Critical Errors in the Microbiology Laboratory

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ASP Program

Infectious Disease Association of California

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

Definitions

Error- the state or condition of being wrong in conduct or judgement

Critical Error – an error that would be expected to have predictable negative outcomes on patient care

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 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

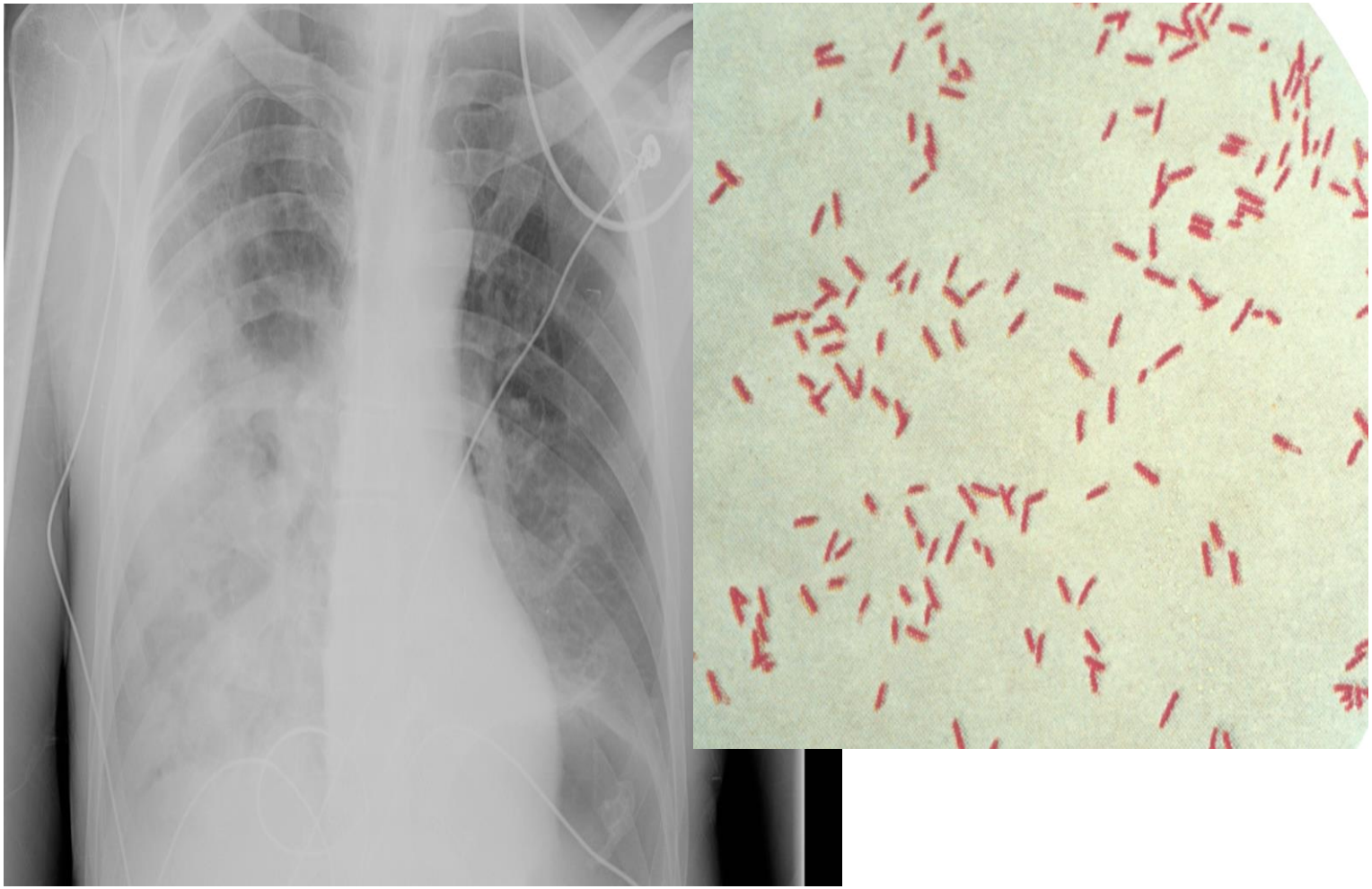
T: 101.2 RR: 22 BP: 104/62 HR: 125 FiO2: 92%

