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Trends in Important Resistant Gram-negative (GN) and Gram-positive (GP) Urine Bacterial Pathogens in Hospitalized Patients in the US: A Multicenter Evaluation from 2013-2018

Thomas Lodise[1]; Steven Gelone[2]; Kalvin Yu[3]; Kalpana Gupta[4]; Maureen Early[2]; Gang Ye[3]; Jennifer Schranz[2]; Vikas Gupta[3]

[1]Albany College of Pharmacy and Health Sciences, Albany, NY; [2]Nabriva Therapeutics US, Inc., King of Prussia, PA, USA; [3]Becton, Dickinson and Company, Franklin Lakes, NJ, USA; [4]Division of Infectious Diseases, Veterans Affairs Boston Healthcare System and Boston University School of Medicine, West Roxbury, Massachusetts

Nabriva Therapeutics
Dublin, Ireland
www.nabriva.com

BACKGROUND

- The US Centers for Disease Control and Prevention (CDC) has identified a number of antibiotic resistant Gram-negative and Gram-positive bacteria as urgent or serious public health threats[1].
  - Urgent antibiotic resistant bacteria threats: carbapenem-resistant Enterobacteriaceae (CRE), drug-resistant *Neisseria gonorrhoeae.*
  - Serious antibiotic resistant bacteria threats: drug-resistant *Acinetobacter,* extended-spectrum cephalosporin- resistant Enterobacteriaceae (ENT), vancomycin-resistant Enterococcus (VRE), drug-resistant *Pseudomonas aeruginosa* (PSA), methicillin-resistant *Staphylococcus aureus* (MRSA).
- Although the US CDC identifies certain antibiotic resistant bacteria as serious or urgent threats, limited data exist regarding the true prevalence of these bacteria in urinary tract infections among adult hospitalized patients.
  - Existing surveillance programs potentially underestimate prevalence owing to limited site participation and clinical specimen availability.
- This study sought to quantify the prevalence and incidence of extended spectrum beta-lactamase (ESBL) ENT, CRE, carbapenem resistant PSA (CR-PSA), VRE, and MRSA in the urine of adult hospitalized patients.

MATERIAL/METHODS

- All hospitalized adult patients with a positive urine culture (first urine isolate of a species per 30-day period) were evaluated from 409 US hospitals in 2013-2018 (BD Insights Research Database, Becton, Dickinson & Company, Franklin Lakes, NJ USA; **Table 1**).
- The following five groups of antibiotic resistant bacteria were examined:
  - ESBL ENT: *Escherichia coli*, *Klebsiella pneumoniae, Klebsiella oxytoca,* and *Proteus mirabilis* isolates confirmed as ESBL positive by commercial laboratory panels OR with intermediate susceptibility or resistance to ceftriaxone, cefotaxime, ceftazidime, or cefepime.
  - CRE: *E. coli, K. pneumoniae, K. oxytoca, P. mirabilis, E. aerogenes, E. cloacae, S. marcescens, C. freundi,* and *M. morganii* isolates with intermediate susceptibility or resistance to imipenem (excluded for *P. mirabilis* and *M. morganii*), meropenem, doripenem, or ertapenem.
  - CR-PSA if intermediate susceptibility or resistance to imipenem, meropenem, or doripenem.
  - VRE if resistant to vancomycin.
  - MRSA if resistant to methicillin/oxacillin.
- Urine isolates were classified as[2]:
  - Community-onset (CO: < 3 days post-inpatient admission and no previous inpatient admission within 14 days).
  - Hospital-onset (HO: ≥ 3 days post-inpatient admission or inpatient admission within 14 days of current admission).
- The resistance rates were evaluate by the following hospital demographics: hospital bed size, teaching or non-teaching status, urban or rural status, and geographic locations (US Department of Health & Human Services (HHS) regions).

Statistical Analysis

- For each antibiotic resistant pathogen classification, the percent of resistance (defined as % of NS per isolates tested) and the rate of resistance (defined as rate of NS per 1000 admissions (all admissions)) were evaluated using the generalized estimating equations (GEE) models with autoregressive variance-covariance structure and hospitals as random effects to account for temporal correlation and within-hospital correlation of data. Hospital characteristics including bed size, urban/rural status, teaching status, and geographic location were considered as covariates in the multi-variable models.

