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Supplementary webappendix

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Supplemental Material

Needs Assessment for Novel Gram-Negative Antibiotics in US Hospitals: a Retrospective Cohort Study

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Supplemental Methods:

Data Source:

Cerner Health Facts Database is a de-identified, longitudinal and relational electronic health record (EHR) data set containing inpatient and outpatient records generated as a by-product of routine care at CERNER EHR client hospitals in the United States. The Cerner Health Facts Database only includes client hospitals that have agreed to share their data for research purposes. It includes over 300 data elements linked to patient encounters including demographics, diagnosis codes, procedure codes, lab results, medication orders and administrations, vital signs, microbiology and specific hospital characteristics. When compared to the nationally-representative Nationwide Inpatient Sample (Healthcare and Cost Utilization Project, Agency for Healthcare Quality and Research), the overall Cerner Health Facts Database contains relatively similar distribution patterns across patient and hospital characteristics, except with an overrepresentation of smaller (<99-bed) hospitals[1]. Data curation (described below) resulted in selection of hospitals with more complete reporting, including microbiology data. This subset of the overall data used for analysis in our study was also comparable to overall US non-federal acute-care hospitals characterized by the American Hospital Association (AHA) Hospital Statistics across a number of center-level characteristics (Table S10), albeit with minor differences in geographic distribution, and a greater contribution of large hospitals to the Cerner Health Facts study cohort.

Data Pruning-Incomplete Reporting:

To mitigate the impact of incomplete reporting–a common occurrence in real-world EHR datasets– we limited analysis to (a) encounters displaying at least one billing diagnosis code, one laboratory test and one medication order and (b) hospitals with less than 50 percent missingness across pharmacy, microbiology, and encounter-level data respectively. See figure S7.

Antibiotic administration:

Concomitant antibiotic administration was used as a proxy for presumed infection in an attempt to select for cultures that were likely to represent presumed infection and decrease the likelihood of cultures representing colonization. Antibiotic administration was defined as a prescription of a gram-positive agent within two days (to capture empiric therapy intent) or gram-negative agents within five days following the index culture (to capture empiric or targeted therapy intent) (Table S3).

Hierarchical Algorithm:

Monomicrobial and polymicrobial samples were merged. Polymicrobial samples were categorized into a single isolate name based on order of resistance profile [Difficult-to-treat resistance (DTR)> Carbapenem-resistant (CR)>Extended-cephalosporin resistant (ECR)] and subsequent remediation was done using ascending alphabetical order. Index cultures were identified based on the most severe resistance profile (DTR>CR>ECR) over each 14-day interval within an encounter. If two site cultures were positive for the same phenotype in a 14-day period, the one with the earliest draw date was selected. For episodes displaying growth of the same strain from multiple sites, the index site was selected in descending hierarchical order of putative treatment duration (bloodstream>lower respiratory>intra-abdominal>skin and soft tissue>urine>other). Hierarchical selection of taxon, site, and phenotype precluded double counting of treatment episodes for which a patient would already be on a treatment regimen. Index cultures were classified based on site and determined to have an associated secondary bloodstream infection if the same organism and resistance phenotype was identified in blood culture within three days of the index culture as adopted from the National Healthcare Safety Network (NHSN) surveillance definitions for identifying healthcare-associated infections.

β-lactam susceptible estimate:

Estimates for the number of episodes and days-of-therapy for non-resistant (i.e., neither DTR, CR, nor ECR) infections respectively were derived, enabling an understanding of treatment opportunities for DTR gram-negative infection (GNI) relative to non-resistant gram-negative infections. DTR episodes were derived by applying the antibiotic administration filter (to select for true infection) and the hierarchical algorithm (to avoid double counting) across all DTR isolates. These DTR isolate and corresponding episode counts were split by site to generate site-specific isolate-to-episode ratios, which were then individually applied to the count of non-resistant isolates for each site to generate the non-resistant episode and days-of-therapy estimates, thereby bypassing the antibiotic administration and hierarchical algorithm steps.

Recursive partition analysis:

The JMP partition platform recursively partitions data according to a relationship between the predictors and response values, creating a decision tree. We used the individual hospital's DTR status (DTR or non-DTR defined by presence or absence of at least 1 DTR isolate among inpatients at that hospital over the study period respectively) as the categorical response variable and hospital's census region, bed size, teaching, urban-rural, and acute status as predictor (explanatory) variables. At each splitting step, the algorithm fits the probabilities estimated for the response levels to choose the explanatory variable minimizing the residual log-likelihood chi-square. The algorithm divides the *X* categories of the explanatory variable into two groups of levels and considers all possible groupings into two levels. The same process is applied to each "child" node in a recursive manner until no further gain can be made. Each branch of the tree ends in a terminal node. Each observation falls into one and exactly one terminal node, and each terminal node is uniquely defined by a set of rules. The probability of being a DTR hospital was estimated at each terminal node.

Number of lives saved calculation:

We sought to calculate the number of lives that would be saved if DTR morality was decreased by 50% with a novel antibiotic. In our DTR cohort there were 292 DTR deaths from 2009-2015. Dividing 292 by 6 results in 49 deaths per year. Using the 80x multiplier extrapolating the CERNER cohort size used in this study to the American Health Association data we estimate that there are 3,920 deaths a year in the US associated with DTR infections, indicating nearly 2000 lives saved per year with a 50% reduction in mortality.

Variable construction:

ICD-codes used to generate mechanical ventilation and neutropenia are provided in supplemental table S11.

Table S1: Organisms of Interest

Taxa Categories	Isolate Names	Taxa Categories	Isolate Names
Achromobacter* species	*Achromobacter piechaudii*	***Escherichia coli*** †	*Escherichia coli*
	Achromobacter species		*Escherichia coli ESBL*
***Acinetobacter baumannii* complex**	*Acinetobacter baumannii*		*Escherichia coli O157*
	Acinetobacter baumannii/haemolyticus		*Escherichia coli, Carbapenem resistant*
Burkholderia* species	*Burkholderia gladioli*	***Klebsiella* species** †	*Klebsiella oxytoca*
	Burkholderia cepacia		*Klebsiella oxytoca ESBL*
	Burkholderia picketti		*Klebsiella pneumoniae*
	Burkholderia sp.		*Klebsiella pneumoniae ESBL*
***Citrobacter* species** †	*Citrobacter amalonaticus*		*Klebsiella pneumoniae ss pneumoniae*
	Citrobacter braakii		*Klebsiella pneumoniae, Carbapenem resistant*
	Citrobacter diversus	***Morganella* species** †	*Morganella morganii*
	Citrobacter farmeri		*Morganella morganii ss morganii*
	Citrobacter freundii		*Morganella morganii ss sibonii*
	Citrobacter koseri (diversus)		*Morganella sp.*
	Citrobacter sedlakii	***Panteoa* species** †	*Panteoa (Enterobacter) agglomerans*
	Citrobacter sp.		*Panteoa sp.*
	Citrobacter werkmanii	***Proteus* species** †	*Proteus mirabilis*
	Citrobacter youngae		*Proteus mirabilis / penneri*
***Enterobacter* species** †	*Enterobacter aerogenes*		*Proteus mirabilis ESBL*
	Enterobacter amnigenus		*Proteus penneri*
	Enterobacter asburiae		*Proteus sp.*
	Enterobacter cancerogenus		*Proteus vulgaris*
	Enterobacter cloacae		*Proteus vulgaris/Proteus penneri*
	Enterobacter cloacae complex	***Providencia* species** †	*Providencia rettgeri*
	Enterobacter gergoviae		*Providencia rustigianii*
	Enterobacter hormaechei		*Providencia sp.*
	Enterobacter intermedium		*Providencia stuartii*
	Enterobacter sakazakii	***Pseudomonas aeruginosa***	*Pseudomonas aeruginosa*
	Enterobacter sp.	***Serratia marcescens*** †	*Serratia marcescens*
	Enterobacter sp., Carbapenem resistant	***Stenotrophomonas maltophilia****	*Stenotrophomonas maltophilia*
	Enterobacter taylorae		

* Taxa not included in overall potential treatment population estimate and only analyzed individually

† Collapsed into *Enterobacteriaceae* spp.

