Critical Microbiology Results for Critical Patients: 2023 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
- I serve as a consultant for: Thermo Fisher Scientific
- I developed the presentation and the opinions presented are my own and do not represent the opinion of the sponsors, the Infectious Disease Association of California, or any public health authority

Case Presentation

- The following descriptions are of 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

Definitions

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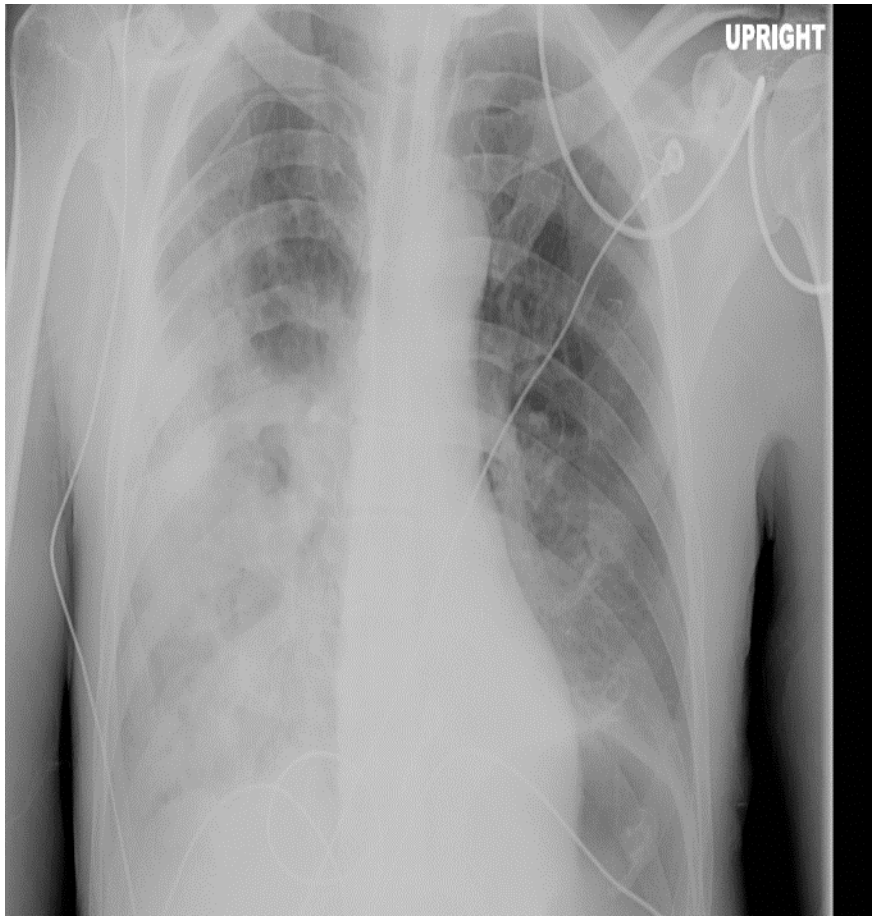
Quality Improvement Opportunity - a change in practice that might improve outcomes, but is not derived from an erroneous practice

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)



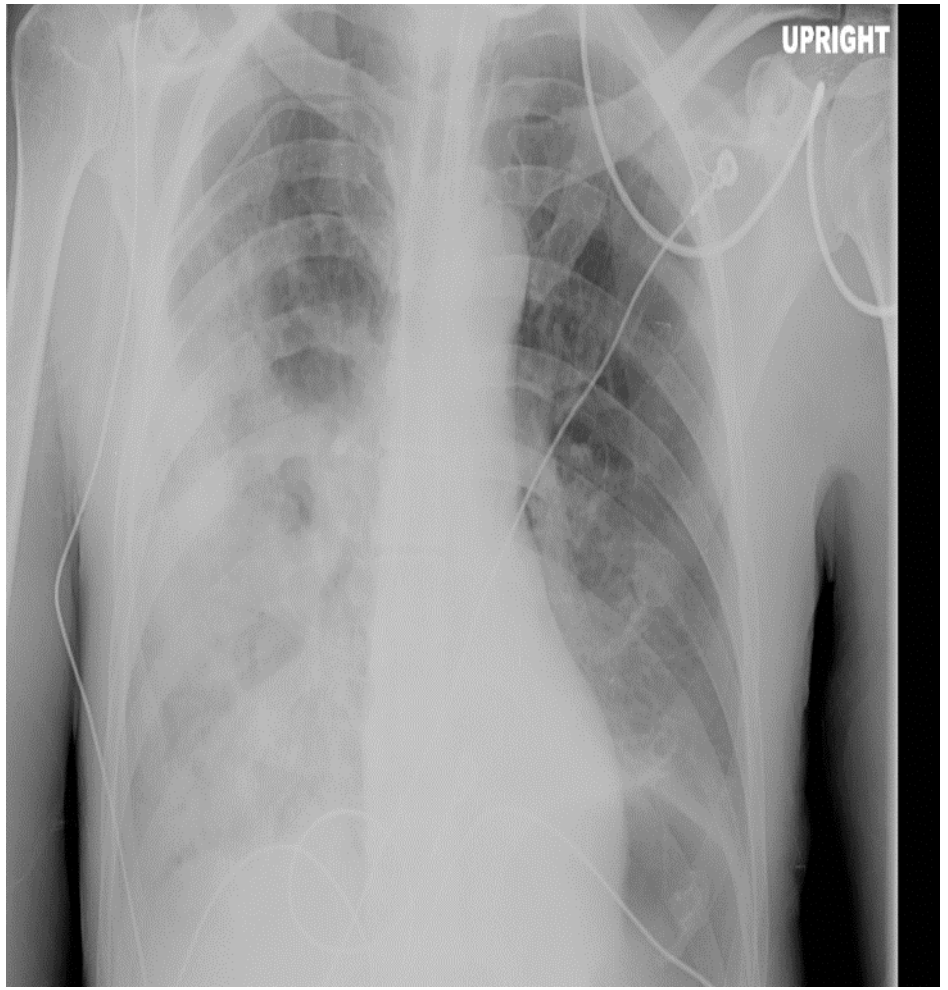
Lucy: Admission Exam

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

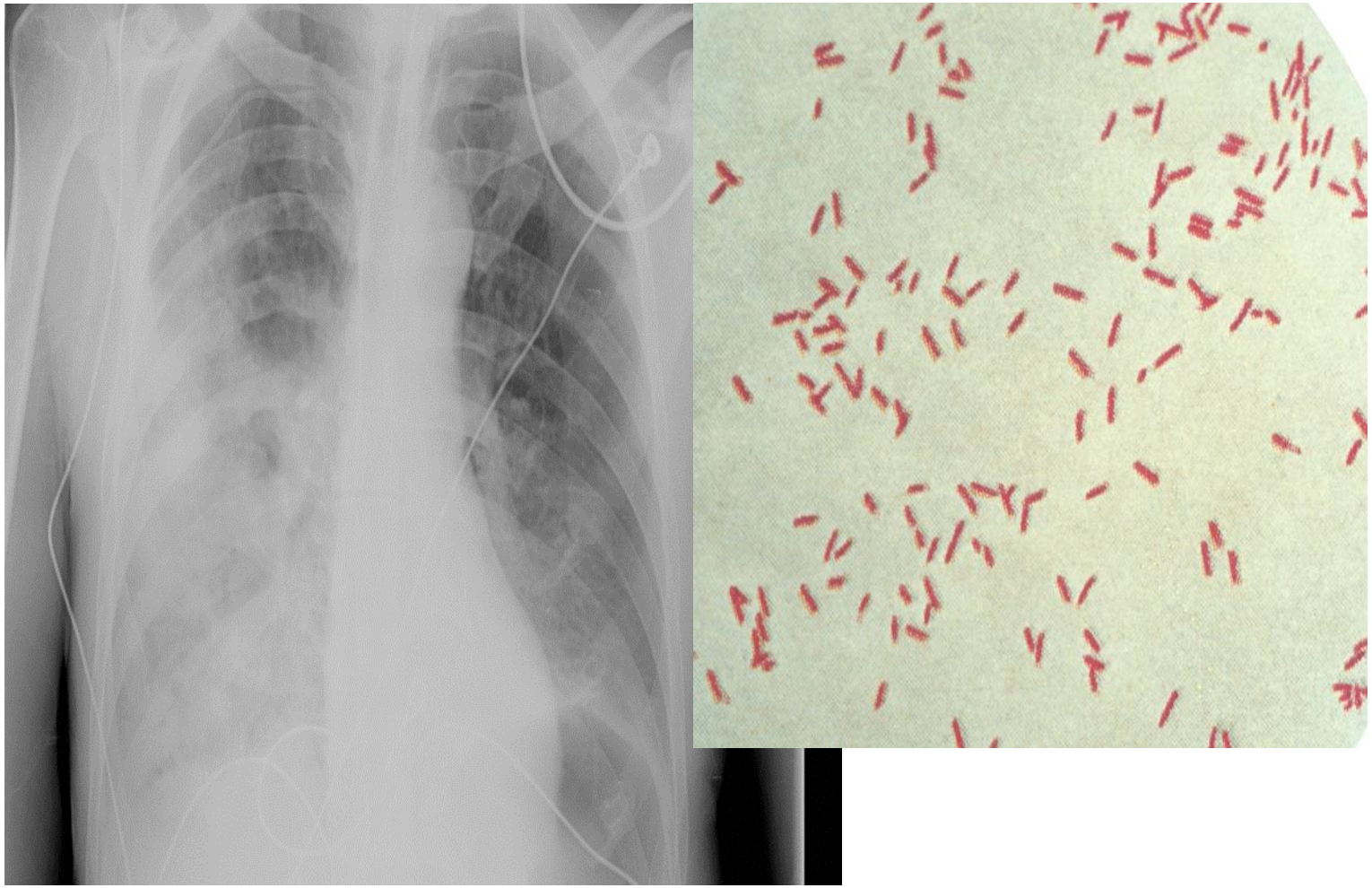
- Intubated, Sedated
- Frail with slight temporal wasting
- JVD was Flat
- Tachycardic, No MRG
- RLL Rhonchi
- Decreased muscle mass
- No Skin Rash

- **PEEP of 12 cm H2O and 80% FiO2**
- **Currently on norepinephrine at 6 mcg/min**

