

# Critical Microbiology Results for Critical Patients 2024 Perspective

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Torrance Memorial Medical Center

# Disclosures

- I am the President and Co-Founder of Expert Stewardship
- I have provided promotional speaker services: Abbvie, Ferring, Nestle Health Science, and Melinta
- I serve as a scientific consultant for ThermoFisher Scientific
- I have no affiliation with Sulbactam-Durlobactam or Innovia Specialty Therapeutics

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- ThermoFisher Scientific had no input, review or guidance into the presentation
- Opinions presented here are my own and do not reflect the opinions of any company, academic institution or public health organization.

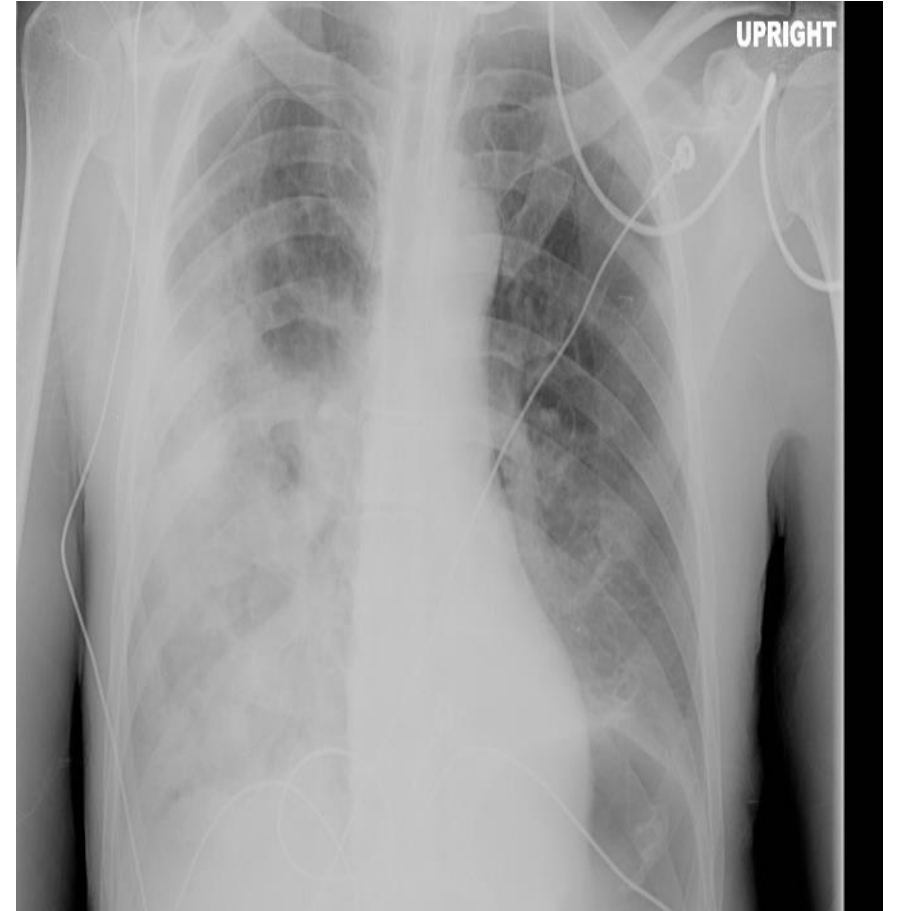
# Case Presentation

- The following descriptions are of a real cases that I or my colleagues have managed
- I will discuss use of antibiotics that may not follow FDA approved indications, but do follow generally accepted clinical practice
- Identifying information has been changed

# Lucy

**65 year old female** with pneumonia that developed on Hospital Day 5. Transferred from OSH for higher level of care.

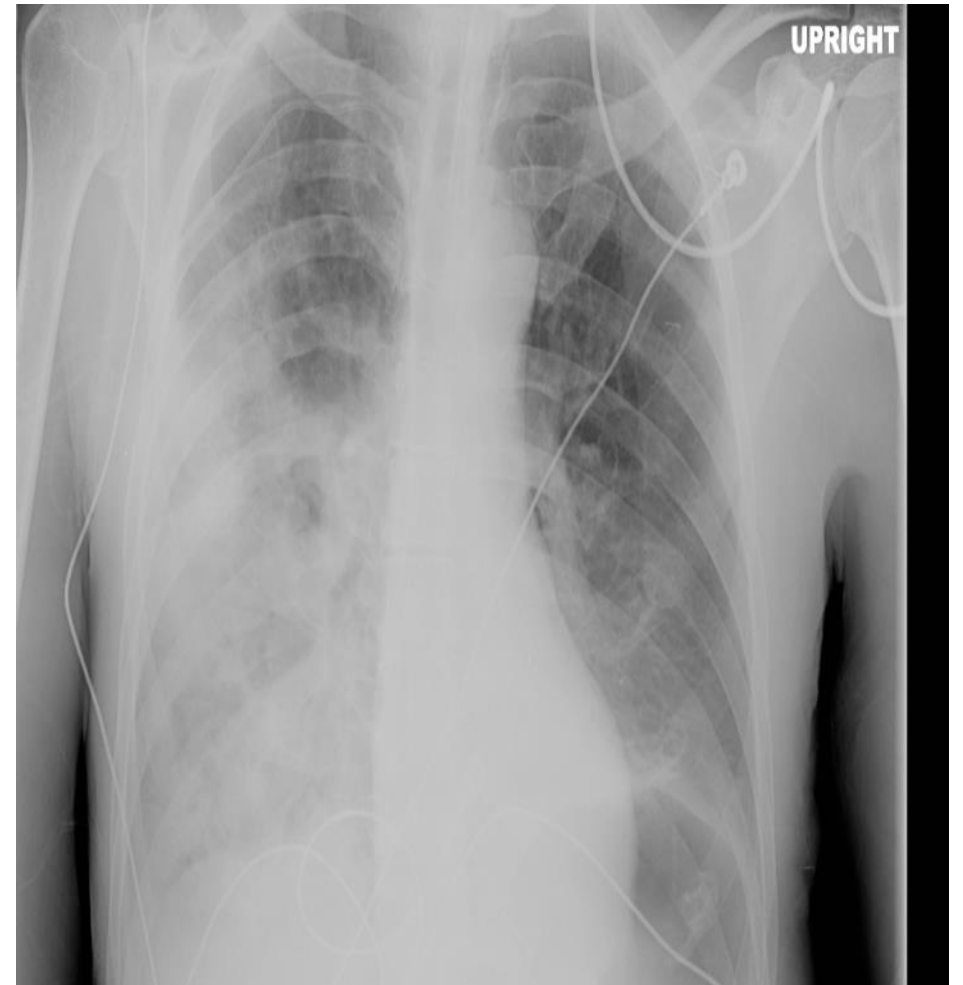
**PMH:** COPD, Bronchiectasis, Diastolic CHF, Recurrent Pneumonia (prior pathogen history unknown)



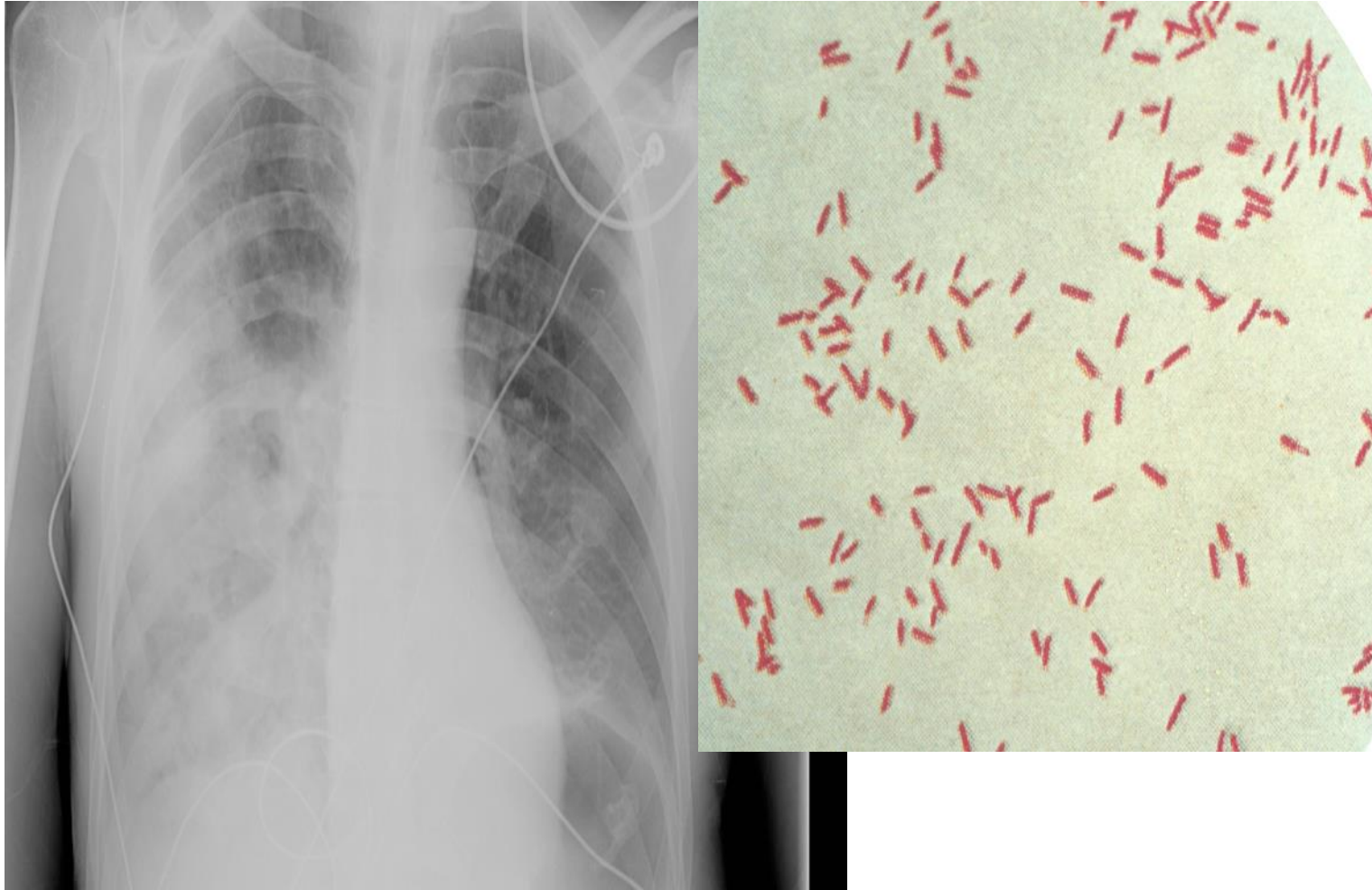
# Lucy: Admission Exam

**T: 101.2 RR: 22 BP: 104/62 HR: 125 FiO2: 92%**

- Intubated, Sedated
  - Frail with slight temporal wasting
  - JVD was Flat
  - Tachycardic, No MRG
  - RLL Rhonchi
  - Decreased muscle mass
  - No Skin Rash
- 
- **PEEP of 12 cm H2O and 80% FiO2**
  - **Currently on norepinephrine at 6 mcg/min**
- 
- **Labs: WBC: 13K, GFR>80, LFTs WNL**

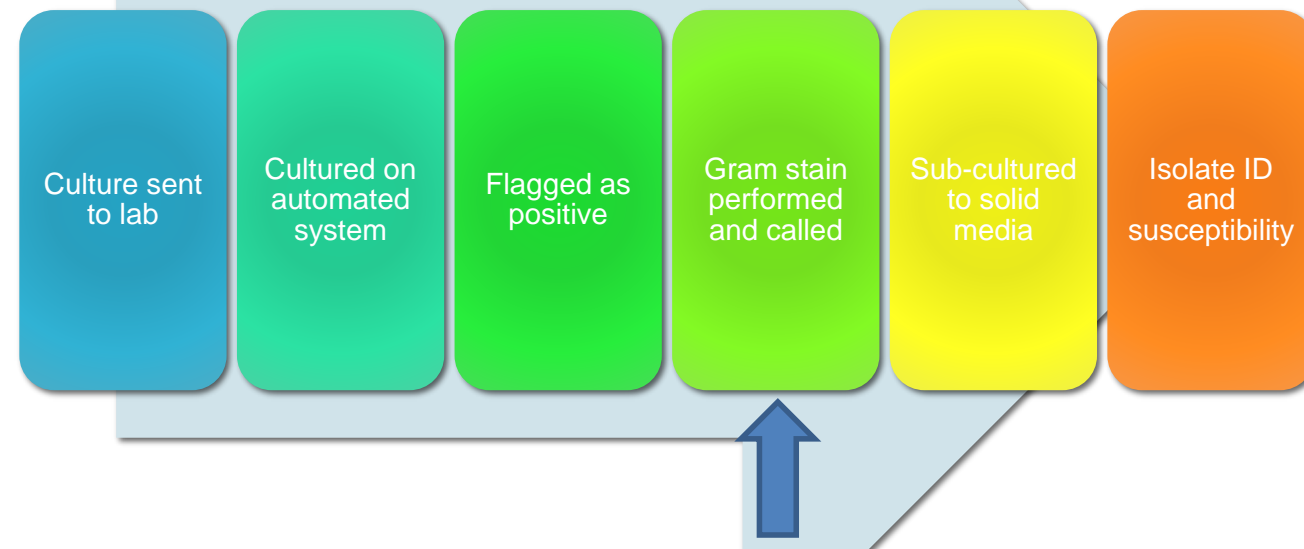


# RLL Pneumonia Gram-Negative Rods



X-Ray Image courtesy of James McKinnell, MD case files  
Gram Stain image: CDC Public Health Image Library

