Comparison of Cefazolin Susceptibilities of *Enterobacterales* with an Automated Susceptibility Testing Platform versus In Vitro Antimicrobial Testing

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BACKGROUND

- In 2011, Clinical and Laboratory Standards Institute (CLSI) revised susceptibility testing breakpoints for the use of parenteral cephalosporins for *Enterobacterales* infections
- This modification was based on data suggesting increased treatment failure secondary to low-level resistance mechanisms not detected by previous breakpoints (MIC ≤8)
- Updated breakpoints may be difficult to implement as many automated susceptibility testing (AST) platforms are limited by the minimum antimicrobial concentration present
  - Vitek®2 (bioMerieux, Durham NC) lowest reportable cefazolin (CFZ) MIC of 4 µg/mL

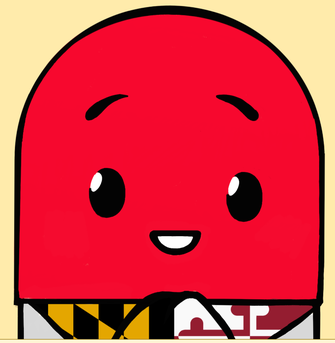
	UMMC Reported Breakpoints for CFZ	CLSI Revised Breakpoints for CFZ*
Susceptible	≤4	≤2
Intermediate	16	4
Resistant	32	≥8

*** = breakpoints for non-urinary sites**

- Current reporting methods may encourage the use of CFZ when isolates may be resistant
- Limited data exists on the impact CFZ use on clinical outcomes in this population

STUDY DESIGN & METHODS

- Retrospective single-center study at University of Maryland Medical Center (UMMC)
- Adult patients with positive blood cultures for CFZ-susceptible *Enterobacterales* from 1/2016 to 9/2018
- **Primary outcome:** rates of CFZ susceptibility for *Enterobacterales* with AST (Vitek®2) vs. manual methods with lower dilutional concentrations
  - Vitek®2 performed at initial admission; version 8.01 and AST-GN74 card
  - MIC Gradient Test Strips (Liofilchem, Waltham, MA) and disk diffusion (BD-BBL, Franklin Lakes, NJ) performed retrospectively on frozen isolates stored at -80^{O}C
- **Secondary outcomes:** clinical outcomes of patients with *Enterobacterale*s bloodstream infections (BSI) who received CFZ vs. alternate therapies
  - Treatment failure: composite of 30-day all-cause inpatient mortality, 30-day recurrent BSI, 60-day recurrent infection with, or infectious complications
  - Infectious complications: local/suppurative complication not present at infection onset or distant complication defined as growth of same initial bacteria
- Statistical analysis:
  - Bivariate analysis used for comparisons including X^2 or Fisher's Exact (FE) Test for nominal variables; Student t-test or Mann Whitney U test for continuous variables
  - Binary logistic regression was used to find independent predictors of clinical failure
    - Variables included were significant on bivariate analysis (p <0.05) or determined to be clinically relevant *a priori*



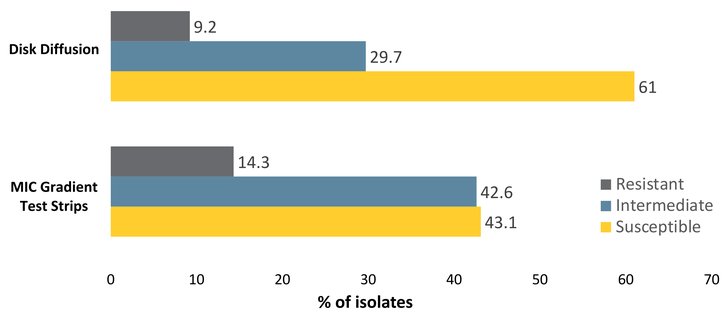
Take-home Points:

AST-reported CFZ susceptibility should be confirmed with additional testing prior to definitive use of CFZ for systemic *Enterobacterales* infections, particularly in patients without source control or ID consult.

