Yılın Ses Getiren Makaleleri

KLİMİK Aylık Toplantısı
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Clinical Infectious Diseases

MAJOR ARTICLE

Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents

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173 Amerikan Hastanesi'nde tedavisi güç Gr(-) Bakteriyemiler: 1.Basamak tedaviye dirençte prevalans,kolaylaştırıcılar retrospektif Kohort analizi

GİRİŞ

- Dirençli bakterilerle

  ABD 23 000 hasta/yıl

  Dünya'da 700 000 hasta/yıl

ÖLÜM

- Plasmid aracılı direnç ve nasokomiyal direnç yayılmakta,

özellikle

- *Enterobacteriaceae,*
- *Pseudomonas aeroginosa*
- *Acinetobacter baumannii* dünya çapında

Hastane salgıları ve tedavi edilemeyen enfeksiyonlara yol açmakta

TANIMLAMALAR

- MDR(multi drug resistant):3≤ antibiyotik grubuna direnç
- XDR(extensively drug-resistant):1-2 antibiyotik hariç tüm antibiyotiklere direnç
- PDR(pandrug resistant): mevcut tüm antibiyotik gruplarına direnç
- DTR (difficult-to-treat resistance)

(ß-laktam, karbapenemler, ß-laktamaz inh ve kinolonlara direnç)

AMAÇ

- Gr (-) kan dolaşımı enfeksiyonlarında, 5 yıllık DTR prevalansının tespit edilerek 1. basamak tedaviye direncin mortaliye etkisi

METOD

- Veri kaynakları ve çalışma grubu:

  2009-2013 arasında, ABD'de 173 hastanede, yatarak tedavi gören, kültür sonuçlarıyla Gr(-) kan dolaşımı enfeksiyonu doğrulanan hastalar retrospektif olarak değerlendirildi.

  Veriler elektronik ortamda HBYS'den temin edildi.

Surveyans bakterileri

- *E.coli*
- *Enterobacter spp,*
- *Klebsiella spp,*
- *P.aeruginosa,*
- *A.baumannii*

DTR tanımı ve CDC tarafından tanımlanan dirençli fenotiplerle olan ilişkisi:

- CR (karbapenem direnci)≥ 1
- ECR(geniş spektrumlu sefolosporin) ≥1
- FQR(florokinolon direnci) ≥1

2015 CDC tanımı

- DTR ise gruplarda duyarlılık ≥ 1

2012 Roberth KOCH inst.

Table 1. Phenotypic Definitions of Difficult-to-Treat Resistance and Centers for Disease Control and Prevention-defined Individual Resistance Phenotype Among 5 Taxa of Gram-negative Bloodstream Infections

Definitions	Agents Included	Defining Criteria
2015 CDC definitions		
Carbapenem resistant[a]	Imipenem, meropenem doripenem ertapenem[b]	Resistance to ≥1 carbapenem (*Escherichia coli, Klebsiella* spp, *Enterobacter* spp); intermediate or resistant to ≥1 carbapenem (*Pseudomonas aeruginosa, Acinetobacter baumannii)*
Extended-spectrum cephalosporin-resistant[a]	Ceftazidime, cefepime, ceftriaxone,[c] cefotaxime[c]	Resistance to ≥1 extended-spectrum cephalosporin
Fluoroquinolone resistant[a]	Ciprofloxacin, levofloxacin, moxifloxacin[c]	Resistance to ≥1 fluoroquinolone
Proposed definition		
Difficult-to-treat resistance	Intermediate or resistant to all reported agents in carbapenem, β-lactam, and fluoroquinolone categories (including additional agents[e] when results available)	

Abbreviation: CDC, Centers for Disease Control and Prevention.

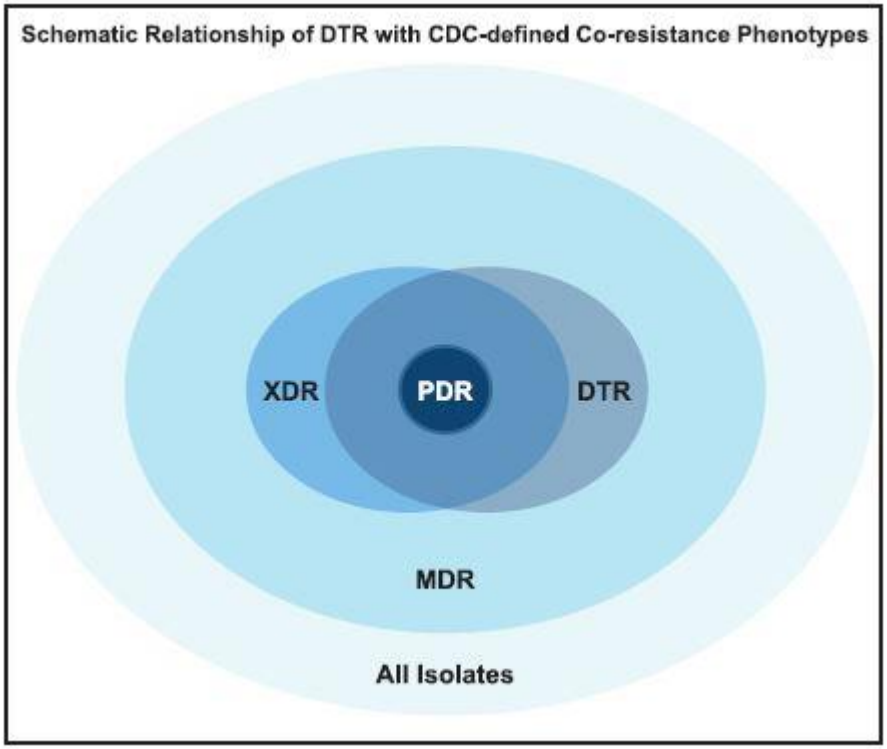
[a]Based on 2015 CDC definitions.

[b]Applicable for Enterobacteriaceae only.

[c]Not applicable for *P. aeruginosa*.

[d]DTR assessment requires in vitro testing against ≥1 carbapenem, ≥1 extended-spectrum cephalosporin, and ≥1 fluoroquinolone.