- **Labs: WBC: 13K, GFR>80, LFTs WNL**

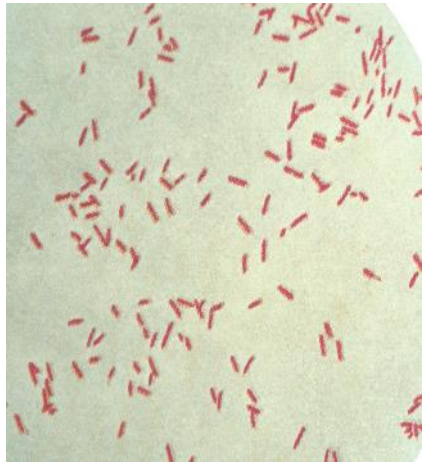


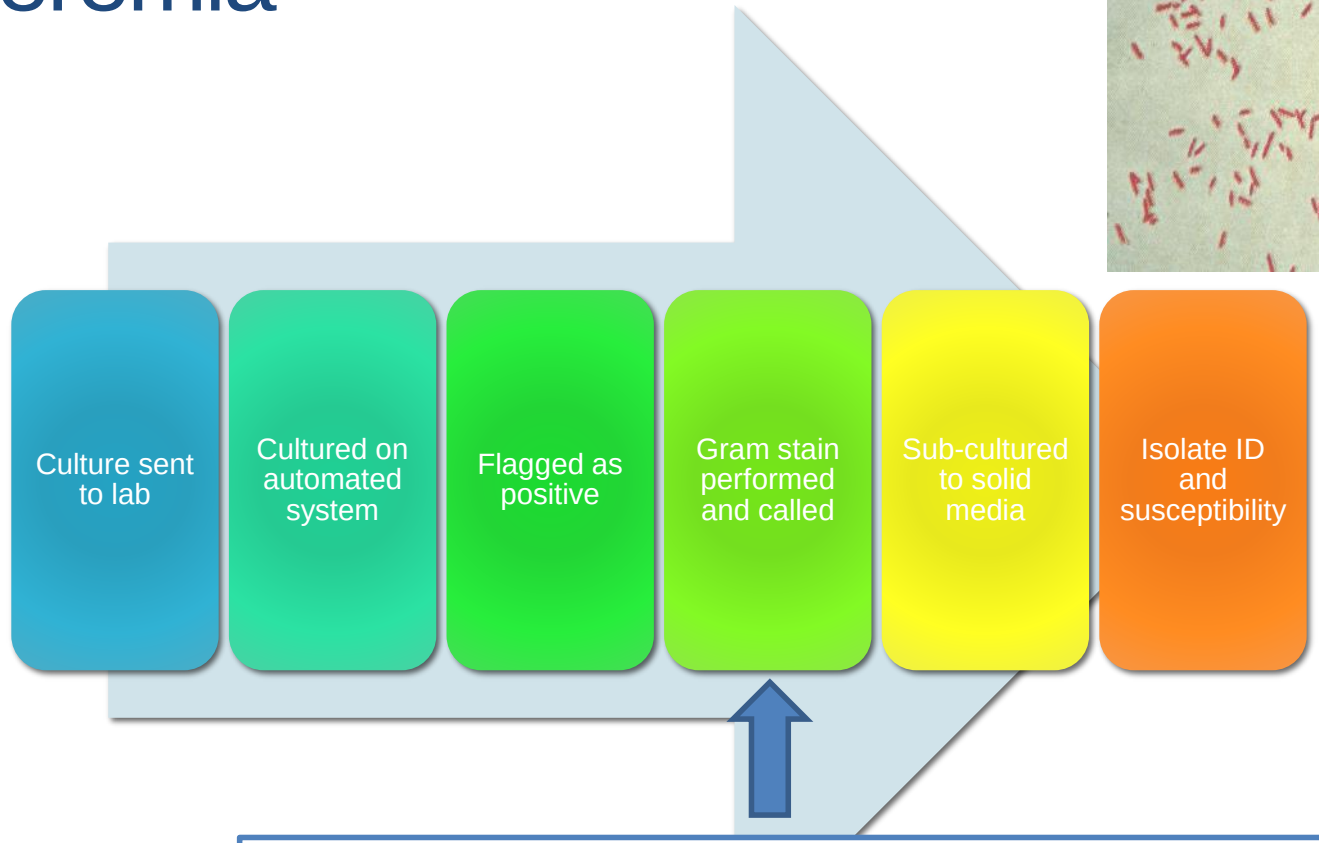
RLL Pneumonia Gram-Negative Rods



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

RLL Pneumonia with Bacteremia



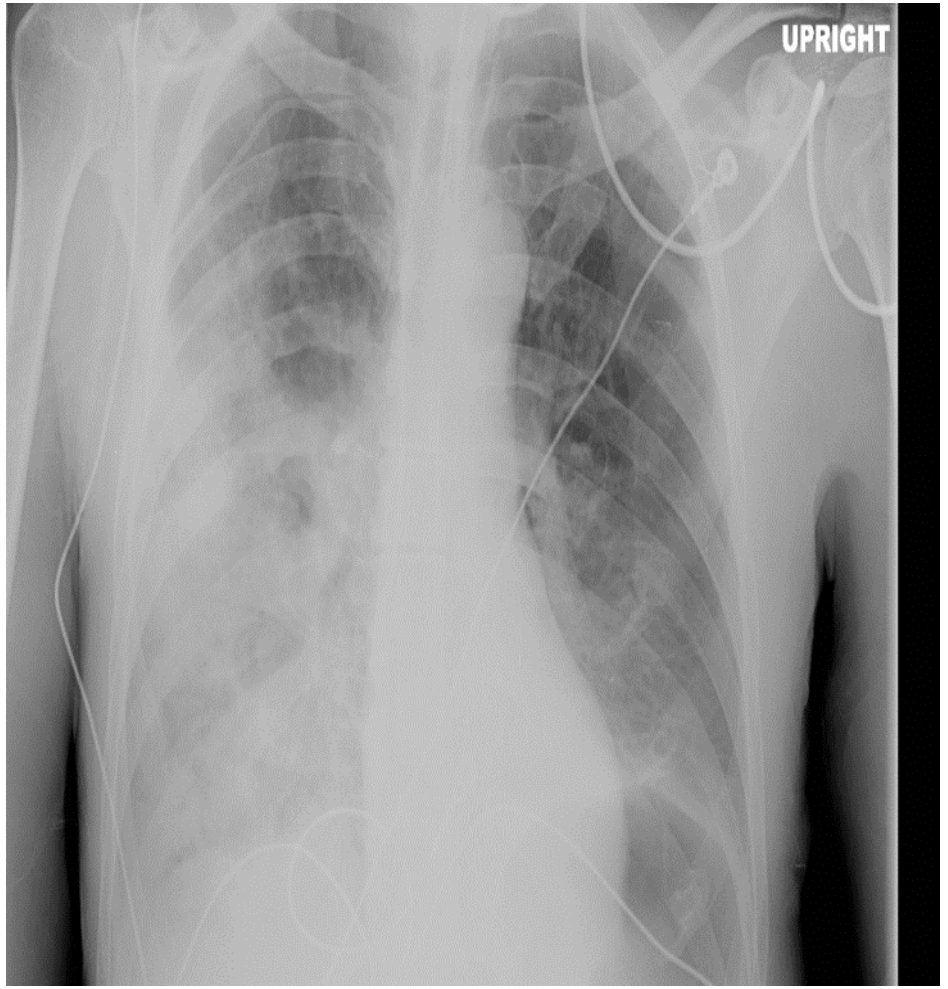


This is where we are with our patient.
We only know we are dealing with a gram negative Rod.

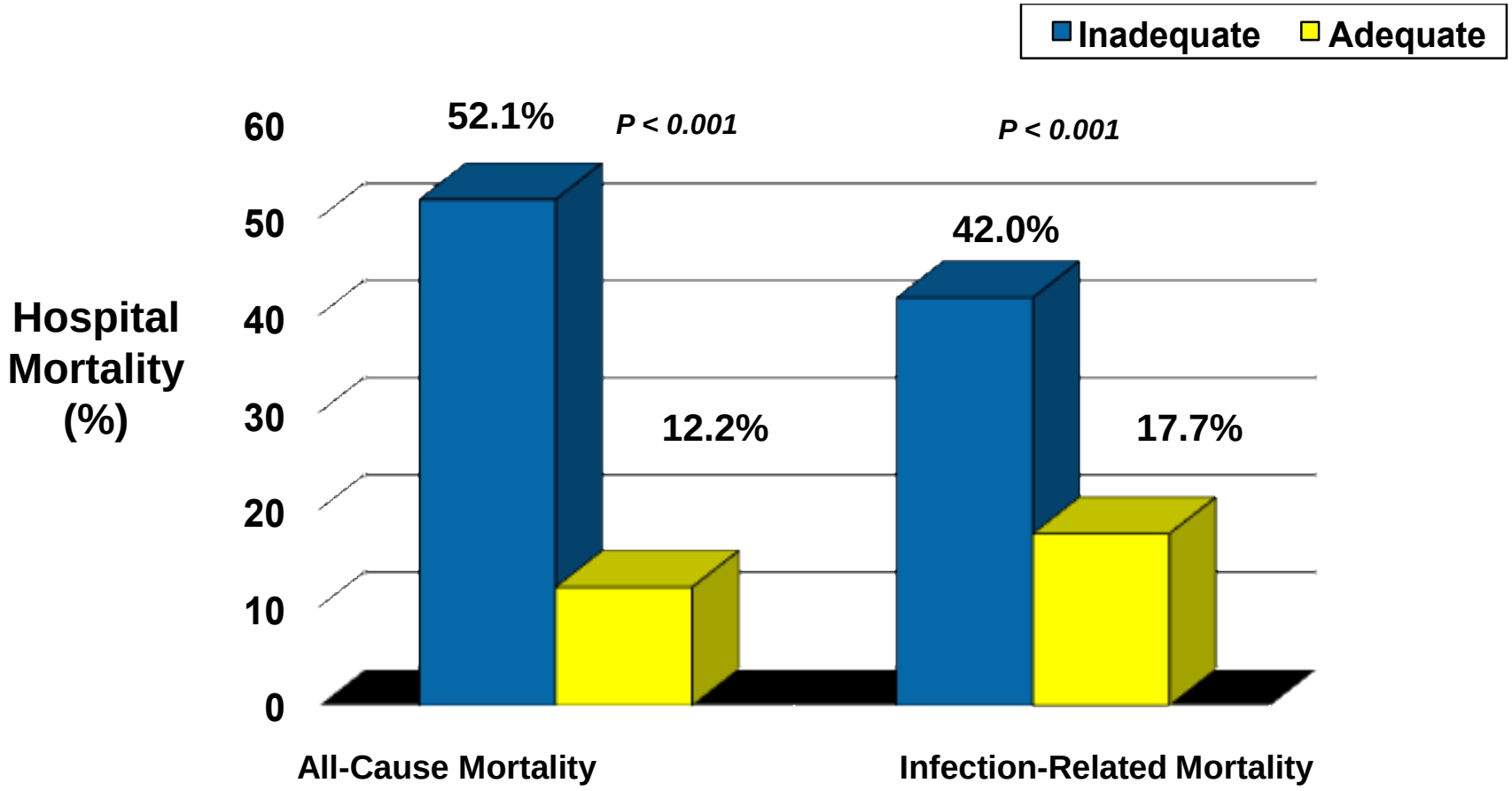
Lucy: Assessment

- 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 or 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?

