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Antibacterial Resistance Lea

Understanding the Molecular Epidemiology of Non-CTX-M ESBL-producing Enterobacterales in the MidAtlantic United States

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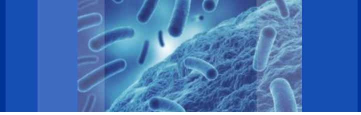
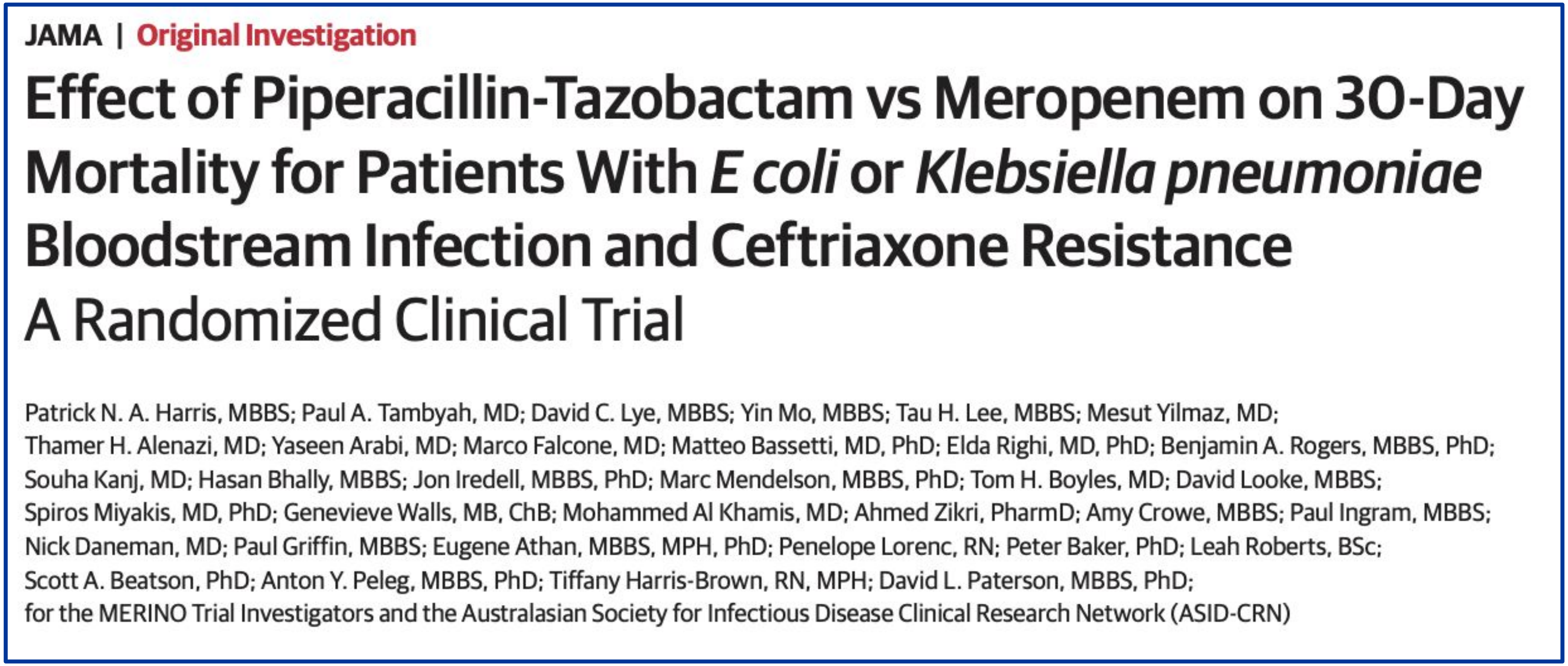
Disclosures

- Nothing to disclose



ESBL-E Primer

- ESBL-E: 197,000 hospitalizations and 9,100 deaths in the United States (2017)
  - Rising compared to other resistance mechanisms
- Multiple ESBL gene families (e.g., $\mathit{bla}_{\text{CTX-M}}$, $\mathit{bla}_{\text{SHV}}$ variants, $\mathit{bla}_{\text{TEM}}$ variants)
  - $\mathit{bla}_{\text{CTX-M}}$ is most common
- Contemporary estimates of the molecular epidemiology of ESBL genes is difficult to estimate
  - FDA cleared tests only detect $\mathit{bla}_{\text{CTX-M}}$ and are limited to blood isolates



JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

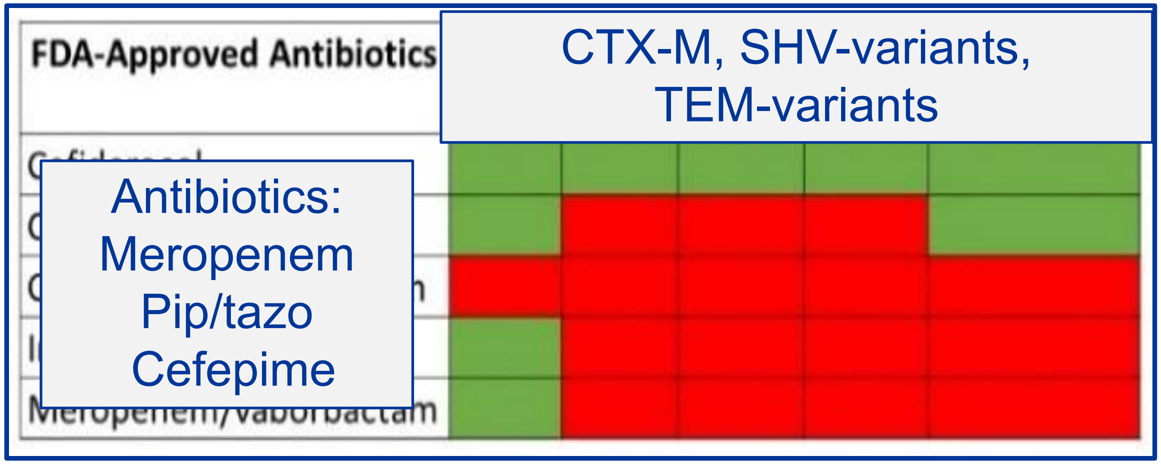
A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

Harris PN, et al. JAMA. 2018;320:984-994.

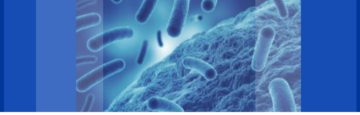
Does knowing the ESBL family matter?

- Unclear if ESBL gene family should guide treatment
  - Ex: Carbapenems
- When molecular data is available, most studies have majority CTX-M ESBL-Es
  - MERINO: 83.5% CTX-M



CTX-M, SHV-variants, TEM-variants

Antibiotics:
Meropenem
Pip/tazo
Cefepime



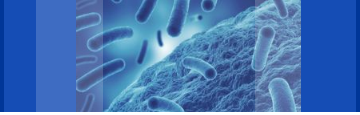
Why is this important?

- Ceftriaxone-R used as a proxy for ESBL production
  - Can lead to overtreatment with carbapenems when organism not actually an ESBL-E
- Other methods can lead to ESBL genes being missed
  - Phenotypic: cefepime-S or pip/tazo-S can be misleading (should still use carbapenems)

Comparing outcomes of non-CTX-M and CTX-M ESBL-E infections

- Clinical outcomes of 30-day mortality and 30-day ESBL-E recurrence
- Exploratory analysis within non-CTX-M cohort
  - Treatment outcomes with meropenem, cefepime or pip/tazo

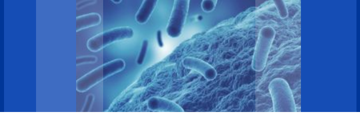
Hareza DA, et al. Clin Infect Dis. 2023. In press.



Methods

- 500 ceftriaxone-resistant Enterobacterales bloodstream isolates
- MALDI-TOF identified species
- MICs were confirmed with BMD
- Whole genome sequencing (WGS) to identify ESBL genes
  - Illumina short-read sequencing

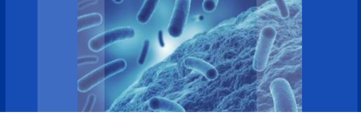
Hareza DA, et al. Clin Infect Dis. 2023. In press.