- 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**

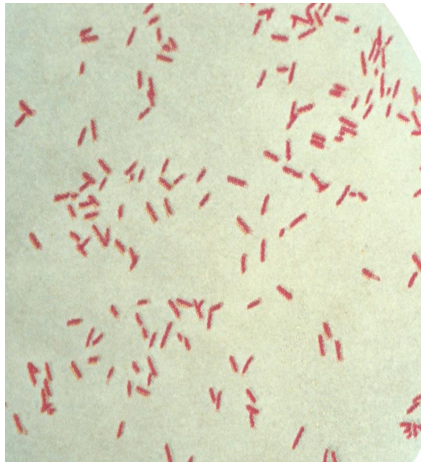
- **Labs: WBC: 13K, GFR>80, LFTs WNL**

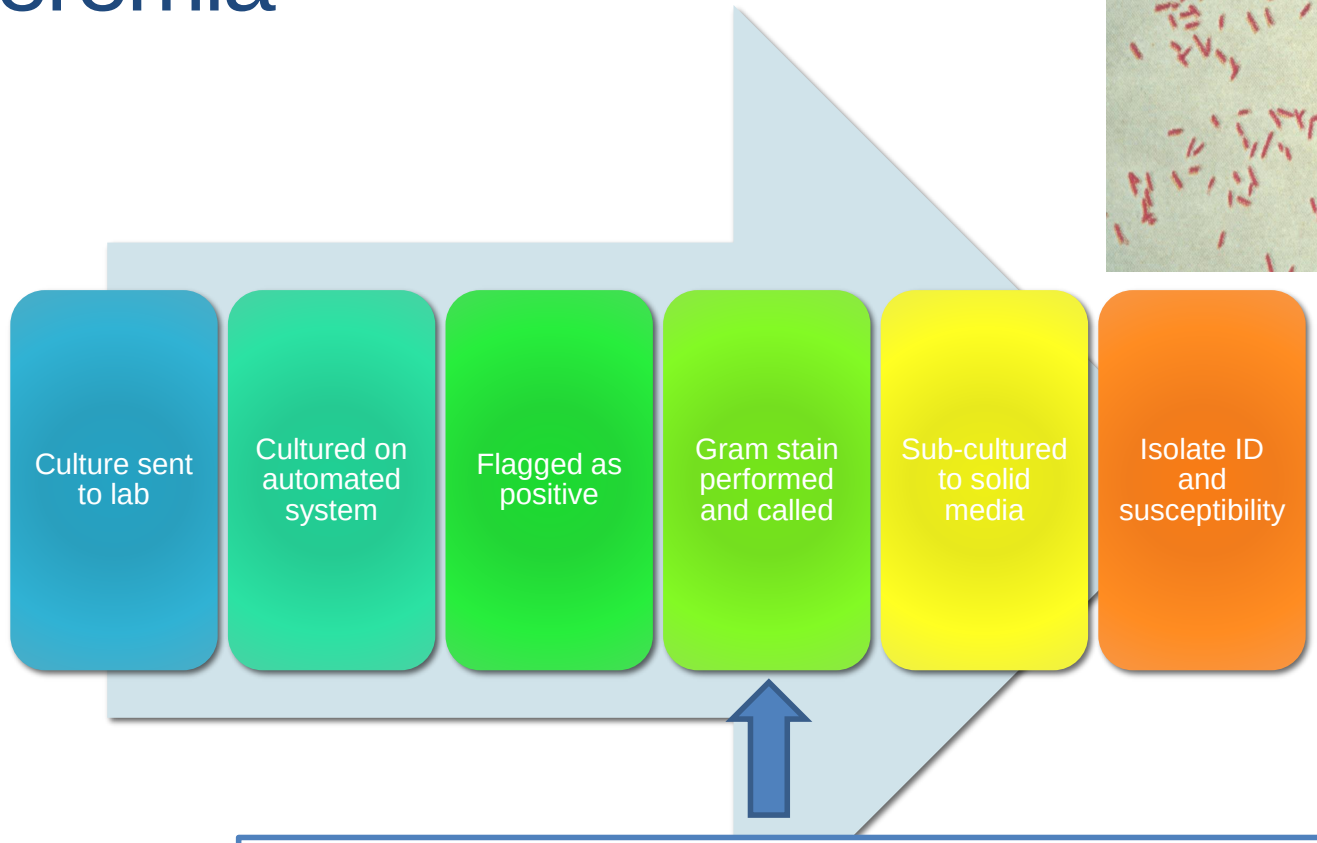
RLL Pneumonia Gram-Negative Rods



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

RLL Pneumonia with Bacteremia





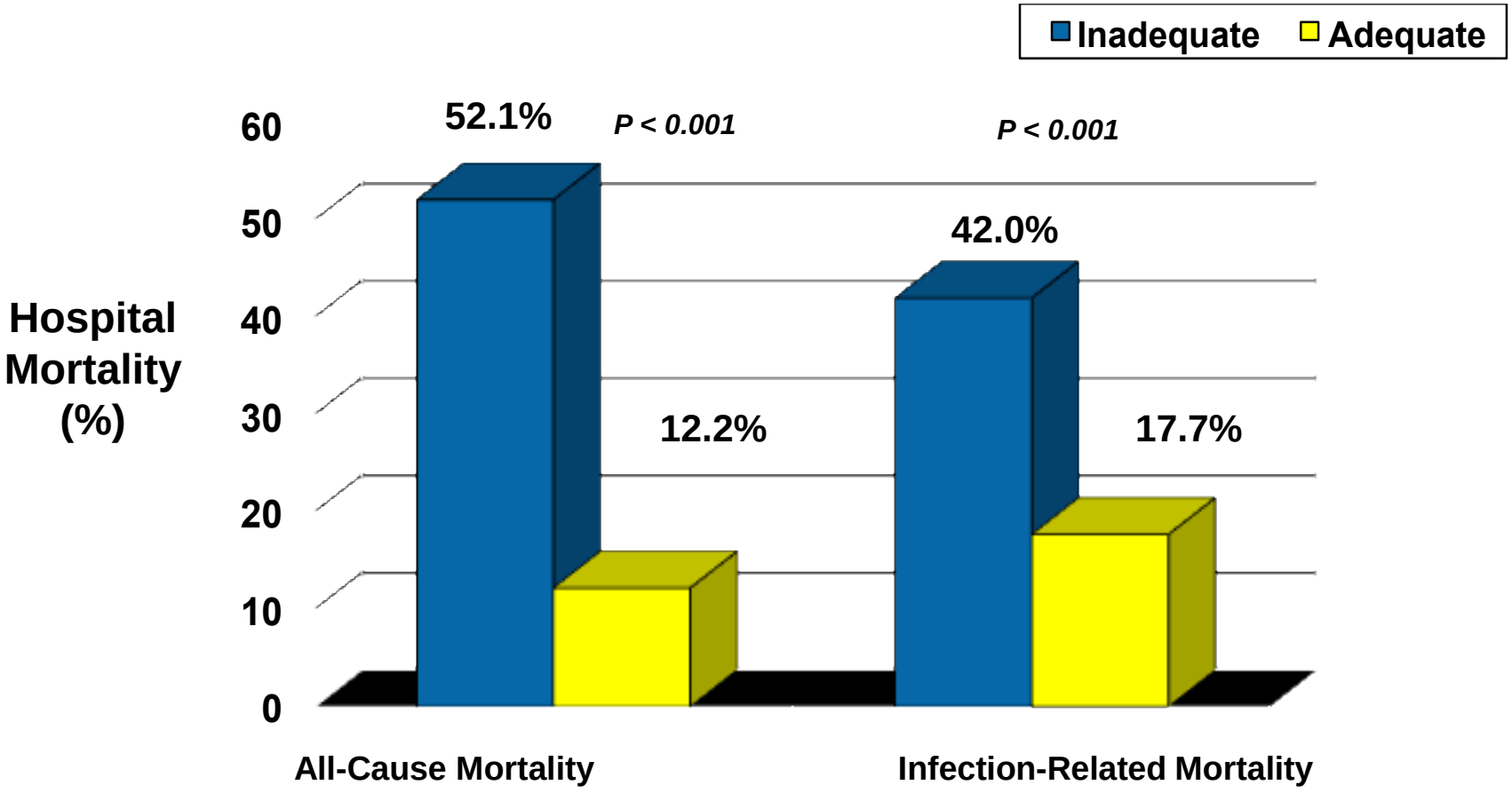
This is where we are with our patient.
We only know we are dealing with a gram negative Rod.

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?**

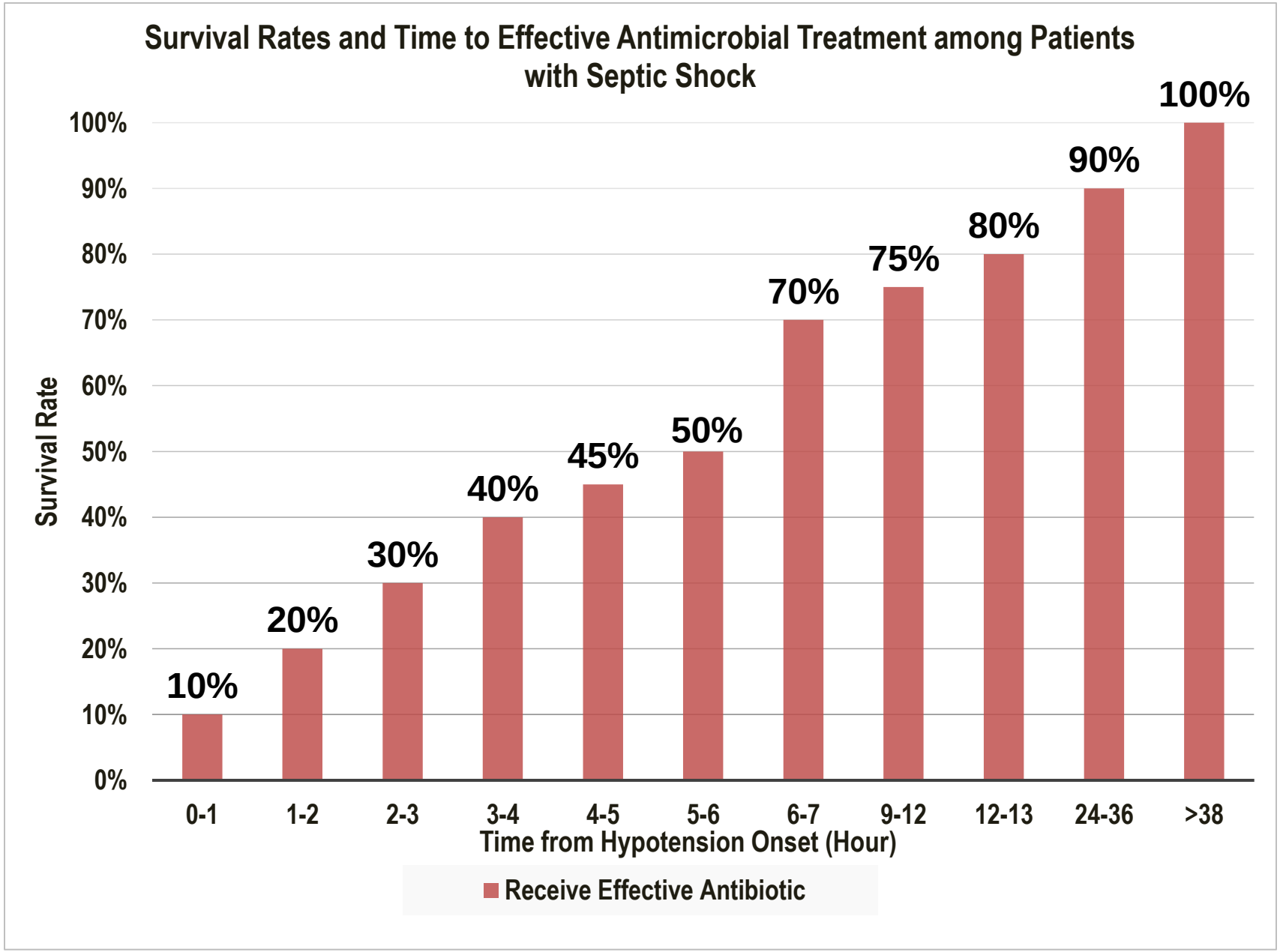
Inadequate antimicrobial therapy associated with higher mortality