# RLL Pneumonia with Bacteremia

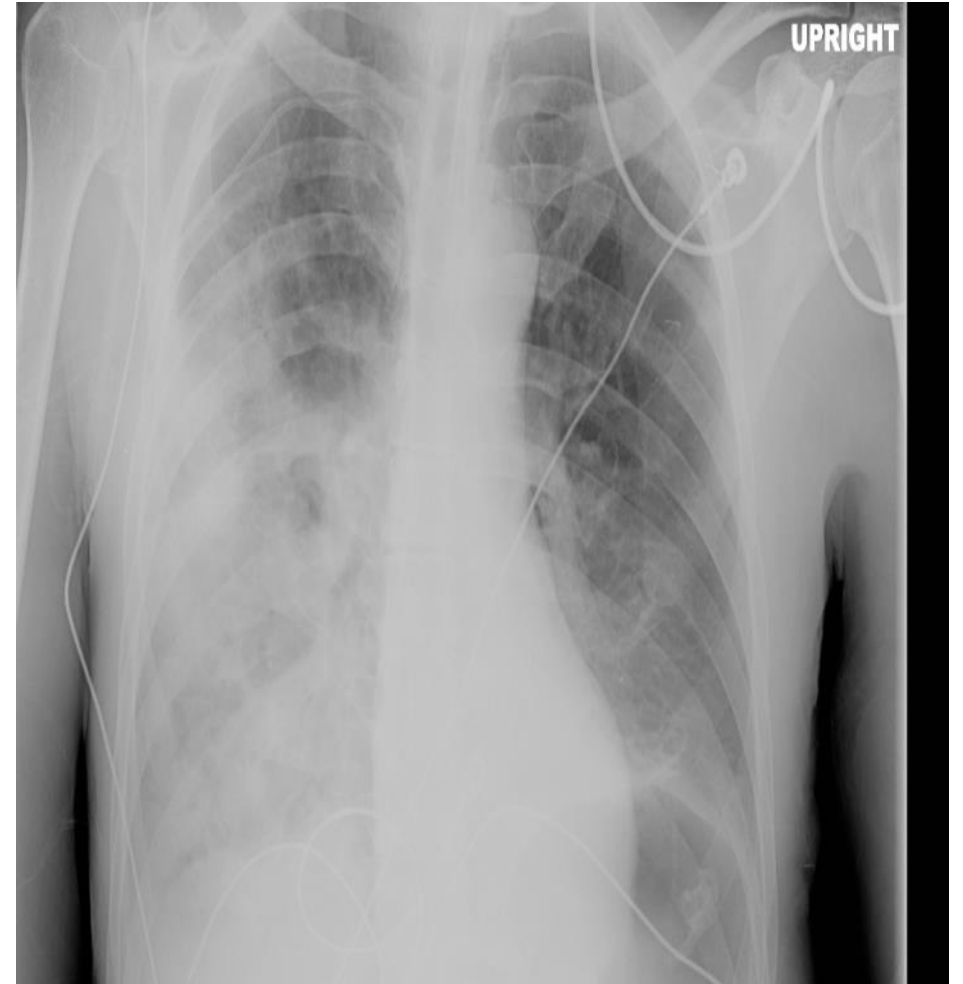


This is where we are with our patient.  
We only know we are dealing with a gram negative Rod.

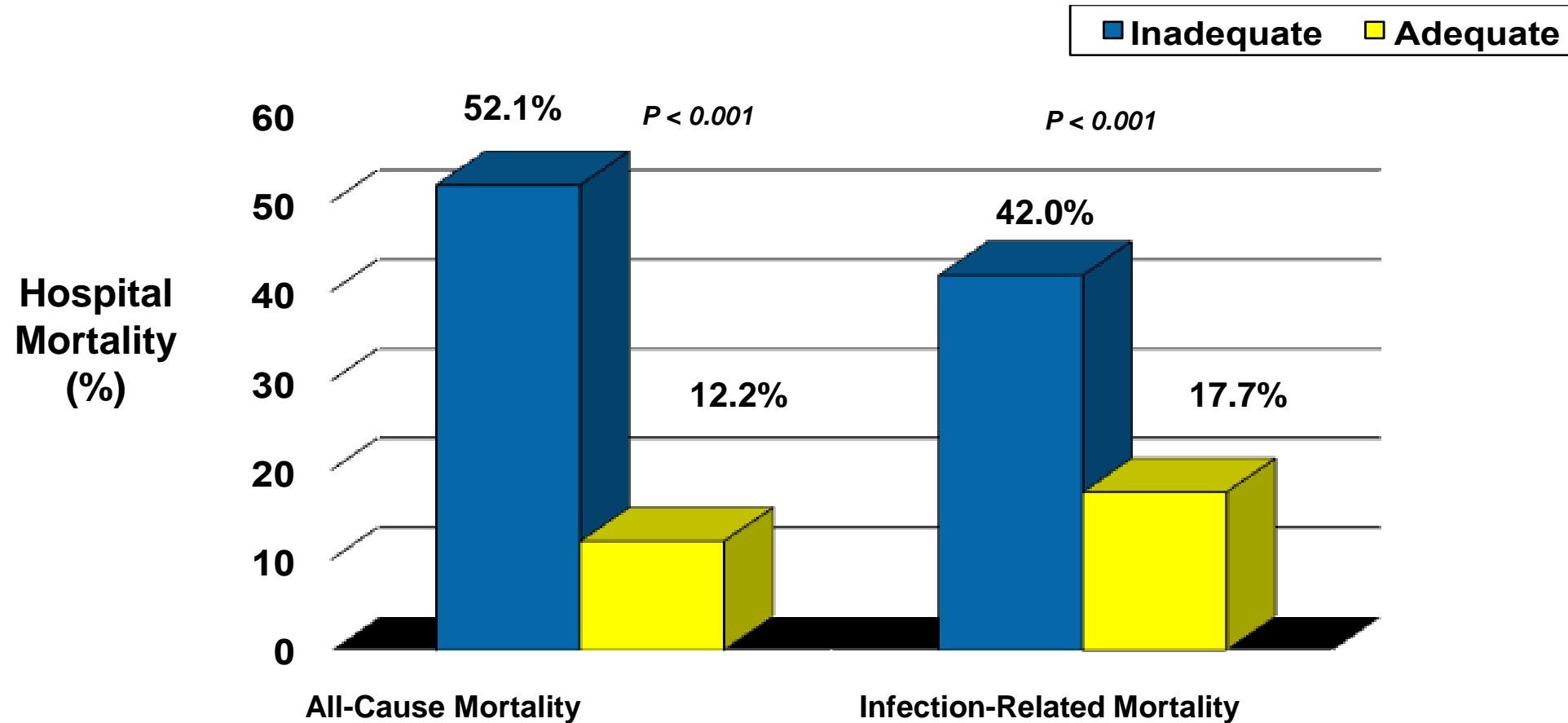


## Lucy: Assessment

- 65 yo transferred to our hospital with sepsis, RLL pneumonia with Gram-negative rods, respiratory failure, retained organ function on vasopressor therapy.
- **How important is correct ABX selection?**



# Inadequate antimicrobial therapy associated with higher mortality



Prospective study (n=2000: 655 with infections)

25% of patients received inadequate treatment

Kollef MH., et al. *Chest*.  
1999;115:462-474.

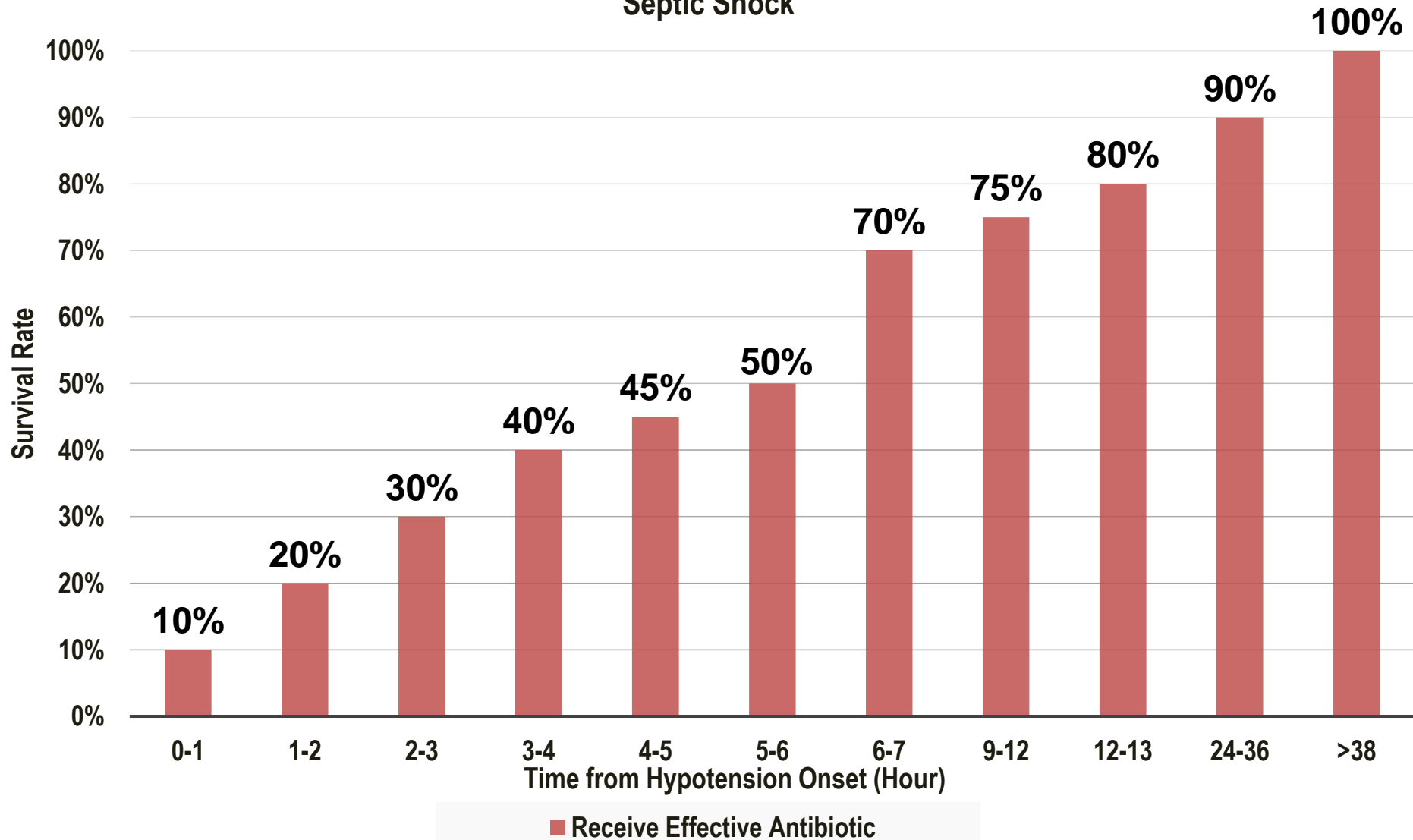
# Antibiotic Selection for Sepsis

- What is the estimated risk of death for bad outcome for my patient while I await identification and sensitivity?
  
- What is the estimated risk that my chosen therapy will not be microbiologically active?

# Antibiotic Selection for Sepsis

- **What is the estimated risk of death for bad outcome for my patient while I await identification and sensitivity?**
  
- What is the estimated risk that my chosen therapy will not be microbiologically active?