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


Schematic Relationship of DTR with CDC-defined Co-resistance Phenotypes
XDR
PDR
DTR
MDR
All Isolates

Çalışma planlanması

- CR,ECR ve FQR duyarlılıkları,
- 30 gün içinde aynı bakteri üremesi tek atak,
- sağlık bakımı ile ilişkili >3 gün hastane yatışı,
- Bakımevinden gelenler veya hemodiyaliz alanlar,daha kısa süre
- Komorbiditeler ve bakteriyeminin kaynağı ICD:9 kodlamasına ve Elixhauser indeksi,

Appendix Table 1. Glossary of diagnosis and procedure codes for source of bacteremia from the International Classification of Diseases Version-9.

Condition	ICD-9 Codes†
Source of Bacteremia*	
Urine	095.4, 099.4, 590, 595.0, 597, 598.0, 599.0
Respiratory	032.0–032.3, 034.0, 098.6, 101, 460–465, 473.0–474.0, 475, 022.1, 031.0, 033, 095.1, 466, 480–487, 510, 511.1, 513, 517.1, 770.0
Abdominal	001–009, 022.2, 095.2, 098.7, 540–542, 566, 567.0–567.2, 569.5, 070, 095.3, 573.1, 573.2, 576.1
Skin and Soft Tissue	680–686
Other site specified/unspecified	All cases not classified by above codes
Ventilator Use	96.70, 96.71, 96.72
Neutropenia	288.0
Healthcare Associated Encounter	
	Isolate day >3
	Admission source from the same or different hospital, skilled nursing facility, ambulatory surgical center, or hospice (claim source code 4, 5, 6, D, E, F)
	Hemodialysis (39.95, V45.11)

Yedek ilaçlar

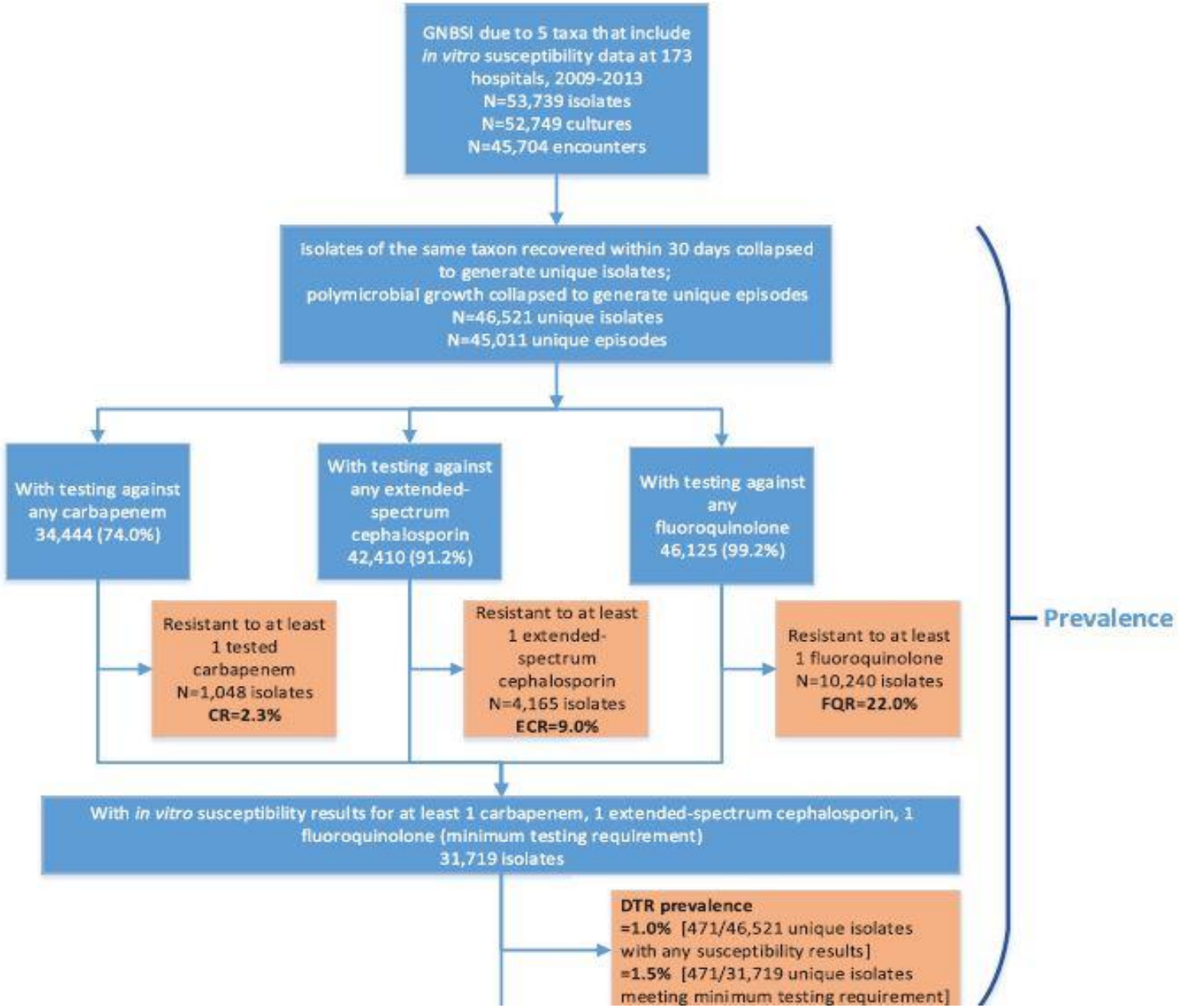
- Aminoglikozidler,
- Colistin /polimiksin
- Tigesiklin