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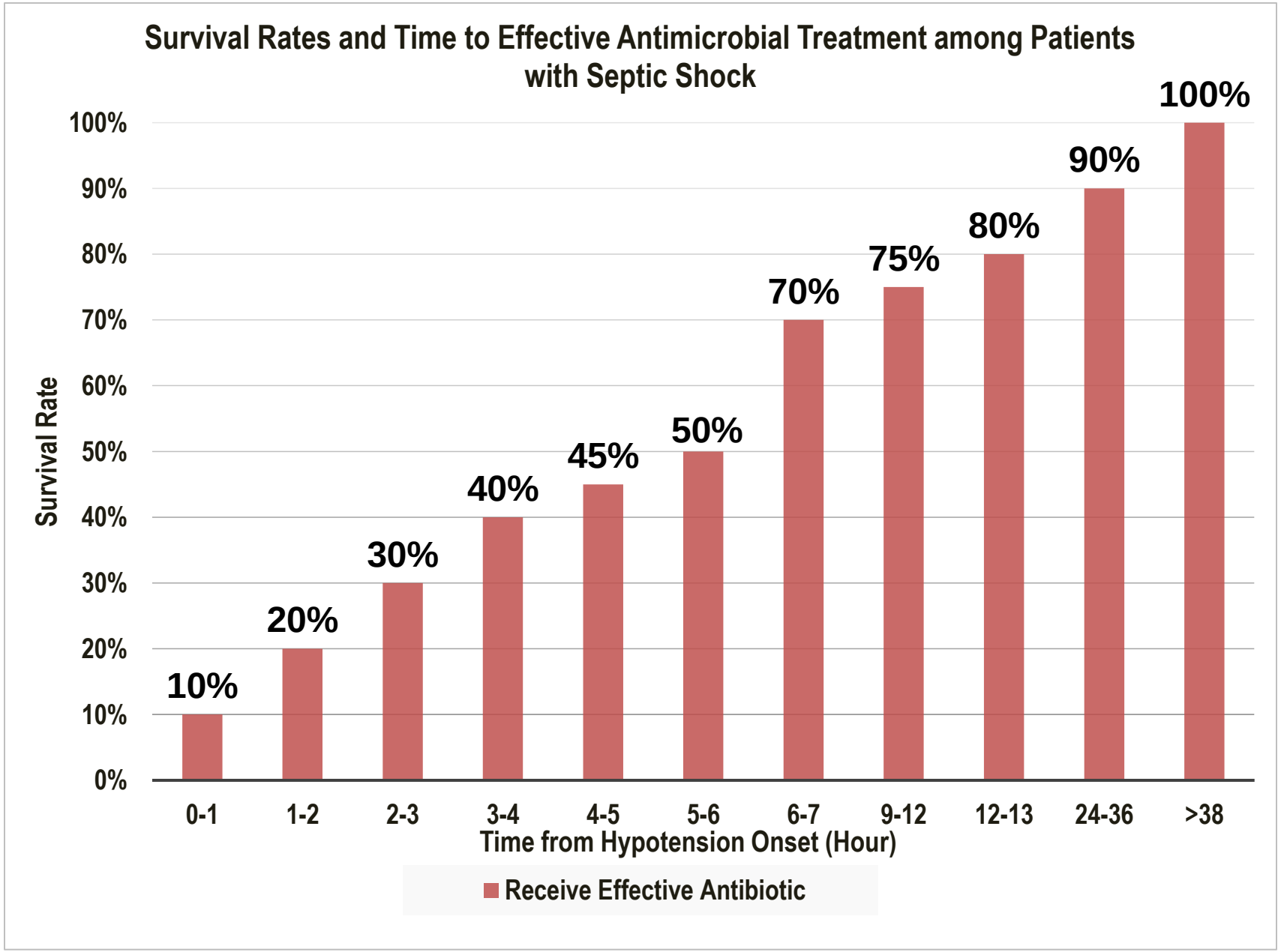

Kumar A, et al. *Crit Care Med* 2006; 1589-1596, Kollef MH., et al. *Chest.* 1999;115:462-474.

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

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

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

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- 3,376 Patients with Bacteremia from 7/2016-6/2020
- Combination of Beta lactam and Vancomycin

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- 3,376 Patients with Bacteremia from 7/2016-6/2020
- Combination of Beta lactam and Vancomycin

- Staphylococcus aureus 22.5% (42% of which was MRSA)
- E. Coli 21%
- Klebsiella 14%

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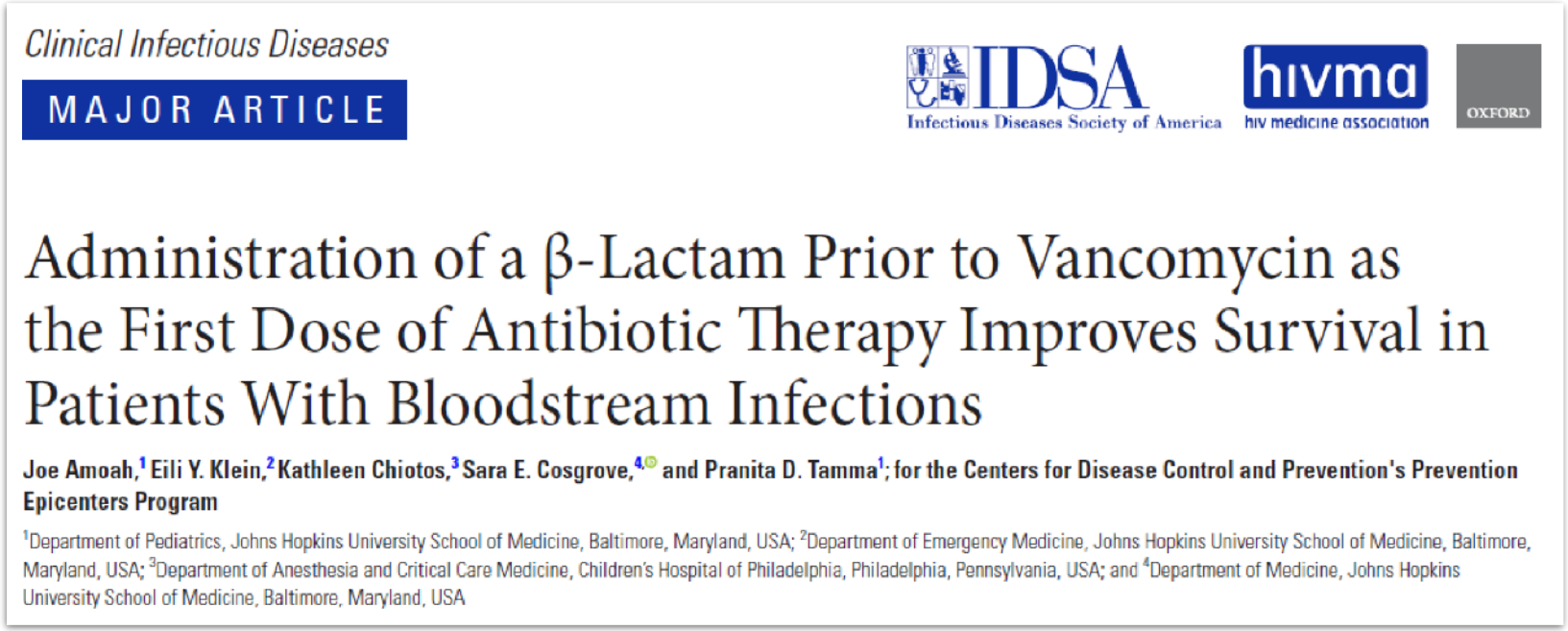

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- 2,685 (79.5%) received Beta Lactam First
  - 47.9% Zosyn
  - 42% Cefepime

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

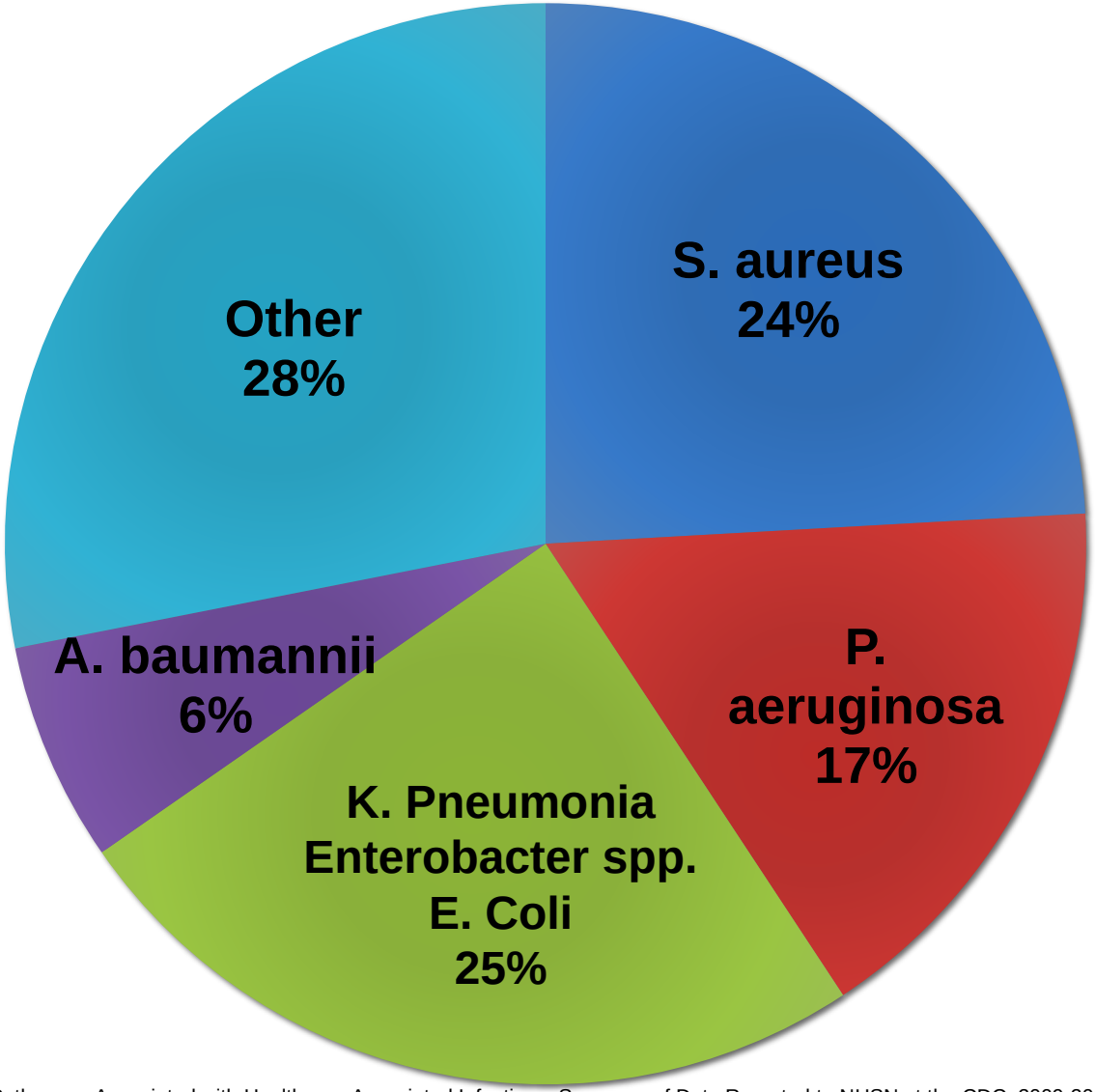
- Beta Lactam First Improved Survival
  - OR 0.48 (0.33-0.69)
  - MRSA 0.93 (0.33-2.62)

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



Sievert et al. Antimicrobial Resistant Pathogens Associated with Healthcare-Associated Infections: Summary of Data Reported to NHSN at the CDC, 2009-2010, ICHE January 2013

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

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

[1] Cefotaxime and ceftriaxone have comparable activity against *Enterobacteriaceae*.