Methods

- 2018–2022 from Johns Hopkins hospitals
- Adult and pediatric patients
- Obtained during routine clinical care
- Clinical chart review performed

Hareza DA, et al. Clin Infect Dis. 2023. In press.



Analysis

- Inverse probability weighting using propensity scores
  - Used in causal inference
  - Goal: Balance of covariates between non-CTX-M and CTX-M groups
  - Addresses bias of known variables

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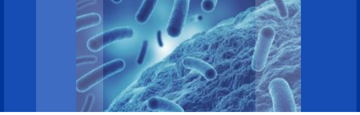


Table 1

Baseline Characteristics	Full Cohort		Inverse Probability Weighted Cohort		
	Non-CTX-M (n=32)	CTX-M (n=364)	Weighted Non-CTX-M (%)	Weighted CTX-M (%)	Standardized Mean Difference
Age ≥65 years, n (%)	14 (43.8)	159 (43.7)	(20.1)	(20.9)	-.105
Severe Immunocompromise, n (%)	8 (25.0)	117 (32.1)	(18.4)	(15.2)	.0745
ICU, n (%)	18 (56.3)	182 (50.0)	(28.4)	(24.2)	.0730
Pitt Bacteremia Score ≥4 on day 1, n (%)	9 (28.1)	89 (24.4)	(15.7)	(11.9)	.115
Charlson comorbidity index ≥5 on day 1, n (%)	13 (40.6)	172 (47.3)	(20.8)	(22.4)	-.143
Carbapenem administered as culture-directed therapy, n (%)	22 (68.8)	335 (92.0)	(48.1)	(43.3)	.0342

Adapted from Hareza DA, et al. Clin Infect Dis. 2023. In press.

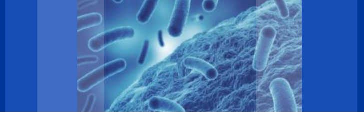


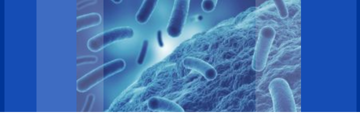
Table 2

Ceftriaxone-R Enterobacterales Molecular Epidemiology				
Organism	**ESBL Family**			
	CTX-M (n=370)	**OXY (n=12)**	**SHV (n=16)**	**VEB (n=5)**
***Enterobacter cloacae* complex**	**5 (1%)**	**0**	**3 (19%)**	**0**
Escherichia coli	**265 (72%)**	**0**	**0**	**0**
Klebsiella aerogenes	**3 (<1%)**	**0**	**1 (6%)**	**0**
Klebsiella oxytoca	**5 (1%)**	**12 (100%)**	**1 (6%)**	**0**
Klebsiella pneumoniae	**88 (24%)**	**0**	**10 (63%)**	**0**
Proteus mirabilis	**3 (<1%)**	**0**	**0**	**5 (100%)**
Providencia stuartii	**1 (<1%)**	**0**	**0**	**0**
Serratia marcescens	**0**	**0**	**1 (6%)**	**0**

*No ESBL genes were found in 20.8% of isolates

**ampC genes were found in 8 (100%) *Citrobacter freundii*, 51 (100%) *E. cloacae* complex, 2 (2%) *K. pneumoniae*, 18 (100%) *K. aerogenes*, 2 (100%) *Morganella morganii*, 1 (11%) *P. mirabilis*, 1 (100%) *P. stuartii*, and 9 (100%) *S. marcescens* isolates

Adapted from Hareza DA, et al. Clin Infect Dis. 2023. In press.