Results: Baseline Demographics and Clinical Characteristics

Characteristics	All Patients (n=238)	CFZ (n=33)	Non-CFZ (n=205)	*P*-value
Age (years), mean ± SD	57 ± 15	54 ± 16	57 ± 16	<0.001
Male, n (%)	137 (57.6)	29 (87.9)	108 (52.7)	< 0.001
CCI, median (IQR)	2 (1, 4)	2 (1, 4)	2 (1, 4)	0.42
BSI in ICU, n (%)	77 (32.3)	11 (33.3)	66 (32.2)	0.89
Organism, n (%)				
Escherichia coli	141 (59.2)	13 (39.4)	128 (62.4)	0.04
Klebsiella spp.	97 (40.8)	20 (60.6)	77 (37.6)	
Source of BSI, n (%)				
Urinary	94 (39.5)	9 (27.3)	85 (41.5)	0.04
Intra-abdominal	60 (25.2)	6 (18.2)	54 (26.3)	
Endovascular	18 (7.6)	6 (18.2)	12 (5.9)	
Skin and soft tissue	15 (6.3)	3 (9.1)	12 (6.9)	
Respiratory	6 (2.5)	2 (6.1)	4 (2)	
Bone/joint	2 (0.8)	1 (3)	1 (0.5)	
Unknown	43 (18.1)	6 (18.2)	37 (18.1)	
ID Consult	151 (63.4)	27 (81.8)	124 (60.5)	0.02
Source Control				
Yes	170 (71.4)	25 (75.8)	145 (70.7)	0.35
No/Unknown	68 (28.6)	8 (24.2)	60 (29.3)	
First Definitive Antibiotic, n (%)				
Ampicillin-sulbactam	8 (3.4)	0 (0)	8 (3.9)	< 0.001
Cefazolin	26 (10.9)	26 (78.8)	0 (0)	
Ceftriaxone	122 (51.3)	5 (15.2)	117 (57.1)	
Cefepime	19 (8)	1 (3)	18 (8.8)	
Meropenem	12 (5)	0 (0)	12 (5.9)	
Piperacillin-tazobactam	24 (10.1)	0 (0)	24 (11.7)	
Quinolones	21 (8.8)	1 (3)	20 (9.8)	
Other	5 (2.1)	0 (0)	5 (2.4)	

CFZ Susceptibility Results by Testing Method in Vitek®2 Susceptible Organisms



***8 isolates with Vitek®2 CFZ MIC of 8 reported as susceptible in EMR**

- 195 microbiologically evaluable (ME):
  - Disk diffusion: 39% of isolates reported as non-susceptible
  - MIC Gradient Test Strip: 56.9% of isolates reported as non-susceptible
- 238 patients → 33 received cefazolin → 24 ME
  - Non-susceptibility of 57.6% to 66.6% by disk or MIC Gradient Test Strip, respectively

Clinical Outcomes, CFZ versus non-CFZ-treated Patients

Outcomes, n (%)	Overall (n=238)	CFZ (n=33)	Non-CFZ (n=205)	*P*-value
Treatment failure*	90 (37.8)	11 (33.3)	79 (38.5)	0.57
30-day mortality	28 (11.8)	2 (6.1)	26 (12.7)	0.42 (Yates)
Recurrent BSI	5 (2.1)	0 (0)	5 (2.4)	NA
Distant complications	26 (10.9)	3 (9.1)	23 (11.2)	0.95 (FE)
30-day readmissions	25 (10.5)	3 (9.1)	22 (10.7)	1 (FE)
30-day *C. difficile* infections	12 (5)	0 (0)	12 (5.6)	NA
60-day recurrent organism	27 (11.3)	4 (12.1)	23 (11.2)	0.88

Logistic Regression Model Independent Predictors of Clinical Failure

Variable	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)
ICU at BSI	2.32 (1.17, 4.62)	<0.001	1.54 (0.59, 3.55)
Urinary source	0.55 (0.28, 1.07)	0.08	--
E. coli	1.54 (0.77, 3.06)	0.22	--
ID consult	0.34 (0.17, 0.71)	0.004	0.37 (0.15, 0.89)
Source Control	0.07 (0.01, 0.31)	<0.001	0.06 (0.13, 0.32)
CFZ Resistant (MIC Gradient Test Strips)	0.78 (0.4, 1.58)	0.51	1.01 (0.38, 2.7)

References:

Turnidge JD et al. *Clin Infect Dis.* 2017;52:917–24; Paterson DL et al. *J Clin Microbiol*. 2011;39:7; Humphries RM et al. *J Clin Microbiol*. 2019;57:e00203-19.