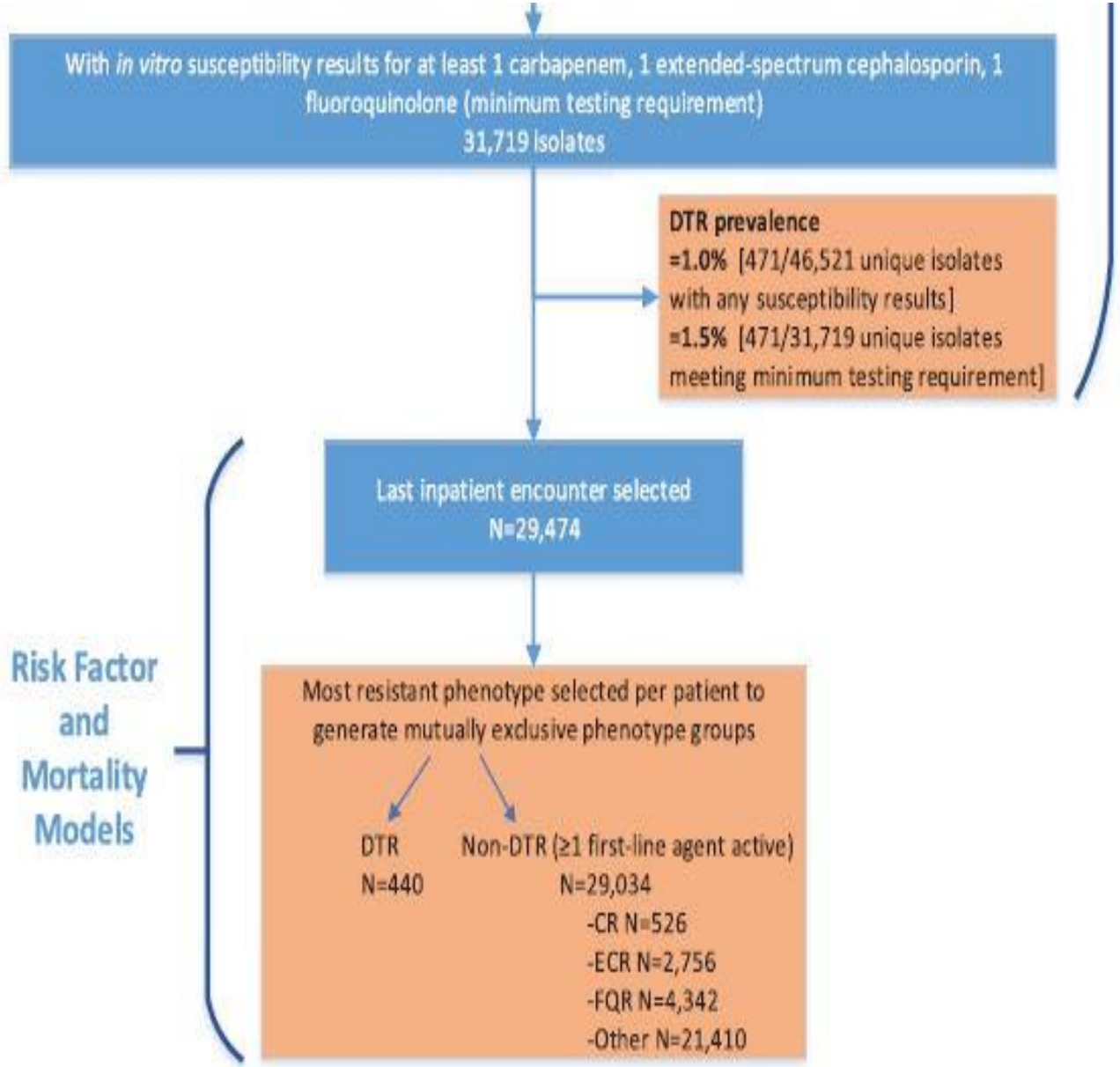
Analiz

- Tek değişkenli ve çoklu değişkenli analiz Poisson regresyonla,
- aRR(atfedilen risk) ve %95 güven aralığı

Appendix Table 2. Hospital reporting patterns within the database by calendar year, 2009-2013.

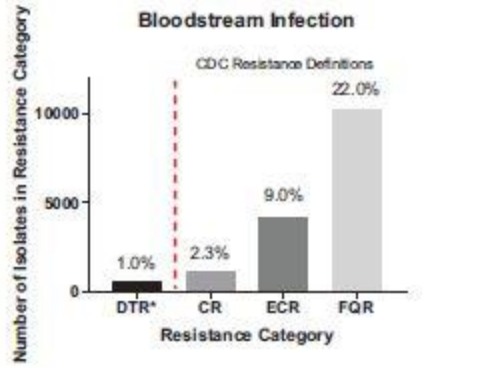
Year	Inpatient encounters (N)	Hospitals with inpatient encounters (N)	Hospitals providing 12 months of data (N, %)	Mean months (SD)	Median months (IQR)
2009	678,822	121	92 (76)	10.6 (2.9)	12 (12-12)
2010	918,803	136	126 (93)	11.6 (1.8)	12 (12-12)
2011	880,985	139	104 (75)	10.8 (2.5)	12 (12-12)
2012	782,295	120	96 (80)	10.8 (3.0)	12 (12-12)
2013	742,549	137	95 (69)	9.8 (3.8)	12 (9-12)


GNBSI due to 5 taxa that include *in vitro* susceptibility data at 173 hospitals, 2009-2013
N=53,739 isolates
N=52,749 cultures
N=45,704 encounters
Isolates of the same taxon recovered within 30 days collapsed to generate unique isolates;
polymicrobial growth collapsed to generate unique episodes
N=46,521 unique isolates
N=45,011 unique episodes
With testing against any carbapenem 34,444 (74.0%)
With testing against any extended-spectrum cephalosporin 42,410 (91.2%)
With testing against any fluoroquinolone 46,125 (99.2%)
Resistant to at least 1 tested carbapenem
N=1,048 isolates
CR=2.3%
Resistant to at least 1 extended-spectrum cephalosporin
N=4,165 isolates
ECR=9.0%
Resistant to at least 1 fluoroquinolone
N=10,240 isolates
FQR=22.0%
With *in vitro* susceptibility results for at least 1 carbapenem, 1 extended-spectrum cephalosporin, 1 fluoroquinolone (minimum testing requirement)
31,719 isolates
DTR prevalence
=1.0% [471/46,521 unique isolates with any susceptibility results]
=1.5% [471/31,719 unique isolates meeting minimum testing requirement]
Prevalence