Antibiogram data source: UCLA Health Infectious Disease

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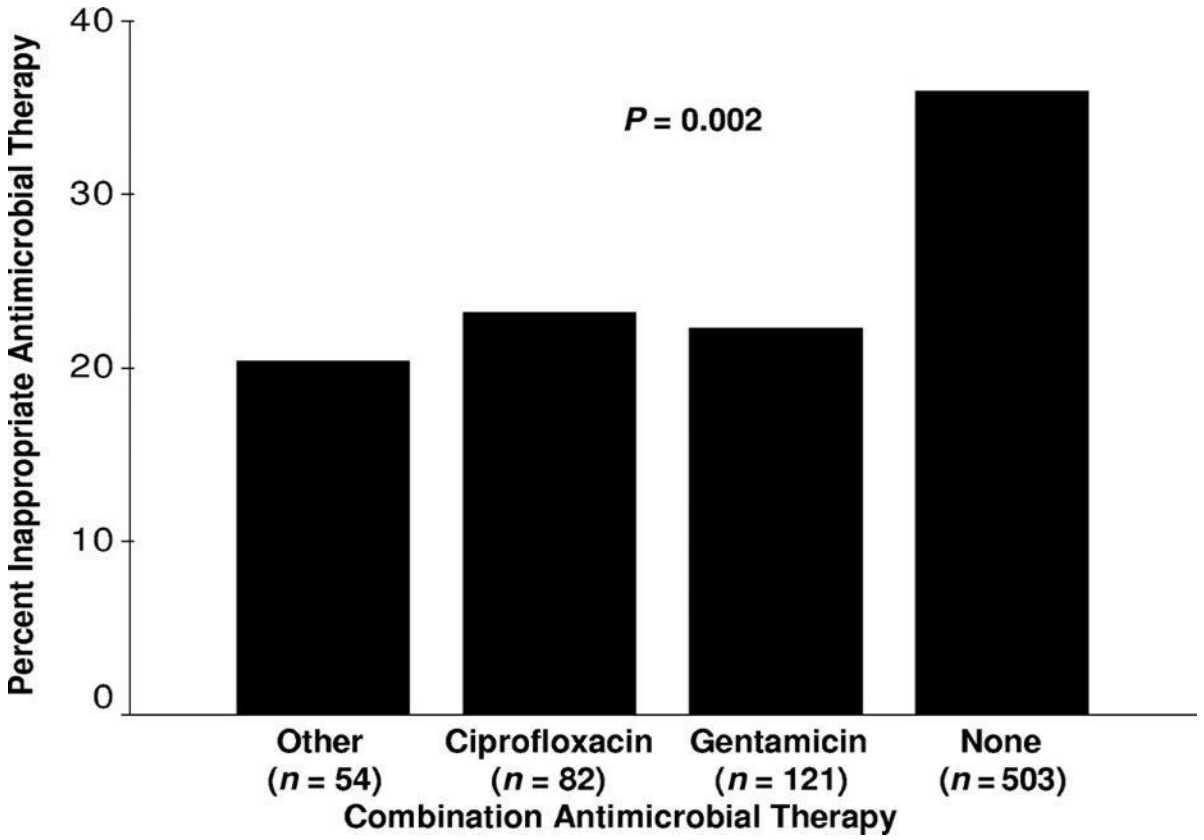
Empiric combination therapy is associated with higher rates of early, appropriate therapy for patients with sepsis due to Gram-negatives

Retrospective study (n=760)



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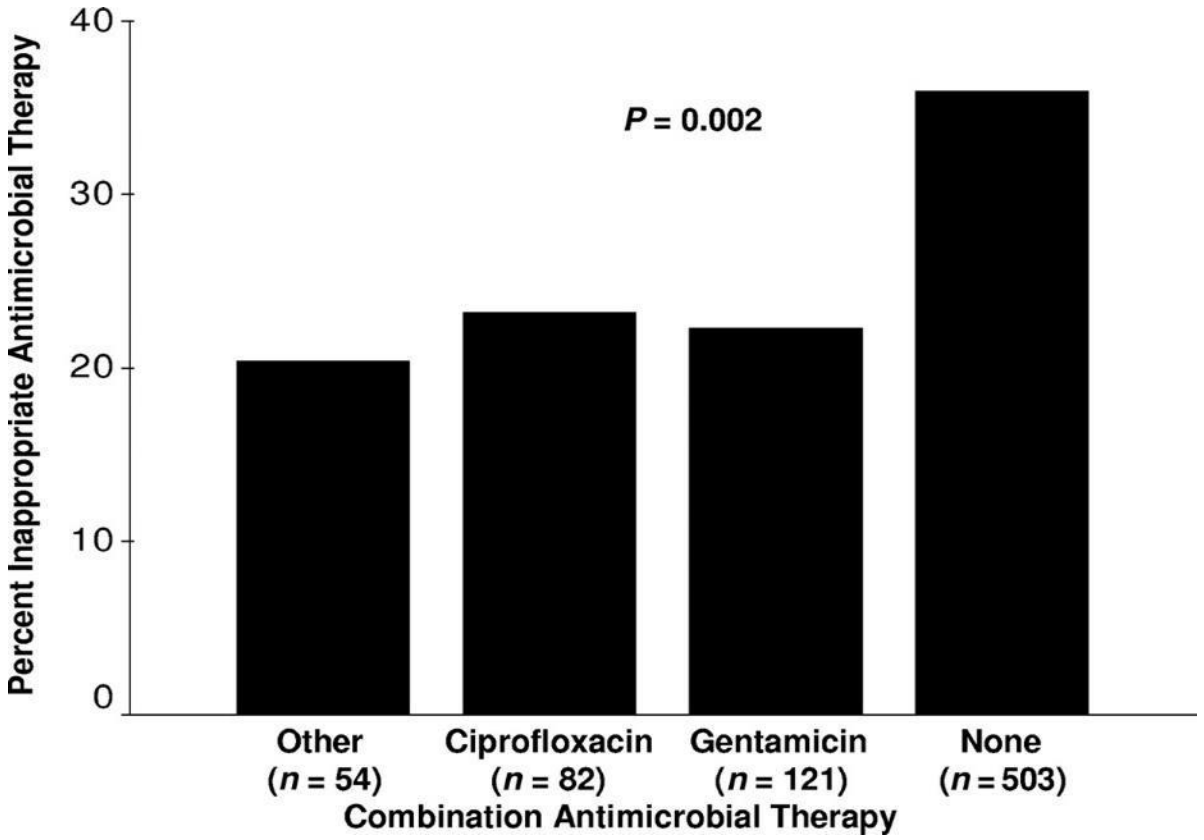

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Citrobacter freundii	37	R[2]	R	76	R	89	–[4]	–[4]	97	99	99	99	89	92	92	81	99
Enterobacter aerogenes	94	R	R	88	R	98	–[4]	–[4]	99	97	99	99	99	99	99	98	98
Enterobacter cloacae	209	R	R	81	R	92	–[4]	–[4]	89	99	99	99	99	99	98	94	85
Escherichia coli	752	41	50	94	59	84	83	79	99	99	99	99	82	85	63	60	99
Klebsiella oxytoca	121	R	64	89	23	95	95	87	98	98	98	99	96	96	94	91	99
Klebsiella pneumoniae	399	R	70	87	71	86	85	84	93	94	94	98	92	88	85	81	97
Morganella morganii	60	R	R	97	R	99	–[4]	–[4]	97	–	98	99	87	98	82	68	R
Proteus mirabilis	197	67	80	99	25	95	97	87	99	–	99	99	90	94	68	67	R
Serratia marcescens	127	R	R	96	R	96	–[4]	–[4]	97	94	96	99	99	96	93	98	R
Acinetobacter baumannii	62	R	62	53	R	58	58	–	R	62	60	67	60	66	56	60	95
Pseudomonas aeruginosa	738	R	R	84	R	88	87	R	R	81	85	96	91	94	78	R	99
Stenotrophomonas maltophilia	84	R	R	R	R	–	30	R	R	R	R	R	R	R	–	99	70
Burkholderia cepacia complex	12[5]	R	R	R	R	R	27	R	R	R	18	R	R	R	36	64	R

[1] Cefotaxime and ceftriaxone have comparable activity against *Enterobacteriaceae*.

Antibiogram data source: UCLA Health Infectious Disease

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

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

[1] Cefotaxime and ceftriaxone have comparable activity against *Enterobacteriaceae*.

