 in 9922**
aztreonam	1.08 (0.98-1.20)	0.11	10 in 38	136 in 9922
cephalexin	**1.41 (1.00-1.98)**	**0.05***	**6 in 38**	309 in 9922
cefazolin	1.06 (0.79-1.41)	0.71	6 in 38	1085 in 9922
cefuroxime	**2.36 (1.37-4.08)**	**0.002****	**4 in 38**	**60 in 9922**
cefaclor	0.07 (NA-NA)	0.99	0 in 38	1 in 9922
ceftriaxone	**1.13 (1.04-1.23)**	**0.004****	**36 in 38**	**2666 in 9922**
ceftazidime	1.14 (0.96-1.34)	0.13	8 in 38	364 in 9922
cefepime	**1.08 (1.04-1.12)**	**<0.001*** **	**104 in 38**	**2667 in 9922**
cefdinir	NA	0.99	0 in 38	6 in 9922
cefoxitin	NA	0.99	0 in 38	44 in 9922
cefotaxime	NA	0.99	0 in 38	158 in 9922
ceftaroline	0.20 (NA-NA)	0.99	0 in 38	1 in 9922
ceftazidime/avibactam	**5.04 (1.25-20.25)**	**0.02***	**1 in 38**	**3 in 9922**
carbapenems	**1.16 (1.08-1.23)**	**<0.001*** **	**46 in 38**	**486 in 9922**
meropenem	**1.20 (1.09-1.32)**	**<0.001*** **	**45 in 38**	**412 in 9922**
ertapenem	1.05 (0.73-1.52)	0.79	1 in 38	74 in 9922
fluoroquinolone	NA	0.99	0 in 38	200 in 9922
ciprofloxacin	NA	0.99	0 in 38	115 in 9922
levofloxacin	NA	0.99	0 in 38	85 in 9922
trimethoprim	NA	0.99	0 in 38	1 in 9922
tmp/smx	1.01 (0.97-1.06)	0.67	21 in 38	2744 in 9922
aminoglycoside	0.85 (0.32-2.29)	0.75	1 in 38	571 in 9922
amikacin	1.55 (0.61-3.96)	0.36	1 in 38	43 in 9922
gentamicin	NA	0.98	0 in 38	444 in 9922
tobramycin	NA	0.99	0 in 38	84 in 9922
nitrofurantoin	NA	0.98	0 in 38	226 in 9922
vancomycin	**1.11 (1.07-1.16)**	**<0.001*** **	**103 in 38**	**3839 in 9922**
linezolid	**1.39 (1.15-1.67)**	**<0.001*** **	**12 in 38**	**127 in 9922**
daptomycin	**1.16 (1.03-1.29)**	**0.01***	**15 in 38**	**127 in 9922**
doxycycline	**1.38 (1.15-1.65)**	**<0.001*** **	**14 in 38**	**180 in 9922**
tetracycline	**1.79 (1.13-2.86)**	**0.01***	**14 in 38**	**11 in 9922**
tigecycline	0.54 (NA-NA)	0.99	0 in 38	1 in 9922
clindamycin	1.15 (0.76-1.74)	0.5	4 in 38	517 in 9922
rifampin	NA	0.99	0 in 38	74 in 9922
azithromycin	**1.29 (1.07-1.55)**	**0.007****	**12 in 38**	**438 in 9922**
erythromycin	1.06 (0.95-1.18)	0.31	8 in 38	337 in 9922
metronidazole	**1.08 (1.03-1.14)**	**0.003****	**47 in 38**	**1703 in 9922**
colistimethate	0.10 (NA-NA)	0.99	0 in 38	29 in 9922
fidaxomicin	0.29 (NA-NA)	0.99	0 in 38	26 in 9922

Risk Factors for Isolation of CPE in LLUH Patients, as Estimated With a Multiple Logistic Regression Model—2020-2021

Factor		OR	p
Age		**1.03 (1.01-1.05)**	**0.001****
Inpatient Antibiotic (received 180 days before isolate collected)			
	β-lactam (no carbapenems)	**1.09 (1.06-1.12)**	**<0.001*****
	carbapenem	**1.15 (1.07-1.23)**	**<0.001*****
	doxycycline	**1.32 (1.10-1.58)**	**0.002***
	tetracycline	**1.65 (1.03-2.63)**	**0.04***