Table S2: Resistance Phenotype Definitions

Definitions	Agents Included	Defining Criteria
Carbapenem Resistance*	imipenem, meropenem, doripenem, ertapenem †	Resistance to ≥1 carbapenem (*Enterobacteriaceae*); intermediate or resistant to ≥1 carbapenem (*Pseudomonas aeruginosa, Acinetobacter baumannii)*
Extended-spectrum cephalosporin-resistance*	ceftazidime, cefepime, ceftriaxone‡, cefotaxime ‡	Resistance to ≥1 extended-spectrum cephalosporin
Difficult-to-treat resistance[2]§		Intermediate or resistant to all reported agents in carbapenem, β-lactam, and fluoroquinolone categories (including additional agents¶,** when results available)

* Based on 2015 Centers for Disease Control definitions

† Applicable for Enterobacteriaceae spp. only

‡ Not applicable for *P. aeruginosa* and *Burkholderia* species

§ DTR assessment requires in vitro testing against >1 carbapenem, >1 extended spectrum cephalosporin, and >1 fluoroquinolone except for *S. maltophilia* which required testing to trimethoprim-sulfamethoxazole and levofloxacin only

¶ Intermediate or resistant to trimethoprim-sulfamethoxazole instead of carbapenems (*S. maltophilia* only).

** Intermediate or resistant to piperacillin-tazobactam and ampicillin-sulbactam (*A. baumannii* only), intermediate or resistant to aztreonam (not applicable for *A. baumannii*). These drugs were only included in the assessment of DTR when results reported.

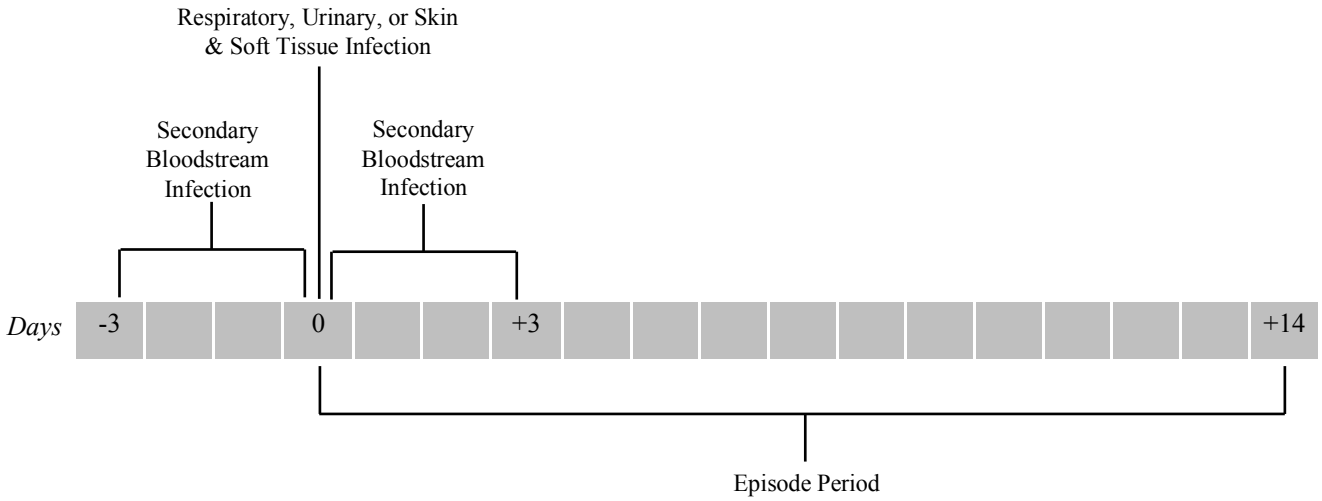
Table S3: Antibiotic Administrations Used as Clinical Indicators of True Infections

Definition	Antibiotics Included
Antibiotic administered on day of or day following index culture (day +1) – selective for Gram-positive organisms*	clindamycin, lincomycin, linezolid, oritavancin, tedizolid, telavancin, vancomycin (intravenous only)
Antibiotics administered on day of or day following index culture (day +1) – selective for Gram-positive organisms at non-respiratory site	daptomycin
Antibiotic administered on day of index culture and/or up to day 5 following the culture (Day +5)—selective for Gram negative organisms†	amikacin, amoxicillin, amoxicillin/clavulanate, ampicillin, ampicillin/sulbactam, azithromycin, aztreonam, cefaclor, cefadroxil, cefamandole, cefazolin, cefdinir, cefditoren, cefepime, cefixime, cefoperazone, cefotaxime, cefotetan, cefoxitin, cefpodoxime, cefprozil, ceftaroline, ceftazidime, ceftazidime/avibactam, ceftibuten, ceftizoxime, ceftolozane/tazobactam, ceftriaxone, cefuroxime, cephalexin, cephapirin, cephradine, chloramphenicol, cinoxacin, ciprofloxacin, clarithromycin, cloxacillin, colistin, dicloxacillin, doripenem, doxycycline, ertapenem, erythromycin, erythromycin/sulfisoxazole, fosfomycin, gatifloxacin, gentamicin, imipenem, kanamycin, metronidazole, mezlocillin, minocycline, moxifloxacin, nafcillin, nitrofurantoin, norfloxacin, ofloxacin, oxacillin, penicillin, piperacillin, polymyxin B, tetracycline, ticarcillin, ticarcillin/clavulanate, tigecycline, tobramycin, trimethoprim/sulfamethoxazole

*Gram-positive agents used on day of culture or the following day consistent with empiric antibiotic therapy and indicating clinician concern for infection in the absence of microbiology data

†Gram-negative agents used on day of culture and/or up to day 5 thereafter to indicate targeted therapy

Figure S1: Operational Schematic of Secondary Bloodstream Infection and Episode Window



Legend: Index cultures were determined by the most resistant isolate (DTR>CR>ECR) in 14-day intervals. Index cultures were classified by site and evaluated for secondary bloodstream infection if there was a positive culture within +/- 3 days with the same organism and phenotype. After the defined episode was established, no further analysis was performed within the 14-day episode period (i.e., if a positive culture was present in the 14-day window meeting one of the resistance phenotypes of interested, it was not included in the overall market size estimate because the episode was already assigned as a treatment opportunity). For encounters that were longer than 14-days, repeat episodes were evaluated in 14-day intervals.