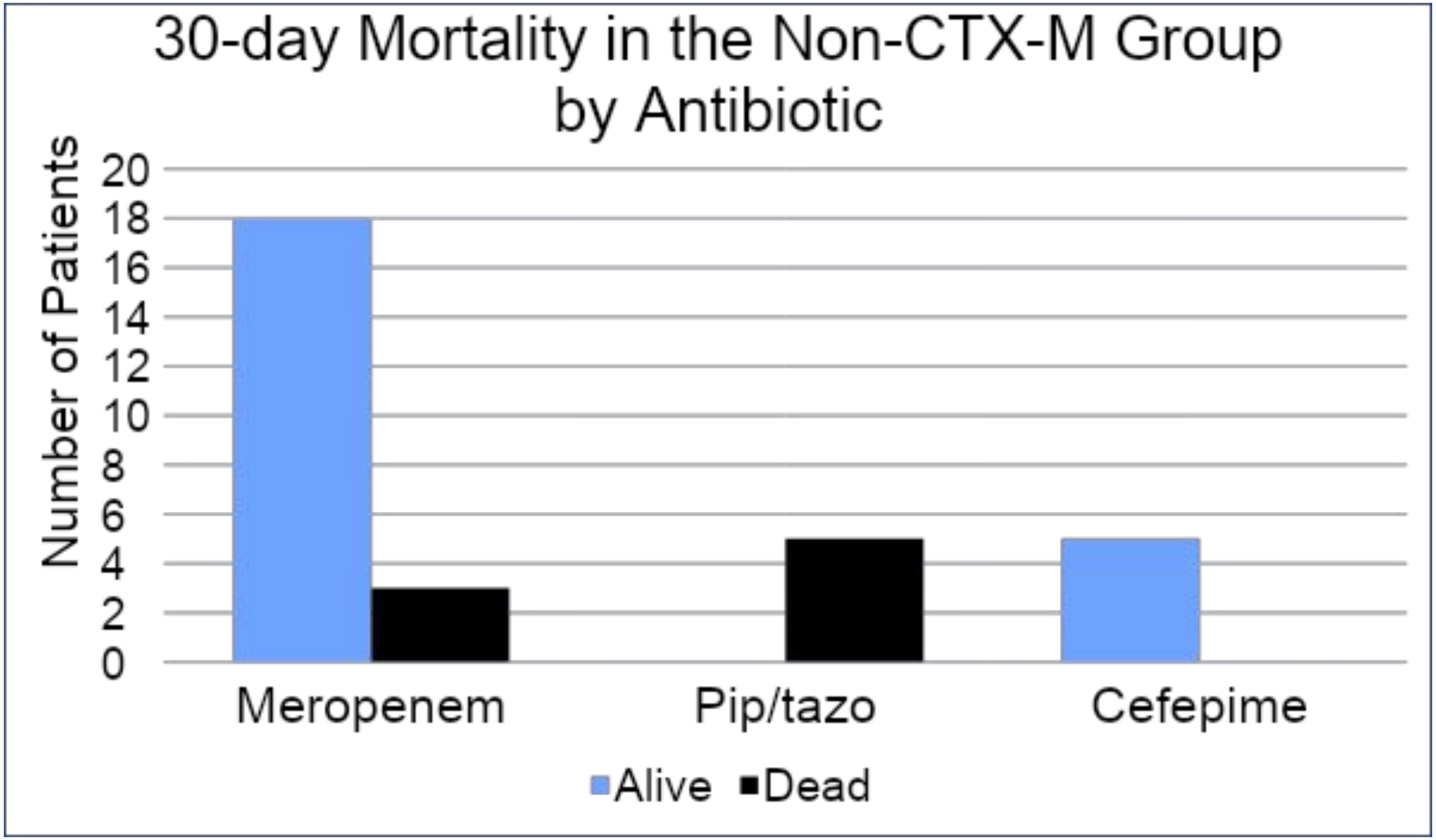
Clinical Outcomes in the IPW Cohort

Outcome	Percent with Outcome	Odds Ratio	95% Confidence Interval	p-value
30-day mortality (non-CTX-M vs CTX-M)	16%	.99	.87-1.11	.83
30-day ESBL-E recurrence (non-CTX-M vs CTX-M)	10%	1.10	.85-1.42	.47

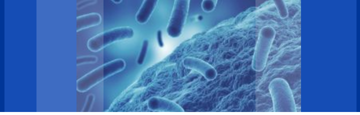
- Similarly concerning outcomes (30-day mortality, ESBL-E recurrence) between non-CTX-M and CTX-M groups

Hareza DA, et al. Clin Infect Dis. 2023. In press.