With *in vitro* susceptibility results for at least 1 carbapenem, 1 extended-spectrum cephalosporin, 1 fluoroquinolone (minimum testing requirement)
31,719 isolates
DTR prevalence
=1.0% [471/46,521 unique isolates with any susceptibility results]
=1.5% [471/31,719 unique isolates meeting minimum testing requirement]
Last inpatient encounter selected
N=29,474
Risk Factor and Mortality Models
Most resistant phenotype selected per patient to generate mutually exclusive phenotype groups
DTR
N=440
Non-DTR (≥1 first-line agent active)
N=29,034
-CR N=526
-ECR N=2,756
-FQR N=4,342
-Other N=21,410

SONUÇLAR

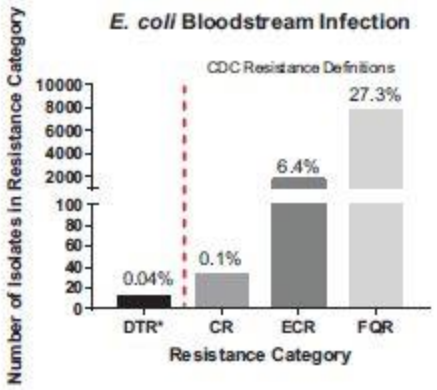
A



DTR (N=471), CR (N=1,048), ECR (N=4,165), FQR (N=10,240)
All percentages were calculated using the total number of BSI isolates as the denominator (N=46,521)

*Most DTR isolates are CR, ECR, and FQR, except:
10 *Enterobacteriaceae* isolates I to all carbapenems tested
13 isolates I to all extended-spectrum cephalosporins tested
6 isolates I to all fluoroquinolones tested

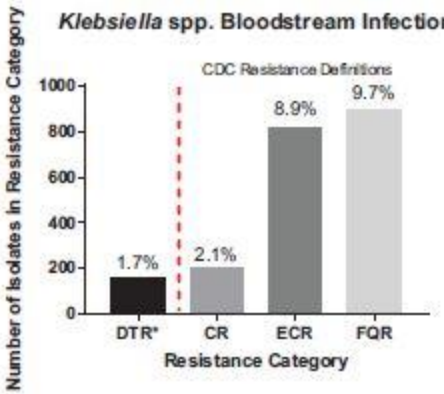
B



DTR (N=12), CR (N=33), ECR (N=1,837), FQR (N=7,803)
All percentages were calculated using the total number of *E. coli* isolates as the denominator (N=28,640)

*All DTR are CR, ECR, and FQR

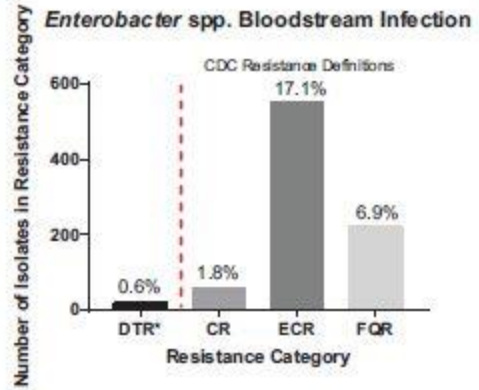
C



DTR (N=155), CR (N=196), ECR (N=816), FQR (N=892)
All percentages were calculated using the total number of *Klebsiella* spp. isolates as the denominator (N=9,168)

*Most DTR isolates are CR, ECR, and FQR, except:
9 isolates I to all carbapenems tested
2 isolates I to all fluoroquinolones tested

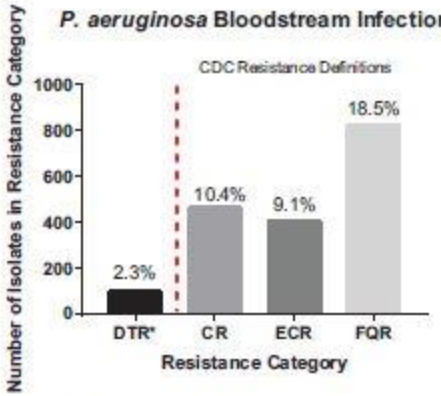
D



DTR (N=20), CR (N=58), ECR (N=552), FQR (N=221)
All percentages were calculated using the total number of *Enterobacter* spp. isolates as the denominator (N=3,221)

*Most DTR isolates are CR, ECR, and FQR, except:
1 isolate I to all carbapenems tested

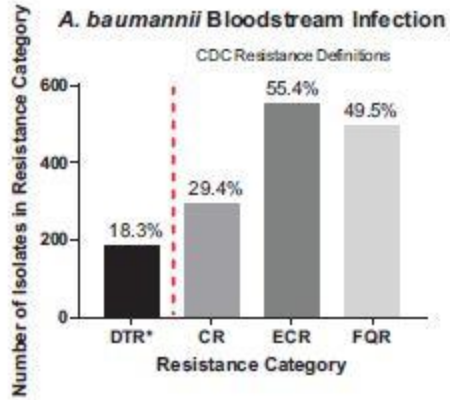
E



DTR (N=101), CR (N=467), ECR (N=407), FQR (N=830)
All percentages were calculated using the total number of *P. aeruginosa* isolates as the denominator (N=4,493)

*Most DTR isolates are CR, ECR, and FQR, except:
12 isolates I to all extended-spectrum cephalosporins tested
4 isolates I to all fluoroquinolones tested

F



DTR (N=183), CR (N=294), ECR (N=553), FQR (N=494)
All percentages were calculated using the total number of *A. baumannii* isolates as the denominator (N=999)