Prospective study (n=2000: 655 with infections)

25% of patients received inadequate treatment

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



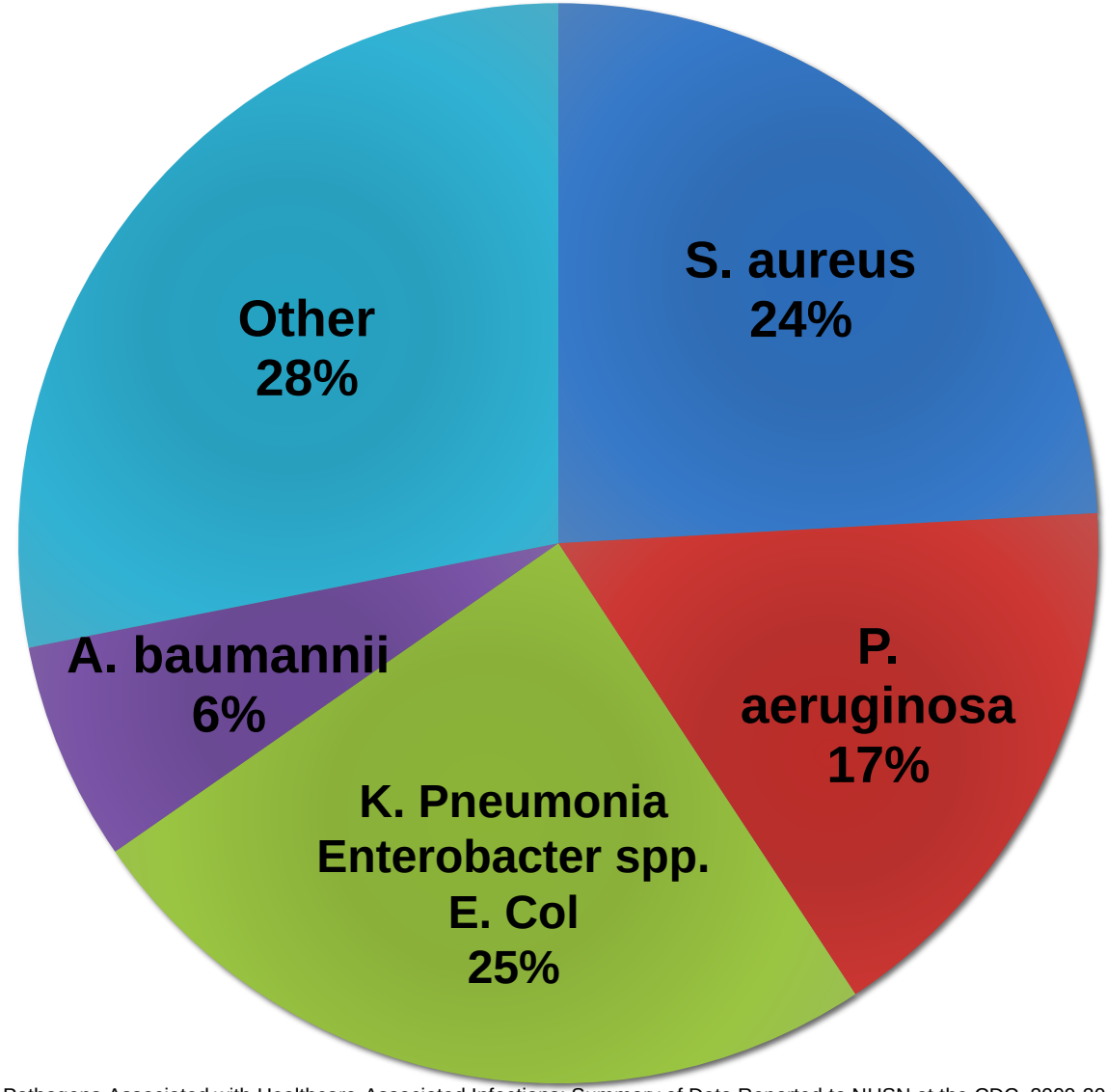
Kumar A, et al. *Crit Care Med* 2006; 1589-1596, Kollef MH., et al. *Chest.* 1999;115:462-474.

Lucy: Assessment

- 65 yo with sepsis, RLL pneumonia with Gram-negative rods, respiratory failure, retained organ function on vasopressor therapy.

- **What Antibiotics Should We Use?**

Bacterial Pathogens Causing HAP



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

That data is cute, but how do we choose the drug to treat the patient?

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

Antibiogram Basics

- Each patient can contribute one isolate to the antibiogram
- The first column represents the number of patient-isolates per year
- Each other column presents the percentage of isolates that are susceptible to each drug

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]
			R	76	R	89	—[4]	—[4]	97	99	99	99	89	92	92	81	99
Enterobacter aerogenes	94		R	88	R	98	—[4]	—[4]	99	97	99	99	99	99	99	98	98
Enterobacter cloacae	209		R	81	R	92	—[4]	—[4]	89	99	99	99	99	99	98	94	85
Escherichia coli	752		50	94	59	84	83	79	99	99	99	99	82	85	63	60	99
Klebsiella oxytoca	121		64	89	23	95	95	87	98	98	98	99	96	96	94	91	99
Klebsiella pneumoniae	399		70	87	71	86	85	84	93	94	94	98	92	88	85	81	97
			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		62	53	R	58	58	—	R	62	60	67	60	66	56	60	95
Pseudomonas aeruginosa	738		R	84	R	88	87	R	R	81	85	96	91	94	78	R	99
Stenotrophomonas maltophilia	64	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*.

2016 Antibiogram data source: UCLA Health Infectious Disease
http://www.pathnet.medsch.ucla.edu/department/cliniclab/microbio/amic.pdf Accessed 11/22/2017

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	3	79	99	99	99	99	82	85	63	60	99
Klebsiella oxytoca	121	R	64	89	23	95	5	87	98	98	98	99	96	96	94	91	99
Klebsiella pneumoniae	399	R	70	87	71	86	5	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	7	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	8	—	R	62	60	67	60	66	56	60	95
Pseudomonas aeruginosa	738	R	R	84	R	88	7	R	R	81	85	96	91	94	78	R	99
Stenotrophomonas maltophilia	84	R	R		R		0	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*.