## Survival Rates and Time to Effective Antimicrobial Treatment among Patients with Septic Shock



*Clinical Infectious Diseases***MAJOR ARTICLE**

## Administration of a $\beta$ -Lactam Prior to Vancomycin as the First Dose of Antibiotic Therapy Improves Survival in Patients With Bloodstream Infections

Joe Amoah,<sup>1</sup> Eili Y. Klein,<sup>2</sup> Kathleen Chiotos,<sup>3</sup> Sara E. Cosgrove,<sup>4</sup> and Pranita D. Tamma<sup>1</sup>; for the Centers for Disease Control and Prevention's Prevention Epicenters Program

<sup>1</sup>Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; <sup>2</sup>Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; <sup>3</sup>Department of Anesthesia and Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; and <sup>4</sup>Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

- 3,376 Patients with Bacteremia from 7/2016-6/2020
- Treated with Beta-lactam and Vancomycin
- Staphylococcus aureus                      22.5% (42% of which was MRSA)
- E. Coli    21%
- Klebsiella spp.                                14%

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- 2,685 (79.5%) received Beta Lactam First
  - 47.9% Zosyn
  - 42% Cefepime

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MAJOR ARTICLE



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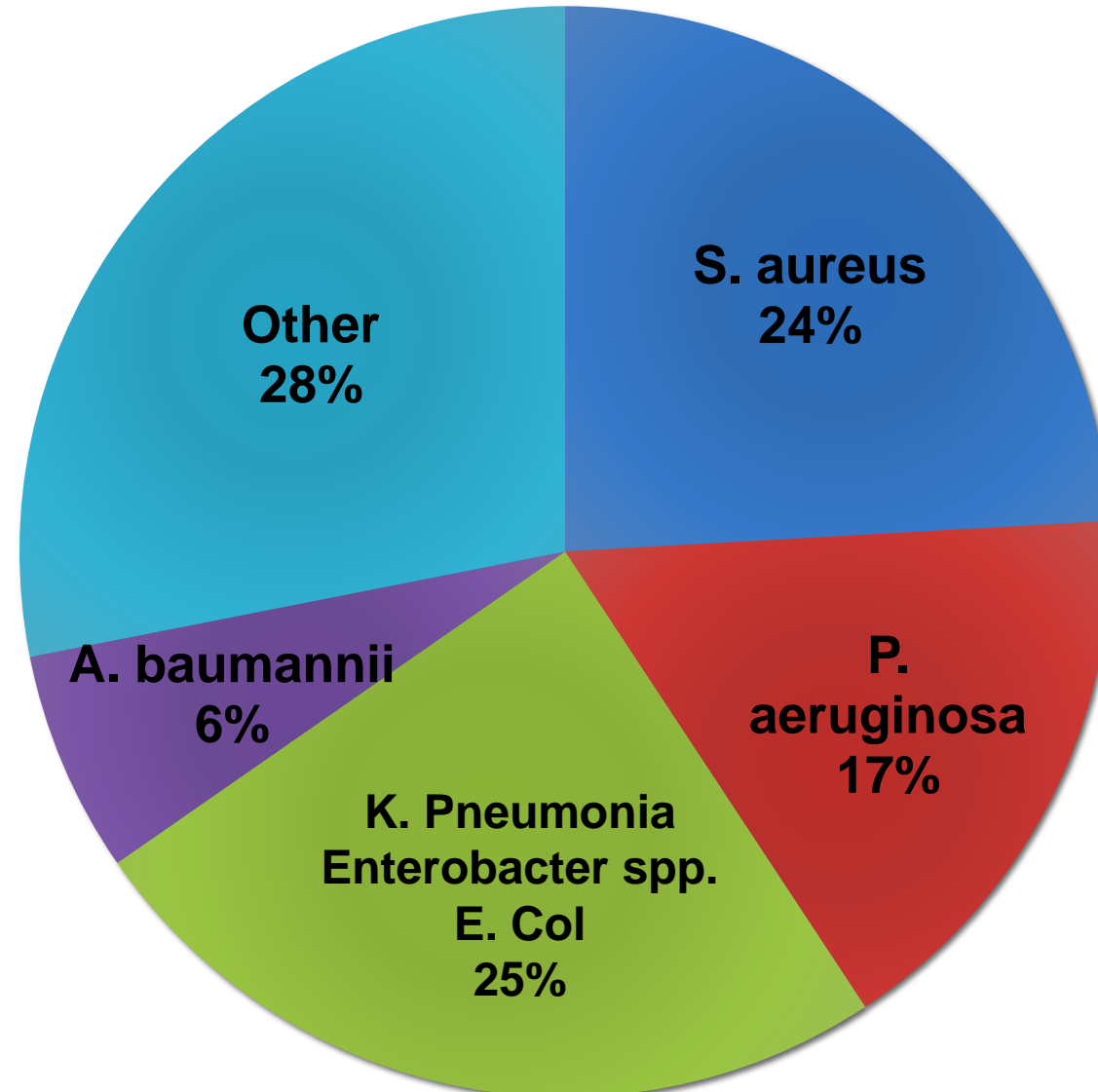
- Beta-Lactam First Improved Survival
  - OR 0.48 (0.33-0.69)
  - MRSA 0.93 (0.33-2.62)



# Antibiotic Selection for Sepsis

- What is the estimated risk of death for bad outcome for my patient while I await identification and sensitivity?
  
- **What is the estimated risk that my chosen therapy will not be microbiologically active?**

# Rank order of Pathogens Causing VAP



**Table 2. Adults (>21 y.o.) Gram-negative Bacteria – Non-Urine Isolates, % Susceptible**

Organism	No. Isolates	Penicillins			Cephalosporins				Carbapenems			Aminoglycosides			Fluoro-quinolone	Other	
		Ampicillin <sup>6</sup>	Ampicillin-Sulbactam <sup>6</sup>	Piperacillin-tazobactam	Cefazolin	Cefepime	Ceftazidime	Ceftriaxone <sup>1</sup>	Ertapenem	Imipenem	Meropenem	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Trimethoprim-sulfamethoxazole	Colistin <sup>7</sup>
<i>Citrobacter freundii</i>	37	R <sup>2</sup>	R	76	R	89	— <sup>4</sup>	— <sup>4</sup>	97	99	99	99	89	92	92	81	99
<i>Enterobacter aerogenes</i>	94	R	R	88	R	98	— <sup>4</sup>	— <sup>4</sup>	99	97	99	99	99	99	99	98	98
<i>Enterobacter cloacae</i>	209	R	R	81	R	92	— <sup>4</sup>	— <sup>4</sup>	89	99	99	99	99	99	98	94	85
<i>Escherichia coli</i>	752	41	50	94	59	84	83	79	99	99	99	99	82	85	63	60	99
<i>Klebsiella oxytoca</i>	121	R	64	89	23	95	95	87	98	98	98	99	96	96	94	91	99
<i>Klebsiella pneumoniae</i>	399	R	70	87	71	86	85	84	93	94	94	98	92	88	85	81	97
<i>Morganella morganii</i>	60	R	R	97	R	99	— <sup>4</sup>	— <sup>4</sup>	97	—	98	99	87	98	82	68	R
<i>Proteus mirabilis</i>	197	67	80	99	25	95	97	87	99	—	99	99	90	94	68	67	R
<i>Serratia marcescens</i>	127	R	R	96	R	96	— <sup>4</sup>	— <sup>4</sup>	97	94	96	99	99	96	93	98	R
<i>Acinetobacter baumannii</i>	62	R	62	53	R	58	58	—	R	62	60	67	60	66	56	60	95
<i>Pseudomonas aeruginosa</i>	738	R	R	84	R	88	87	R	R	81	85	96	91	94	78	R	99
<i>Stenotrophomonas maltophilia</i>	84	R	R	R	R	—	30	R	R	R	R	R	R	R	—	99	70
<i>Burkholderia cepacia complex</i>	12 <sup>5</sup>	R	R	R	R	R	27	R	R	R	18	R	R	R	36	64	R

<sup>1</sup> Cefotaxime and ceftriaxone have comparable activity against *Enterobacteriaceae*.

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<i>Stenotrophomonas maltophilia</i>	84	R	R	R	R	—	30	R	R	R	R	R	R	R	—	99	70
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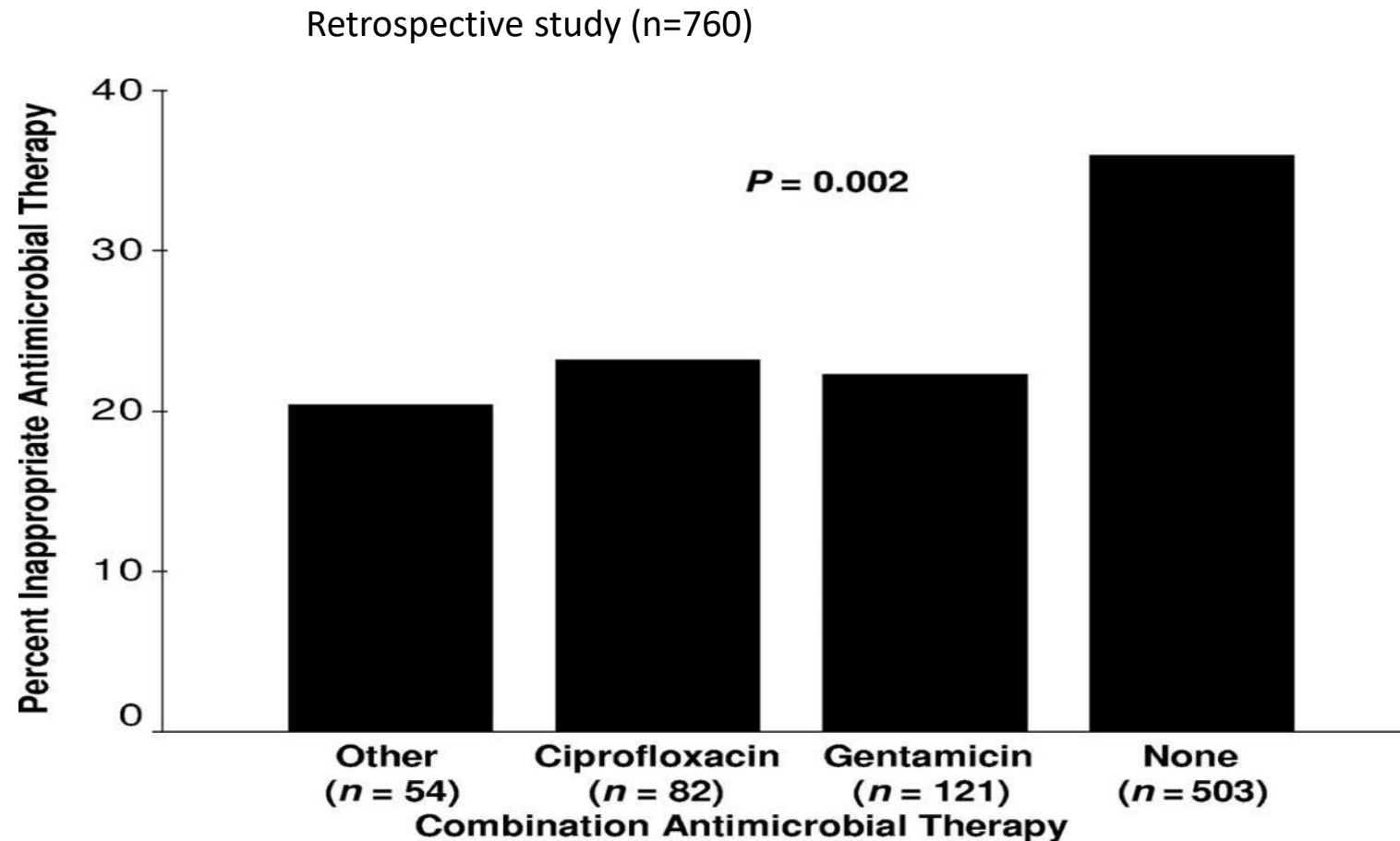
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<i>Burkholderia cepacia complex</i>	12 <sup>5</sup>	R	R	R	R	R	27	R	R	R	18	R	R	R	36	64	R

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## Empiric combination therapy is associated with higher rates of early, appropriate therapy for patients with sepsis due to Gram-negatives



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<i>Burkholderia cepacia complex</i>	12 <sup>5</sup>	R	R	R	R	R	27	R	R	R	18	R	R	R	36	64	R

<sup>1</sup> Cefotaxime and ceftriaxone have comparable activity against *Enterobacteriaceae*.