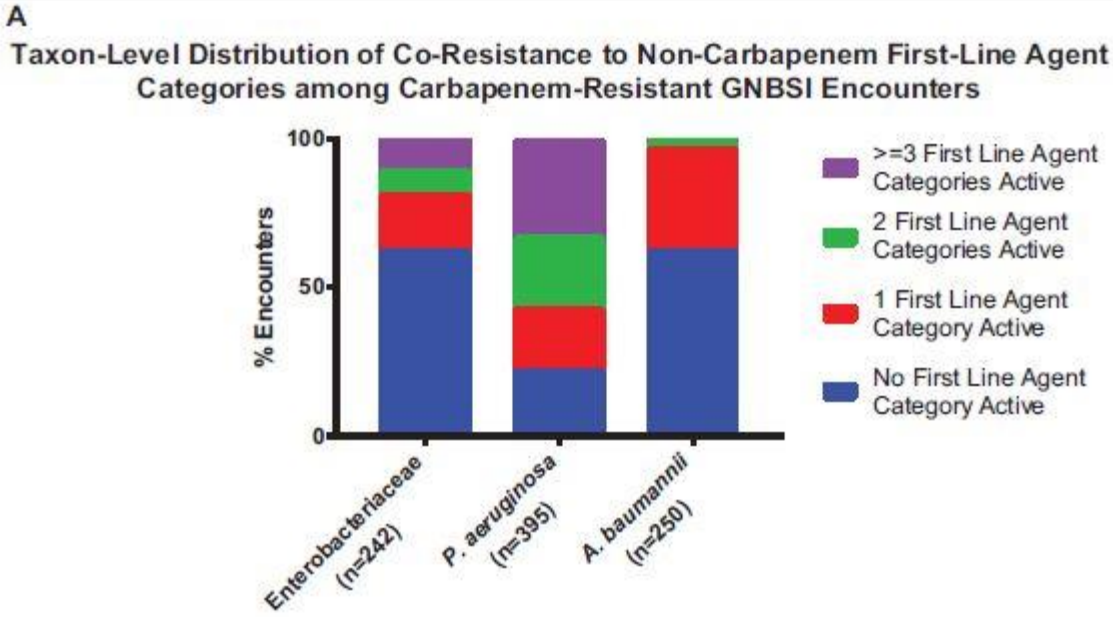
*Most DTR isolates are CR, ECR, and FQR, except:
1 isolate I to all extended-spectrum cephalosporins tested

Characteristic	Mutually Exclusive Categories of Unique Encounters With GNBSI Isolates, No. (%)[a]				
	No First-line Agent Active	≥1 First-line Agent Active			
	DTR (n = 440)	CR (n = 526)	ECR (n = 2756)	FQR (n = 4342)	Other (Nonresistant) (n = 21 410)
Patient-level characteristics					
Patient demographics					
Age group, y					
<18	<5 (NR)[b]	9 (1.7)	50 (1.8)	30 (0.7)	634 (3.0)
18–44	59 (13.4)	62 (11.8)	251 (9.1)	328 (7.6)	2284 (10.7)
45–64	166 (37.7)	194 (36.9)	838 (30.4)	1259 (29)	5976 (27.9)
>64	214 (48.6)	261 (49.6)	1617 (58.7)	2725 (62.8)	12 516 (58.5)
Sex					
Male	222 (50.5)	292 (55.5)	1443 (52.4)	2253 (51.9)	9238 (43.2)
Female	218 (49.6)	234 (44.5)	1313 (47.6)	2089 (48.1)	12 172 (56.9)
Race					
White	280 (63.6)	352 (66.9)	1717 (62.3)	2985 (68.8)	15 240 (71.2)
Black	101 (23.0)	119 (22.6)	537 (19.5)	815 (18.8)	3418 (16.0)
Hispanic/other	59 (13.4)	55 (10.5)	502 (18.2)	542 (12.5)	2752 (12.9)
Encounter characteristics					
Admission year					
2009	83 (18.9)	105 (20.0)	427 (15.5)	813 (18.7)	3529 (16.5)
2010	101 (23.0)	110 (20.9)	564 (20.5)	984 (22.7)	4726 (22.1)
2011	104 (23.6)	105 (20.0)	537 (19.5)	963 (22.2)	4773 (22.3)
2012	84 (19.1)	117 (22.2)	558 (20.3)	822 (18.9)	4518 (21.1)
2013	68 (15.5)	89 (16.9)	670 (24.3)	760 (17.5)	3864 (18.1)
Elixhauser comorbidity index, median (IQR)	6 (4, 8)	5, (3, 7)	5 (3, 7)	4 (3, 6)	4 (3, 6)
APR DRG risk of mortality[c]					
Minor	5 (1.1)	16 (3.0)	169 (6.1)	357 (8.2)	2541 (11.9)
Moderate	23 (5.2)	43 (8.2)	360 (13.1)	711 (16.4)	4315 (20.2)
Major	99 (22.5)	127 (24.1)	845 (30.7)	1423 (32.8)	6926 (32.4)
Extreme	313 (71.1)	340 (64.6)	1382 (50.2)	1851 (42.6)	7625 (35.6)
ICU stay	321 (73.0)	328 (62.4)	1401 (50.8)	1845 (42.5)	8547 (39.9)
Ventilator use	226 (51.4)	220 (41.8)	606 (22.0)	651 (15.0)	2919 (13.6)
Neutropenia	12 (2.7)	19 (3.6)	60 (2.2)	122 (2.8)	663 (3.1)

