Extended Spectrum β-lactamase Non-susceptibility Is Increasing Over Time In Patients Hospitalized With Culture Positive Urinary Enterobacterales

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ABSTRACT

Background: Antimicrobial resistance of gram negative uropathogens to existing first line therapies has made selection of empiric therapy for patients presenting with a complicated urinary tract infection (cUTI) more challenging. A better understanding of the rate of change of susceptibilities to these antibiotics may better help to gauge the effectiveness of stewardship interventions as well as identify antibacterial classes that remain under selection pressure.

Materials/methods: This retrospective study examined the antimicrobial susceptibility of non-duplicate (first isolate of a species in 30 days) Enterobacterales urine isolates from hospitalized adult patients collected from 2013 through of 2018. Reporting institutions consisted of US hospitals in the BD Insights Research Database (Becton, Dickinson and Company, Franklin Lakes, NJ), which provides geographical representation across the US and includes small and large hospitals in urban and rural areas. The proportion of non-duplicate urine isolates that were non-susceptible (%NS) to the target class was then determined by year of collection.

Results:

Year	Hospitals	β-lactam		ESBL		FQ		Nitrofurantoin		T/S	
		Tested	%NS	Tested	%NS	Tested	%NS	Tested	%NS	Tested	%NS
	n	n		n		n		n		n	
2013	233	121,570	63.4	111,737	9.3	121,570	30.5	121,570	28.1	121,570	27.1
2014	268	138,802	62.8	127,631	10.0	138,802	30.6	138,802	27.9	138,802	26.7
2015	297	153,810	62.2	141,717	11.0	153,810	30.9	153,810	26.2	153,810	27.1
2016	340	174,744	61.7	160,728	11.4	174,744	29.7	174,744	24.2	174,744	26.9
2017	355	185,258	60.8	170,628	12.0	185,258	28.5	185,258	24.3	185,258	26.2
2018	331	167,390	60.7	153,775	12.3	167,390	27.3	167,390	25.2	167,390	25.7

Conclusions: Relative to the rates of resistance in 2013, non-susceptibility to β-lactams, trimethoprim-sulfamethoxazole (T/S), fluoroquinolones (FQ) and nitrofurantoin have stabilized. Organisms vulnerable to extended spectrum β-lactamases (ESBL) however have increased over this period, suggesting that reliance on empiric therapy with β-lactams over other antibiotics may further limit the utility of this class over time.

INTRODUCTION

- Antimicrobial resistance of gram negative uropathogens to existing first line therapies has made selection of empiric therapy for patients presenting with a complicated urinary tract infection (cUTI) more challenging.
- A better understanding of the rate of change of susceptibilities to these antibiotics may better help to gauge the effectiveness of stewardship interventions as well as identify antibacterial classes that remain under selection pressure.

METHODS

- Retrospective study of hospitalized adult patients with culture-positive urinary Enterobacterales collected from 2013-2018
- Examined the antimicrobial susceptibility of non-duplicate (first isolate of a species in 30 days) Enterobacterales urine isolates from hospitalized adult patients collected from 2013 through of 2018.
- Reporting institutions consisted of US hospitals in the BD Insights Research Database (Becton, Dickinson and Company, Franklin Lakes, NJ), which provides geographical representation across the US and includes small and large hospitals in urban and rural areas.
- The proportion of non-duplicate urine isolates that were non-susceptible (%NS) to the target class was then determined by year of collection.
- Estimates of antimicrobial resistance were assessed per 1000 Admissions over time and by Hospital Demographics

RESULTS

Table 1: Distribution of Study Hospitals

Characteristic	# Hospitals	
	N	%
Overall	369	100
Year[a]		
2013	233	63
2014	268	73
2015	297	81
2016	340	92
2017	355	96
2018	331	90
Bed size		
<100	100	27
100-300	164	44
>300	105	29
Urban/Rural		
Rural	89	24
Urban	280	76
Teaching status		
Non-teaching	265	72
Teaching	104	28
HHS region[b]		
Region 1 (New England)	6	2
Region 2 (East coast)	37	10
Region 3 (East)	16	4
Region 4 (Southeast)	91	25
Region 5 (Central north)	80	22
Region 6 (Central south)	77	21
Region 7 (Midwest)	4	1
Region 8 (Midwest)	13	4
Region 9 (Southwest)	32	9
Region 10 (Northwest)	13	4