**Table 2. Adults (>21 y.o.) Gram-negative Bacteria – Non-Urine Isolates, % Susceptible**

Organism	No. Isolates	Penicillins			Cephalosporins				Carbapenems			Aminoglycosides			Fluoro-quinolone	Other	
		Ampicillin <sup>6</sup>	Ampicillin-Sulbactam <sup>6</sup>	Piperacillin-tazobactam	Cefazolin	Cefepime	Ceftazidime	Ceftriaxone <sup>1</sup>	Ertapenem	Imipenem	Meropenem	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Trimethoprim-sulfamethoxazole	Colistin <sup>7</sup>
<i>Citrobacter freundii</i>	37	R <sup>2</sup>	R	76	R	89	– <sup>4</sup>	– <sup>4</sup>	97	99	99	99	89	92	92	81	99
<i>Enterobacter aerogenes</i>	94	R	R	88	R	98	– <sup>4</sup>	– <sup>4</sup>	99	97	99	99	99	99	99	98	98
<i>Enterobacter cloacae</i>	209	R	R	81	R	92	– <sup>4</sup>	– <sup>4</sup>	89	99	99	99	99	99	98	94	85
<i>Escherichia coli</i>	752	41	50	94	59	84	83	79	99	99	99	99	82	85	63	60	99
<i>Klebsiella oxytoca</i>	121	R	64	89	23	95	95	87	98	98	98	99	96	96	94	91	99
<i>Klebsiella pneumoniae</i>	399	R	70	87	71	86	85	84	93	94	94	98	92	88	85	81	97
<i>Morganella morganii</i>	60	R	R	97	R	99	– <sup>4</sup>	– <sup>4</sup>	97	–	98	99	87	98	82	68	R
<i>Proteus mirabilis</i>	197	67	80	99	25	95	97	87	99	–	99	99	90	94	68	67	R
<i>Serratia marcescens</i>	127	R	R	96	R	96	– <sup>4</sup>	– <sup>4</sup>	97	94	96	99	99	96	93	98	R
<i>Acinetobacter baumannii</i>	62	R	62	53	R	58	58	–	R	62	60	67	60	66	56	60	95
<b><i>Pseudomonas aeruginosa</i></b>	738	R	R	84	R	88	87	R	R	<b>81</b>	<b>85</b>	96	91	<b>94</b>	78	R	99
<i>Stenotrophomonas maltophilia</i>	84	R	R	R	R	–	30	R	R	R	R	R	R	R	–	99	70
<i>Burkholderia cepacia complex</i>	12 <sup>5</sup>	R	R	R	R	R	27	R	R	R	18	R	R	R	36	64	R

<sup>1</sup> Cefotaxime and ceftriaxone have comparable activity against *Enterobacteriaceae*.

## Combination Antibioigram from UCLA

Information provided for two-drug combination does NOT imply synergism, antagonism or likely activity in vivo; 1142 patients, includes the most resistant

	Amikacin (97) <sup>1</sup>	Gentamicin (92)	Tobramycin (95)	Ciprofloxacin (80)
Cefepime (90)	99 <sup>2</sup>	97	97	95
Meropenem (87)	98	96	97	92
Piperacillin- tazobactam (86)	99	97	97	93
Ciprofloxacin (80)	98	95	96	-

\*Includes pediatrics and adults

1. Percent susceptible for individual drug in parenthesis
2. Percent susceptible for either or both drugs (eg, %S to amikacin and/or cefepime)

Adapted from antibiogram data source: UCLA Health Infectious Disease

# Antibiotic Selection for Sepsis

- 65 yo with sepsis, RLL pneumonia, respiratory failure, but retained organ function.
- Zosyn 3.375 gm IV q8H (over 3H)
- Tobramycin 350mg IV q24H



# Hospital Antibigram Limitations

- Favors observations in earlier part of calendar year
- Traditional antibiograms cannot provide interpretable data for combination therapy approaches
- Does not adjust for specific patient risk factors, including prior antibiotic exposure, history of MDROs, and length of stay in the hospital or location in the hospital
- **Provides no information on resistance from outside hospitals**

# Quality Improvement Opportunity

- Take advantage of available data to provide better prediction scoring to clinicians



BACTERIOLOGY



## Risk Factors for Colistin Resistance among Gram-Negative Rods and *Klebsiella pneumoniae* Isolates

Stefan E. Richter,<sup>a,b</sup> Loren Miller,<sup>c</sup> Daniel Z. Uslan,<sup>d</sup> Douglas Bell,<sup>e</sup> Karol Watson,<sup>b,f</sup> Romney Humphries,<sup>g\*</sup> James A. McKinnell<sup>c</sup>

Open Forum Infectious Diseases

MAJOR ARTICLE



## Risk Factors for Development of Carbapenem Resistance Among Gram-Negative Rods

Stefan E. Richter,<sup>1,2,g</sup> Loren Miller,<sup>3</sup> Jack Needleman,<sup>4</sup> Daniel Z. Uslan,<sup>5</sup> Douglas Bell,<sup>6</sup> Karol Watson,<sup>1,2</sup> Romney Humphries,<sup>7,a</sup> and James A. McKinnell<sup>3</sup>

<sup>1</sup>Division of Cardiology, <sup>2</sup>NIH BD2K Center of Excellence, <sup>3</sup>Infectious Disease Clinical Outcome Research Unit, Los Angeles Biomedical Research Institute at Harbor-UCLA, <sup>4</sup>Department of Health Policy and Management, <sup>5</sup>Division of Infectious Disease, <sup>6</sup>Division of Internal Medicine, and <sup>7</sup>Division of Pathology & Laboratory Medicine, University of California, Los Angeles, Los Angeles, California\*Present affiliation: Accelerate Diagnostics, Tucson, Arizona

# Our Patient Came from an OSH!!!

Data presented as: Percent Susceptible (# of Isolates Tested)	# of all isolates tested (# of hospitals reporting)	Ampicillin	Ampicillin/ Sulbactam	Piperacillin/ Tazobactam	Ceftriaxone	Ceftazidime	Cefepime	Cefazolin	Ertapenem	Imipenem	Meropenem	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Levofloxacin	Trimethoprim/ Sulfamethoxazole	Nitrofurantoin	Minocycline	Tigecycline
Acinetobacter baumannii	2,723 75	R	43 2,084	27 1,776	10 1,320	27 1,894	40 1,139	R	R	27 1,120	39 1,436	36 1,925	37 2,661	40 2,084	27 2,030	26 1,985	48 2,287	-	79 154	79 424
Citrobacter freundii	1,720 45	R	R	83 1,604	79 1,629	80 1,370	98 1,579	R	100 1,100	98 361	98 1,329	99 1,517	92 1,720	92 916	91 1,490	90 801	82 1,683	95 1,443	-	100 254
Citrobacter koseri	561 19	R	90 85	99 549	96 527	97 383	99 483	93 498	100 248	99 161	100 364	99 450	99 561	97 427	99 372	98 450	96 550	86 542	-	100 61
Enterobacter sp.	8,911 71	R	R	81 8508	79 7918	81 6816	96 8044	R	95 5333	94 2138	99 6770	99.5 7207	97 8818	97 5022	96 7331	95 4605	92 8510	35 5735	-	99 1650
Escherichia coli	143,153 82	38 15,318	50 59,750	94 135,592	87 136,184	89 118,505	89 128,176	83 123,386	100 89,252	100 27,115	100 11,374	99 123,826	88 142,208	83 67,642	73 122,656	67 69,750	67 141,267	96 129,730	-	100 8,523
Klebsiella oxytoca	3,248 49	R	66 1,693	93 2,844	93 2,842	96 2,448	97 2,772	53 2,604	100 1,890	100 717	100 2,408	100 2,679	96 2,948	94 1,692	95 2,588	95 1,358	91 2,780	85 2,046	-	100 479
Klebsiella pneumoniae	30,629 80	R	71 13,763	87 24,936	85 25,145	86 20,712	87 23,744	81 21,631	96 15,606	90 6,529	97 19,382	95 24,501	90 25,802	84 15,356	86 21,942	84 13,646	83 24,970	35 20,500	-	93 1,948
Morganella morganii	2,300 53	R	10 1,362	96 2,223	85 2,037	78 1,747	96 2,077	R	100 1,300	55* 439	99 1,599	99 2,119	73 2,240	85 1,325	63 1,876	54 1,401	56 2,178	R	-	R
Proteus mirabilis	19,503 80	70 17,791	77 9,969	97 17,599	87 17,582	91 14,857	92 16,487	74 16,657	99 10,454	69* 2,583	97 13,057	99 15,833	83 18,733	82 11,239	67 15,154	62 11,572	68 18,603	R	-	R
Pseudomonas aeruginosa	23,921 83	R	R	85 23,524	R	81 20,258	85 21,045	R	R	80 12,142	84 17,770	96 22,185	85 23,575	93 21,464	73 19,554	65 16,206	R	R	-	R
Serratia marcescens	2,668 58	R	R	94 1,876	90 2,376	92 2,047	95 2,401	R	99 1,462	96 555	97 1,987	96 2,417	97 2,663	79 1,707	87 2,330	86 1,581	98 2,256	R	-	99.6 550
Stenotrophomonas	1,970	R	R	R	R	46	-	R	R	R	R	R	R	R	-	81	92	-	98	R

## LA County Regional Antibioqram

# Antibiotic Selection for Sepsis

- 65 yo with sepsis, RLL pneumonia, respiratory failure, but retained organ function.
- Zosyn 3.375 gm IV q8H (over 3H)
- Tobramycin 350mg IV q24H





## *K. Pneumoniae* from OSH Blood CX

<b>Antimicrobial</b>	<b>Susceptibility</b>
<b>Cefepime</b>	<b>S-DD (4)</b>
<b>Ceftazidime</b>	<b>R</b>
<b>Ceftriaxone</b>	<b>R</b>
<b>Tobramycin</b>	<b>R</b>
<b>Pip/Tazo</b>	<b>S</b>
<b>Meropenem</b>	<b>S</b>
<b>Tigecycline</b>	<b>R</b>

## 2 Days After Consult

- Lucy still on ventilator, max FiO<sub>2</sub>, high positive ventilatory pressures
- Persistent Fevers
- Increased Sputum production
- Max pressors, increased over last 24 hours

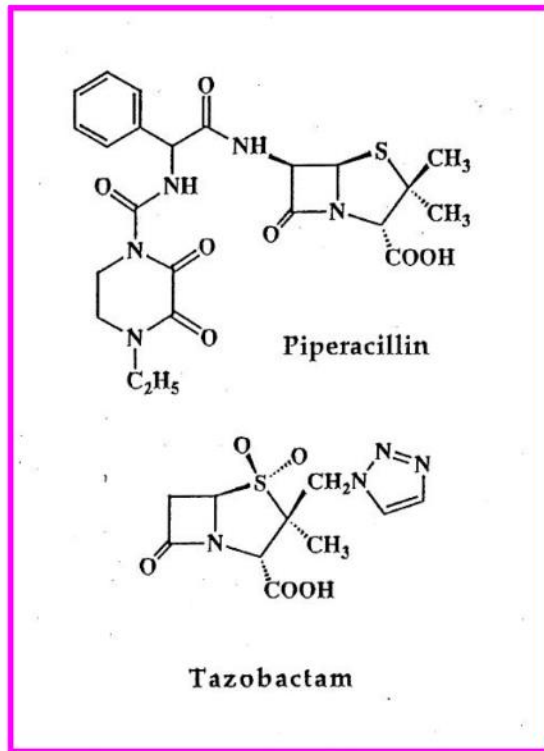
# Why is Lucy getting sicker?

## *K. Pneumoniae* is almost certainly an ESBL Producer

Antimicrobial	Susceptibility
Cefepime	S-DD (4)
Ceftazidime	R
Ceftriaxone	R
Tobramycin	R
Pip/Tazo	S
Meropenem	S
Tigecycline	R

Based on these susceptibility results, this isolate is likely an ESBL producer and Pip/Tazo is not recommended for use in this patient