Table S4a: Conservative Empiric Therapy Estimate

	Episodes*	DOT	DOT/10,000 Encounters
1 Day of Colistin/Polymyxin B[†]	1,728	1,728	5·8
2 Days of Colistin/Polymyxin B	37	74	0·2
Total Colistin/Polymyxin B	**1,765**	**1,802**	**6·0**

Table S4b: Liberal Empiric Therapy Estimate

	Episodes*	DOT	DOT/10,000 Encounters
1 Day of Colistin/Polymyxin B[†]	1,728	1,728	5·8
2 Days of Colistin/Polymyxin B	37	74	0·2
1 Day of Aminoglycosides[‡§]	12,414	12,414	41·4
2 Days of Aminoglycosides	4,218	8,436	28·2
Total Empiric Therapy	**18,397**	**22,652**	**75·6**

Table S4c: Additional Empiric Antibiotics[¶] not Included in Overall Analysis

	Episodes*	DOT	DOT/10,000 Encounters
1 Day of Tigecycline	271	271	0·9
2 Days of Tigecycline	270	540	1·8
3 Days of Tigecycline	234	702	2.3
3 Days of Colistin/Polymyin-B	35	105	0.4
3 Days of Aminoglycosides	2026	6078	20.3

* Episodes with multiple instances of 2-days or less within a 14-day period were excluded as were episodes where the last day of antibiotic administration and discharge day were the same.

† Colistin and polymyxin B mapped as a single variable in dataset

‡ Aminoglycosides include amikacin, gentamicin, and tobramycin

§ Encounters admitted to an obstetric service or with a diagnosis code for non-tuberculosis mycobacterial infections were removed due to potential non-DTR indications for aminoglycoside therapy

¶ Investigated for prevalence within dataset but not included in overall analysis

Table S5: Treatment Opportunities for Gram Negative Active Antibiotic Against β-Lactam Susceptible Infections Using Conservative* and Liberal† Treatment Durations

	Culture Site	Site-specific episode-to-isolate ratio‡	Raw Isolate Count§	Confirmed Infection Episodes¶	DOT of Confirmed Infections
Conservative Treatment Duration	Urinary (5 DOT)	0·56	99,645	55,637	27,8187
	Intra-abdominal (7 DOT)	0·57	8,072	4,567	31,969
	Lower Respiratory (8 DOT)	0·60	19,232	11,513	92,108
	Skin Soft Tissue (5 DOT)	0·58	17,145	9,957	49,786
	Other (5 DOT)	0·41	4,067	1,675	8,373
	Bloodstream (14 DOT)	0·79	20,999	16,673	233,416
	Total	**0·59**	**169,160**	**100,022**	**693,839**
	Per 10,000 encounters	**--**	**564·6**	**333·8**	**2,315.7**
Liberal Treatment Duration	Urinary (14 DOT)	0·56	99,645	55,637	778,923
	Intra-abdominal (14 DOT)	0·57	8,072	4,567	63,939
	Lower Respiratory (14 DOT)	0·60	19,232	11,513	161,189
	Skin Soft Tissue (14 DOT)	0·58	17,145	9,957	139,402
	Other (14 DOT)	0·41	4,067	1,675	23,445
	Bloodstream (14 DOT)	0·79	20,999	16,673	233,416
	Total	**0·59**	**169,160**	**100,022**	**1,400,313**
	Per 10,000 encounters	**--**	**564·6**	**333·8**	**4,673.5**

* Conservative treatment duration as per guideline review and clinical practice recommendations.[3-6] Since no guidelines exist for bacteremia a 14-day treatment course was selected arbitrarily.

† Treatment duration of 14 days for all sites.

‡ The site-specific episode-to-isolate ratios were derived from the site-specific drop from DTR isolates to episode counts after the application of both antibiotic administration filter and hierarchical algorithm. 2,288 DTR isolates were identified prior to antibiotic administration and hierarchical algorithms (754 urinary, 76 intra-abdominal, 897 lower respiratory, 260 skin soft tissue, 102 other, 199 bloodstream) which were used to calculate the site-specific multiplier based on the confirmed infection episode counts shown in Table 1.

§Raw infection isolates is the total number of isolates prior to antibiotic administration and hierarchical algorithm.

¶Confirmed infections episodes is calculated by multiplying the raw infection isolates by the infection confirmation rate.

Table S6: Demographics of DTR-GNI Encounters by Presumed Site of Infection

	Blood	Lower Respiratory	Urinary	Skin & Soft Tissue	Intra-abdominal	All Sites*
Age Category – no.(%)						
0 years	0 (0)	2 (0·4)	0 (0)	0 (0)	0 (0)	2 (0·2)
1-17 years	5 (3·2)	22 (4·1)	7 (1·7)	1 (0·7)	1 (2·3)	37 (2·8)
18-44 years	31 (19·7)	110 (20·6)	67 (16·4)	32 (21·6)	4 (9·3)	259 (19·5)
45-64 years	59 (37·6)	175 (32·8)	126 (30·9)	52 (35·1)	18 (41·9)	447 (33·6)
65+ years	62 (39·5)	225 (42·1)	208 (51)	63 (42·6)	20 (46·5)	584 (43·9)
Gender – no.(%)						
Female	58 (36·7)	229 (42·6)	204 (48·5)	68 (45)	22 (51·2)	604 (44·7)
Male	100 (63·3)	308 (57·4)	217 (51·5)	83 (55)	21 (48·8)	748 (55·3)
Race – no.(%)						
Black	60 (38)	121 (22·5)	130 (30·9)	68 (45)	10 (23·3)	411 (30·4)
White	81 (51·3)	338 (62·9)	260 (61·8)	71 (47)	27 (62·8)	797 (58·9)
Other	17 (10·8)	78 (14·5)	31 (7·4)	12 (7·9)	6 (14)	144 (10·7)
ICU Admission on Culture Day – no.(%)	56 (35·4)	213 (39·7)	76 (18·1)	34 (22·5)	12 (27·9)	407 (30·1)
Neutropenia – no.(%)	7 (4·4)	3 (0·6)	4 (1)	1 (0·7)	0 (0)	15 (1·1)
Mechanical Ventilation – no. (%)	58 (36·7)	221 (41·2)	70 (16·6)	21 (13·9)	7 (16·3)	391 (28·9)
Isolate Name – no.(%)						
Acinetobacter baumannii	48 (30·4)	167 (31·1)	75 (17·8)	65 (43)	12 (27·9)	387 (28·6)
Escherichia coli	5 (3·2)	3 (0·6)	19 (4·5)	3 (2)	2 (4·7)	32 (2·4)
Enterobacter spp.	4 (2·5)	7 (1·3)	18 (4·3)	4 (2·6)	1 (2·.3)	36 (2·7)
Klebsiella spp.	61 (38·6)	82 (15·3)	181 (43)	26 (17·2)	11 (25·6)	368 (27·2)
Other *Enterobacteriaceae spp.*[†]	2 (1·3)	3 (0·6)	4 (1)	6 (4)	0 (0)	15 (1·1)
Pseudomonas aeruginosa	38 (24·1)	275 (51·2)	124 (29·5)	47 (31·1)	17 (39·5)	514 (38)
Patient Deceased – no.(%)	62 (39·2)	120 (22·4)	42 (10)	17 (11·3)	8 (18·6)	254 (18·8)
Elixhauser – median(IQR)	4 (3-4)	4 (3-4)	4 (3-4)	4 (3-4)	3 (3-4)	4 (2-6)
Culture-day SOFA Score – median(IQR)	4 (3-5)	3 (3-5)	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-5)
Census Region – no.(%)						
Midwest	29 (18·4)	45 (8·4)	57 (13·5)	38 (25·2)	8 (18·6)	182 (13·5)
Northeast	44 (27·.9)	162 (30·2)	141 (33·5)	29 (19·2)	9 (20·9)	390 (28·8)
South	79 (50)	254 (47·3)	191 (45·5)	77 (51)	19 (44·2)	644 (47·6)
West	6 (3·8)	76 (14·2)	32 (7·6)	7 (4·6)	7 (16·3)	136 (10·1)
Bed Size Range – no.(%)						
<100	6 (9·1)	30 (5·6)	21 (5·0)	4 (2·6)	1 (2·3)	66 (4·9)
100-299	44 (11·7)	129 (24·0)	121 (28·7)	56 (37·1)	14 (32·6)	376 (27·8)
300+	108 (11·9)	378 (70·4)	279 (66·3)	91 (60·3)	28 (67·6)	910 (67·3)
Urban Hospital – no.(%)	114 (72·2)	374 (69·7)	309 (73·4)	133 (88·1)	30 (69·8)	992 (73·4)
Teaching Facility – no.(%)	135 (85·4)	433 (80·6)	337 (80·1)	132 (87·4)	32 (74·4)	1097 (81·1)