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

Organism	No. Isolates	Penicillins			Cephalosporins				Carbapenems			Aminoglycosides			Fluoro-quinolone	Other	
		Ampicillin	Ampicillin-sulbactam	Piperacillin-tazobactam	Cefazolin	Cefepime	Ceftazidime	Ceftriaxone[1]	Ertapenem	Imipenem	Meropenem	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Trimethoprim–sulfamethoxazole	Colistin
Citrobacter freundii	40	R[2]	R	88	R	93	—[3,4]	—[4]	90	93	95	99	83	93	85	73	99
Enterobacter aerogenes	63	R	R	79	R	95	—[4]	—[4]	98	95	99	99	99	99	98	98	99
Enterobacter cloacae	172	R	R	81	R	92	—[4]	—[4]	95	99	99	99	98	98	97	91	79
Escherichia coli	441	41	50	92	89	84	83	79	98	99	99	98	79	81	58	55	99
Klebsiella oxytoca	102	R	86	91	91	95	95	92	98	99	99	99	95	97	96	91	99
Klebsiella pneumoniae	299	R	72	88	71	86	84	82	93	93	93	94	90	87	85	76	98
Morganella morganii	29[5]	R	R	97	R	99	—[4]	—[4]	99	—	99	99	76	90	69	66	R
Proteus mirabilis	117	74	87	99	34	95	97	92	99	—	99	99	87	93	71	70	R
Serratia marcescens	99	R	R	98	R	99	—[4]	—[4]	99	97	99	99	99	99	93	99	R
Acinetobacter baumannii	49	R	69	49	R	63	61	—	R	74	71	74	65	69	63	67	94
Pseudomonas aeruginosa	498	R	R	87	R	89	90	R	R	80	86	95	92	96	78	R	99
Stenotrophomonas maltophilia	53	R	R	R	R	—	32	R	R	R	R	R	R	R	—	94	45
Burkholderia cepacia complex	12[5]	R	R	R	R	R	42	R	R	R	42	R	R	R	58	92	R

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

[2] R = intrinsic resistance.

[3] — = Not routinely tested and/or not applicable.

[4] 3rd generation cephalosporins should not be used for serious infections.

[5] Calculated from fewer than the standard recommendation of 30 isolates.

2016 Antibiogram data source: UCLA Health Infectious Disease
http://www.pathnet.medsch.ucla.edu/department/cliniclab/microbio/amic.pdf Accessed 11/22/2017

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

Organism	No. Isolates	Penicillins			Cephalosporins				Carbapenems			Aminoglycosides			Fluoro-quinolone	Other	
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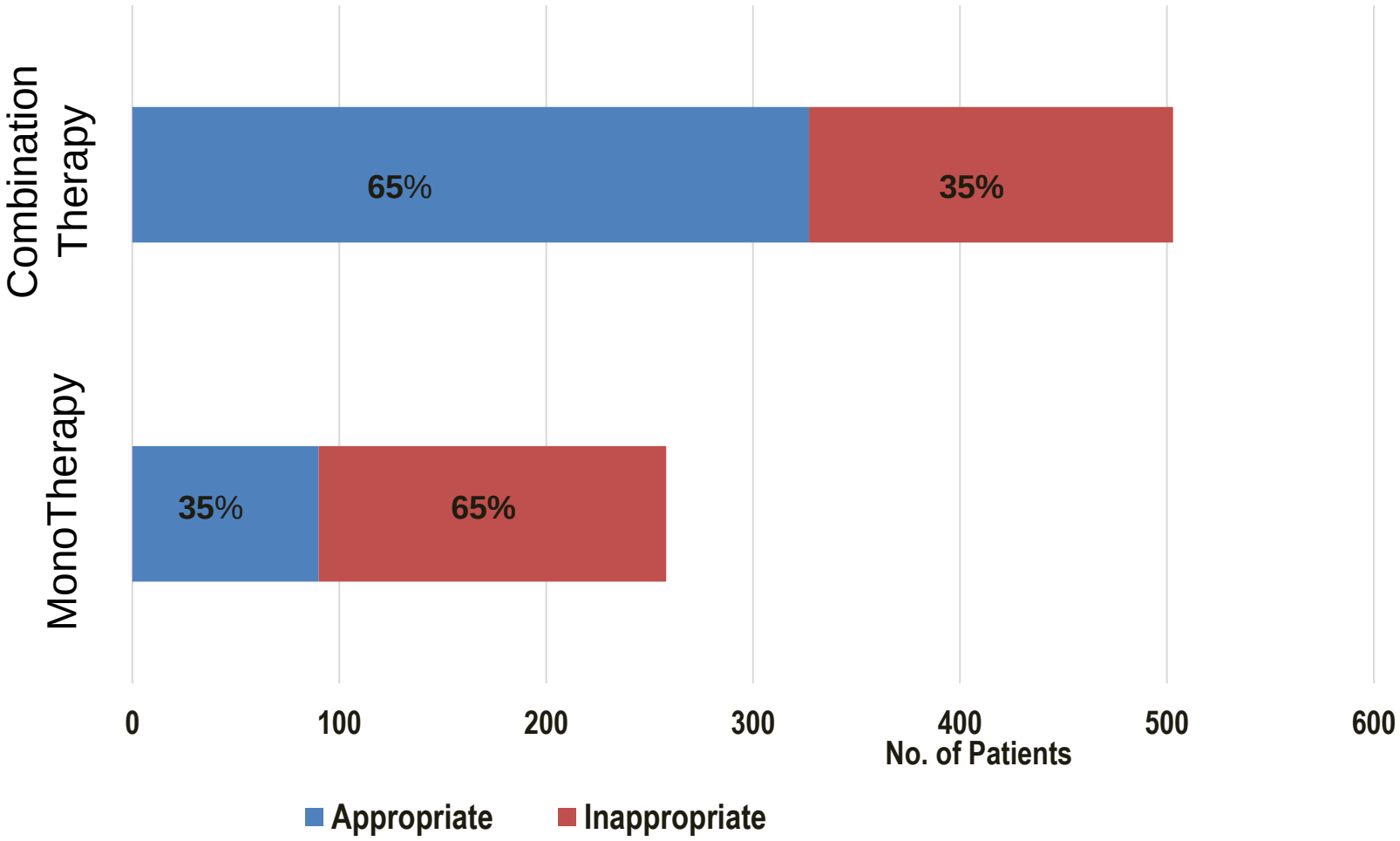
Citrobacter freundii	37	R[2]	R	76	R	89	–[4]	–[4]	97	99	99	99	89	92	92	81	99
Enterobacter aerogenes	94	R	R	88	R	98	–[4]	–[4]	99	97	99	99	99	99	99	98	98
Enterobacter cloacae	209	R	R	81	R	92	–[4]	–[4]	89	99	99	99	99	99	98	94	85
Escherichia coli	752	41	50	94	59	84	83	79	99	99	99	99	82	85	63	60	99
Klebsiella 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*.

2016 Antibiogram data source: UCLA Health Infectious Disease
http://www.pathnet.medsch.ucla.edu/department/cliniclab/microbio/amic.pdf Accessed 11/22/2017

Empiric Combination Therapy Is Associated with Higher Rates of Early, Appropriate Therapy for Patients with Sepsis Due to Gram-negatives



Micek S T et al. *Antimicrob. Agents Chemother*. 2010;54:1742-1748.

Antibiotic Selection for Sepsis

- What is the estimated risk that my chosen therapy will not be microbiologically active?

- What is the estimated risk of death for bad outcome for my patient while I await identification and sensitivity?

Assessment and Plan

- 65 yo with sepsis, RLL pneumonia, respiratory failure, but retained organ function.
- Meropenem 2 gm q8H (over 3H)
- Tobramycin 350mg IV q24H

Using the Antibiogram for Stewardship

- Do we really need to use a carbapenem in combination therapy here?