Antibiogram data source: UCLA Health Infectious Disease

Combination Antibiogram 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)[1]	Gentamicin (92)	Tobramycin (95)	Ciprofloxacin (80)
Cefepime (90)	99[2]	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

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Antibiotic Selection for Sepsis

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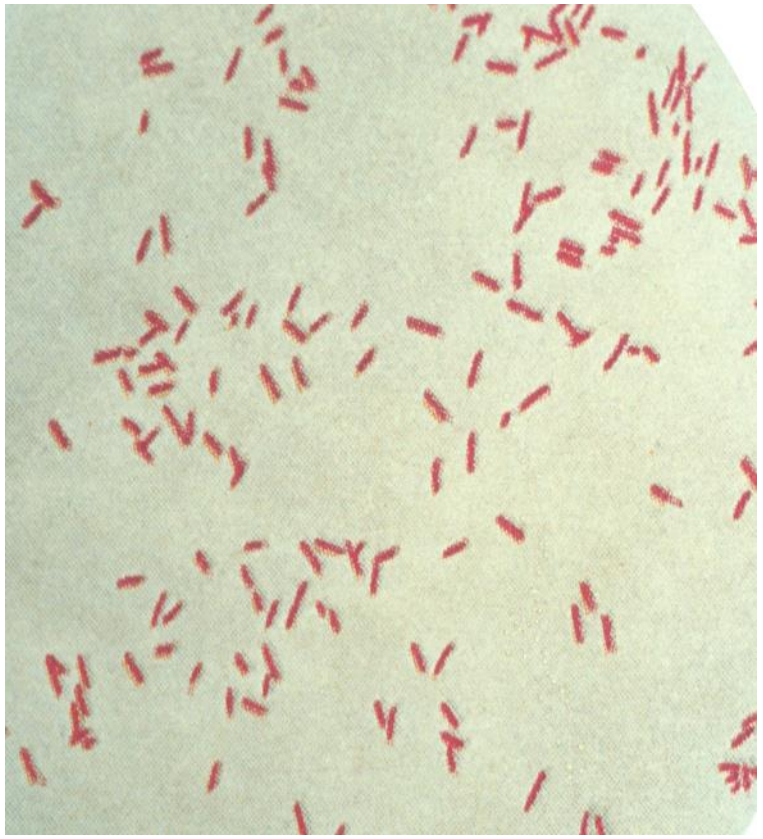


Hospital Antibiogram Limitations

- 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**

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

LA County Regional Antibiogram

Quality Improvement Opportunity

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

Quality Improvement Opportunity

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

Quality Improvement Opportunity

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

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

BACTERIOLOGY

Check for updates

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

Stefan E. Richter,[a,b] Loren Miller,[c] Daniel Z. Uslan,[d] Douglas Bell,[e] Karol Watson,[b,f] Romney Humphries,[g*] James A. McKinnell[c]

Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

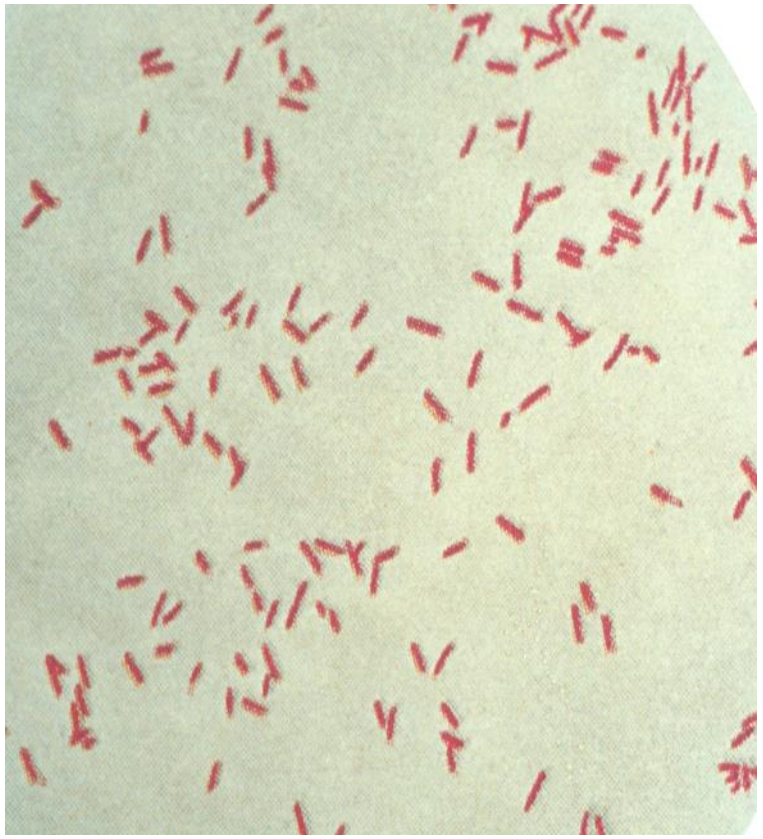
Risk Factors for Development of Carbapenem Resistance Among Gram-Negative Rods

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

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

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

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

2 Days After Consult

- Lucy still on ventilator, max FiO2, high positive ventilatory pressures
- Persistent Fevers
- Increased Sputum production
- Max pressors, increased over last 24 hours

Why is Lucy getting sicker?

https://www.idsociety.org/practice-guideline/amr-guidance/

K. Pneumoniae is almost certainly an ESBL Producer

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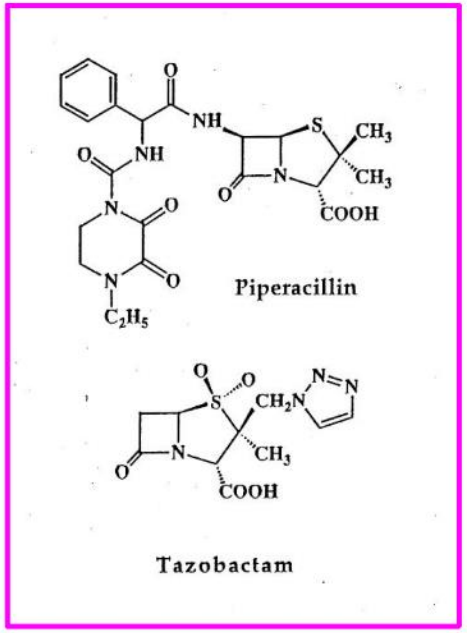
Pip/Tazo	S
Meropenem	S
Tigecycline	R

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

Piperacillin-Tazobactam



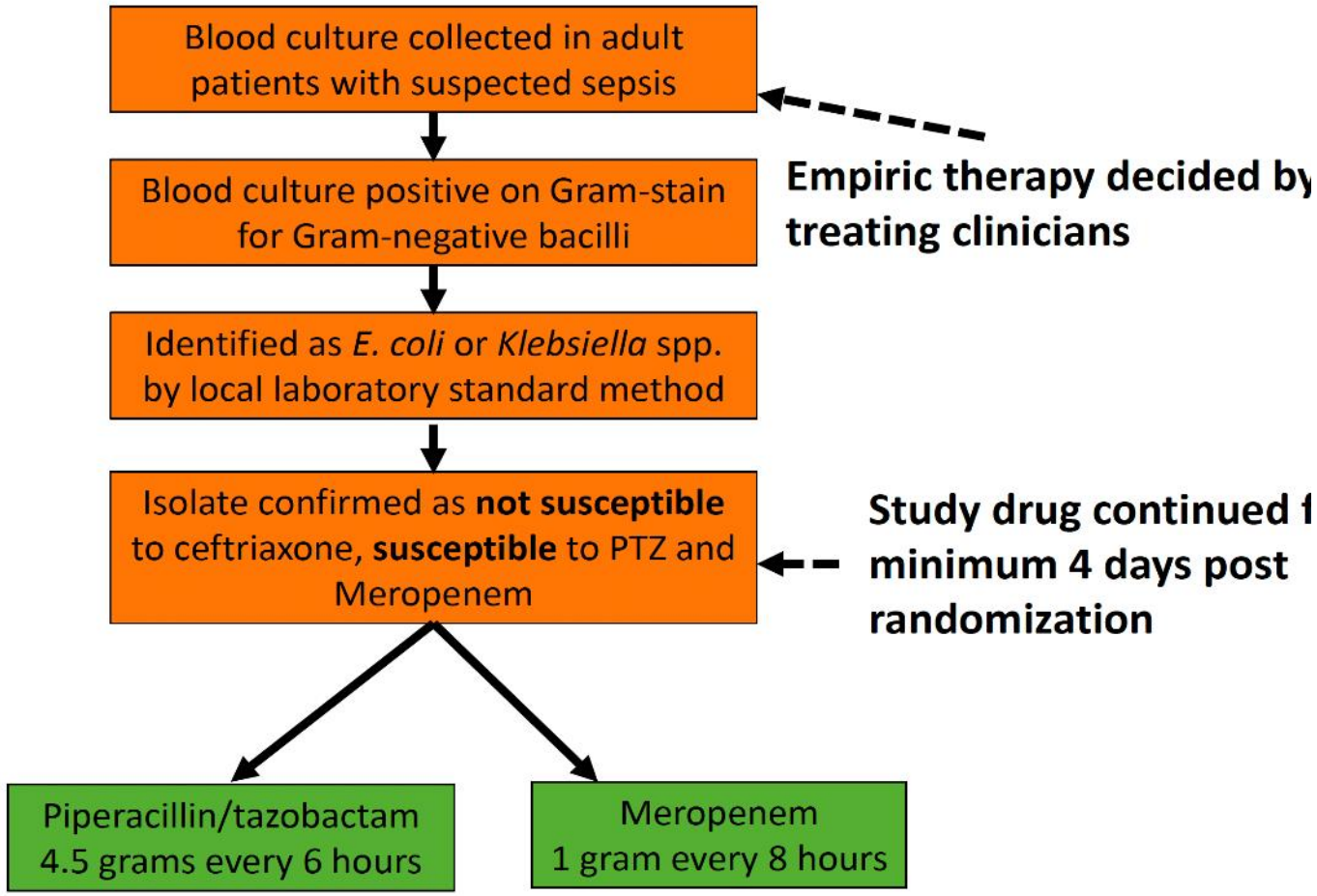
- 1981 - piperacillin approved
- 1993 - piperacillin-tazobactam approved for skin and skin structure and intra-abdominal infections
  - BEFORE ESBLs were wide-spread
  - CLSI never included editing pip-tazo as "R" if ESBL detected, but many do this in practice
- Tazobactam – inhibit activity of ESBLs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

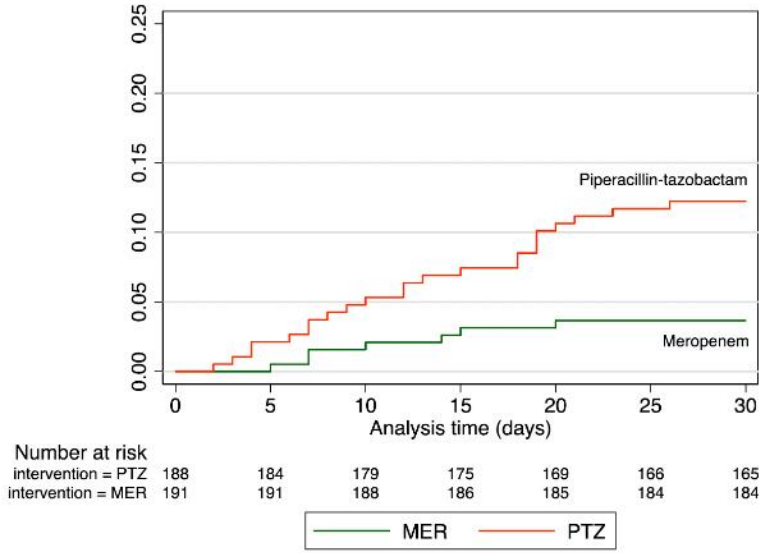


Harris PNA, et al. JAMA. 2018;320:984-994

Merino Trial – Zosyn Associated with Risk of Death

MERINO Trial: "no"