*Inclusive of those infections not categorized as blood, lower respiratory, urinary, skin & soft tissue, or intra-abdominal

[†]Composed of *Citrobacter* spp., *Morganella* spp., *Panteoa* spp., *Proteus* spp., *Providencia* spp., *Serratia marcescens*

Table S7: Treatment Opportunities for Gram Negative Active Antibiotic Against DTR, CR, and ECR Phenotypes for Individual Enterobacteriaceae spp.*†‡

Citrobacter spp.	DTR		CR		ECR	
Culture Site	**Episodes**	**DOT**	**Episodes**	**DOT**	**Episodes**	**DOT**
Urinary (5 DOT)	2	10	6	30	287	1435
Intra-abdominal (7 DOT)	0	0	0	0	10	70
Respiratory (8 DOT)	2	16	2	16	24	192
Skin Soft Tissue (5 DOT)	1	5	2	10	20	100
Other (5 DOT)	0	0	0	0	6	30
Primary Blood Stream (14 DOT)	2	28	1	14	23	322
Secondary Blood Stream (14 DOT)	0	0	0	0	2	28
Total	7	59	11	70	372	2177
DOT per 10,000 Encounters		0·20		0·23		7·3

Panteoa spp.	DTR		CR		ECR	
Culture Site	**Episodes**	**DOT**	**Episodes**	**DOT**	**Episodes**	**DOT**
Urinary (5 DOT)	0	0	0	0	5	25
Intra-abdominal (7 DOT)	0	0	0	0	0	0
Respiratory (8 DOT)	0	0	0	0	2	16
Skin Soft Tissue (5 DOT)	1	5	0	0	1	5
Other (5 DOT)	0	0	0	0	0	0
Primary Blood Stream (14 DOT)	0	0	5	70	2	28
Secondary Blood Stream (14 DOT)	0	0	0	0	0	0
Total	1	5	5	70	10	74
DOT per 10,000 Encounters		0·02		0·23		0·25

Enterobacter spp.	DTR		CR		ECR	
Culture Site	**Episodes**	**DOT**	**Episodes**	**DOT**	**Episodes**	**DOT**
Urinary (5 DOT)	18	90	53	265	699	3495
Intra-abdominal (7 DOT)	1	7	16	112	66	462
Respiratory (8 DOT)	8	64	19	152	313	2504
Skin Soft Tissue (5 DOT)	4	20	8	40	152	760
Other (5 DOT)	2	10	6	30	32	160
Primary Blood Stream (14 DOT)	3	42	15	210	128	1792
Secondary Blood Stream (14 DOT)	1	14	0	0	31	434
Total	37	247	117	809	1421	9607
DOT per 10,000 Encounters		0·82		2·7		32·1

Proteus spp.	DTR		CR		ECR	
Culture Site	**Episodes**	**DOT**	**Episodes**	**DOT**	**Episodes**	**DOT**
Urinary (5 DOT)	1	5	46	230	370	1850
Intra-abdominal (7 DOT)	0	0	3	21	11	77
Respiratory (8 DOT)	0	0	11	88	51	408
Skin Soft Tissue (5 DOT)	2	10	11	55	88	440
Other (5 DOT)	0	0	3	15	12	60
Primary Blood Stream (14 DOT)	0	0	7	98	34	476
Secondary Blood Stream (14 DOT)	0	0	0	0	19	266
Total	3	15	81	507	585	3577
DOT per 10,000 Encounters		0·05		1·7		11·9

Escherichia coli	DTR		CR		ECR	
Culture Site	**Episodes**	**DOT**	**Episodes**	**DOT**	**Episodes**	**DOT**
Urinary (5 DOT)	19	95	59	295	3182	15910
Intra-abdominal (7 DOT)	2	14	8	56	123	861
Respiratory (8 DOT)	4	32	5	40	230	1840
Skin Soft Tissue (5 DOT)	3	15	1	5	154	770
Other (5 DOT)	0	0	1	5	40	200
Primary Blood Stream (14 DOT)	5	70	6	84	402	5628
Secondary Blood Stream (14 DOT)	0	0	0	0	250	3500
Total	33	226	80	485	4381	28709
DOT per 10,000 Encounters		0·75		1·6		95·8

Serratia spp.	DTR		CR		ECR	
Culture Site	**Episodes**	**DOT**	**Episodes**	**DOT**	**Episodes**	**DOT**
Urinary (5 DOT)	1	5	4	20	30	150
Intra-abdominal (7 DOT)	0	0	1	7	2	14
Respiratory (8 DOT)	0	0	8	64	48	384
Skin Soft Tissue (5 DOT)	1	5	3	15	21	105
Other (5 DOT)	0	0	3	15	12	60
Primary Blood Stream (14 DOT)	0	0	4	56	16	224
Secondary Blood Stream (14 DOT)	0	0	0	0	3	42
Total	2	10	23	177	132	979
DOT per 10,000 Encounters		0·03		0·59		3·3