[a]The numbers of hospitals across years do not add up to the total (369) and may change from year to year. [b]HHS regions (US territories were not included) are defined below:
Region 1 (New England): Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont.
Region 2 (East coast): New Jersey, New York.
Region 3 (East): Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia.
Region 4 (Southeast): Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee.
Region 5 (Central north): Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin.
Region 6 (Central south): Arkansas, Louisiana, New Mexico, Oklahoma, and Texas.
Region 7 (Midwest): Iowa, Kansas, Missouri, and Nebraska.
Region 8 (Midwest): Colorado, Montana, North Dakota, South Dakota, Utah, and Wyoming.
Region 9 (Southwest): Arizona, California, Hawaii, and Nevada.
Region 10 (Northwest): Alaska, Idaho, Oregon, and Washington.

RESULTS

Table 2: Regional Comparison of Antibiotic Susceptibility for Enterobacterales from Inpatient Urinary Isolates

HHS region	Beta-lactam			ESBL positive			Fluoroquinolone			Nitrofurantoin			Trimethoprim-sulfamethoxazole		
	Tested	NS	%NS	Tested	NS	%NS	Tested	NS	%NS	Tested	NS	%NS	Tested	NS	%NS
	n	n	Mean (SD)	n	n	Mean (SD)	n	n	Mean (SD)	n	n	Mean (SD)	n	n	Mean (SD)
Region 1	11,618	6,656	53.1 (15.2)	10,554	946	7.3 (5.3)	11,618	2,386	18.2 (9.2)	11,618	2,838	23.3 (9.4)	11,618	2,253	16.3 (8.4)
Region 2	102,888	66,710	64.0 (9.6)	94,943	12,719	12.3 (7.6)	102,888	31,061	29.1 (8.6)	102,888	27,600	28.5 (10.0)	102,888	27,698	25.8 (7.7)
Region 3	41,170	25,813	62.0 (8.7)	37,430	3,447	9.1 (4.8)	41,170	11,574	28.7 (7.3)	41,170	10,328	26.7 (10.8)	41,170	9,489	23.0 (6.5)
Region 4	262,554	171,565	65.0 (11.6)	240,739	28,797	11.6 (6.5)	262,554	80,293	31.5 (9.1)	262,554	74,413	26.3 (9.9)	262,554	70,321	27.2 (8.1)
Region 5	201,995	116,094	57.8 (11.3)	185,513	17,134	9.2 (6.0)	201,995	57,778	28.5 (8.8)	201,995	50,917	25.4 (9.5)	201,995	51,480	25.3 (8.2)
Region 6	200,832	126,356	62.0 (12.7)	185,480	22,973	12.1 (6.9)	200,832	64,652	32.2 (9.6)	200,832	52,135	25.5 (9.5)	200,832	60,272	30.1 (8.6)
Region 7	1,830	1,009	57.5 (14.3)	1,695	119	7.1 (7.3)	1,830	478	20.4 (12.5)	1,830	437	21.0 (13.1)	1,830	455	22.5 (13.8)
Region 8	11,085	6,216	55.9 (11.9)	10,125	630	6.4 (5.2)	11,085	1,971	18.0 (7.8)	11,085	2,188	20.0 (10.5)	11,085	1,980	18.5 (8.2)
Region 9	79,522	52,613	65.0 (9.7)	73,866	14,931	17.0 (14.8)	79,522	24,809	29.9 (8.0)	79,522	20,472	25.7 (7.3)	79,522	24,034	29.8 (6.7)
Region 10	28,080	16,376	58.2 (7.6)	25,871	1,936	7.4 (5.4)	28,080	5,859	20.1 (6.6)	28,080	6,795	24.1 (7.3)	28,080	5,499	19.4 (6.0)
Total	941,574	589,408	62.6	866,216	103,632	12	941,574	280,861	29.8	941,574	248,123	26.4	941,574	253,481	26.9

Table 3: Proportion of Urine Isolates Non-susceptible to Target Class by Year of Collection

Year	Hospitals	β-lactam		ESBL positive		FQ		Nitrofurantoin		T/S	
		Tested	%NS	Tested	%NS	Tested	%NS	Tested	%NS	Tested	%NS
	n	n		n		n		n		n	
2013	233	121,570	63.4	111,737	9.3	121,570	30.5	121,570	28.1	121,570	27.1
2014	268	138,802	62.8	127,631	10.0	138,802	30.6	138,802	27.9	138,802	26.7
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2017	355	185,258	60.8	170,628	12.0	185,258	28.5	185,258	24.3	185,258	26.2
2018	331	167,390	60.7	153,775	12.3	167,390	27.3	167,390	25.2	167,390	25.7