- Piperacillin-tazobactam failed to demonstrate non-inferiority compared with meropenem
- Analysis showed NO relation to MIC



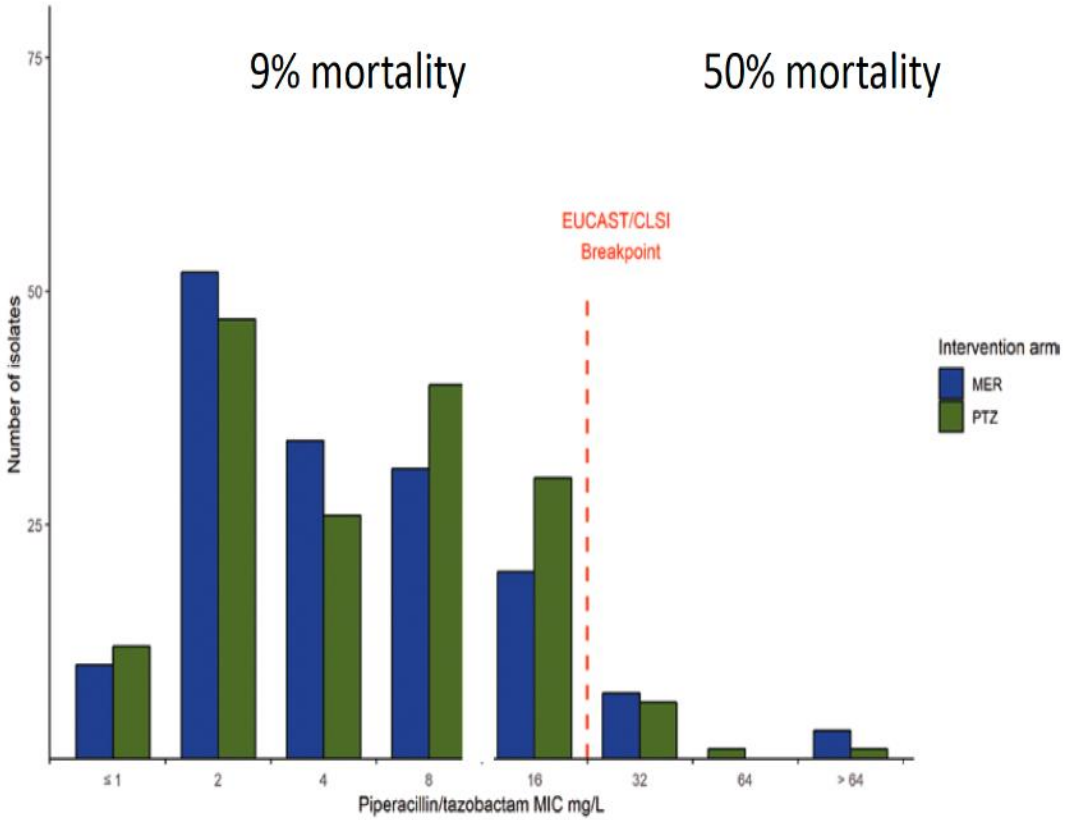
	Mortality 30 days n/total (%)		Risk difference % (1-sided 97.5% CI)[c]	*P* value for non-inferiority
	Piperacillin-tazobactam	Meropenem		
Primary analysis	23/187 (12.3)	7/191 (3.7)	8.6 (-∞ to 14.5)	.90
Per-protocol analysis	18/170 (10.6)	7/186 (3.8)	6.8 (-∞ to 12.8)	.76

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

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

Inaccurate Local Lab Contributed to Poor Drug Choice

Patient isolates re-tested by BMD



MERINO re-analyzed by BMD MICs

	Bivariate Analysis		Multivariate Analysis	
Variable	OR	*P*	aOR	*P*
Log_2(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)[a]	<.001	1.7 (1.3–2.2)[a]	<.001

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

[a]Calculated for each numerical increase in Charlson Comorbidity Score.

Henderson A, et al. Clin Infect Dis. 2020 Oct 27:ciaa1479

Correct Drug Choice Would have Saved Lives

	Bivariate Analysis		Multivariate Analysis	
Variable	OR	*P*	aOR	*P*
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Henderson A, et al. Clin Infect Dis 2020; PMID: 33106863

Correct Drug Choice Would have Saved Lives

Node 0 All patients		
	%	N
Survived	88.5	139
Died	11.5	18
Total	100	157

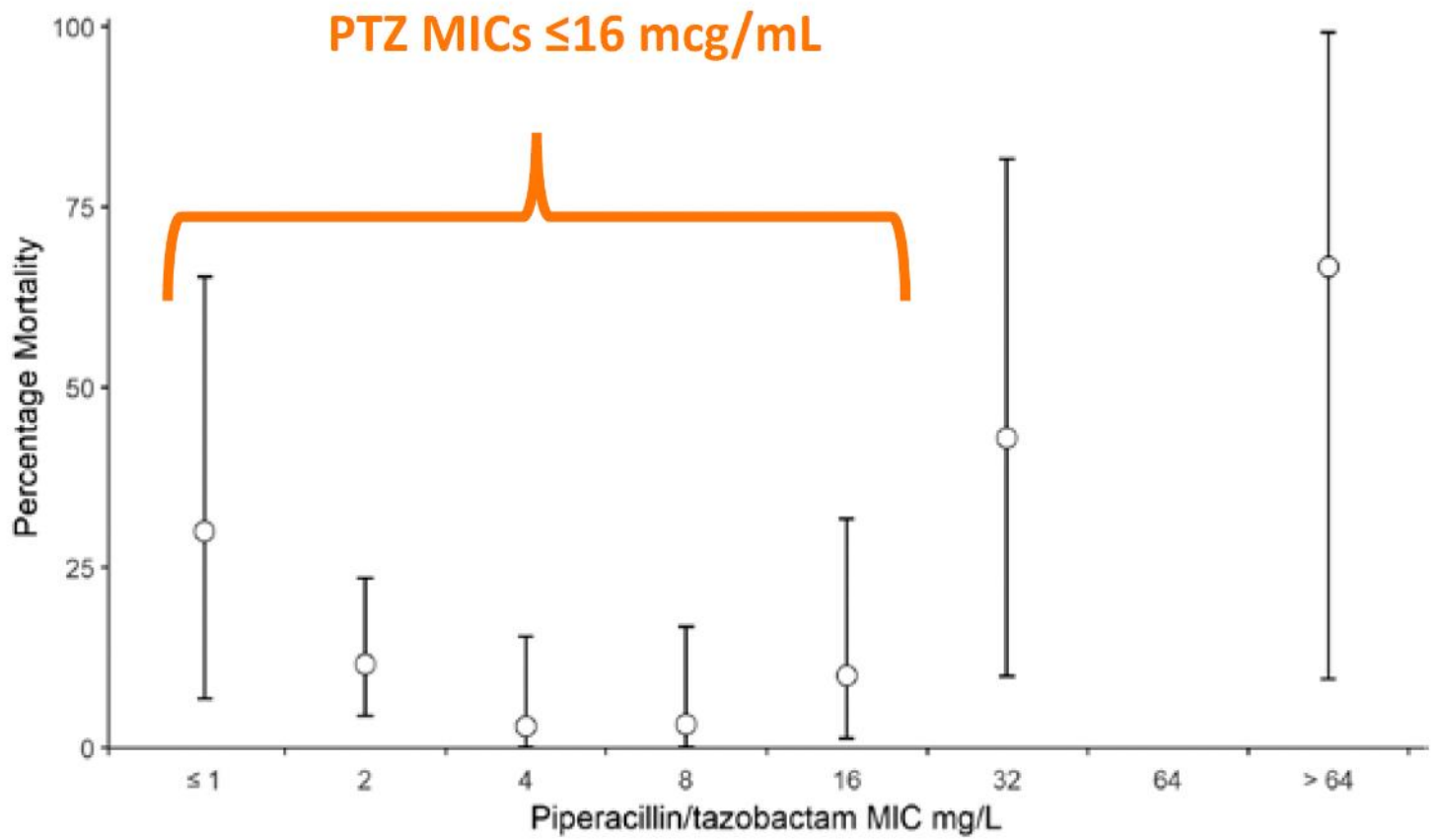
Piperacillin/Tazobactam
MIC

Node 1 MIC 1, 2, 4, 8, 16 mg/L		
	%	N
Survived	91.0	134
Died	9.0	13
Total	100	147

Node 2 MIC 32, 64, 128 mg/L		
	%	N
Survived	50.0	5
Died	50.0	5
Total	100	10

Henderson A, et al. Clin Infect Dis 2020; PMID: 33106863

New Breakpoint Justification



Henderson A, et al. Clin Infect Dis 2020; PMID: 33106863

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
CLSI 2022	≤8#	16*	≥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

Poll Question

- Have you updated your susceptibility breakpoint for Piperacillin-Tazobactam to <8?
  - Yes
  - No
  - Not Sure

CRITICAL ERRORS

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

Why would anyone use the old CLSI breakpoints?