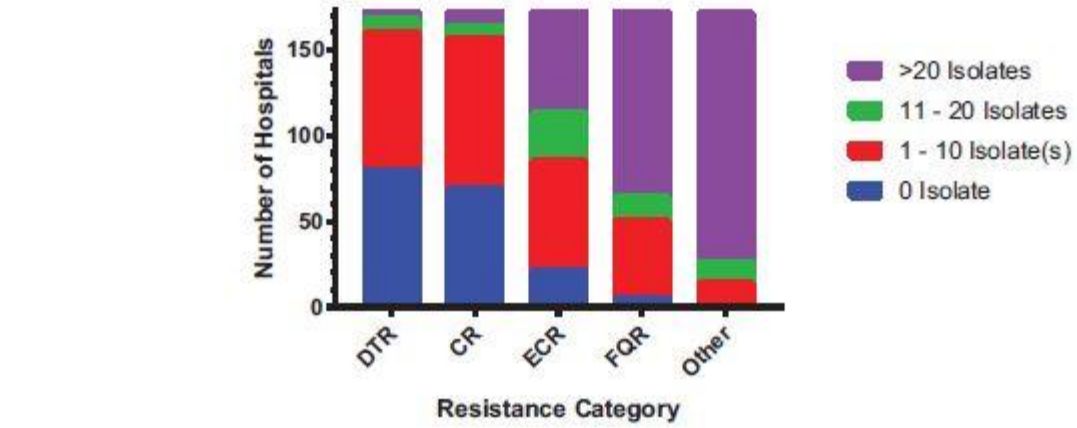
Characteristic	Mutually Exclusive Categories of Unique Encounters With GNBSI Isolates, No. (%)[a]				
	No First-line Agent Active	≥1 First-line Agent Active			
	DTR (n = 440)	CR (n = 526)	ECR (n = 2756)	FQR (n = 4342)	Other (Nonresistant) (n = 21 410)
Isolated taxon					
Escherichia coli	10 (2.3)	18 (3.4)	1542 (56.0)	3777 (87)	12 595 (58.8)
Klebsiella spp.	127 (28.9)	36 (6.8)	469 (17.0)	129 (3.0)	4280 (20.0)
Enterobacter spp.	15 (3.4)	36 (6.8)	349 (12.7)	41 (0.9)	1535 (7.2)
Pseudomonas aeruginosa	88 (20.0)	307 (58.4)	154 (5.6)	272 (6.3)	2219 (10.4)
Acinetobacter baumannii	157 (35.7)	93 (17.7)	114 (4.1)	11 (0.3)	226 (1.1)
Multiorganism	43 (9.8)	36 (6.8)	128 (4.6)	112 (2.6)	555 (2.6)
Bacteremia source[d]					
Urinary only	98 (22.3)	114 (21.7)	1135 (41.2)	2128 (49.0)	9599 (44.8)
Respiratory only	70 (15.9)	93 (17.7)	232 (8.4)	300 (6.9)	1710 (8.0)
Abdominal only	27 (6.1)	32 (6.1)	170 (6.2)	267 (6.2)	1433 (6.7)
Skin and soft tissue only	13 (3.0)	29 (5.5)	84 (3.1)	85 (2.0)	456 (2.1)
Other site	89 (20.2)	128 (24.3)	575 (20.9)	825 (19.0)	5318 (24.8)
Multisite	143 (32.5)	130 (24.7)	560 (20.3)	737 (17.0)	2894 (13.5)
Healthcare associated[e]	285 (64.8)	325 (61.8)	1118 (40.6)	1141 (26.3)	4835 (22.6)
Discharge status					
Death[f]	190 (43.2)	183 (34.8)	609 (22.1)	795 (18.3)	3161 (14.8)
Discharge to an institution	230 (52.3)	276 (52.5)	1594 (57.8)	2162 (49.8)	8731 (40.8)
Other[g]	20 (4.6)	67 (12.7)	553 (20.1)	1385 (31.9)	9518 (44.5)

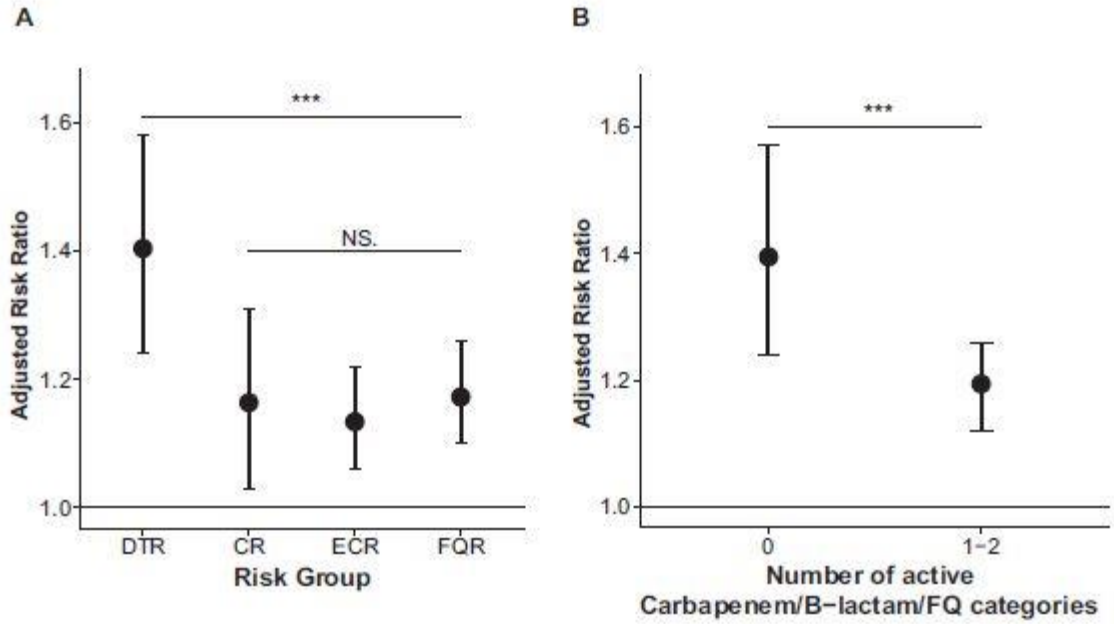
Characteristic	Mutually Exclusive Categories of Unique Encounters With GNBSI Isolates, No. (%)[a]				
	No First-line Agent Active	≥1 First-line Agent Active			
	DTR (n = 440)	CR (n = 526)	ECR (n = 2756)	FQR (n = 4342)	Other (Nonresistant) (n = 21 410)
Hospital characteristics					
Bed capacity, No.					
≤299	141 (32.1)	172 (32.7)	859 (31.2)	1596 (36.8)	8533 (39.9)
300–499	158 (35.9)	159 (30.2)	1022 (37.1)	1421 (32.7)	6284 (29.4)
≥500	141 (32.1)	195 (37.1)	875 (31.8)	1325 (30.5)	6593 (30.8)
Urban hospital	426 (96.8)	487 (92.6)	2599 (94.3)	3924 (90.4)	19 249 (89.9)
Teaching hospital	258 (58.6)	317 (60.3)	1267 (46.0)	2049 (47.2)	10 166 (47.5)
Region					
East North Central	88 (20.0)	88 (16.7)	353 (12.8)	681 (15.7)	3540 (16.5)
East South Central	31 (7.1)	19 (3.6)	74 (2.7)	219 (5.0)	797 (3.7)
Middle Atlantic	91 (20.7)	135 (25.7)	502 (18.2)	545 (12.6)	2501 (11.7)
Mountain	26 (5.9)	30 (5.7)	104 (3.8)	126 (2.9)	839 (3.9)
New England	8 (1.8)	21 (4.0)	119 (4.3)	175 (4.0)	998 (4.7)
Pacific	36 (8.2)	40 (7.6)	480 (17.4)	591 (13.6)	3249 (15.2)
South Atlantic	112 (25.5)	133 (25.3)	735 (26.7)	1160 (26.7)	5275 (24.6)
West North Central	13 (3.0)	25 (4.8)	128 (4.6)	301 (6.9)	1799 (8.4)
West South Central	35 (8.0)	35 (6.7)	261 (9.5)	544 (12.5)	2412 (11.3)