# Piperacillin-Tazobactam



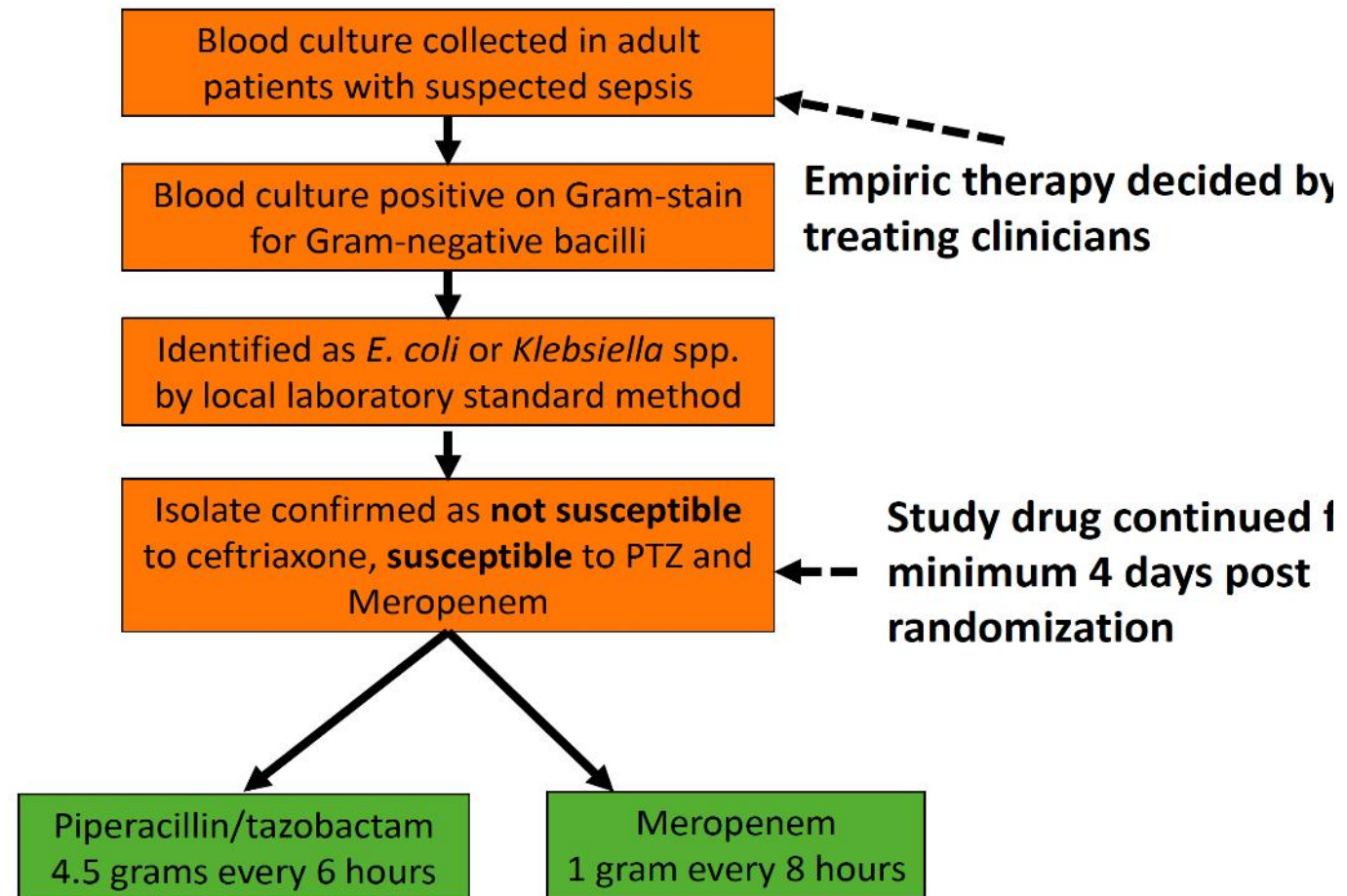
- 1981 - **piperacillin** approved
- 1993 - **piperacillin-tazobactam** approved for skin and skin structure and intra-abdominal infections
  - BEFORE ESBLs were wide-spread
  - CLSI never included editing pip-tazo as “R” if ESBL detected, but many do this in practice
- Tazobactam – inhibit activity of ESBLs
- Piperacillin - penicillin

	Susceptible	Intermediate	Resistant
CLSI 2021 & FDA	≤16µg/mL	32 to 64 µg/mL	≥128µg/mL

# Merino Trial Design

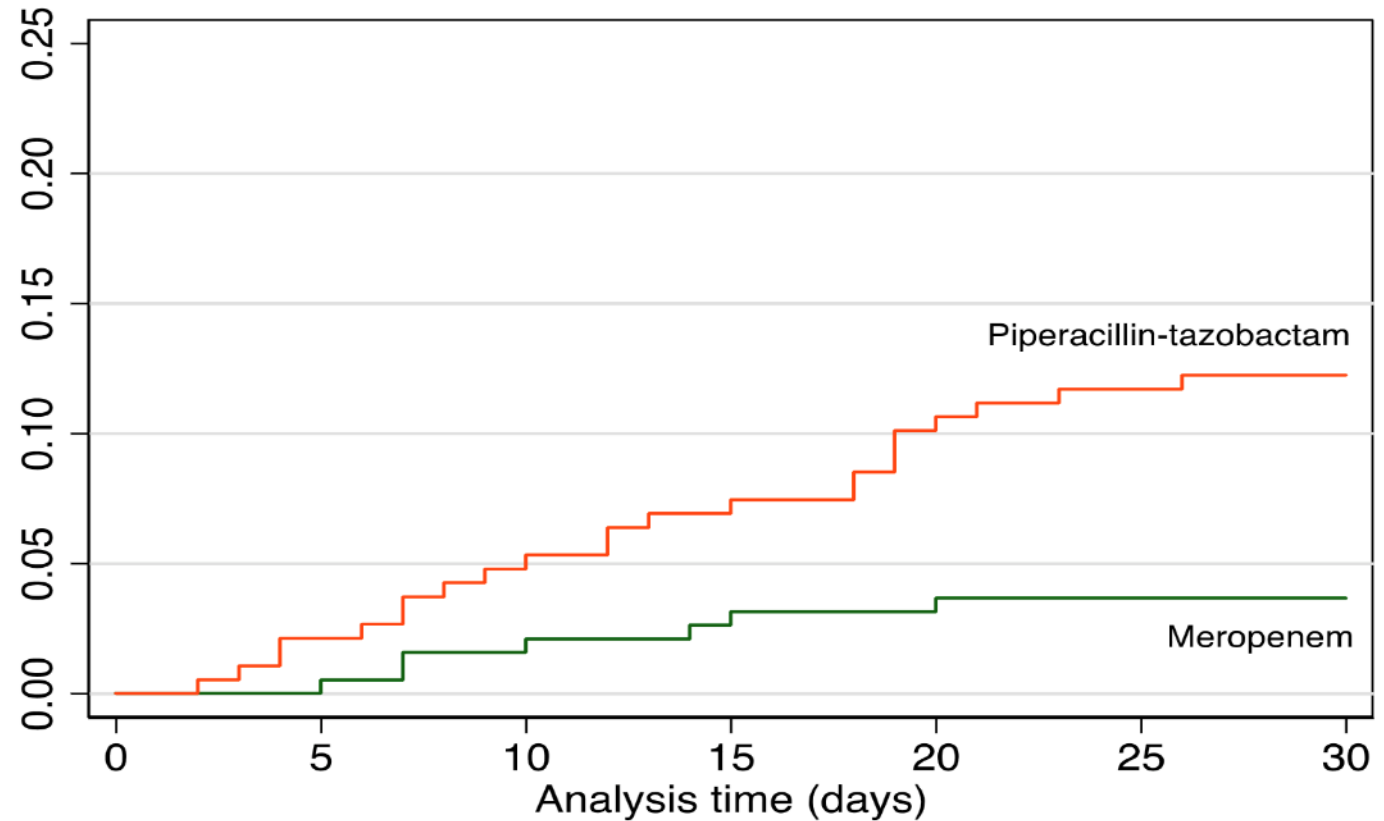
MERINO Trial:

Can pip-tazo be used for ESBL isolates?



# Merino Trial – P/T Associated with Risk of Death

**Study Stopped  
Early by DSMB for  
Harm and Futility!!**



Number at risk

intervention = PTZ 188      184      179      175      169      166      165

intervention = MER 191      191      188      186      185      184      184

— MER — PTZ

# Merino Trial – P/T Associated with Risk of Death

	Mortality 30 days n/total (%)		Risk difference % (1-sided 97.5% CI) <sup>c</sup>	P value for non- inferiority
	Piperacillin-tazobactam	Meropenem		
Primary analysis	23/187 (12.3)	7/191 (3.7)	8.6 (-∞ to 14.5)	.90
Per-protocol analysis	18/170 (10.6)	7/186 (3.8)	6.8 (-∞ to 12.8)	.76

**Risk difference 8.6% [one sided 97.5% CI: -∞ to 14.5%]**



# Merino Trial – P/T Associated with Risk of Death

	Mortality 30 days n/total (%)		Risk difference % (1-sided 97.5% CI) <sup>c</sup>	P value for non- inferiority
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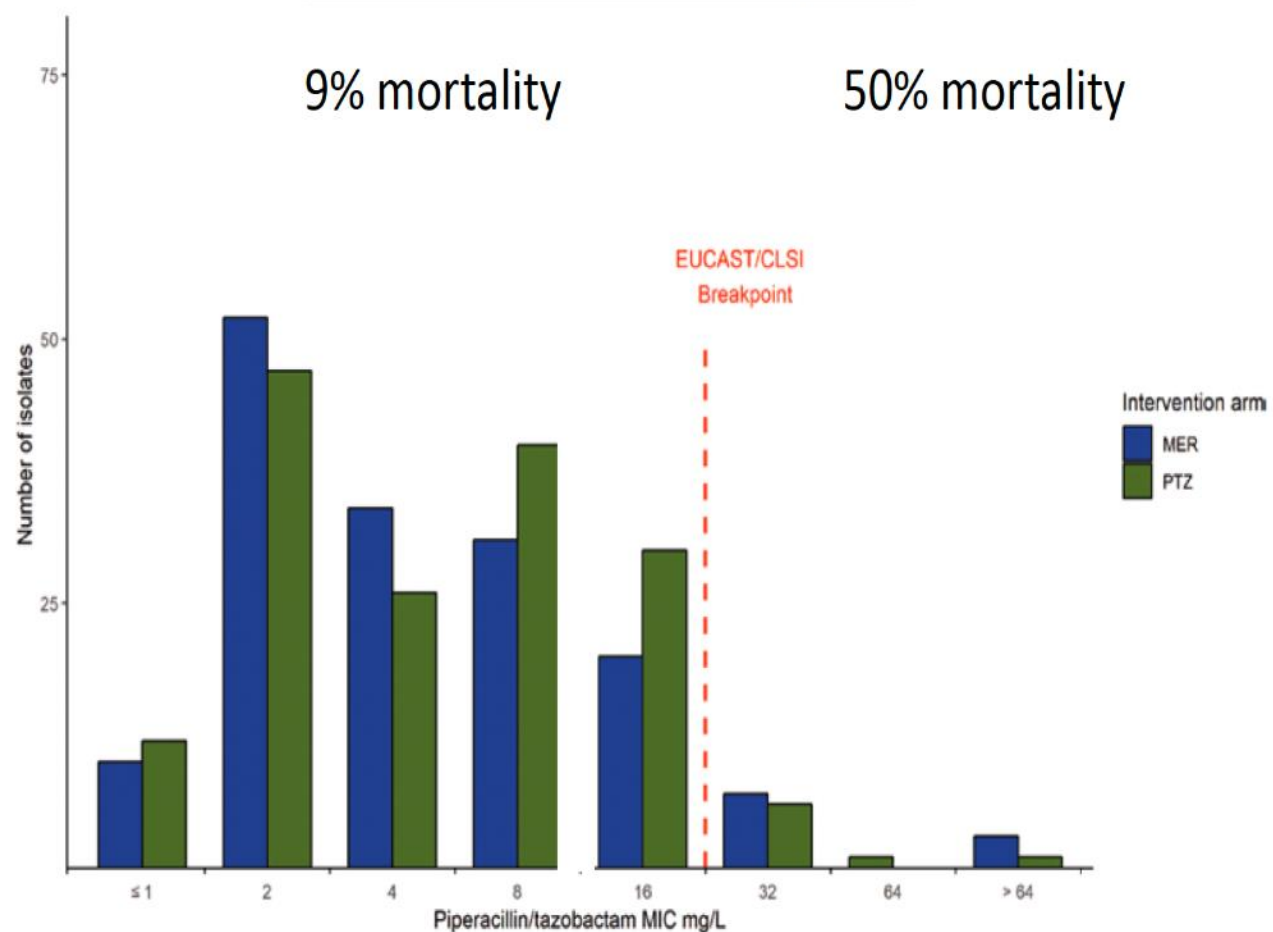
**Risk difference 8.6% [one sided 97.5% CI: -∞ to 14.5%]**

JAMA. 2018;320(10):984-994

**Failure of Zosyn (Pip-Tazo) did not seem to be related to MIC of the infecting isolate**

# Inaccurate Local Lab Contributed to Poor Drug Choice

## Patient isolates re-tested by BMD



## MERINO re-analyzed by BMD MICs

Variable	Bivariate Analysis		Multivariate Analysis	
	OR	P	aOR	P
Log <sub>2</sub> (MIC)	1.2 (0.9–1.6)	.20	...	
MIC > 16 mg/L	10.3 (2.6–41.9)	<.001	14.9 (2.8–872)	.002
UTI source	0.4 (0.2–1.1)	.09	0.6 (0.2–1.8)	.3
Charlson comorbidity score	1.6 (1.3–2.0) <sup>a</sup>	<.001	1.7 (1.3–2.2) <sup>a</sup>	<.001

Abbreviations: aOR, adjusted odds ratio; MIC, minimum inhibitory concentration; UTI, urinary tract infection.

<sup>a</sup>Calculated for each numerical increase in Charlson Comorbidity Score.