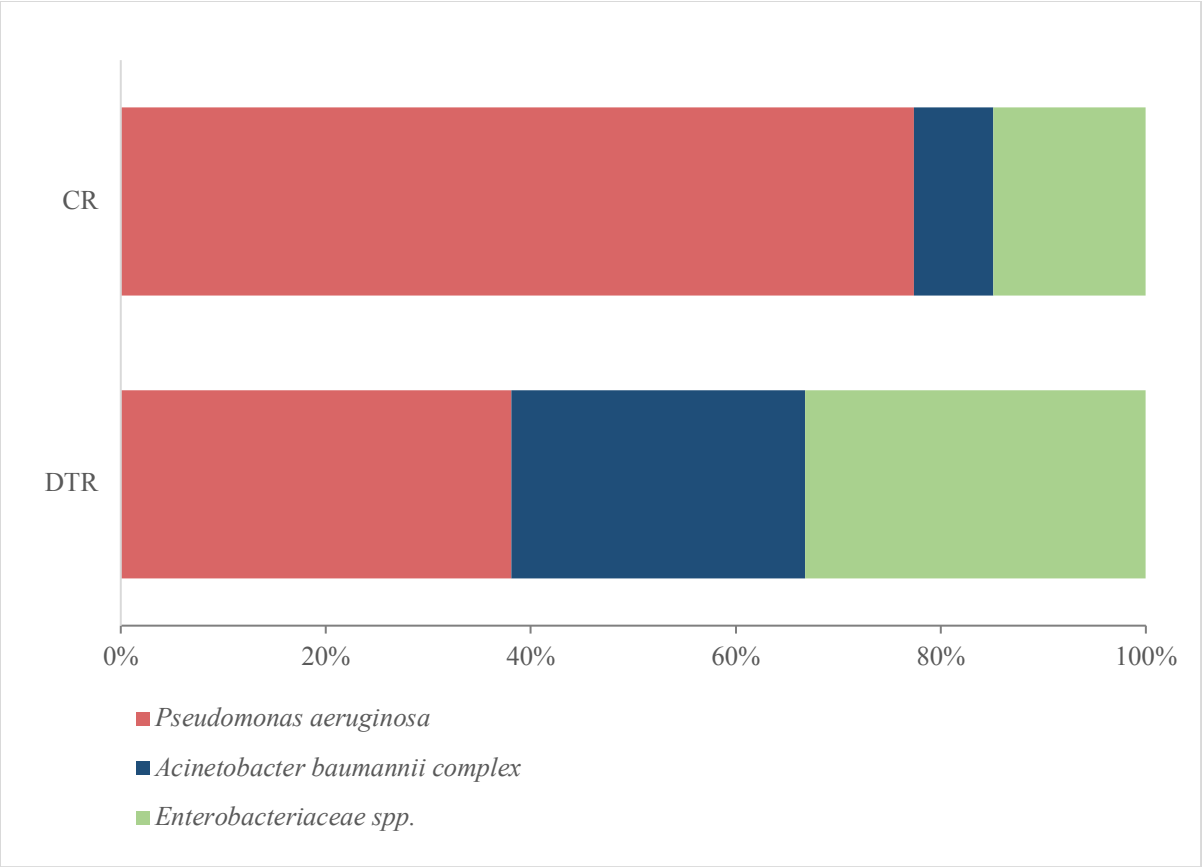
Klebsiella spp.	DTR		CR		ECR	
Culture Site	**Episodes**	**DOT**	**Episodes**	**DOT**	**Episodes**	**DOT**
Urinary (5 DOT)	181	905	32	160	853	4265
Intra-abdominal (7 DOT)	11	77	5	35	32	224
Respiratory (8 DOT)	84	672	22	176	221	1768
Skin Soft Tissue (5 DOT)	26	130	5	25	93	465
Other (5 DOT)	8	40	3	15	23	115
Primary Blood Stream (14 DOT)	42	588	14	196	146	2044
Secondary Blood Stream (14 DOT)	19	266	4	56	49	686
Total	371	2678	85	663	1417	9567
DOT per 10,000 Encounters		8·9		2·2		31·9

Providencia spp.	DTR		CR		ECR	
Culture Site	**Episodes**	**DOT**	**Episodes**	**DOT**	**Episodes**	**DOT**
Urinary (5 DOT)	0	0	10	50	55	275
Intra-abdominal (7 DOT)	0	0	1	7	1	7
Respiratory (8 DOT)	1	8	3	24	13	104
Skin Soft Tissue (5 DOT)	0	0	4	20	19	95
Other (5 DOT)	0	0	0	0	6	30
Primary Blood Stream (14 DOT)	0	0	1	14	9	126
Secondary Blood Stream (14 DOT)	0	0	1	14	2	28
Total	1	8	20	129	105	665
DOT per 10,000 Encounters		0·03		0·43		2·2

Morganella spp.	DTR		CR		ECR	
Culture Site	**Episodes**	**DOT**	**Episodes**	**DOT**	**Episodes**	**DOT**
Urinary (5 DOT)	0	0	9	45	108	540
Intra-abdominal (7 DOT)	0	0	0	0	4	28
Respiratory (8 DOT)	0	0	3	24	13	104
Skin Soft Tissue (5 DOT)	1	5	1	5	25	125
Other (5 DOT)	0	0	0	0	3	15
Primary Blood Stream (14 DOT)	0	0	3	42	14	196
Secondary Blood Stream (14 DOT)	0	0	1	14	1	14
Total	1	5	17	130	168	1022
DOT per 10,000 Encounters		0·02		0·43		3·4

*Hierarchical algorithm for generating market size estimates was applied to individual datasets that included only the organism of interest
†All categories (DTR, CR, and ECR) are mutually exclusive groups (DTR category excludes any isolates that are only carbapenem resistant
‡Conservative treatment duration as per guideline review and clinical practice recommendations. Since no specific guidelines exist for bacteremia due to antibiotic-resistant gram-negative pathogens, a 14-day treatment course was selected arbitrarily [3-6]

Figure S2: Species Level Comparisons of DTR-GNI and CR-GNI



Legend: Species level comparisons were done between GNI with DTR and CR phenotypes. *Pseudomonas aeruginosa* makes up a disproportionally higher percentage of the CR market (77%) as compared to the DTR market (38%) implying that there are a significant number of CR-*Pseudomonas aeruginosa* infections that have a first line agent available. DTR and CR are treated as mutually exclusive groups (the CR category excludes any isolates that classify as DTR).

Table S8: DTR-GNI Treatment Opportunities for *Stenotrophomonas* maltophilia*, *Burkholderia spp.*, and *Achromobacter spp.* ¶

	Stenotrophomonas maltophilia				*Burkholderia* spp.		*Achromobacter* spp.	
Culture Site	**Episodes†**	**DOT†**	**Additional Episodes‡**	**DOT‡**	**Episodes**	**DOT**	**Episodes**	**DOT**
Urinary (5 DOT)	2	10			0	0	0	0
Intra-abdominal (7 DOT)	0	0			0	0	0	0
Lower Respiratory (8 DOT)	15	120			19	152	11	88
Skin Soft Tissue (5 DOT)	1	5			0	0	0	0
Other (5 DOT)	0	0			0	0	0	0
Primary Bloodstream (14 DOT)	1	14	8§	112	1	14	0	0
Secondary Bloodstream (14 DOT)	0	0			0	0	0	0
Total	**19**	**149**	**8**	**112**	**19**	**152**	**11**	**88**
Days of therapy per 10,000 encounters		**0·50**		**0·37**		**0·51**		**0·29**

*Hierarchical algorithm for generating market size estimates was applied to a dataset that included only the organism of interest individually