Should we use meropenem for non-CTX-M ESBL-E infections?



Hareza DA, et al. Clin Infect Dis. 2023. In press.



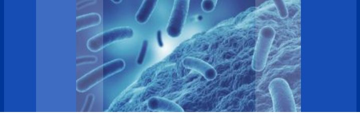
Conclusions

- Meropenem associated with improved 30-day mortality within the non-CTX-M group
- Overall Conclusion
    - Potential benefit of early diagnostics and issues with using MICs alone to guide treatment

Hareza DA, et al. Clin Infect Dis. 2023. In press.

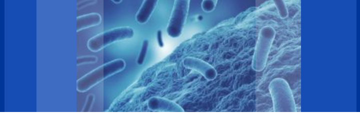
Limitations

- Observational data
  - Residual confounding
- Small sample size
- Only hospitals in Maryland



Next Steps

- Continue to study clinical outcomes and molecular epidemiology of non-CTX-M ESBL-Es
- Expand the 500-isolate cohort
- Increase geographic reach



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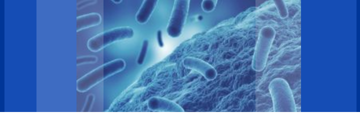


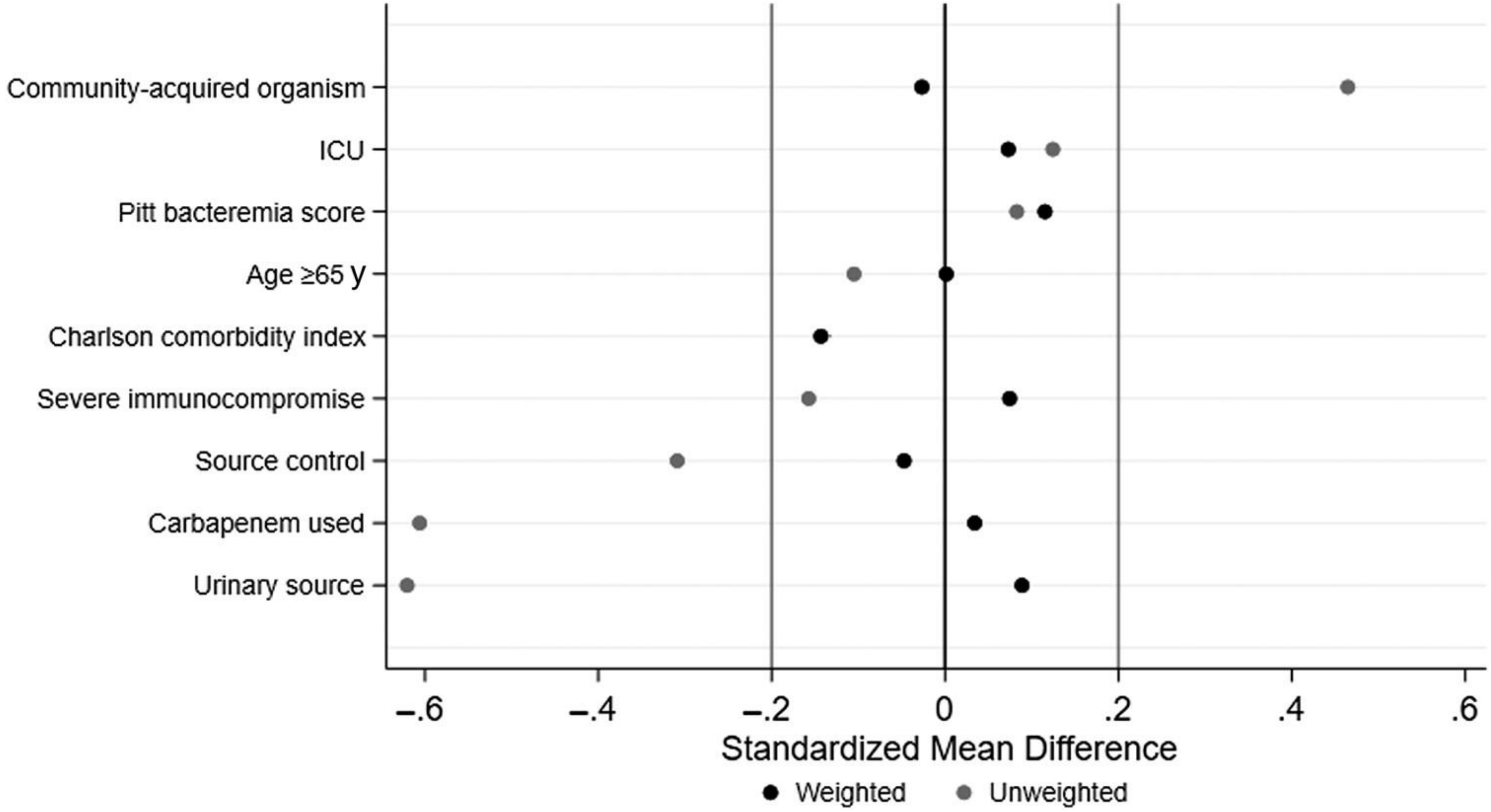
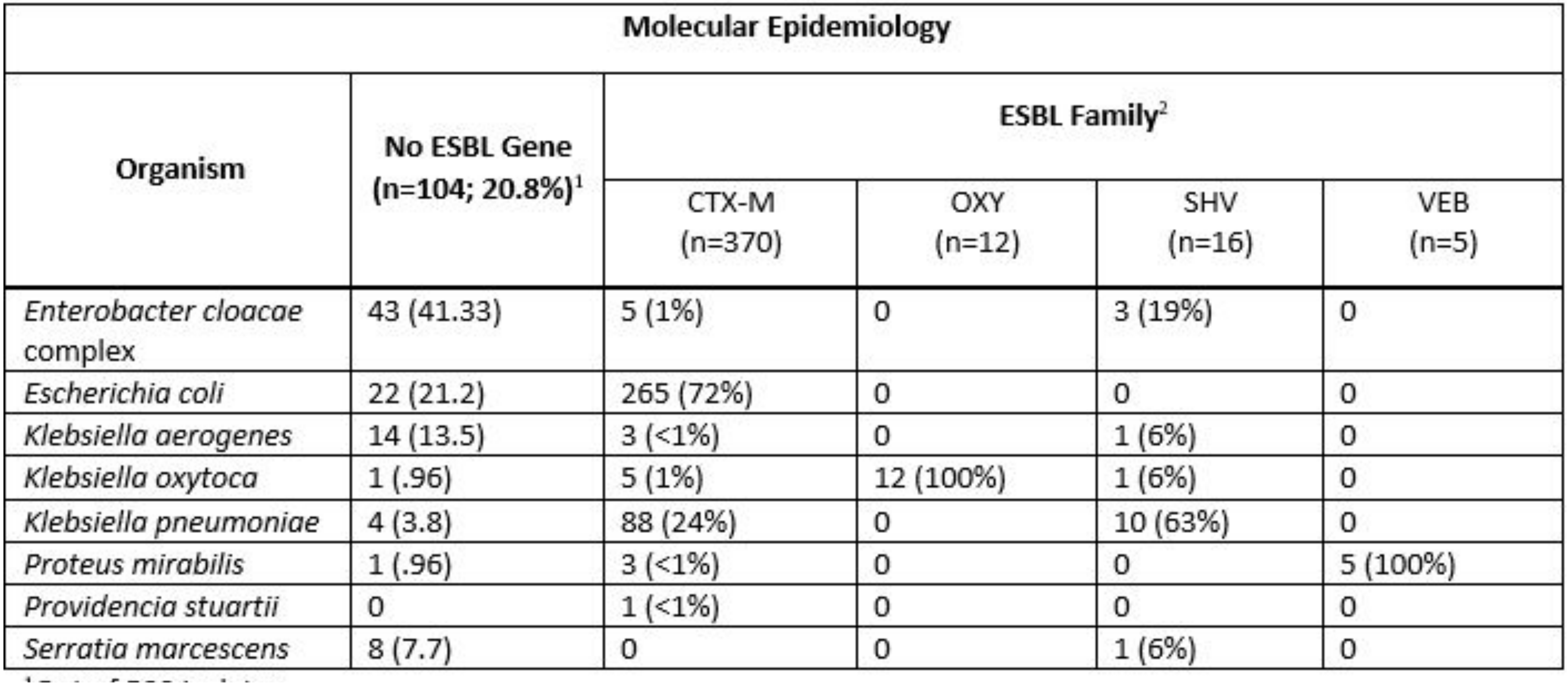