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

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		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

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)				
Meropenem (87)				
Piperacillin-tazobactam (86)				
Ciprofloxacin (80)				

*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 2016 Antibiogram data source: UCLA Health Infectious Disease
http://www.pathnet.medsch.ucla.edu/department/cliniclab/microbio/amic.pdf Accessed 11/22/2017

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 2016 Antibiogram data source: UCLA Health Infectious Disease
http://www.pathnet.medsch.ucla.edu/department/cliniclab/microbio/amic.pdf Accessed 11/22/2017

Assessment and Plan

- 65 yo with sepsis, RLL pneumonia, respiratory failure, but retained organ function.
- Piperacillin-Tazobactam 4.5 gm q8 Hours (over 2H)
- Tobramycin 350mg IV q24

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**

Quality Improvement Opportunity

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

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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

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

Assessment and Plan

- 65 yo with sepsis, RLL pneumonia, respiratory failure, but retained organ function.
- Meropenem 2 gm q8H (over 3H)
- Tobramycin 350mg IV q24H

K. Pneumoniae from OSH Blood CX

Antimicrobial	Susceptibility
Ciprofloxacin	R
Pip/Tazobactam	R
TMP/SMX	R
Gentamicin	R
Colistin	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

K. pneumoniae from Local Laboratory

Antimicrobial	Susceptibility
Ciprofloxacin	R
Pip/Tazobactam	R
Gentamicin	R
Colistin	R
Meropenem	R
Tigecycline	R

Delayed Antimicrobially Active Therapy (DAT) Increases Risk of Death by 2-3 Fold!!

Lodise et al 2018.

K. pneumoniae final results

Antimicrobial	Susceptibility
Meropenem	**R**
Meropenem MIC	**2**

Why was there a discrepancy in Results?

OSH using old breakpoints, local hospital uses current breakpoints!

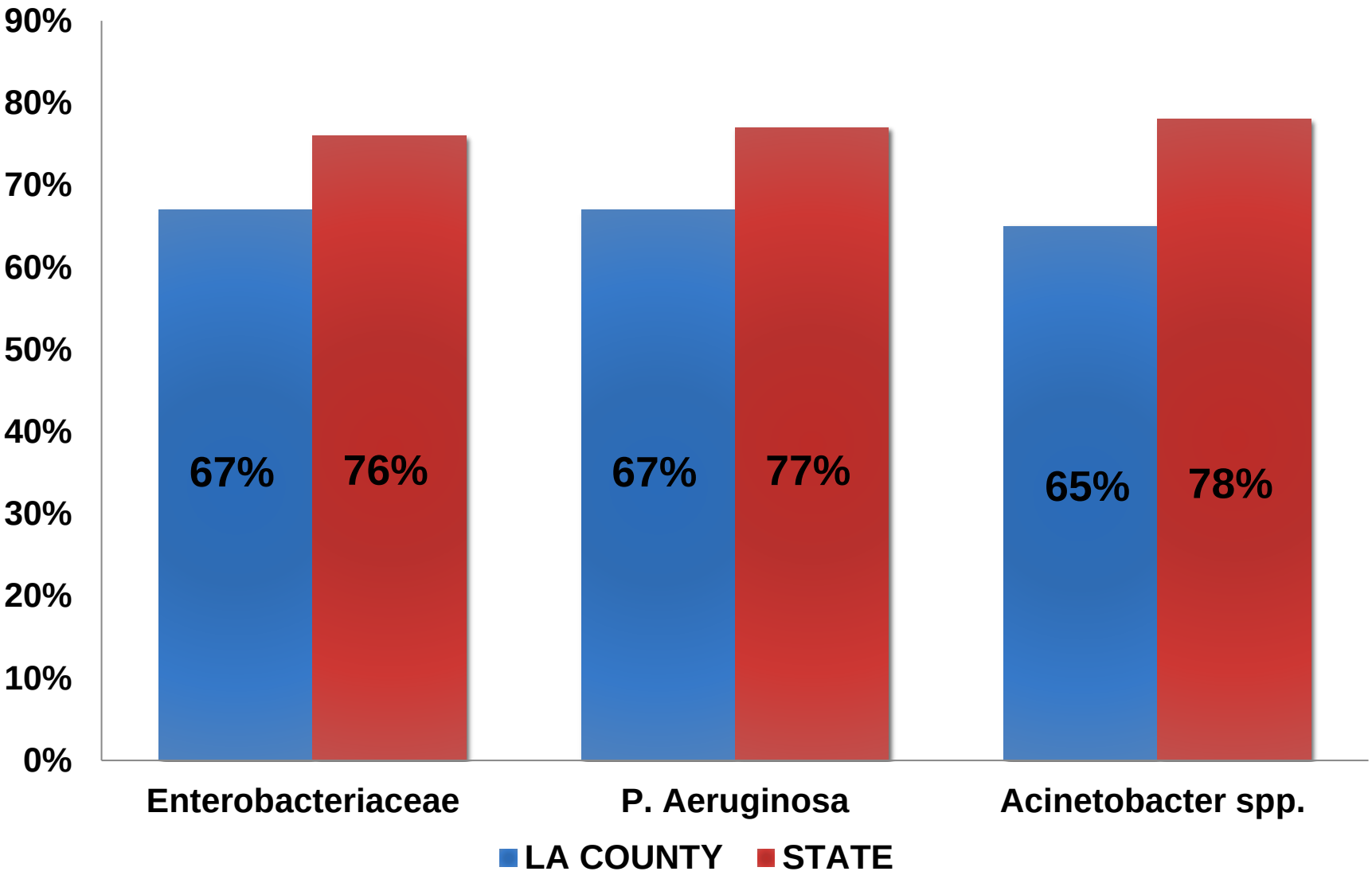
Enterobacteriaceae breakpoints

	Current Breakpoints (M100-S22) MIC (ug/mL)			Previous Breakpoints (M100-S19) MIC (ug/mL)		
Antibiotic	**Susceptible**	**Intermediate**	**Resistant**	**Susceptible**	**Intermediate**	**Resistant**
Ertapenem	**<0.25**	**0.5**	**≥1**	≤2	4	≥8
Imipenem	**≤1**	**2**	**≥4**	≤4	8	≥16
Meropenem	**≤1**	**2**	**≥4**	≤4	8	≥16

Use of Updated breakpoints is supported by the CLSI, FDA, CDC, and IDSA

Humphries et al. J Clin Microbiology, 2015.

Survey of Hospital Use of Current CLSI breakpoints



Humphries et al. CID 2018, McKinnell et al. ID Week 2017

K. pneumoniae final results

Antimicrobial	Susceptibility
Meropenem	R
Meropenem MIC	2

Do we really care if the MIC is <=1 versus 2-4 mcg/ml?

JCM
Journals.ASM.org

Clinical Outcomes of *Enterobacteriaceae* Infections Stratified by Carbapenem MICs

Twisha S. Patel, Jerod L. Nagel
Departments of Pharmacy Services and Clinical Sciences, University of Michigan Health System and College of Pharmacy, Ann Arbor, Michigan, USA

- Matched cohort analysis of adult patients
- Enterobacteriaceae infections treated with carbapenems
- Compared MIC of 2-8 mcg/ml versus ≤1 mcg/ml

Patel et al. Journal of Clinical Medicine. 2015

Does knowing the MIC matter?