A


Taxon-Level Distribution of Co-Resistance to Non-Carbapenem First-Line Agent Categories among Carbapenem-Resistant GNBSI Encounters
% Encounters
100
50
0
Enterobacteriaceae (n=242)
P. aeruginosa (n=395)
A. baumannii (n=250)
>=3 First Line Agent Categories Active
2 First Line Agent Categories Active
1 First Line Agent Category Active
No First Line Agent Category Active

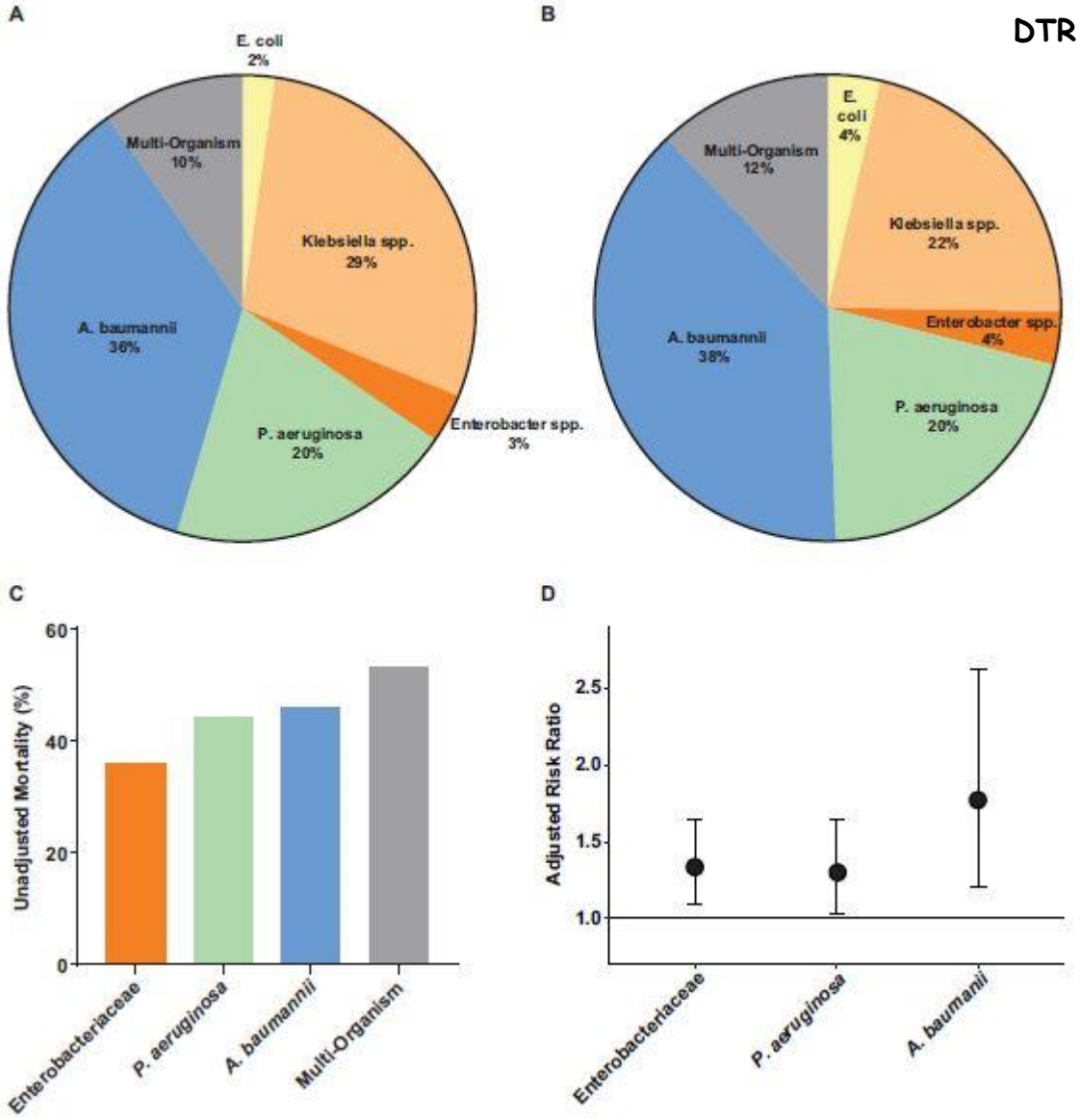
B


Distribution of Resistance Isolates among 173 Hospitals
Number of Hospitals
150
100
50
0
DTR
CR
ECR
FQR
Other
Resistance Category
>20 Isolates
11 - 20 Isolates
1 - 10 Isolate(s)
0 Isolate

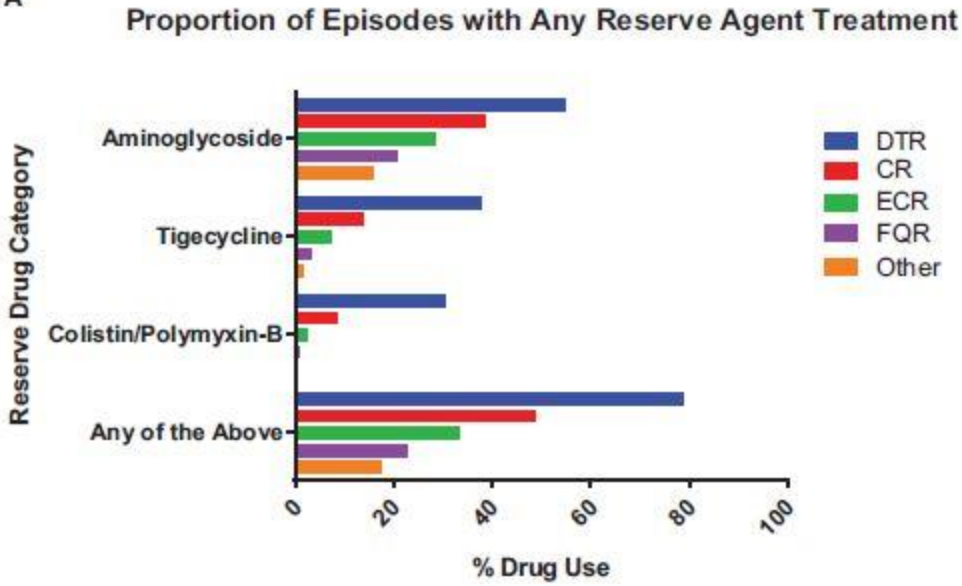

A
***
NS.
1.6
1.4
1.2
1.0
Adjusted Risk Ratio
DTR
CR
ECR
FQR
Risk Group
B
***
1.6
1.4
1.2
1.0
Adjusted Risk Ratio
0
1−2
Number of active
Carbapenem/B−lactam/FQ categories