Community-acquired organism
ICU
Pitt bacteremia score
Age ≥65 y
Charlson comorbidity index
Severe immunocompromise
Source control
Carbapenem used
Urinary source
−.6
−.4
−.2
0
.2
.4
.6
Standardized Mean Difference
● Weighted
● Unweighted

Table 1

Baseline Characteristics	Full Cohort		Inverse Probability Weighted Cohort		
	Non-CTX-M (n=32)	CTX-M (n=364)	Weighted Non-CTX-M (%)	Weighted CTX-M (%)	Standardized Mean Difference
Age, median (IQR)	52.2 (33.5-75.8)	61.9 (47.9-73.3)	39.7 (32.6-70.7)	61.8 (47.4-73.3)	--
Age ≥ 65 years, n (%)	14 (43.8)	159 (43.7)	(20.1)	(20.93)	-.1050117
Male sex, n (%)	20 (62.5)	186 (51.1)	(39.4)	(24.7)	--
Severe immunocompromise, n (%)	8 (25.0)	117 (32.1)	(18.4)	(15.2)	.0744809
ICU, n (%)	18 (56.3)	182 (50.0)	(28.4)	(24.2)	.0729625
Pitt Bacteremia Score ≥ 4 on day 1, n (%)	9 (28.1)	89 (24.4)	(15.7)	(11.9)	.1153025
Charlson comorbidity index ≥ 5 on day 1, n (%)	13 (40.6)	172 (47.3)	(20.8)	(22.4)	-.1431494
Source of bacteremia, n (%)					--
Intra-abdominal	8 (25.0)	110 (30.2)	(8.8)	(15.1)	--
Respiratory	4 (12.5)	17 (4.7)	(1.5)	(2.4)	--
Skin or soft skin	2 (6.3)	22 (6.0)	(2.0)	(2.9)	--
Urinary tract	7 (21.9)	184 (50.5)	(27.5)	(23.1)	.0888232
Source control by end of antibiotic therapy, n (%)	24 (75.0)	317 (87.1)	(44.0)	(41.1)	-.0472916
Carbapenem administered as culture-directed therapy, n (%)	22 (68.8)	335 (92.0)	(48.1)	(43.3)	.0341912
Community-acquired organism group, n (%)	27 (84.4)	335 (92.0)	(51.1)	(46.3)	-.0267189

Adapted from Hareza DA, et al. Clin Infect Dis. 2023. In press.



Molecular Epidemiology					
Organism	**No ESBL Gene (n=104; 20.8%)[1]**	**ESBL Family[2]**			
		CTX-M (n=370)	OXY (n=12)	SHV (n=16)	VEB (n=5)
Enterobacter cloacae complex	43 (41.33)	5 (1%)	0	3 (19%)	0
Escherichia coli	22 (21.2)	265 (72%)	0	0	0
Klebsiella aerogenes	14 (13.5)	3 (<1%)	0	1 (6%)	0
Klebsiella oxytoca	1 (.96)	5 (1%)	12 (100%)	1 (6%)	0
Klebsiella pneumoniae	4 (3.8)	88 (24%)	0	10 (63%)	0
Proteus mirabilis	1 (.96)	3 (<1%)	0	0	5 (100%)
Providencia stuartii	0	1 (<1%)	0	0	0
Serratia marcescens	8 (7.7)	0	0	1 (6%)	0

Most Common Serotypes by Organism

Organism	Serotype	Frequency
E. coli	131	168
	648	13
	69	7
	1193	7
	410	5
	93	1
K. pneumoniae	307	18
	17	9
	348	9
	405	8
	93	6
	15	4
	628	5
K. aerogenes	15	1