RESULTS

- Across the 6-year study period, there were more than 24.5 million admissions reported from 409 US hospitals accounting for 1,351,329 non-duplicate urine isolates: 1,016,642 were ENT, 87,450 were PSA, 205,258 were enterococci, and 41,979 were *S. aureus.*
- The 30-day non-duplicate urine isolates tested were 934,642 for ESBL (77.8% CO vs. 22.2% HO), 1,016,642 for CRE (76.7% CO vs. 23.3% HO), 87,450 for CR-PSA (58.6% CO vs. 41.4% HO), 205,258 for VRE (58.6% CO vs. 41.4% HO), and 41,979 for MRSA (75.4% CO vs. 24.6% HO) **(Table 1)**.
- For the respective isolates tested for the 6 year period the average percent (standard deviation) were 10.9% (7.7) for ESBL ENT, 0.8% (1.5) for CRE, 12.6% (17.4) for CR-PSA, 17.3% (18.2) for VRE, and 55.0% (29.0) for MRSA **(Table 1)**.
- For the 6 year period the average rate of NS per 1000 admissions (standard deviation) were 4.7 (4.1) for ESBL, 0.35 (0.7) for CRE, 0.48 (0.8) for CR-PSA, 1.5 (1.8) for VRE, and 1.2 (1.3) for MRSA.
- There was a significant increase in percent ESBL among ENT from 2013 to 2018 ($P < 0.0001$) whereas CR-PSA and MRSA decreased during the same time period (all $P < 0.0043$) **(Table 1, Figure 1)**. The same was true after stratifying by CO versus HO settings.
- The annual NS rate per 1000 admission trends for ESBL ENT was increasing ($P <.0001$) and the anuual rate per 1000 admissions trend for CRE was also increasing but not statistically significant (P=0.081). The rate trends for CR-PSA, VRE, and MRSA were decreasing (all $P < 0.05$) **(Table 1, Figure 1).**
  - For CO isolates there was a significant increase in rate per 1000 admissions for CRE ($P = 0.0237$) and ESBL ($P < 0.0001$).
  - For HO isolates there was a significant increase in rate per 1000 admissions for ESBL ($P < 0.0001$) and a significant decrease in CR-PSA ($P < 0.0001$), MRSA ($P < 0.0001$) and VRE ($P < 0.0001$).

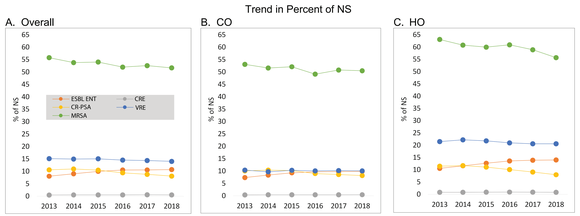
RESULTS (continued)

Table 1. Summary (unadjusted) Statistics of Admissions, Urine Isolates, Resistance (%NS and per 1000 Admissions) over Time and by Hospital Characteristics.