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

21st Century Cures allows recognition of MANY CLSI breakpoints by FDA…. But not all

FDA and CLSI Breakpoints

FDA and CLSI independently set breakpoints for new drugs

- FDA - as part of New Drug Approval process → listed on STIC website
- CLSI - if the drug sponsor requests CLSI breakpoints (optional) → listed in M100

- When breakpoints differ or are updated, CLSI may request FDA to recognize CLSI BP via Rationale Document submission

CLSI breakpoint published in M100

⇩

CLSI develops and submits "rationale document" to FDA

FDA options:

- Accept CLSI breakpoint → refer to M100 on STIC website
- Do not accept CLSI breakpoint → publish exception on STIC website
- Do not accept CLSI breakpoint but come to alternate BP → publish FDA breakpoint on STIC website

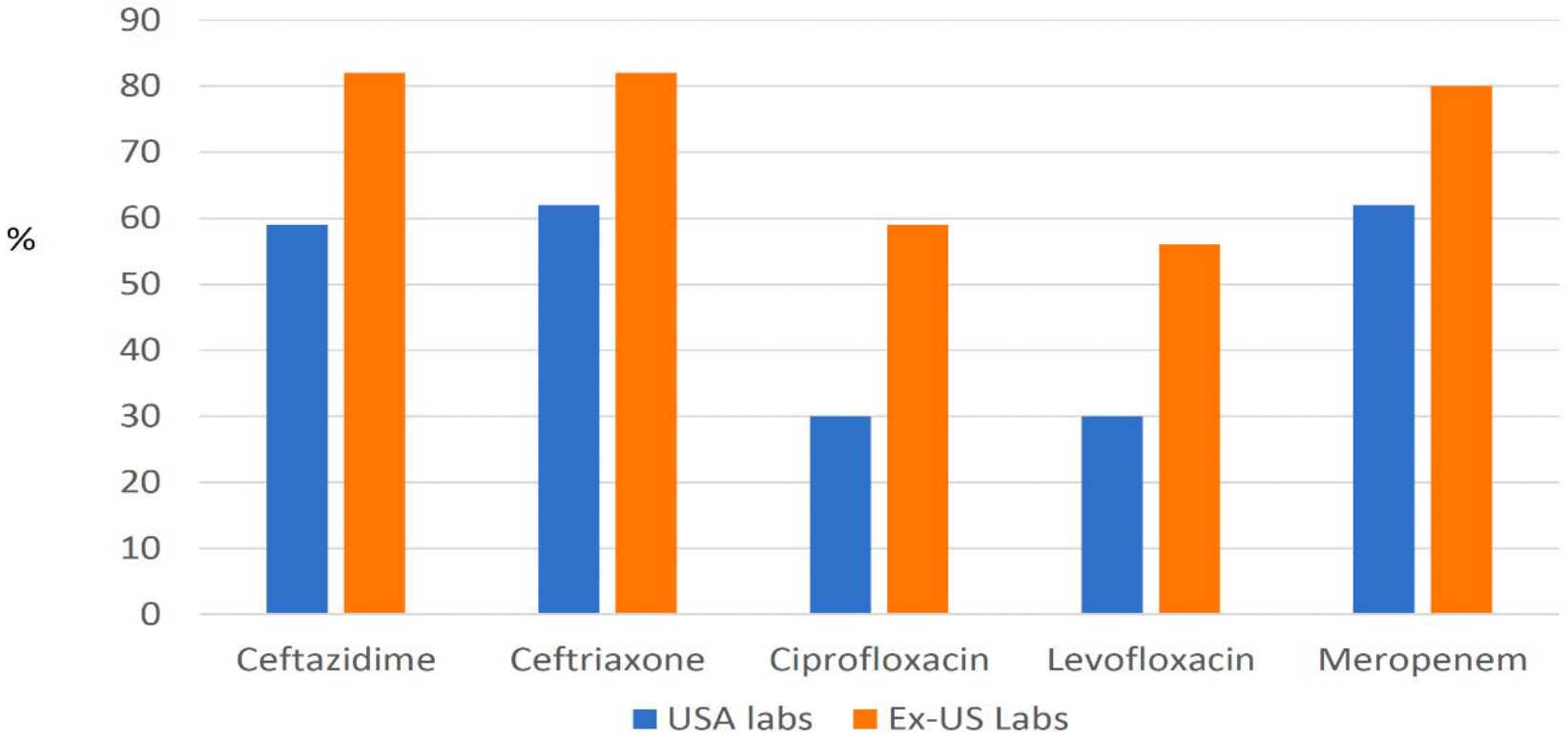
STIC, Susceptibility Test Interpretive Criteria

Differences Between Existing FDA and CLSI Breakpoints

>100 differences between FDA and CLSI (M100) breakpoints

	Examples
FDA has breakpoint, CLSI does not	• Tigecycline, omadacycline
CLSI has breakpoint, FDA does not	• Colistin, *E. faecium* daptomycin
Only one has a disk breakpoint	• Ceftazidime for *Acinetobacter* spp.
Differences in the categories	• Cefepime "S-DD"
Differences in the breakpoints	• Piperacillin-tazobactam for Enterobacterales

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



P<0.001 for all

Simner et al. 2022. OFID. 9(3):ofac007

Local Laboratory CAN update breakpoints

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- Obtain Reference Bacterial Strains
  - FDA has reference panels

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- Save Lives

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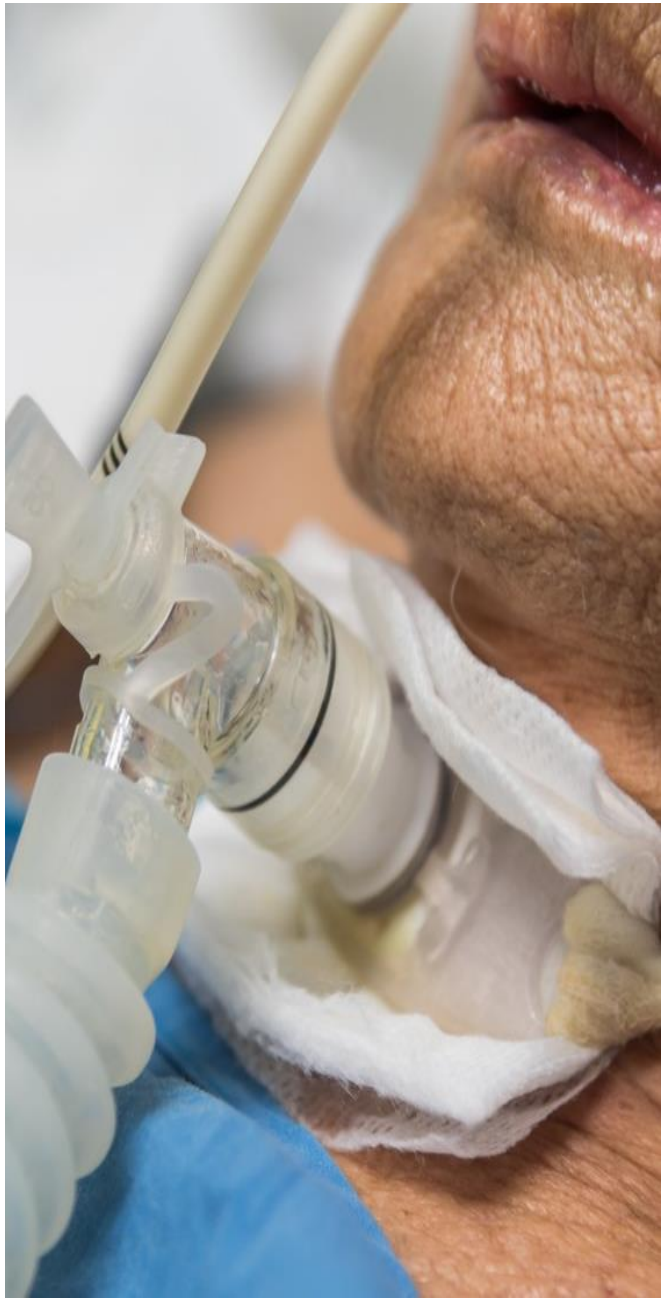
  - FDA has reference panels
- Laboratory runs a verification or validation study to update the breakpoints
  - https://clsi.org/meetings/ast/breakpoints-in-use-toolkit/
  - AST manufacturer can also be helpful in this process
- Save Lives
- LA County Department of Public Health Assisted in Carbapenem Breakpoint Updates for their Hospitals

Lucy

77 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)



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

https://www.idsociety.org/practice-guideline/amr-guidance/

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- Penicillin Binding Protein Mutations

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

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

Culture 1

	Acinetobacter baumannii	
Drug	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

	Acinetobacter baumannii			
Drug	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		
Delafloxcin				>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		

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- 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 use ampicillin Sulbactam

Antibiotic Strategy

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- **High Dose Ampicillin-Sulbactam**

Dose	Daily SUL	AMP/SUL regimen
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

Antibiotic Strategy

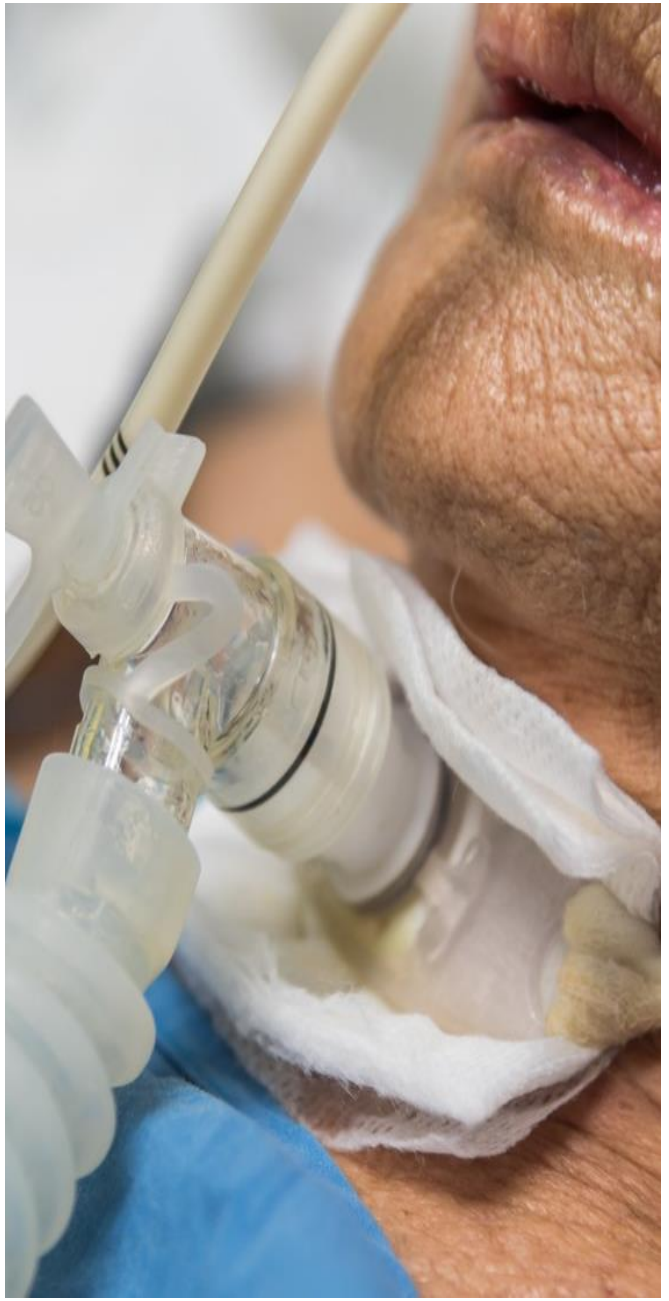
- High Dose Ampicillin-Sulbactam
- TMP/SMX
- Eravacycline
- Did not try Minocycline or Omadacycline
- ~~Cefiderocol~~
- ~~Delafloxacin~~

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.