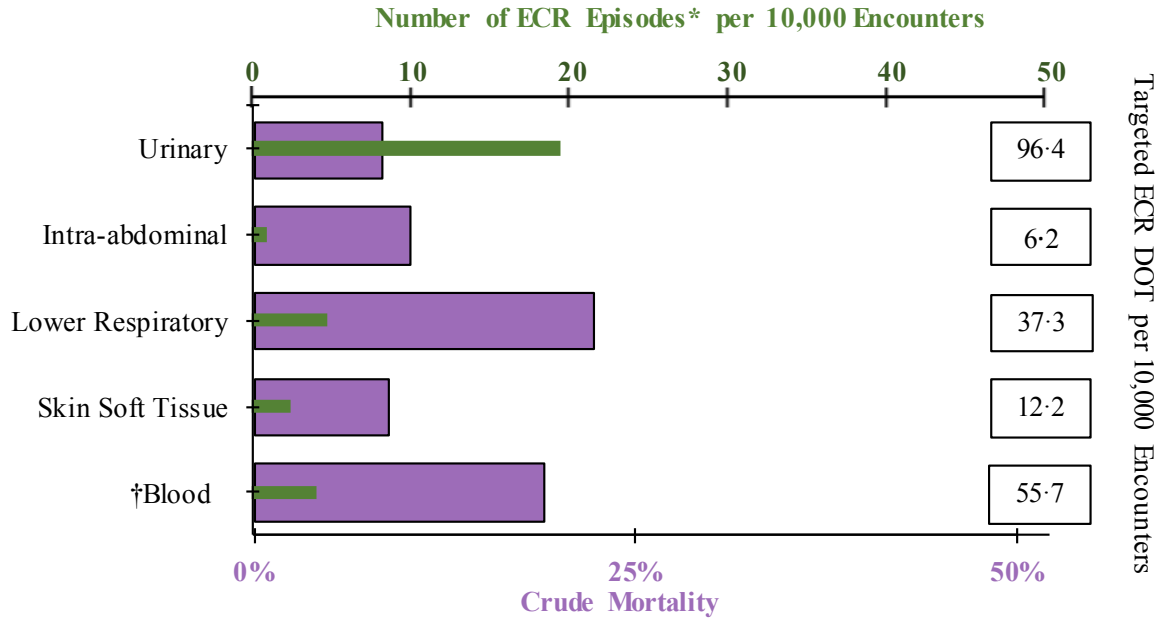
¶ There were 3,652 *Stenotrophomas maltophilia*, 315 *Burkholderia* spp., and 128 *Achromobacter* spp. isolates prior to hierarchical selection of resistant isolates

†Trimethoprim-sulfamethoxazole resistance required to meet DTR definition, testing for carbapenem resistance not required

‡Trimethoprim-sulfamethoxazole resistance not required (modified DTR definition for *Stenotrophomonas maltophilia* bloodstream isolates), testing for carbapenem resistance not required

§When trimethoprim-sulfamethoxazole resistance is not required 8 additional bloodstream infections were identified for a total of 9 primary bloodstream infections.

Figure S3: Episodes and Targeted Treatment Opportunities for ECR-GNI and Crude Mortality



Legend: Mortality estimates were compared with prevalence of ECR infection by site. Thin dark green bars represent ECR episodes per 10,000 encounters by site. Thick purple bars represent associated ECR mortality. While lower respiratory had the highest mortality, urinary was the most prevalent.

* Includes all infection types per site. "Other" infection site not included in this visualization.

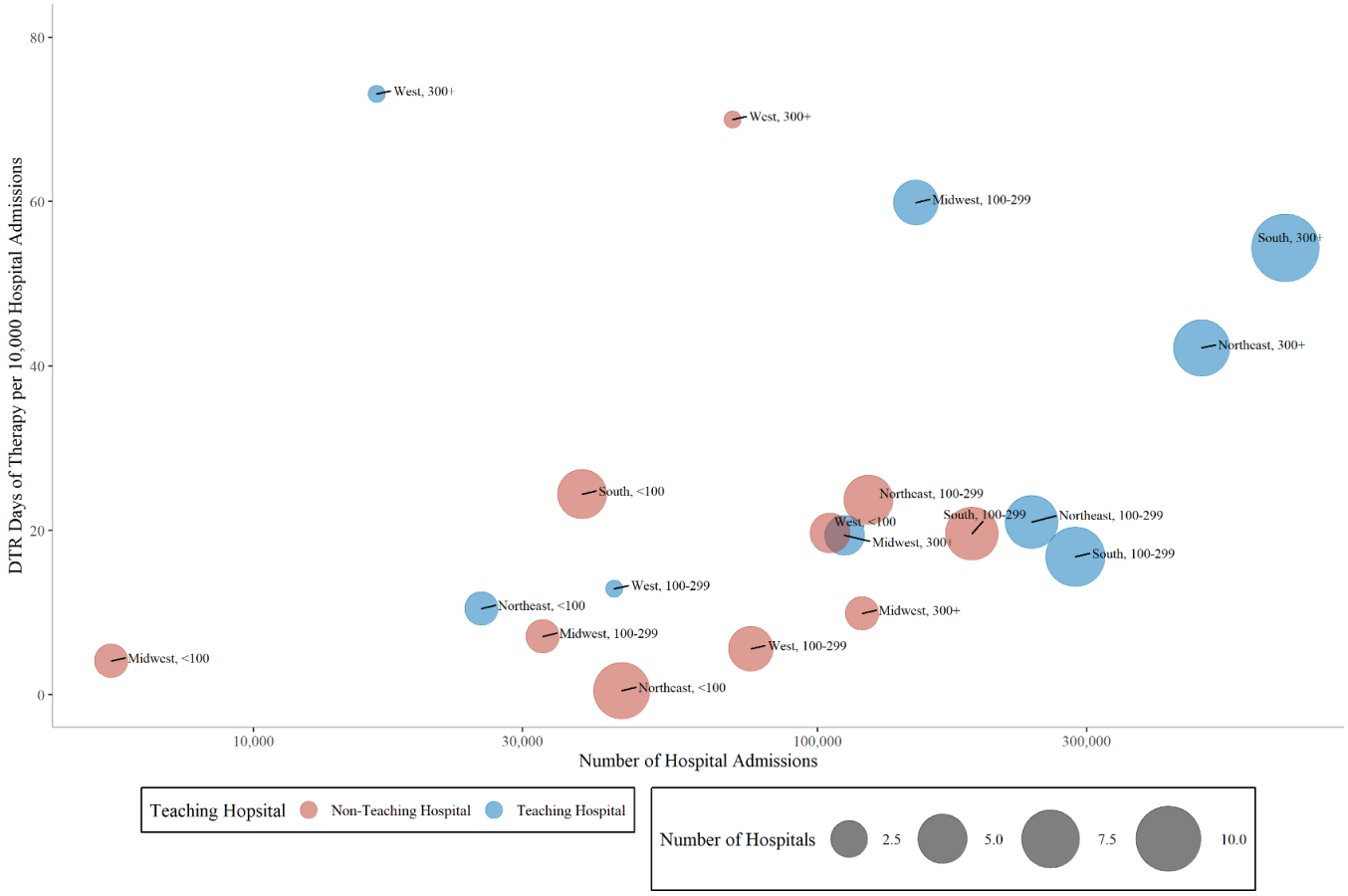
† 39 of 226 (17·3%) bloodstream infections are secondary to urinary (n=25), lower respiratory (n=7), skin and soft tissue (n=5), and intra-abdominal (n=2) sites