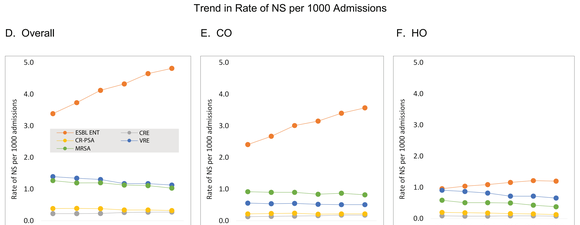
	Hospital Demographics		% NS					Per 1000 Admissions				
	Facilities	Admissions	ESBL	CRE	CR-PSA	VRE	MRSA	ESBL	CRE	CR-PSA	VRE	MRSA
			%NS (SD)*, (n/N)	%NS (SD)*, (n/N)	%NS (SD)*, (n/N)	%NS (SD)*, (n/N)	%NS (SD)*, (n/N)	Rate/1000 Adms	Rate/1000 Adms	Rate/1000 Adms	Rate/1000 Adms	Rate/1000 Adms
Characteristic	n (%)	n	n	n	n	n	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Overall			10.9 (7.7) (109,179/934,642)	0.77 (1.5) (8,737/1,016,642)	12.6 (17.4) (11,564/87,450)	17.3 (18.1) (38,719/205,258)	54.9 (29.0) (23,099/41,979)	4.7 (4.1)	.35 (.7)	.48 (.8)	1.5 (1.8)	1.2 (1.3)
CO	409	24,530,091	10.1 (7.7) (79,234/727,091)	0.64 (1.4) (5,285/780,137)	12.4 (19.3) (6,453/51,281)	13.0 (17.6) (16,021/120,176)	53.0 (31.3) (16,865/31,839)	3.5 (3.4)	.23 (.5)	.30 (.6)	.7 (1.0)	.9 (1.1)
HO			14.3 (14.4) (29,945/207,551)	1.27 (3.7) (3,452/236,505)	12.9 (21.7) (5,111/36,169)	23.8 (24.0) (22,698/85,082)	60.7 (38.7) (6,234/10,340)	1.2 (1.4)	.12 (.3)	.22 (.5)	.9 (1.3)	.5 (.7)
Year[a]												
2013	239 (58.4%)	3,025,887	9.1 (6.2) (10,681/113,300)	75 (1.4) (993/123,280)	13.6 (17.6) (1,625/10,958)	18.8 (19.3) (5,412/27,912)	57.8 (27.5) (3,213/5,563)	3.8 (3.2)	.32 (.6)	.49 (.7)	1.7 (1.7)	1.2 (1.1)
2014	274 (67.0%)	3,425,934	9.9 (7.5) (13,381/128,284)	76 (1.6) (1,173/139,554)	14.4 (19.4) (1,752/11,753)	18.1 (17.9) (5,800/30,371)	57.0 (28.8) (3,403/6,094)	4.1 (3.6)	.32 (.7)	.54 (.9)	1.7 (1.9)	1.2 (1.2)
2015	317 (77.5%)	3,939,061	10.6 (8.3) (17,430/148,898)	72 (1.4) (1,397/161,738)	13.6 (17.7) (2,037/13,927)	17.9 (18.7) (6,639/34,180)	55.6 (29.4) (3,916/6,994)	4.5 (4.3)	.31 (.6)	.51 (.7)	1.6 (1.9)	1.3 (1.6)
2016	373 (91.2%)	4,538,489	11.0 (8.0) (21,409/174,723)	76 (1.4) (1,650/190,209)	12.3 (17.1) (2,074/15,804)	16.3 (17.2) (6,929/37,468)	53.5 (29.0) (4,251/7,874)	4.7 (4.1)	.34 (.6)	.45 (.8)	1.4 (1.9)	1.1 (1.1)
2017	399 (97.6%)	4,976,960	11.7 (8.1) (23,897/191,791)	84 (1.5) (1,841/208,385)	11.6 (16.4) (2,167/17,923)	17.0 (17.8) (7,302/39,402)	54.9 (28.9) (4,469/8,231)	5.2 (4.6)	.39 (.7)	.44 (.7)	1.4 (1.7)	1.2 (1.3)
2018	376 (91.9%)	4,623,760	12.0 (7.4) (22,381/177,646)	79 (1.5) (1,713/193,476)	11.2 (16.8) (1,909/17,085)	16.5 (18.1) (6,637/35,925)	52.1 (29.8) (3,847/7,223)	5.3 (4.1)	.39 (.9)	.45 (.8)	1.4 (1.7)	1.1 (1.1)
HHS region[b]												
Region 2 (East coast)	43 (10.5%)	2,591,664	12.3 (7.2) (13,273/103,114)	1.66 (2.4) (1,780/111,762)	12.4 (15.6) (1,325/10,585)	20.0 (12.7) (5,479/25,936)	55.0 (26.1) (2,634/4,860)	5.0 (3.3)	.71 (1.0)	.50 (.6)	2.1 (1.8)	1.1 (.9)
Region 3 (East)	18 (4.4%)	818,166	8.7 (5.0) (3,358/38,383)	74 (1.2) (398/42,205)	7.8 (14.5) (289/3,480)	16.0 (11.5) (1,743/9,175)	52.0 (26.6) (964/1,809)	5.2 (3.7)	.45 (.8)	.33 (.6)	2.2 (2.1)	1.6 (1.3)
Region 4 (Southeast)	94 (23.0%)	6,347,177	11.4 (6.4) (28,928/247,068)	72 (1.3) (2,308/289,384)	12.6 (17.2) (3,317/24,741)	14.5 (16.3) (8,837/54,029)	59.7 (29.2) (6,699/11,335)	5.3 (3.9)	.36 (.8)	.53 (.8)	1.4 (1.7)	1.3 (1.2)
Region 5 (Central north)	96 (23.5%)	6,217,821	9.2 (6.5) (21,349/224,944)	78 (1.3) (2,162/245,262)	12.6 (16.5) (2,724/20,502)	23.1 (23.7) (11,392/49,534)	54.5 (28.8) (5,390/9,970)	3.7 (3.6)	.33 (.6)	.47 (.8)	1.8 (2.3)	1.2 (1.7)
Region 6 (Central south)	75 (18.3%)	4,562,851	12.0 (6.9) (21,505/173,317)	68 (1.3) (1,175/187,797)	15.8 (19.8) (2,292/14,899)	15.3 (14.8) (6,456/37,142)	55.2 (30.2) (3,845/6,977)	5.1 (4.2)	.30 (.7)	.53 (.7)	1.3 (1.3)	1.1 (1.2)
Region 9 (Southwest)	33 (8.1%)	2,023,989	16.7 (14.5) (15,739/80,158)	85 (1.2) (758/86,286)	15.2 (17.3) (1,314/7,466)	20.0 (17.4) (3,236/16,658)	50.3 (26.4) (2,093/4,108)	7.2 (6.5)	.36 (.5)	.58 (.8)	1.5 (1.3)	1.1 (.9)
Region 10 (Northwest)	18 (4.4%)	998,459	6.7 (5.2) (2,568/35,875)	20 (1.0) (59/39,067)	2.7 (9.0) (73/2,864)	8.0 (14.8) (425/5,679)	49.3 (29.6) (738/1,558)	2.6 (2.1)	.07 (.3)	.08 (.3)	.5 (.9)	1.0 (1.0)
Regions 1, 7, 8 (New England & Midwest)	32 (7.8%)	969,964	6.8 (5.2) (2,459/31,783)	.26 (.9) (77/34,879)	9.9 (19.9) (230/2,913)	12.5 (15.8) (1,131/7,105)	*45.5 (31.2) (735/1,562)*	2.3 (2.0)	.09 (.3)	.29 (.7)	1.0 (1.5)	.9 (1.0)