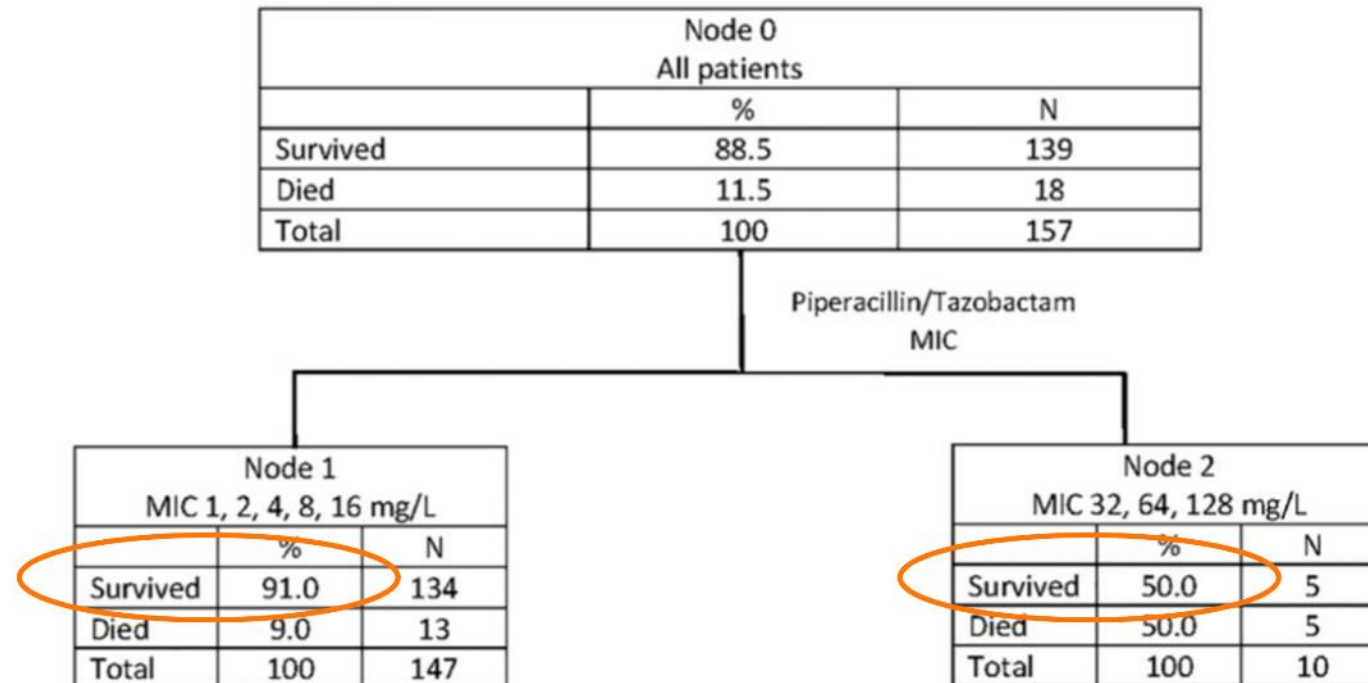
# Correct Microbiology Results Would have Saved Lives

Variable	Bivariate Analysis		Multivariate Analysis	
	OR	<i>P</i>	aOR	<i>P</i>
Log <sub>2</sub> (MIC)	1.2 (0.9–1.6)	.20	...	
MIC > 16 mg/L	10.3 (2.6–41.9)	<.001	14.9 (2.8–87.2)	.002
UTI source	0.4 (0.2–1.1)	.09	0.6 (0.2–1.8)	.3
Charlson comorbidity score	1.6 (1.3–2.0) <sup>a</sup>	<.001	1.7 (1.3–2.2) <sup>a</sup>	<.001

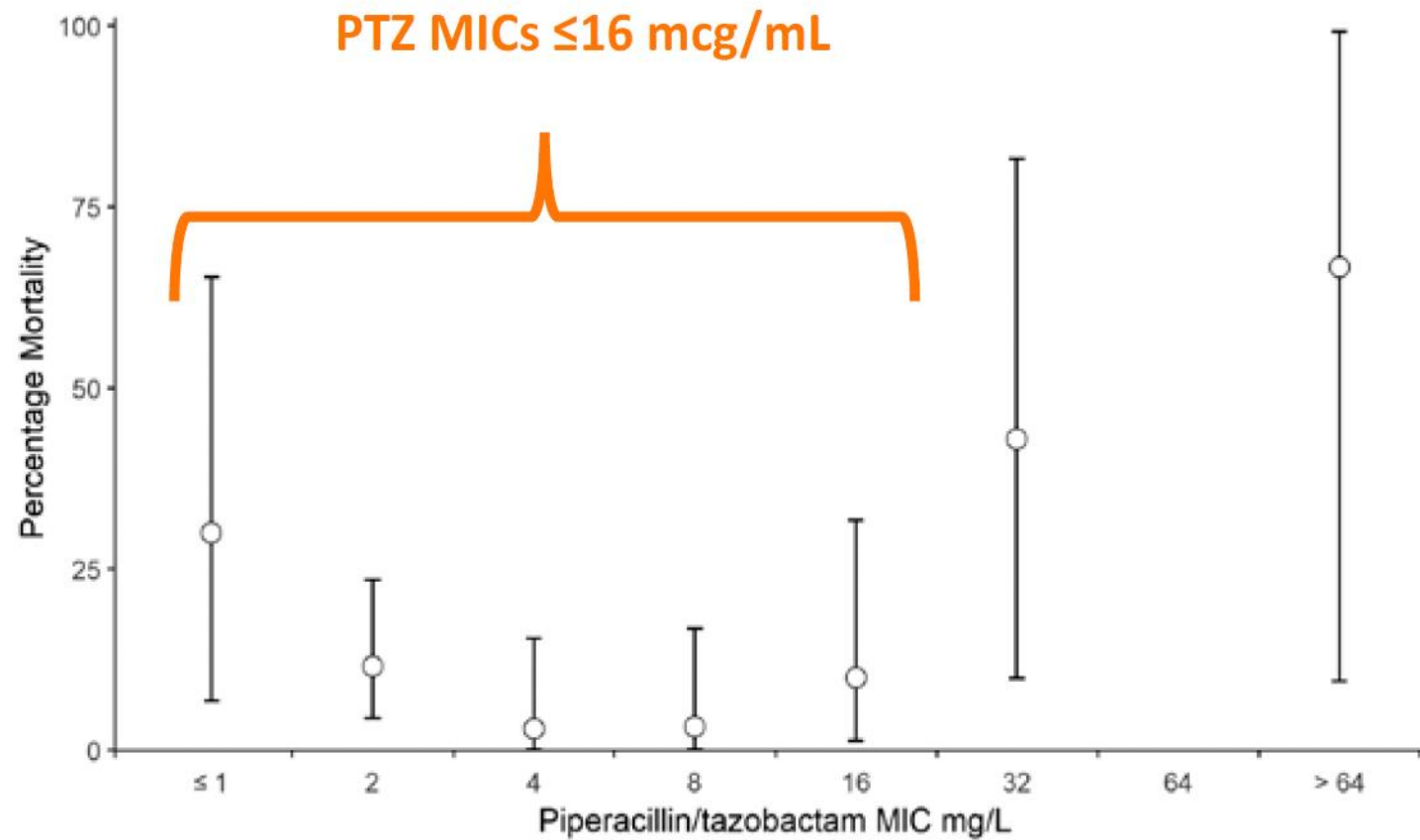
Abbreviations: aOR, adjusted odds ratio; MIC, minimum inhibitory concentration; UTI, urinary tract infection.

<sup>a</sup>Calculated for each numerical increase in Charlson Comorbidity Score.

# Correct Microbiology Results Would have Saved Lives



# Breakpoint Update Justification



# New Breakpoint for Zosyn

Parameter	
Microbiology	≤8 µg/mL is the ECV
Clinical data	≤16 µg/mL is associated with reduced mortality risk
PK/PD	≤8 or ≤16 µg/mL result in reasonable target attainment

	Susceptible µg/mL	Susceptible Dose- dependent µg/mL	Resistant µg/mL
CLSI	≤16	32 to 64	≥128
FDA	≤16	32 to 64	≥128
EUCAST	≤8	--	>8
<b>CLSI 2022</b>	≤8 <sup>#</sup>	16 <sup>*</sup>	≥32

Breakpoint of ≤16 µg/mL for susceptible avoided due to testing concerns

SDD vs I to promote extended infusion option  
EUCAST assessment that 16 is ATU

# CRITICAL ERRORS

- **Failure to use Current Breakpoints Increases Patient's Risk of Death**

## Breakpoint situation: U.S.



### Standards Organization

- Used by most U.S. laboratories
- "best practices" for laboratories
- Breakpoints in M100, M45



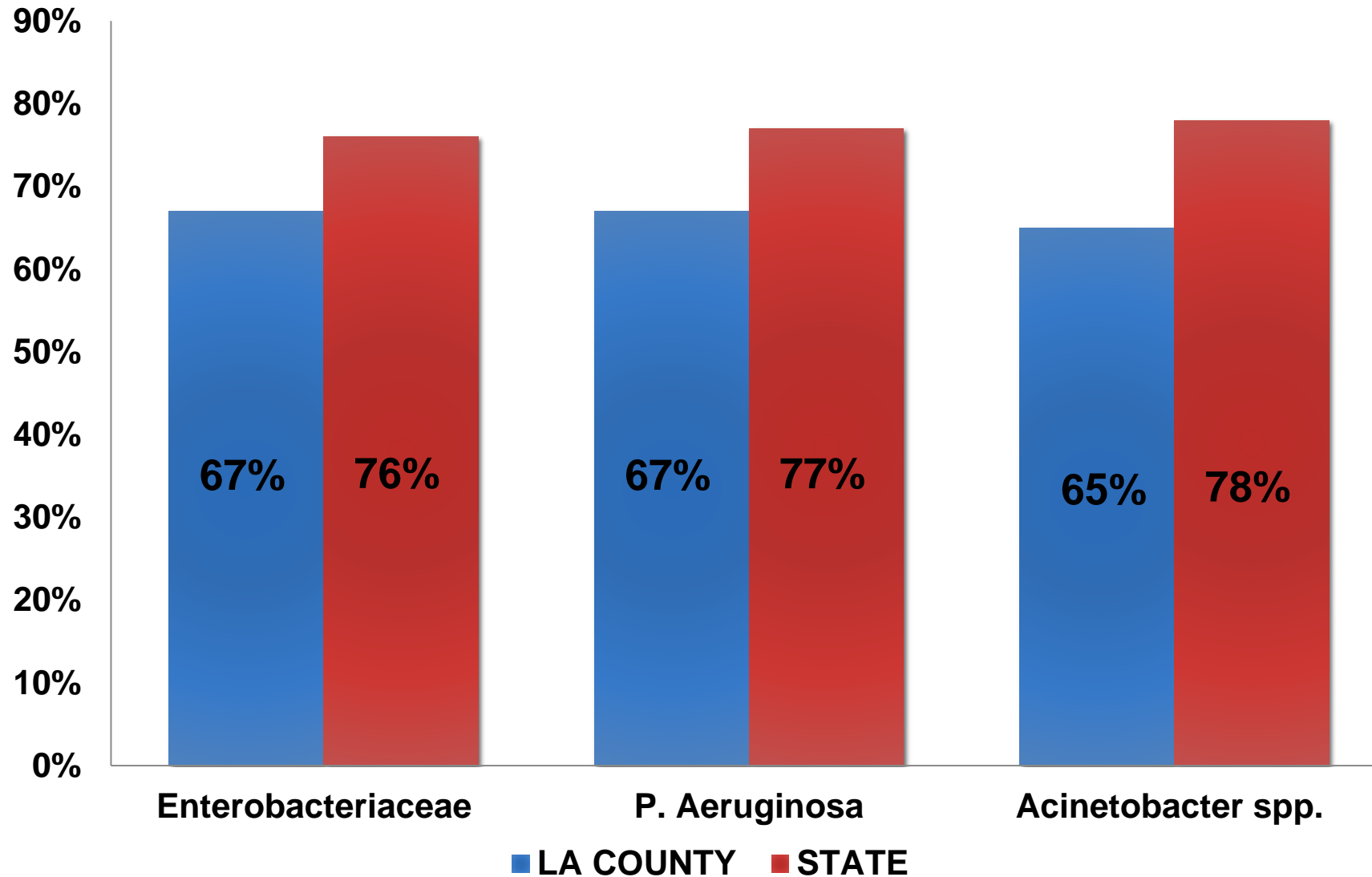
### Regulatory

- FDA breakpoints **MUST** be used by FDA-cleared AST instruments
- Breakpoints listed on "STIC" website