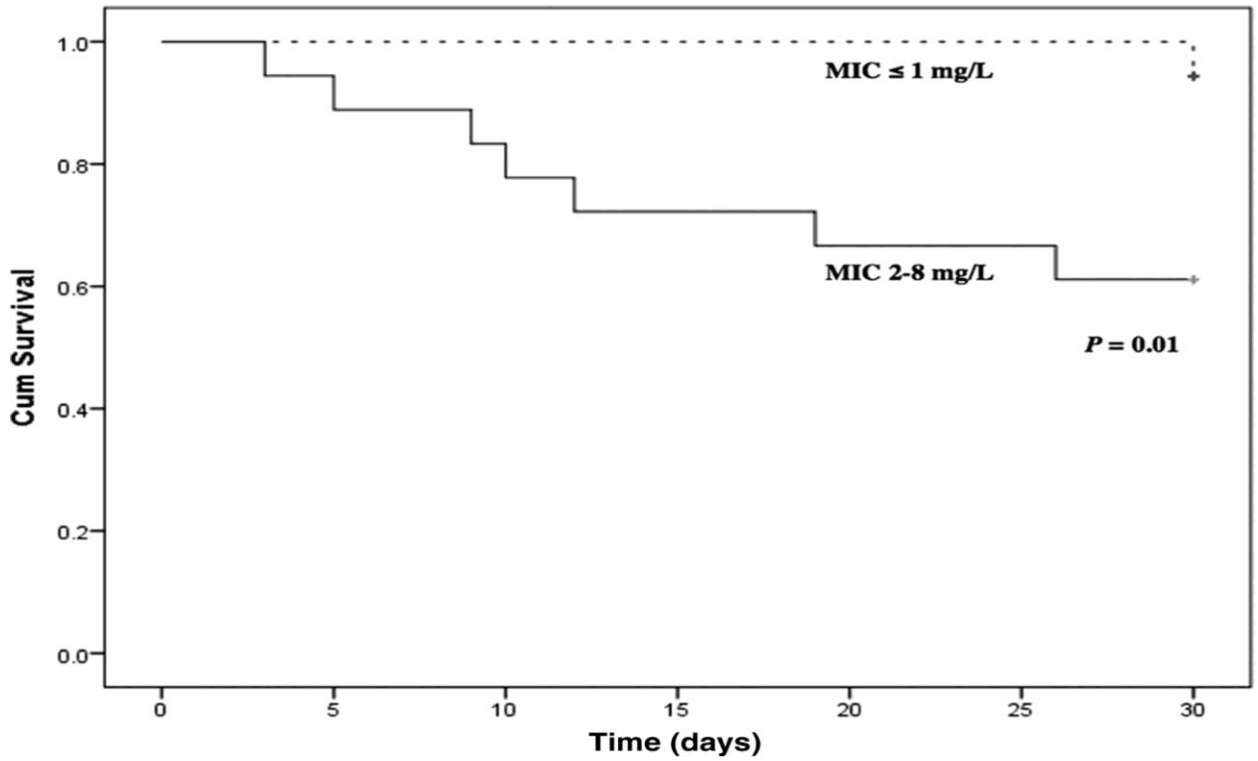


TABLE 3 Clinical outcomes stratified by carbapenem MIC

Outcome	Value		*P* value
	MIC of ≤1 mg/liter	MIC of 2–8 mg/liter	
No. of patients with 30-day mortality/total number of patients (%)	1/18 (5.6)	7/18 (38.9)	0.04
Mean total hospital length of stay ± SD, in days	34.4 ± 25	57.6 ± 45	0.06
Mean ICU length of stay ± SD, in days	21.7 ± 19	56.6 ± 44	<0.01
No. of patients with 30-day hospital readmission/total number of patients (%)	3/17 (17.6)	3/11 (27.3)	0.65

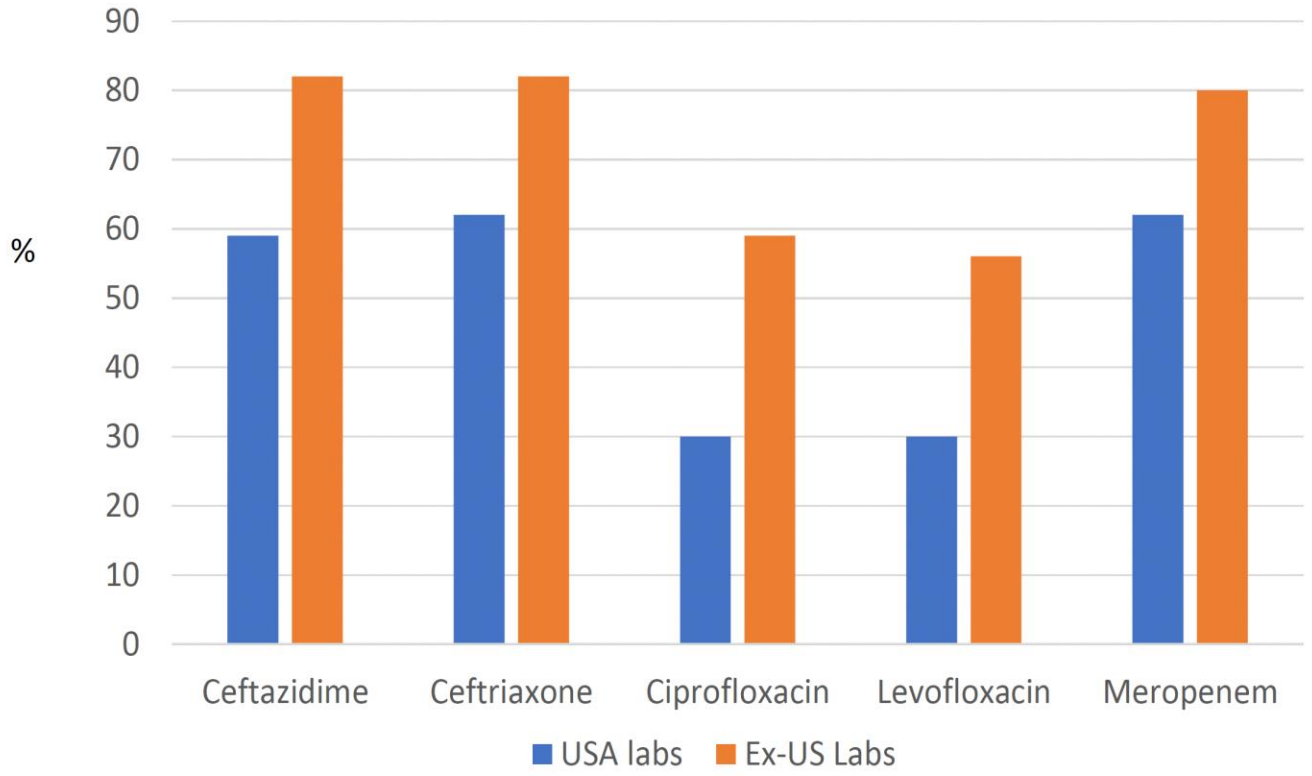
Patel et al. Journal of Clinical Medicine. 2015

CRITICAL ERRORS

- **Failure to use current breakpoints increases patients risk of death**

Why would anyone use the old CLSI breakpoints?

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

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

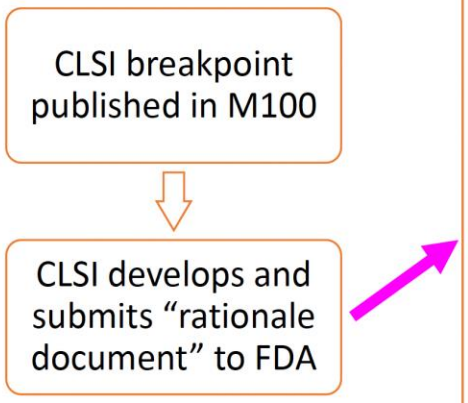
21st Century Cures allows recognition of MANY CLSI breakpoints by FDA…. But not all

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



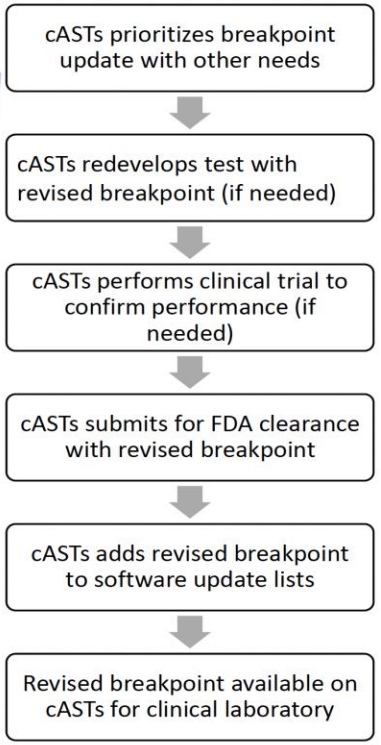
FDA options:

- 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

Breakpoint Uodates

How does this work for devices?