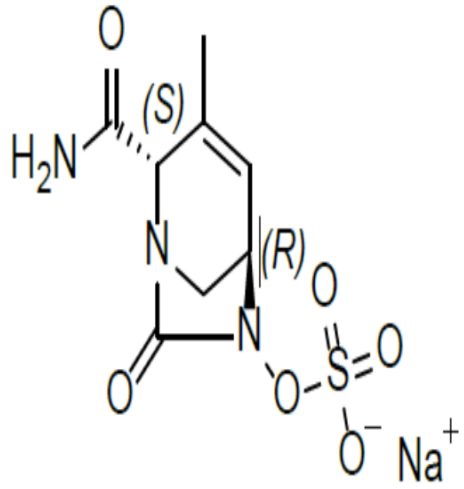
PMH: Pulmonary Fibrosis (not on oxygen)

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

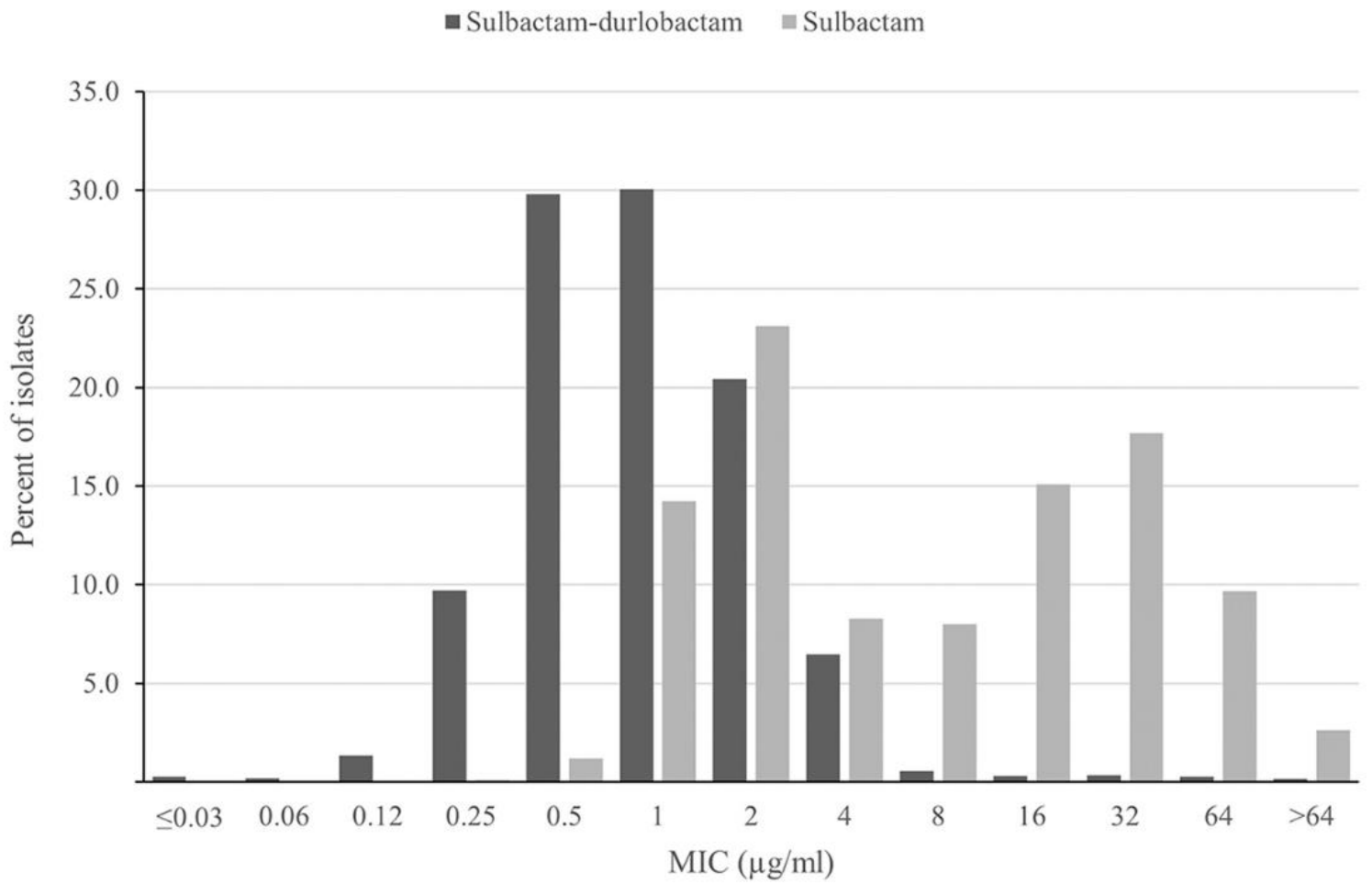
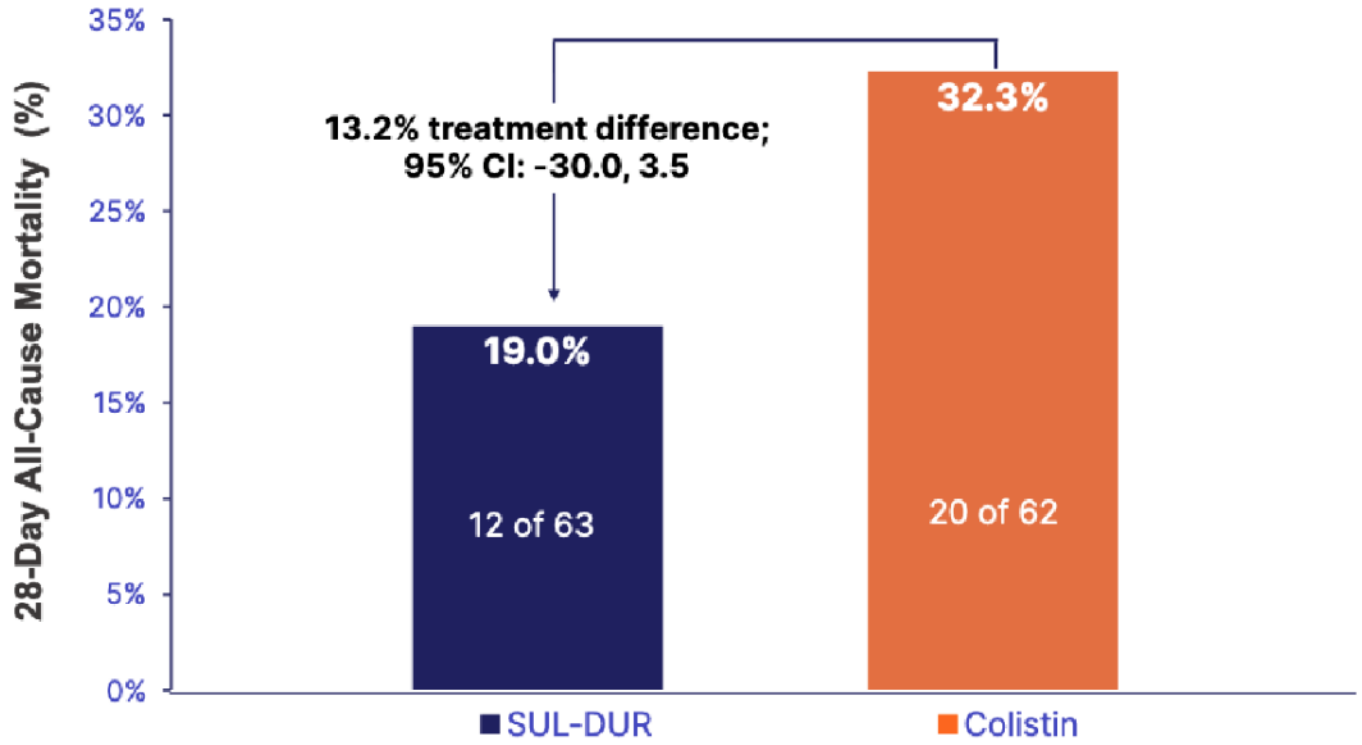


FIG 1 Sulbactam-durlobactam (black bars) and sulbactam (gray bars) MIC distributions for 5,032 isolates of *Acinetobacter baumannii-calcoaceticus* complex (ABC) species collected globally from 2016 to 2021.

Sulbactam-Durlobactam is Indicated for treatment of HAP/VAP

As expected only really active against A. Baumannii

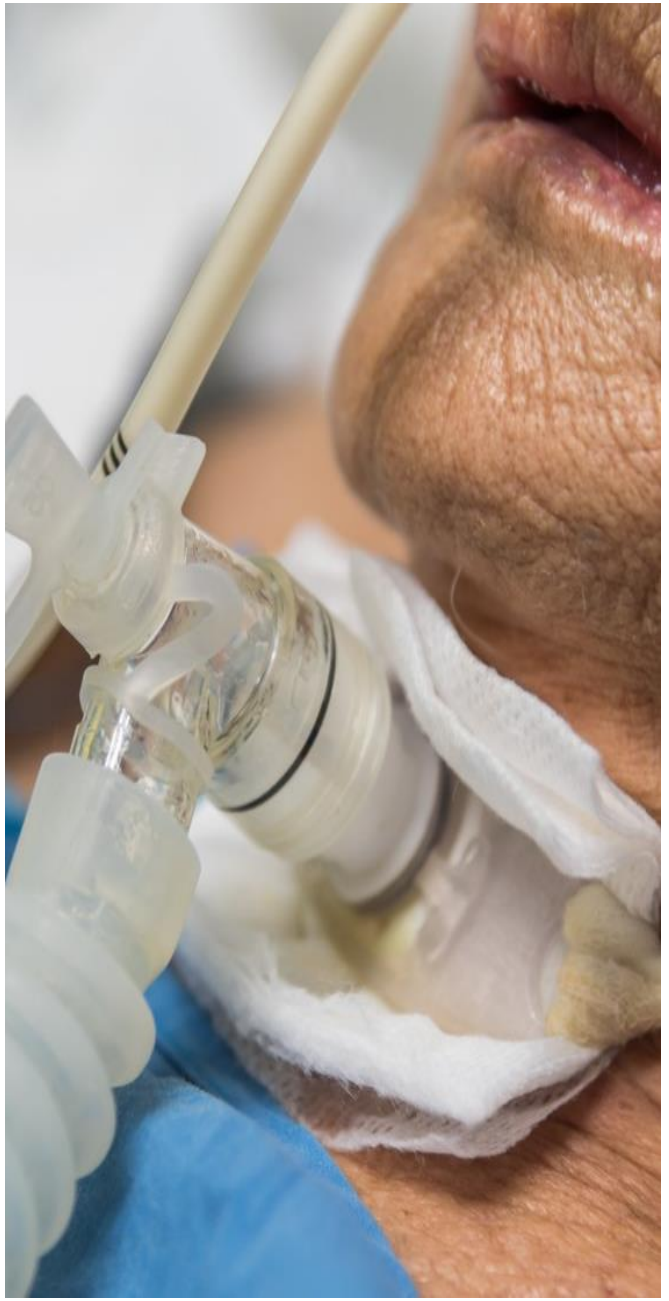


McLeod SM, et al. Id Week 2023

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