* The numbers of hospitals across years do not add up to 409 and may change from year to year.
[b]HHS regions are defined in the below (US territories were not included. Some regions were combined due to small subgroup sample size to facilitate analysis.).
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.

Figure 1. GEE Model Adjusted Percent of NS and Rate of NS per 1000 Admissions (Urine isolates) over Time (Year).



% of NS	ESBL ENT			CRE			CR-PSA			VRE			MRSA		
	Overall	CO	HO	Overall	CO	HO	Overall	CO	HO	Overall	CO	HO	Overall	CO	HO
Trend	Increase	Increase	Increase	Stable	Stable	Stable	Decrease	Decrease	Decrease	Stable	Stable	Stable	Decrease	Decrease	Decrease
P	<.0001	<.0001	<.0001	0.8784	0.4586	0.9590	<.0001	0.0063	<.0001	0.7852	0.9131	0.7733	0.0043	0.0248	0.0160



Rate of NS	ESBL ENT			CRE			CR-PSA			VRE			MRSA		
	Overall	CO	HO	Overall	CO	HO	Overall	CO	HO	Overall	CO	HO	Overall	CO	HO
Trend	Increase	Increase	Increase	Stable	Increase	Stable	Decrease	Stable	Decrease	Decrease	Stable	Decrease	Decrease	Stable	Decrease
P	<.0001	<.0001	0.0001	0.0813	0.0237	0.838	0.0486	0.6725	<.0001	0.0029	0.5372	<.0001	0.0004	0.1041	<.0001

Limitations

- These data were collected from the laboratory information system feeds provided by participating hospitals and relied on interpretive results reported at each facility.
- These data were collected and analyzed from the perspective of unique non-duplicate collected cultures and not from the perspective of unique patients.
- While the goal was to understand the volume and frequency of these organisms in clinical urine cultures with antimicrobial ordered across a large number of geographical diverse institutions, delineating true infections with symptoms and clinical acumen was beyond the scope of this study.

CONCLUSIONS

- In this large-scale study of patients in US hospitals, the incidence per 1000 admissions of non-duplicate urine isolates was highest for ESBLs followed by VRE, MRSA, CR-PSA and CRE.
- The percentage and rate per 1000 admissions of non-duplicate urine ESBL among ENT significantly increased in both the CO and HO settings between 2013 and 2018 and there was a significant increase in rate per 1000 admissions for CO CRE.
- There was a significant decrease in CR-PSA, MRSA and VRE between 2013 and 2018.
- This analysis during the first 5 years after the CDC published Antimicrobial Stewardship Program guidelines highlights an increasing ESBL rate in Community Onset (“admission period”) urine isolates while other drug resistant pathogens are relatively stable and continue to persist. Stewardship programs may be able to use this type of epidemiological information to better inform optimal therapy choices.

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