Process may take ~ 5 years

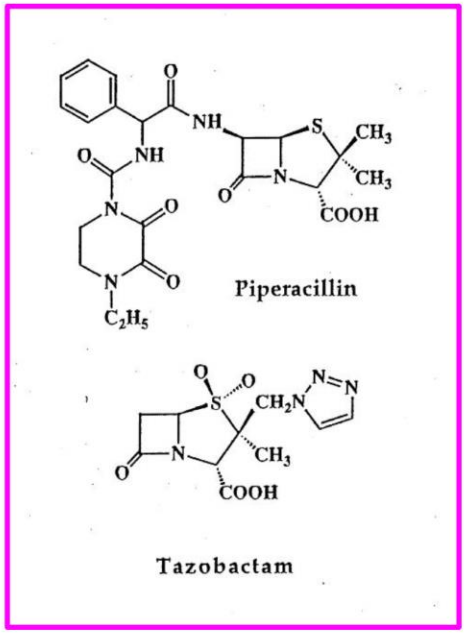
BP, breakpoint
cAST, commercial antimicrobial susceptibility test (e.g., Vitek2, Microscan)

"The FDA and CLSI have supported the 2010 CLSI breakpoints for Enterobacteriaceae.

FDA cannot mandate that AST manufacturers update breakpoints.

AST manufacturers do not want to spend the $$ to updated their breakpoints with the FDA."

Piperacillin-Tazobactam

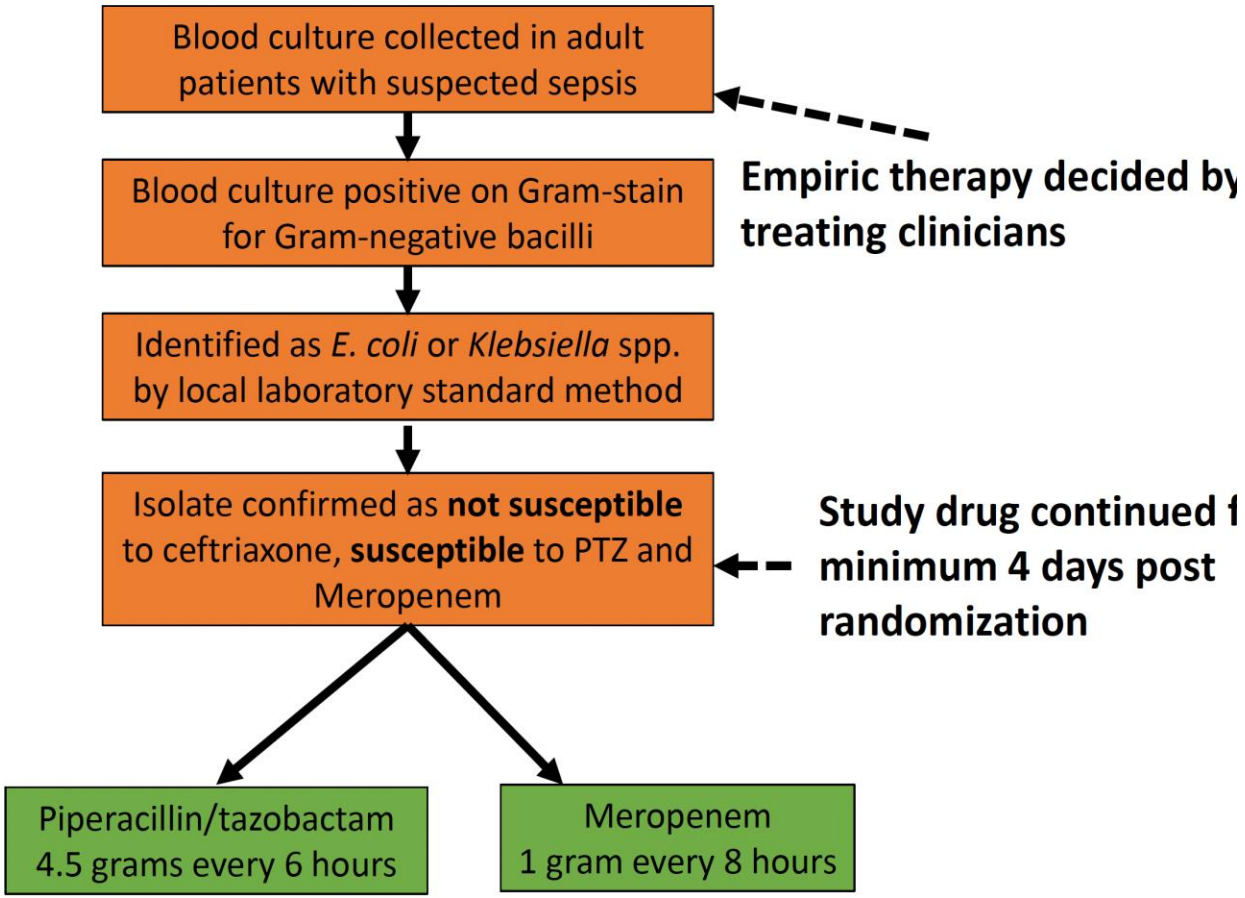


- 1981 - piperacillin approved
- 1993 - piperacillin-tazobactam approved for skin and skin structure and intra-abdominal infections
  - BEFORE ESBLs were wide-spread
  - CLSI never included editing pip-tazo as "R" if ESBL detected, but many do this in practice
- Tazobactam – inhibit activity of ESBLs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

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

MERINO Trial:

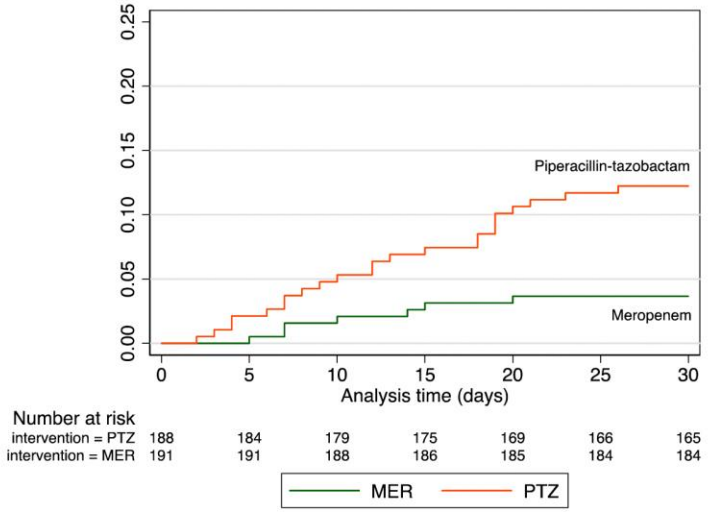
Can pip-tazo be used for ESBL isolates?