Table S9: Reliability Adjusted DTR-GNI DOT Rates and Absolute Burden by Hospital Characteristics

	Reliability Adjusted		Unadjusted	
Hospital Category	**DOT/10k Encounters**	**Absolute DOT**	**DOT/10k Encounters**	**Absolute DOT**
West, 300+ Beds, Teaching Hospital	73·1	121	73·8	122
West, 300+ Beds, Non-Teaching Hospital	70·0	495	70·2	496
Midwest, 100-299 Beds, Teaching Hospital	59·9	895	59·9	896
South, 300+ Beds, Teaching Hospital	54·4	3,678	54·5	3,682
Northeast, 300+ Beds, Teaching Hospital	42·2	2,024	42·2	2,025
South, <100 Beds, Non-Teaching Hospital	24·4	93	24·5	184
Northeast, 100-299 Beds, Non-Teaching	23·7	292	23·7	293
Northeast, 100-299 Beds, Teaching	21·0	504	21·0	503
West, <100 Beds, Non-Teaching Hospital	19·7	207	19·7	253
South, 100-299 Beds, Non-Teaching Hospital	19·6	368	19·6	384
Midwest, 300+ Beds, Teaching Hospital	19·4	217	19·4	269
South, 100-299 Beds, Teaching Hospital	16·8	482	16·8	481
West, 100-299 Beds, Teaching Hospital	12·9	56	12·8	56
Northeast, <100 Beds, Teaching Hospital	10·5	27	10·4	29
Midwest, 300+ Beds, Non-Teaching Hospital	9·9	119	9·8	118
Midwest, 100-299 Beds, Non-Teaching Hospital	7·1	23	6·9	29
West, 100-299 Beds, Non-Teaching Hospital	5·6	43	5·5	49
Midwest, <100 Beds, Non-Teaching Hospital	4·1	2	3·7	10
Northeast, <100 Beds, Non-Teaching Hospital	0·5	2	--	0

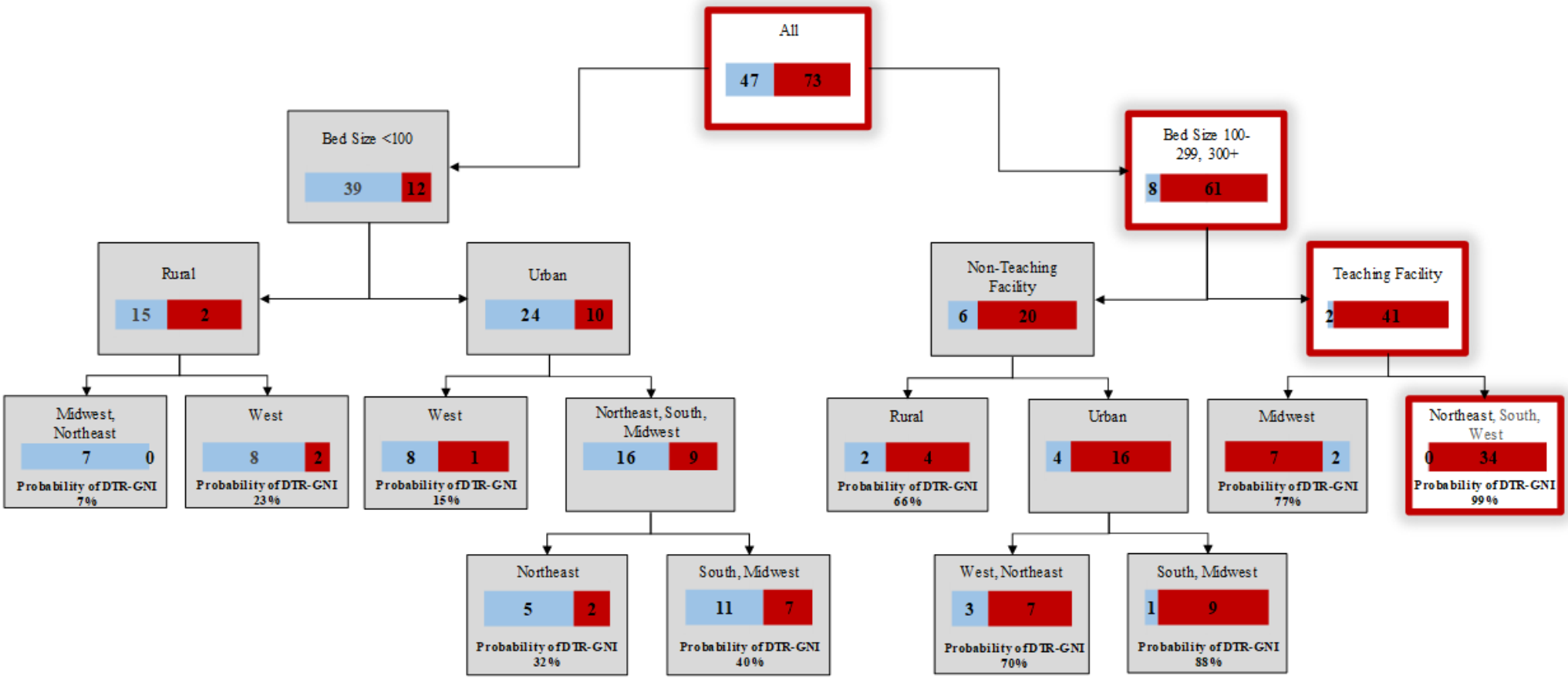
Legend: All 120 hospitals with presumed infections were grouped based on hospital characteristics including hospital size, teaching status, and region. Reliability adjustments were performed using random effects logistic regression to evaluate DTR-DOT rates of treatment opportunities by hospital characteristics. This method shrinks estimates towards the mean based on the reliability of individual hospital estimates. Teaching hospitals with bed size in the West had the highest rate of DTR-DOT while teaching hospitals from the south with 300+ beds had the highest absolute burden. Confidence intervals not calculated because of random effects model.

Figure S4: Plot of DTR Days of Therapy Rates by Hospital Admissions and Characteristics