Risk Factors for Isolation of ESBL-producing Enterobacterales in LLUH Patients, as Estimated With a Multiple Logistic Regression Model—2020-2021

Factor		OR	p
Gender	female	REF	
	male	**2.48 (1.86-3.30)**	**<0.001*****
Age		**1.01 (1.01-1.02)**	**<0.001*****
Organism			
	Escherichia	REF	
	Citrobacter	NA (NA-NA)	0.98
	Enterobacter	NA (NA-NA)	0.98
	Klebsiella	0.78 (0.56-1.09)	0.14
	Morganella	NA (NA-NA)	0.99
	Proteus	0.78 (0.43-1.41)	0.42
	Providentia	NA (NA-NA)	0.99
	Serratia	NA (NA-NA)	0.98
Inpatient Antibiotic (received 180 days before isolate collected)			
	β-lactam (no carbapenems)	**1.06 (1.04-1.09)**	**<0.001*****
	carbapenem	**1.09 (1.02-1.16)**	**0.006****
	vancomycin	**1.05 (1.00-1.09)**	**0.04***

Discussion

- The positive association between receipt of β-lactams and isolation of β-lactamase producing Enterobacterales is consistent with selective pressure β-lactams apply on bacteria, allowing CPE and ESBL-producing bacteria to predominate.
- The positive association with age may be a marker for past exposure to β-lactam antibiotics or nosocomial infection with β-lactamase producing Enterobacterales
- The mechanism of the independent association of receipt of doxycycline and tetracycline with CPE, and vancomycin with ESBL-producing Enterobacterales is unclear as these antibiotics do not provide reliable coverage of Enterobacterales, but may be due to confounding
- Identification of risk factors for isolation of β-lactamase producing Enterobacterales could inform a stratified random sampling method for surveillance of resistant Enterobacterales in entire hospital populations that may have resource limitations.

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References

1. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States. Atlanta, GA: US Department of Health and Human Services, 2019.
2. Jernigan JA, et al. Multidrug-Resistant Bacterial Infections in U.S. Hospitalized Patients, 2012-2017. N Engl J Med. 2020;382(14):1309-19.
3. Goodman K, et al. A clinical decision tree to predict whether a bacteremic patient is infected with an extended-spectrum β-lactamase–producing organism. Clinical Infectious Diseases. 2016;63(7):896-903.
4. Park YS, et al. Clinical and Microbiologic Characteristics of Cephalosporin-Resistant Escherichia coli at Three Centers in the United States. Antimicrobial Agents and Chemotherapy. 2012;56(4):1870-6.
5. Liu EW, et al. Clinical and demographic features associated with infections with extended-spectrum β-lactamase–producing Escherichia coli in a health system in Maine, 2017. Antimicrobial Stewardship & Healthcare Epidemiology. 2021;1(7):1-3.
6. Marchaim D, et al. Recent exposure to antimicrobials and carbapenem-resistant Enterobacteriaceae: the role of antimicrobial stewardship. Infect Control Hosp Epidemiol. 2012;33(8):817-30.
7. Schwaber MJ, et al. Predictors of carbapenem-resistant Klebsiella pneumoniae acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother. 2008;52(3):1028-33.
8. Falagas ME, et al. Risk factors of carbapenem-resistant Klebsiella pneumoniae infections: a matched case control study. J Antimicrob Chemother. 2007;60(5):1124-30. Epub 2007/09/22.
9. Kwak YG, et al. Risk factors for the acquisition of carbapenem-resistant Klebsiella pneumoniae among hospitalized patients. Microb Drug Resist. 2005;11(2):165-9.
10. Prabaker K, et al. Transfer from high-acuity long-term care facilities is associated with carriage of Klebsiella pneumoniae carbapenemase-producing Enterobacteriaceae: a multihospital study. Infect Control Hosp Epidemiol. 2012;33(12):1193-9.
11. Lin MY, et al. The importance of long-term acute care hospitals in the regional epidemiology of Klebsiella pneumoniae carbapenemase-producing Enterobacteriaceae. Clin Infect Dis. 2013;57(9):1246-52.
12. Tischendorf J, et al. Risk of infection following colonization with carbapenem-resistant Enterobactericeae: A systematic review. Am J Infect Control. 2016;44(5):539-43.