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

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%]

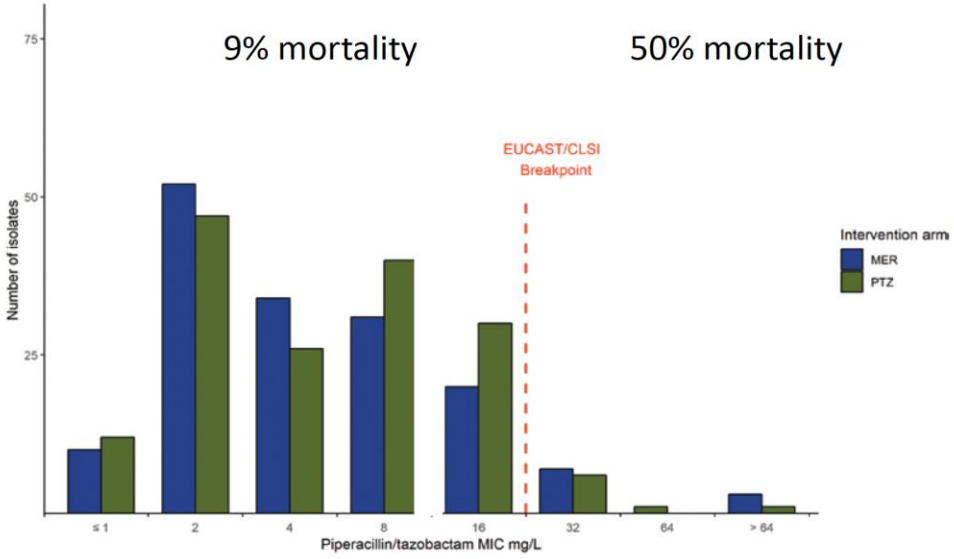
JAMA. 2018;320(10):984-994

What happened?

Patients enrolled based on susceptibility results from local labs
- **Mostly Vitek 2**
- **Repeat testing by reference BMD = many patients had pip-tazo resistant infections**

Patient isolates re-tested by BMD

9% mortality 50% mortality



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

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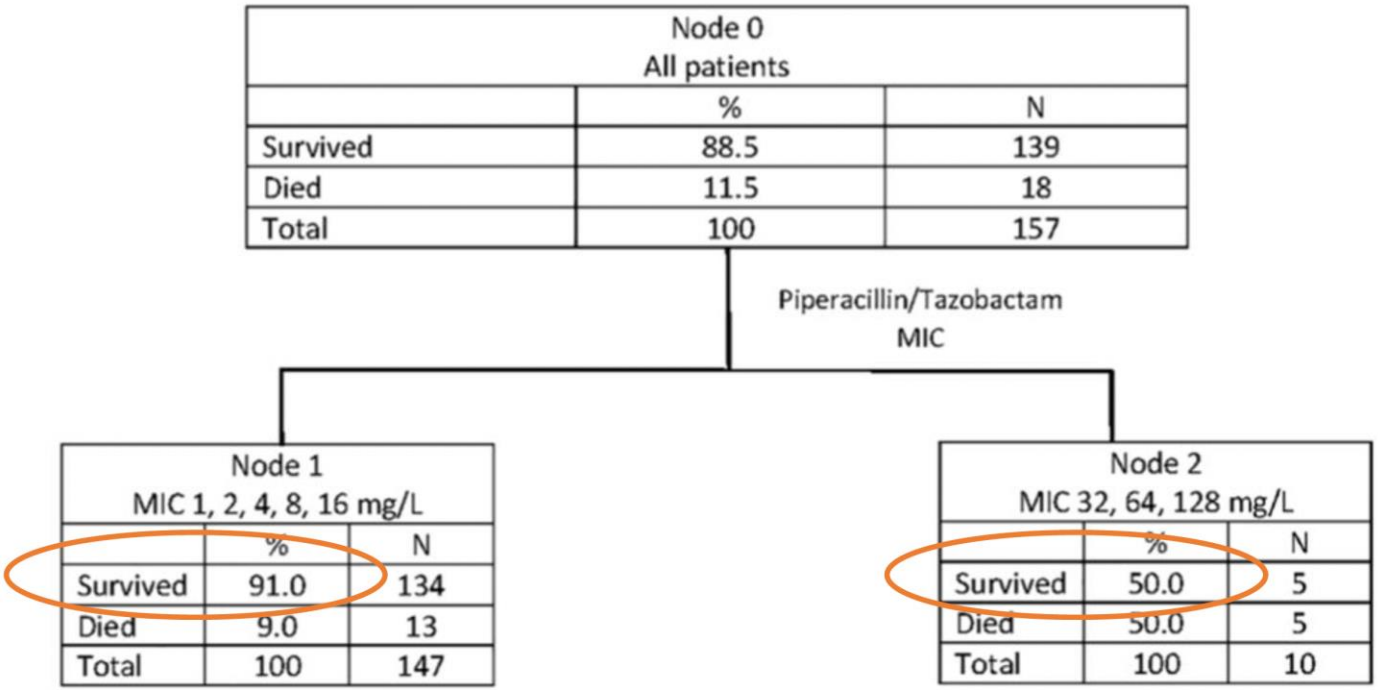
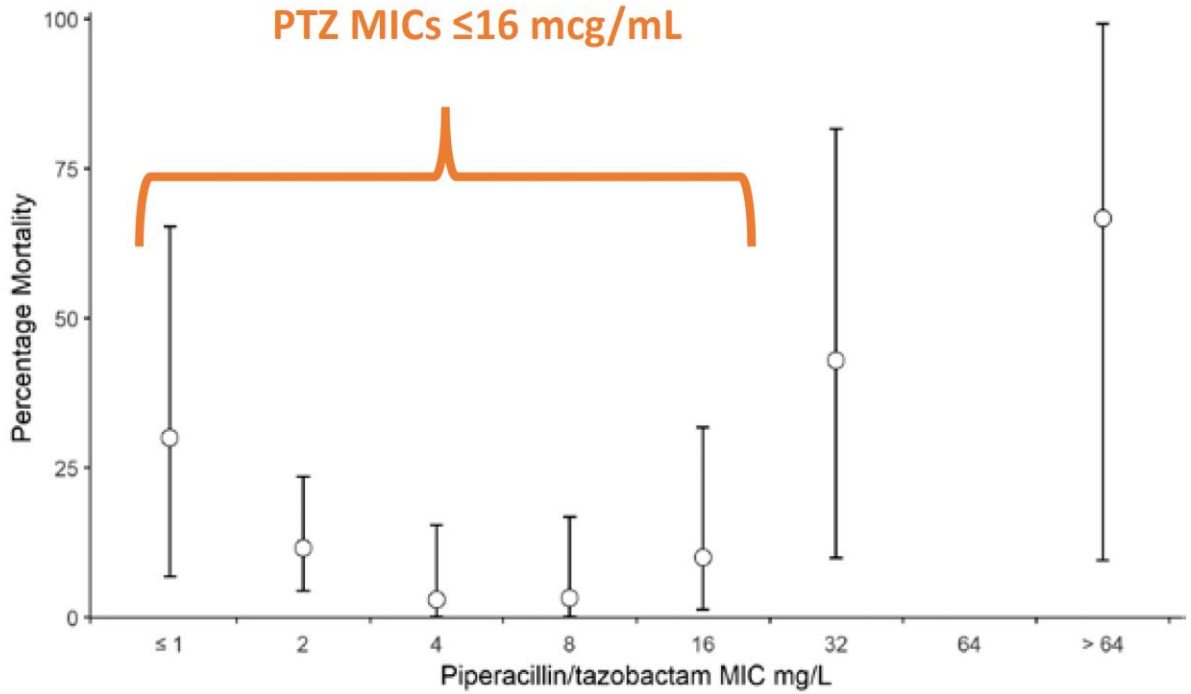
Henderson A, et al. Clin Infect Dis 2020; PMID: 33106863



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

MERINO: Reference MIC & Association with Mortality



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

Breakpoint summary

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

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

Local Laboratory CAN update breakpoints

- Obtain Reference Bacterial Strains
  - 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

BREAKING NEWS FLASH

- Aminoglycosides for Pseudomonas – gone?
- Combination therapy?

Summary

- Discrepancy between CLSI and FDA Breakpoints is the product of clunky FDA regulation of Automated Susceptibility Testing Devices
- Failure to Resolve the Breakpoint Discrepancy has Resulted in Increased and Needless Patient Mortality – Documented in Clinical Trials and Not Quantified in Clinical Practice
- ASP Programs Need to Include at Least Annual Review and Routine Breakpoint Updates with Their Microbiology Laboratory
- Public Health may Play a Role in Standardizing Treatment