Table 4: Antibiotic Susceptibility and ESBL Status for Enterobacterales from Inpatient Urinary Isolates By Hospital Demographics in Multivariate Analysis

Characteristic	Beta-Lactam	ESBL	Fluoroquinolone	Nitrofurantoin	Trimethoprim-sulfamethoxazole
	Resistance percent	Resistance percent	Resistance percent	Resistance percent	Resistance percent
Bed size					
< 100	61.5 (59.9-63.0)	9.3 (8.5-10.2)	26.4 (25.2-27.7)	25.2 (24.0-26.4)	24.0 (23.0-25.0)
100-300	62.4 (60.2-64.6)	10.7 (8.8-13.0)	26.4 (25.0-27.9)	25.8 (24.0-27.6)	24.6 (23.5-25.8)
> 300	59.3 (56.7-61.8)	8.6 (7.5-9.9)	26.1 (24.5-27.9)	24.0 (22.2-25.9)	24.7 (23.3-26.1)
Urban/Rural					
Rural	61.9 (59.6-64.2)	9.5 (8.1-11.0)	26.4 (24.8-28.1)	24.9 (23.3-26.6)	24.7 (23.4-26.0)
Urban	60.2 (58.8-61.6)	9.6 (8.8-10.4)	26.2 (25.0-27.4)	25.0 (23.8-26.3)	24.2 (23.2-25.2)
Teaching status					
Non-teaching	61.3 (59.6-63.1)	10.3 (9.0-11.8)	26.7 (25.4-28.0)	25.3 (24.0-26.6)	24.4 (23.3-25.4)
Teaching	60.8 (58.7-62.9)	8.8 (7.8-9.8)	26.0 (24.5-27.5)	24.7 (22.9-26.6)	24.5 (23.3-25.7)

Table 5: Antibiotic Susceptibility for Enterobacterales from Inpatient Urinary Isolates Over Time in Multivariate Analysis

Year	Beta-Lactam	ESBL	Fluoroquinolone	Nitrofurantoin	Trimethoprim-sulfamethoxazole
	Resistance % (range)	Resistance % (range)	Resistance % (range)	Resistance % (range)	Resistance % (range)
2013	61.5 (59.9-63.1)	8.0 (7.1-8.9)	26.8 (25.5-28.2)	26.9 (25.5-28.3)	24.5 (23.5-25.5)
2014	61.6 (60.0-63.2)	8.7 (7.7-9.8)	27.1 (25.7-28.4)	26.7 (25.2-28.2)	24.5 (23.5-25.5)
2015	61.7 (60.2-63.3)	9.6 (8.5-10.9)	27.5 (26.2-28.8)	25.1 (23.7-26.5)	25.0 (24.0-26.0)
2016	61.2 (59.6-62.7)	10.4 (9.3-11.6)	26.7 (25.5-27.9)	23.3 (22.1-24.6)	24.5 (23.5-25.6)
2017	60.2 (58.7-61.8)	10.4 (9.5-11.5)	25.7 (24.5-26.9)	23.5 (22.3-24.7)	24.3 (23.3-25.3)
2018	60.1 (58.6-61.6)	10.2 (9.3-11.2)	24.3 (23.1-25.5)	24.6 (23.4-25.8)	23.8 (22.8-24.7)

CONCLUSIONS

- Relative to the rates of resistance in 2013, non-susceptibility to β-lactams, trimethoprim-sulfamethoxazole (T/S), fluoroquinolones (FQ) and nitrofurantoin (NFT) have stabilized.
- Organisms vulnerable to extended spectrum β-lactamases (ESBL) however have increased over this period.
- There is no difference in resistance by quarter, bedsize, urban/rural, teaching/non-teaching hospital
- There is some regional variability in resistance, but all regions have levels of resistance for all oral antibiotics tested that are at the border of or above 30%; only 3 of the 10 regions are not already at 20% for all oral agents tested
- The high national resistance rates for oral antibiotic agents against urinary Enterobacterales isolates highlights the major concern for oral stepdown options for patients with cUTI

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