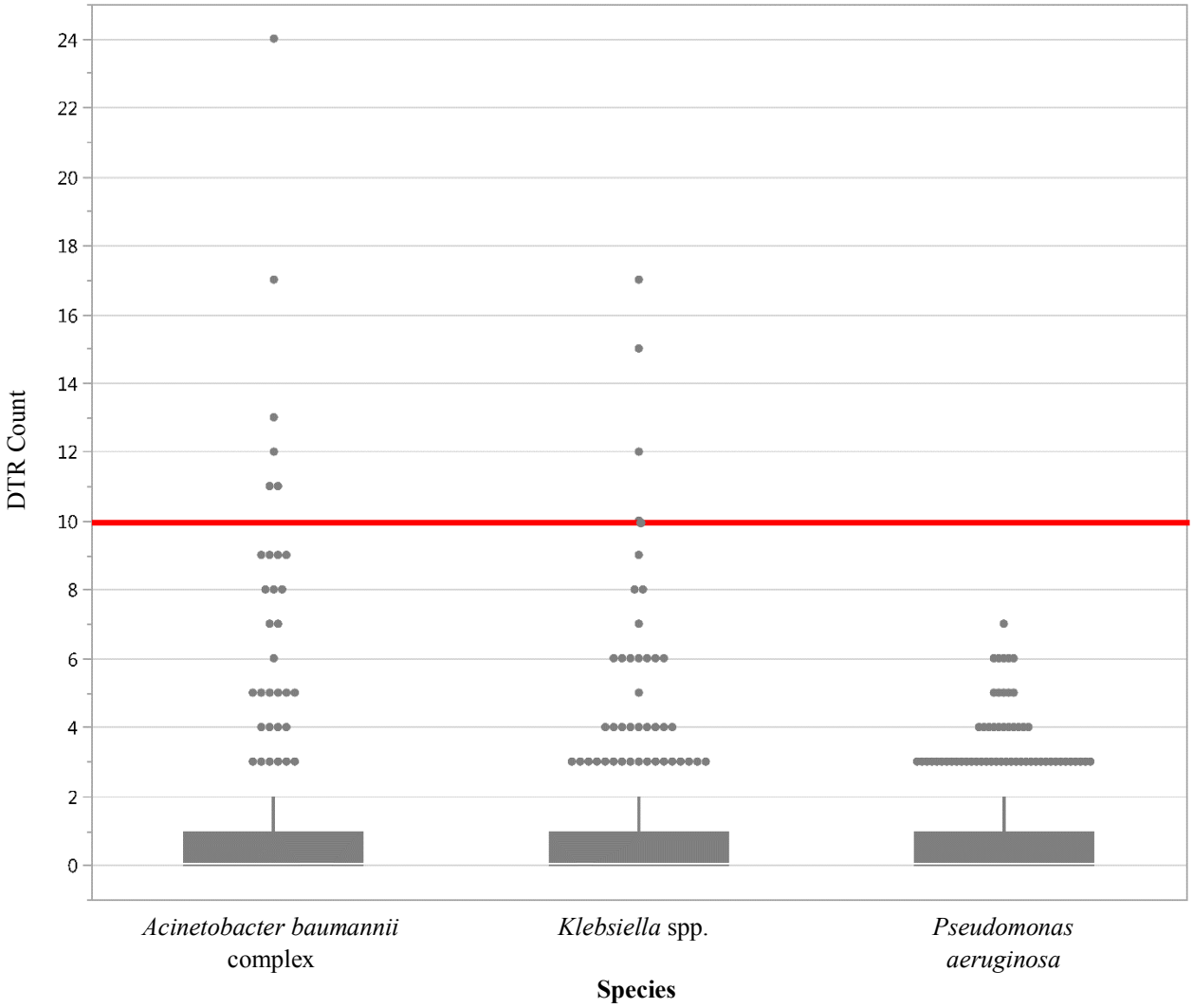
Legend: Hospitals were grouped based on teaching status, bed-size, and geographic region. Random effects logistic regression was used to calculate an adjusted DTR DOT rate per 10,000 DOT encounters for each hospital group. The size of each circle indicates the number of hospitals represented in each group. Blue circles indicate teaching hospitals and red indicate non-teaching. The highest rate of DTR was observed in teaching hospitals in the west with 300+ beds (adjusted rate of 73·1 DTR episodes/10,000 DOT).

Figure S5: Partitioning Analysis Evaluating Hospital Characteristics Associated with Likelihood of Encountering a DTR-GNI



Legend: Recursive partition analysis was used to build a decision tree to predict hospital characteristics associated with the likelihood a hospital would encounter at least one episode of DTR-GNI. Each node represents an individual partition in which variables are conditionally selected based on results of prior node. Percentage displayed in each terminal node represents the probability of having a DTR-GNI encounter at a hospital with the respective characteristics as partitioned. Of the 120 hospitals with a presumed infection episode 73 had at least one DTR-GNI from 2009-2015 and 47 had no DTR episodes. The factor most associated with likelihood of DTR episodes at a hospital was bed size ≥100.

Figure S6: Boxplot Distribution of Difficult-to-Treat Resistance (DTR) Episodes per Hospital by Quarter



Legend: Hospitals were clustered and evaluated by quarter to identify species-level outbreaks. The red line represents a *post hoc* "outbreak threshold" defined as hospital quarters with 10 or more DTR episodes per organism. DTR-*Acinetobacter baumannii* complex was the species with the highest number of episodes in a single quarter (24) and six hospital quarters with outbreaks across 2 hospitals. DTR-*Klebsiella* species had a maximum of 17 per quarter and four hospital quarters with an outbreak across 2 hospitals, while *Pseudomonas aeruginosa* had a maximum of seven per quarter and no hospital outbreaks.

Table S10: Comparison of *Cerner Healthfacts* Database Cohort Hospital Characteristics with American Hospital Association (AHA) Hospital Statistics

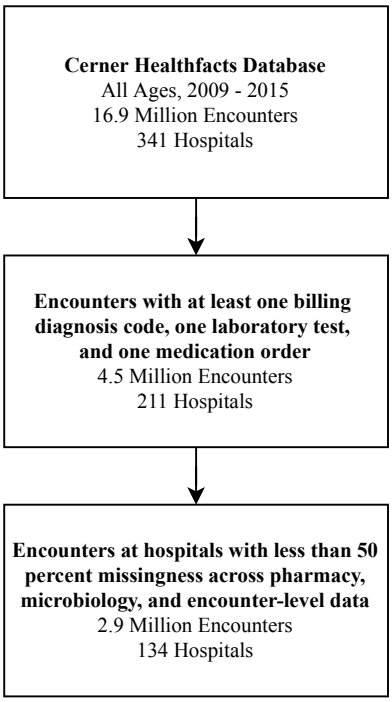
Characteristics	Cerner Hospitals in Study		AHA – 2015*	
	N	%	N	%
	132		5,280	
Region				
Midwest	27	20	1,510	29
Northeast	32	24	648	12
South	44	33	2,133	40
West	29	22	989	19
Urban Location	101	77	3,393	64
Teaching Status				
Non-Teaching	81	61	3,450	65
Teaching†	51	39		
Major Teaching‡			267	5
Minor Teaching§			1,563	30
Bed Capacity				
<100	58	44	2,941	56
100-299	45	34	1,552	29
300+	29	22	787	15

* AHA community hospitals defined as nonfederal, short-term care hospitals open to the general public regardless of teaching status[7]
†affiliated with an *Association of American Medical Colleges (*AAMC) accredited medical school
‡member of AAMC's Council of Teaching Hospitals
§medical school affiliation reported to *American Medical Association (*AMA), training approved by *American Osteopathic Association (*AOA), at least 1 *Accreditation Council for Graduate Medical Education* (ACGME) accredited program.

Table S11: ICD Codes Used to Define Mechanical Ventilation and Neutropenia

Type	Mechanical Ventilation	Neutropenia
ICD 9	96·7	288·00
	96·71	288·04
	96·72	
ICD 10	5A1935Z	D70·3
	5A1945Z	D70·9
	5A1955Z	

Figure S7: Data Curation Effects on Study Population



Legend: The flowchart presents the stepwise drop in the sample size of the study population with each data curation step using rules set *a priori* to maximize use of more complete data at the encounter and hospital level.

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