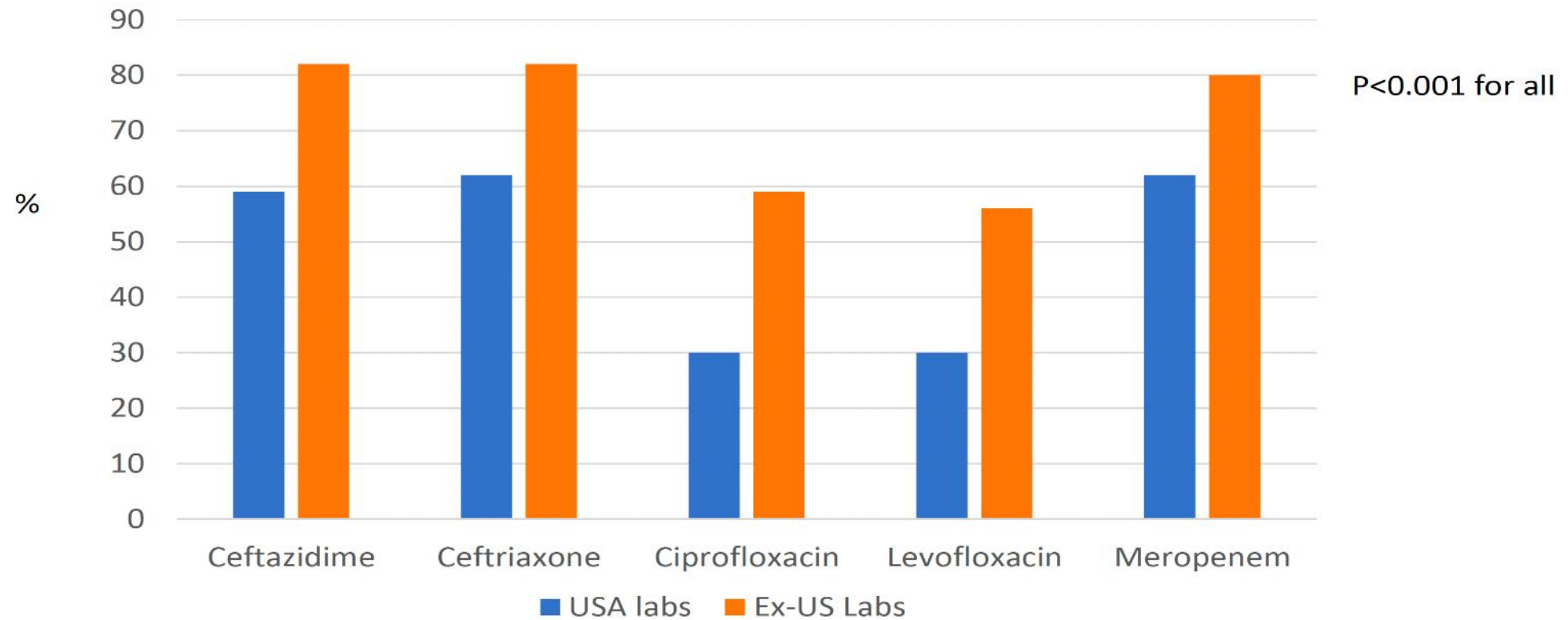
21<sup>st</sup> Century Cures allows recognition of MANY CLSI breakpoints by FDA.... But not all



## Survey of Hospital Use of Current CLSI breakpoints for Carbapenems



## Use of current Enterobacterales breakpoints: U.S. vs. International CAP-Accredited Labs



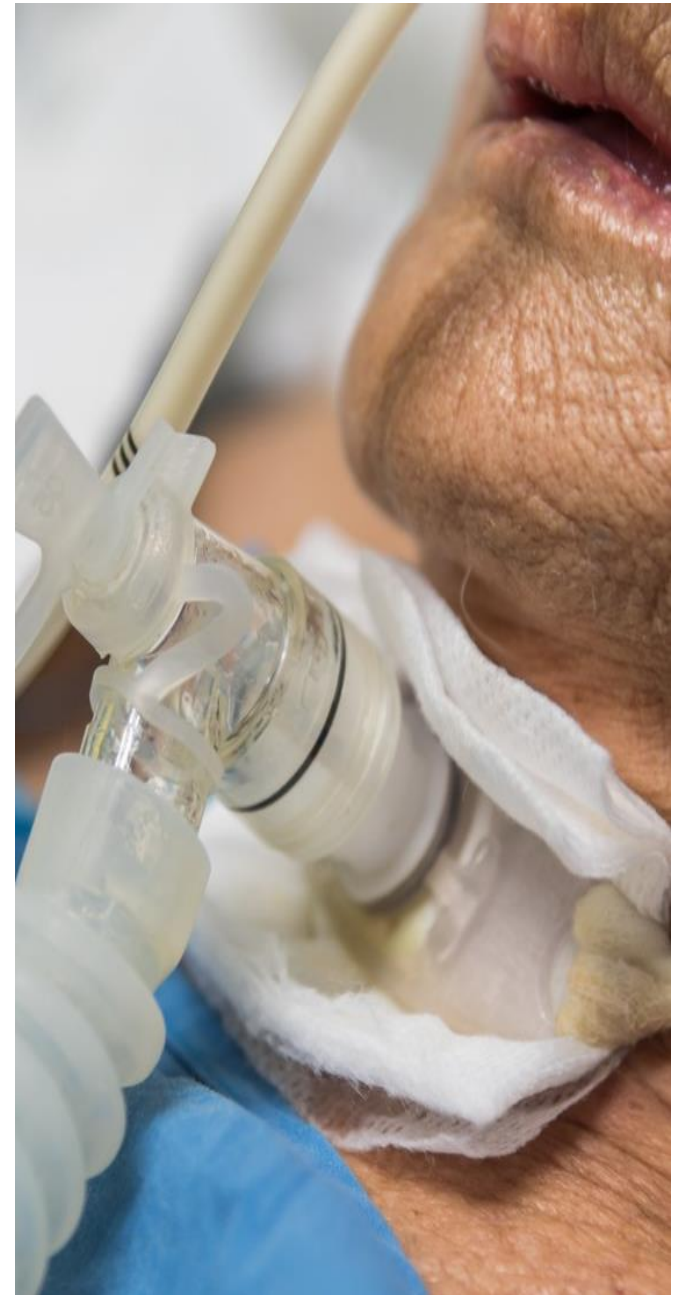
# Local Laboratory must update breakpoints

- Obtain Reference Bacterial Strains
  - FDA has reference panels
- Laboratory must update their own machines
  - <https://clsi.org/meetings/ast/breakpoints-in-use-toolkit/>
  - AST manufacturer can also be helpful in this process
- Save Lives
- LA County Department of Public Health Assisted in Carbapenem Breakpoint Updates for their Hospitals

# Patty

**67 year old female** with pulmonary fibrosis currently in the ICU with severe bacterial pneumonia and a deep neck skin infection.

**PMH:** Pulmonary Fibrosis (not on oxygen), No significant healthcare exposure in last four years



## *A. Baumannii* from Sputum, BAL, and Multiple Surgical Specimens from Neck

## *A. Baumannii* resistance mechanisms are complicated

- Amp-C, Oxa 23, Oxa 24/40, *A. baumannii* derived cephalosporinases (ADCs), and other beta-lactamases (including NDM and IMP)
- Porin Loss
- Efflux Pumps (Tet and AdeABC )
- Penicillin Binding Protein Mutations

## *A. Baumannii* from Sputum, BAL, and Multiple Surgical Specimens from Neck

<b>Antimicrobial</b>	<b>Susceptibility</b>
<b>Amp/Sul</b>	<b>R</b>
<b>Pip/Tazobactam</b>	<b>R</b>
<b>Gentamicin</b>	<b>R</b>
<b>Colistin</b>	<b>R</b>
<b>Meropenem</b>	<b>R</b>
<b>Tigecycline</b>	<b>R</b>

# Culture 1

Drug	<b>Acinetobacter baumannii</b>	
	MIC Interp	MIC
Amikacin	R	>32
Ampicillin/Sulbactam	R	>16
Cefepime	R	>16
Ceftazidime	R	>16
Ceftazidime/Avibactam	NI	>16
Ceftolozane/Tazobactam	NI	>16
Ciprofloxacin	R	>2
Gentamicin	I	>8
Imipenem	R	>8
Meropenem	R	>8
Minocycline	I	8
Piperacillin/Tazobactam	R	>64
Tetracycline	R	>8
Tigecycline	NI	≤1
Tobramycin	R	>8
Trimethoprim/Sulfa	R	>2



# Culture 2

Drug	<b>Acinetobacter baumannii</b>			
	MIC Interp	MIC	Kirby-Bauer	MIC
Amikacin	R	>32		
Ampicillin/Sulbactam	NI	>16		
Cefepime	R	>16		
Cefiderocol			NS	
Ceftazidime	R	>16		
Ceftazidime/Avibactam		>16		
Ceftolozane/Tazobactam		>16		
Ciprofloxacin	R	>2		
Delafloxacin				>1
Eravacycline				1.0
Gentamicin	I	>8		
Imipenem	R	>8		
Imipenem/Relebactam				>16
Meropenem	R	>8		
Meropenem/Vaborbactam				>16
Minocycline	I	8		
Omadacycline				4
Piperacillin/Tazobactam	R	>64		
Plazomicin				>4
Tetracycline	NI	>8		
Tigecycline	NI	4		
Tobramycin	R	>8		
Trimethoprim/Sulfa	S	<=2		

# Antibiotic Strategy

- High Dose Ampicillin-Sulbactam
- TMP/SMX
- Eravacycline
- Did not try Minocycline or Omadacycline
- ~~Cefiderocol~~
- ~~Delafloxacin~~

# Antibiotic Strategy

- **High Dose Ampicillin-Sulbactam**
- Interestingly it is the Sulbactam Component with Microbiologic Activity Against the CRAB
- Sulbactam is an Ambler Class A serine beta-lactamase inhibitor
- Sulbactam is also a Beta-Lactam Antibacterial against PBP1 and PBP3 inhibition of *A. baumannii*
- Based on drug availability and susceptibility testing, we still used ampicillin Sulbactam

# Antibiotic Strategy

- **High Dose Ampicillin-Sulbactam**

# Antibiotic Strategy

- **High Dose Ampicillin-Sulbactam**

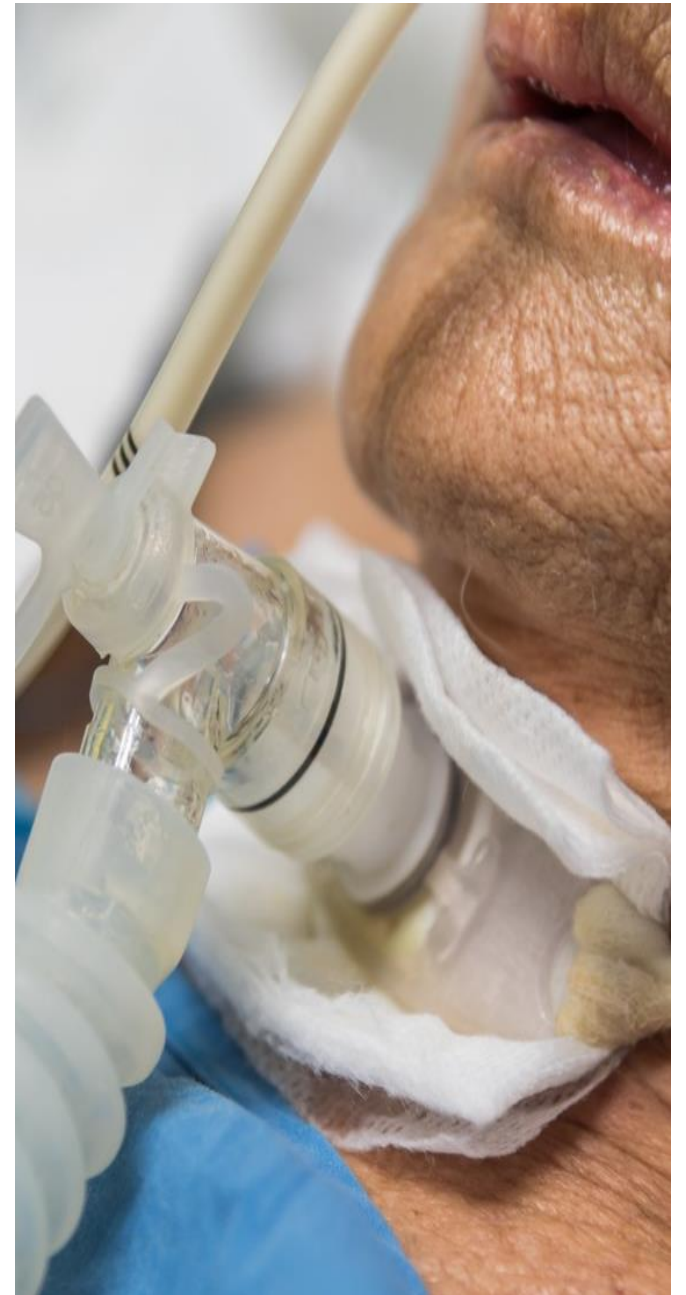
<b>Dose</b>	<b>Daily SUL</b>	<b>AMP/SUL regimen</b>
FDA-approved (max dose)	4 g	2/1 g q6h over 30 mins
IDSA high-dose (low end)	6 g	2/1 g IV q4h over 30 mins
IDSA high-dose (high end)	9 g	6/3 g IV q8h over 4 hours

# Lucy

**77 year old female** with pulmonary fibrosis currently in the ICU with severe bacterial pneumonia and a deep neck skin infection due to CRAB.