DTR n:440

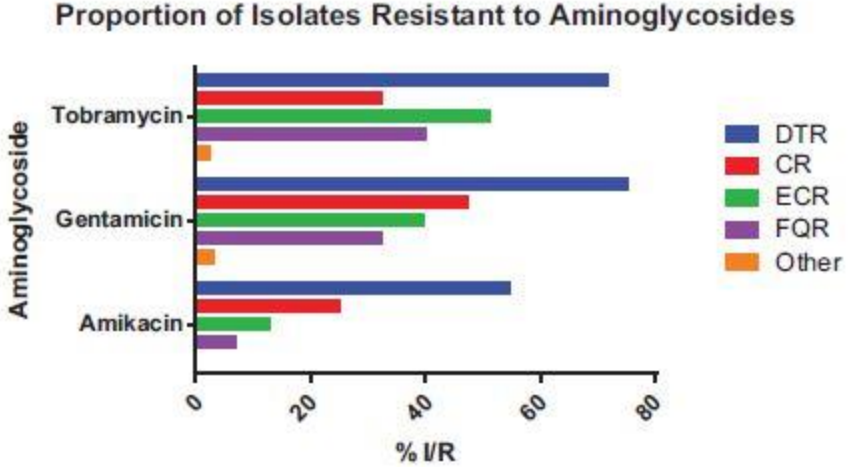
DTR X n:190



A


Proportion of Episodes with Any Reserve Agent Treatment
Reserve Drug Category
Aminoglycoside
Tigecycline
Colistin/Polymyxin-B
Any of the Above
0
20
40
60
80
100
% Drug Use
DTR
CR
ECR
FQR
Other

B


Proportion of Isolates Resistant to Aminoglycosides
Aminoglycoside
Tobramycin
Gentamicin
Amikacin
0
20
40
60
80
% I/R
DTR
CR
ECR
FQR
Other

Sonuçları özetlersek

- Geleneksel tanımlamalar, klinikle örtüşmemekte, yatak başı tdv ye yol göstermez,
- DTR direnci %1 tespit edilmiş,
- Aminoglikozidler en sık kullanılan alternatif
- DTR'li hastalarda aminoglikozid,tigesiklin ve kolimisin/polimikasin B tercih edilmiş,
- DTR'lerde mortalite belirgin olarak artmış,
- Mortalite CR,ECR ve FQR her üç grupta da artmış ancak aralarında anlamlı farkı yok
- *Enterobactericaea spp 'da* DTR ve CR korele

Kısıtlamalar

1-Ulusal veri için yetersiz

2-Hastanelerde kaynak kontrolünün yeterli yapılıp yapılmadığı ve yeterli diyagnostik araştırma ?

3- Komorbiditesi olan hastalıkları ayrımları net yapılmadı

4- Uzun dönem etki ve ABD dışındaki ülkeler için yorum yapamayız

5- DTR için standart yöntemler olmadığından tanısı yetersiz ,

6- Yeni antibiyotikler çıktıkca revizyon gerekecektir.

Background. Resistance to all first-line antibiotics necessitates the use of less effective or more toxic "reserve" agents. Gram-negative bloodstream infections (GNBSIs) harboring such difficult-to-treat resistance (DTR) may have higher mortality than phenotypes that allow for ≥1 active first-line antibiotic.

Methods. The Premier Database was analyzed for inpatients with select GNBSIs. DTR was defined as intermediate/resistant in vitro to all ß-lactam categories, including carbapenems and fluoroquinolones. Prevalence and aminoglycoside resistance of DTR episodes were compared with carbapenem-resistant, extended-spectrum cephalosporin-resistant, and fluoroquinolone-resistant episodes using CDC definitions. Predictors of DTR were identified. The adjusted relative risk (aRR) of mortality was examined for DTR, CDC-defined phenotypes susceptible to ≥1 first-line agent, and graded loss of active categories.

Results. Between 2009–2013, 471 (1%) of 45 011 GNBSI episodes at 92 (53.2%) of 173 hospitals exhibited DTR, ranging from 0.04% for *Escherichia coli* to 18.4% for *Acinetobacter baumannii*. Among patients with DTR, 79% received parenteral aminoglycosides, tigecycline, or colistin/polymyxin-B; resistance to all aminoglycosides occurred in 33%. Predictors of DTR included urban healthcare and higher baseline illness. Crude mortality for GNBSIs with DTR was 43%; aRR was higher for DTR than for carbapenem-resistant (1.2; 95% confidence interval, 1.0–1.4; $P = .02$), extended-spectrum cephalosporin-resistant (1.2; 1.1–1.4; $P = .001$), or fluoroquinolone-resistant (1.2; 1.0–1.4; $P = .008$) infections. The mortality aRR increased 20% per graded loss of active first-line categories, from 3–5 to 1–2 to 0.

Conclusion. Nonsusceptibility to first-line antibiotics is associated with decreased survival in GNBSIs. DTR is a simple bedside prognostic measure of treatment-limiting coresistance.

Keywords. gram-negative bacteria; antimicrobial resistance; mortality.

Sonuç

- XDR ve MDR günlük uygulamada tedavi de klinisyene yeteri kadar yol göstermemekte, pratik uygulamada DTR tanımlaması hem hastanın surveyi hem de tedavi seçenekleri açısından yol gösterici olacaktır.


İyi seneler……