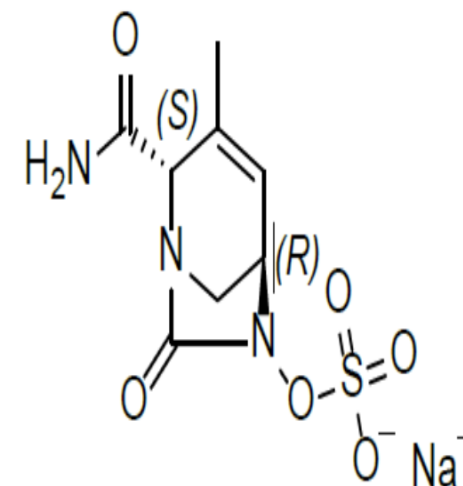
**PMH:** Pulmonary Fibrosis (not on oxygen)

**Hospital Course:** 8 surgical interventions, recurrent bouts of severe respiratory failure, intermittent pressors – never on ECMO, but clinical course continued to deteriorate



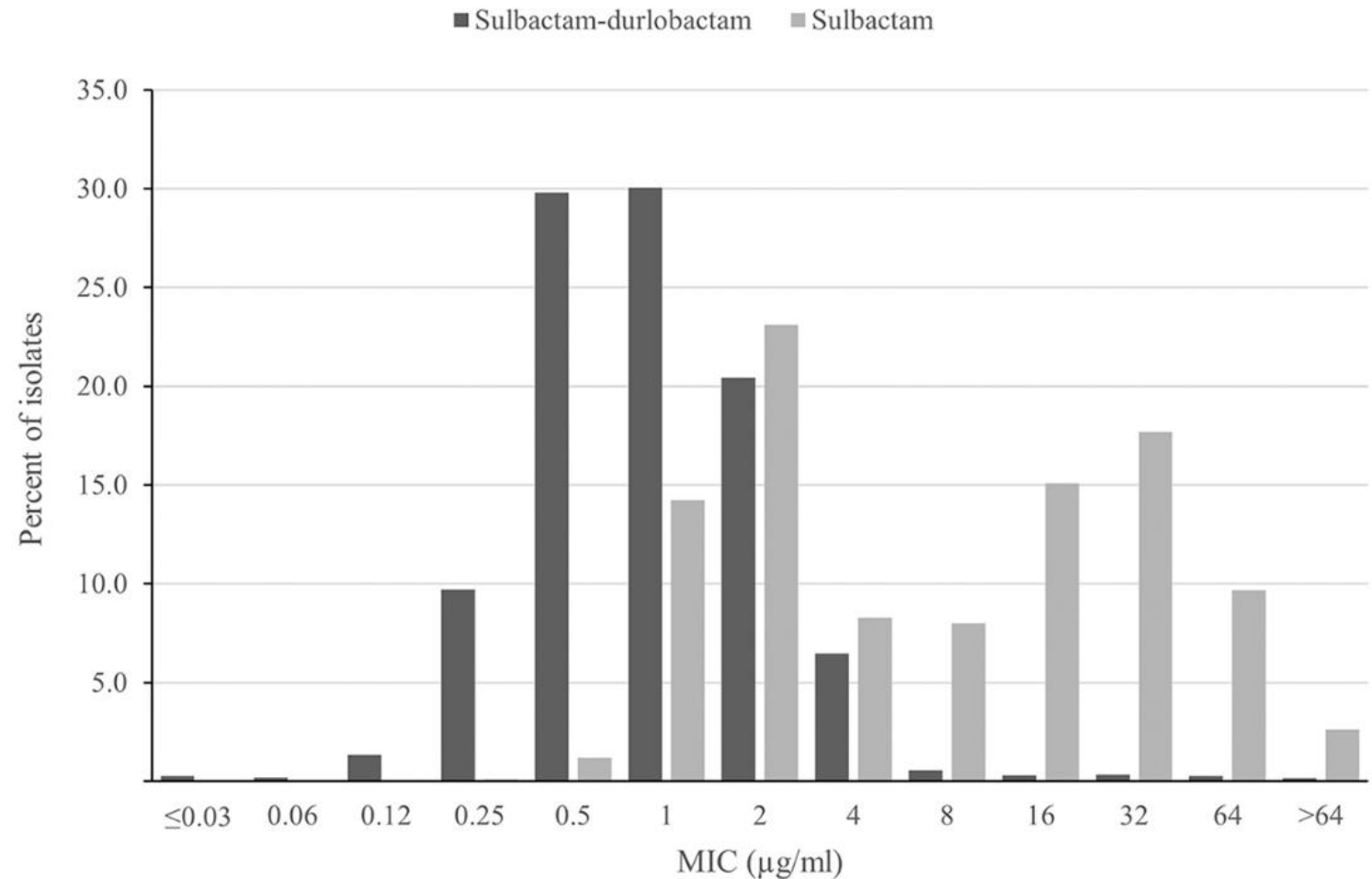
# Sulbactam-Durlobactam is a Novel Antimicrobial with Activity Against CRAB

- Durlobactam is a diazabicyclooctane non-beta-lactam, beta-lactamase inhibitor
- Protects Sulbactam from degradation by certain serine-beta-lactamases
- Durlobactam has no activity



## Sulbactam-Durlobactam is a new antimicrobial with activity against CRAB

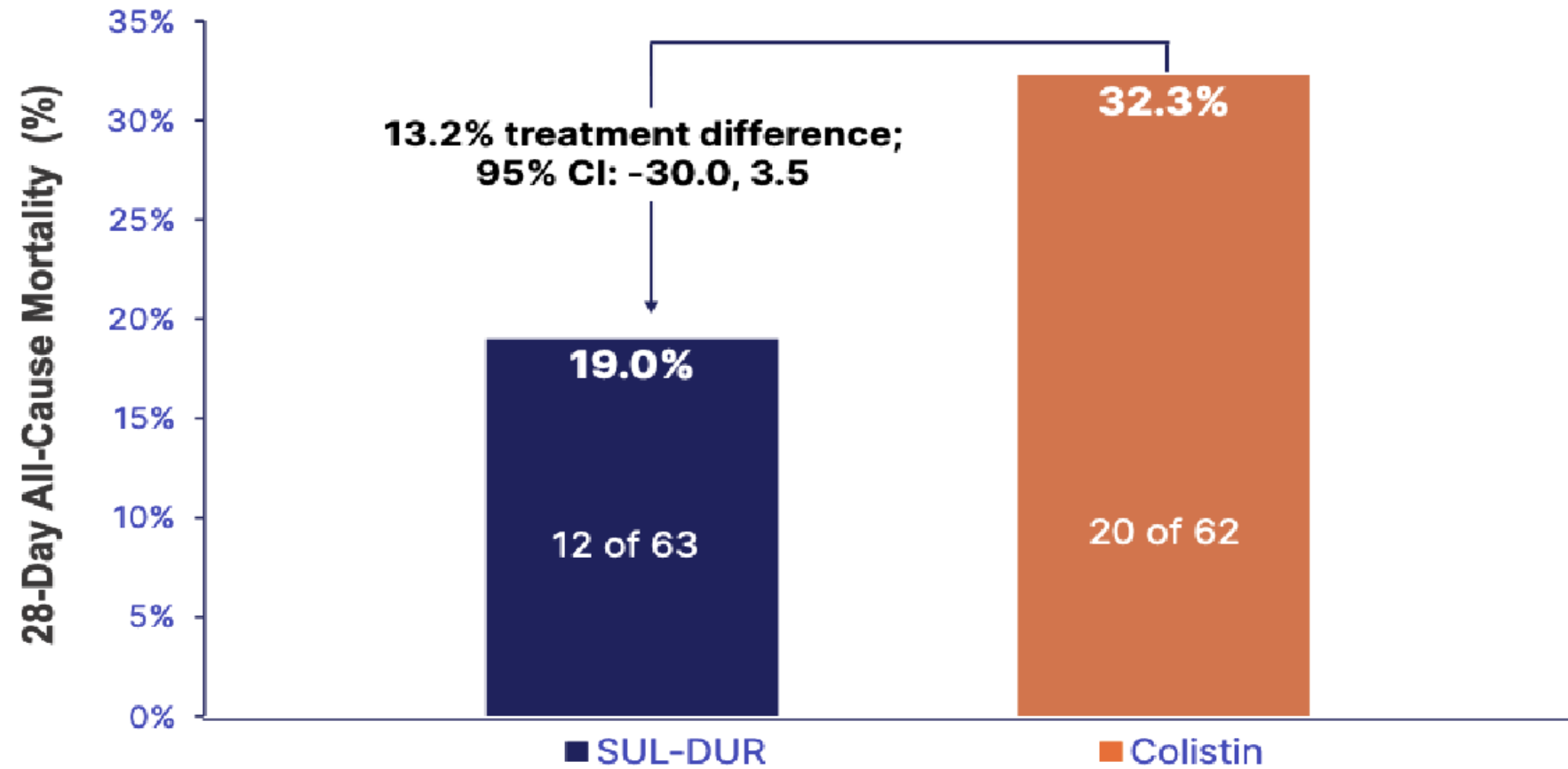
Karlowsky JA, et al. AAC 202



**FIG 1** Sulbactam-durlobactam (black bars) and sulbactam (gray bars) MIC distributions for 5,032 isolates of *Acinetobacter baumannii-calcoaceticus* complex (ABC) species collected globally from 2016 to 2021.



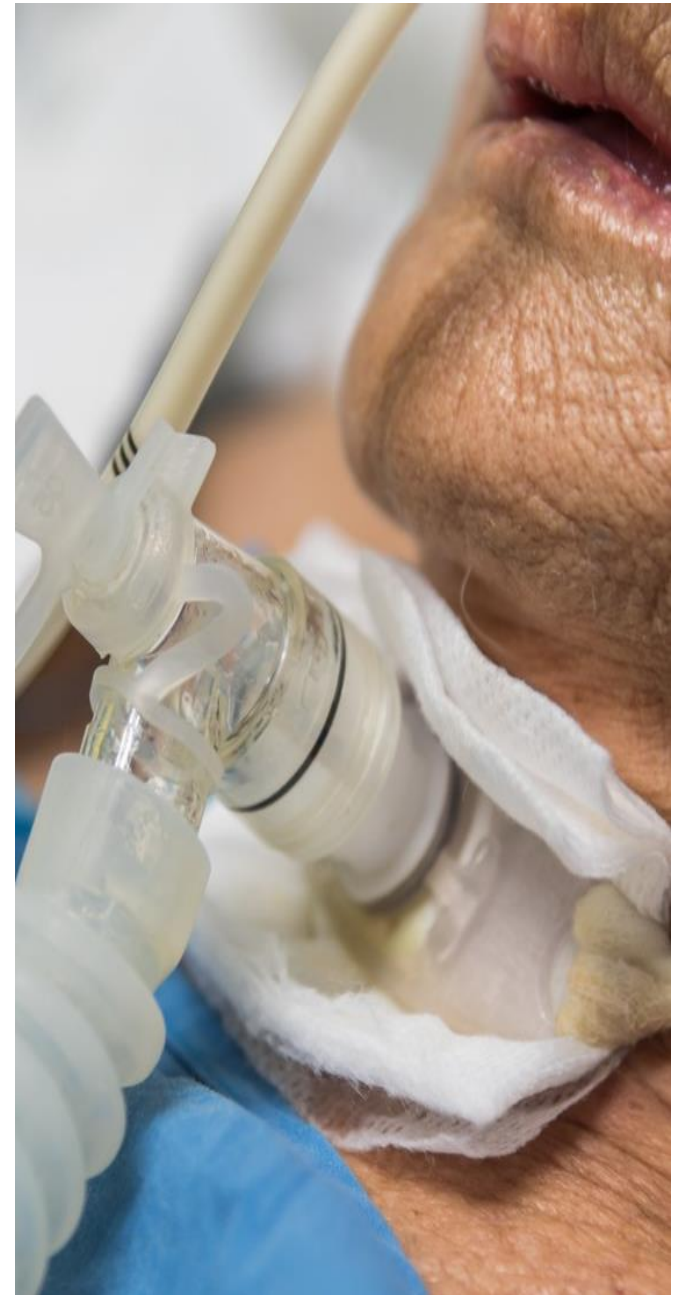
## Sulbactam-Durlobactam is Indicated for treatment of HAP/VAP



# Lucy

**Hospital Course:** 8 surgical interventions, recurrent bouts of severe respiratory failure, intermittent pressors – never on ECMO

**Hospital Completion:** Patient's Pneumonia and Neck Infection Resolved after 19 days of Sulbactam-Durlobactam Therapy



# Summary

- The Clinical Microbiology Laboratory still plays a critical role in the acute management of patients
- Microbiology Laboratories must realize that accuracy in the Local Laboratory will impact outcomes as proven in the Merino Trial
- Expanded Capacity for Testing Novel Antimicrobial Agents is Crucial
- Knowledge of Novel Antimicrobials is Crucial for Management of Patients