# Critical Microbiology Results for Critical Patients: 2023 Perspective

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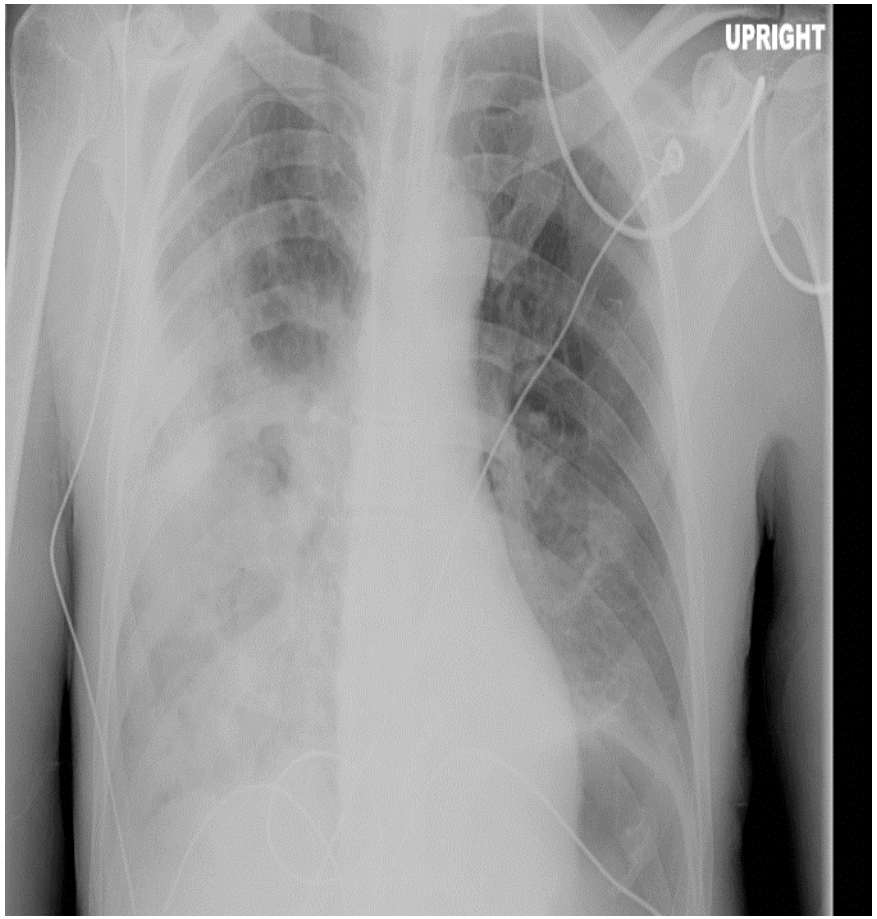
**Quality Improvement Opportunity** - a change in practice that might improve outcomes, but is not derived from an erroneous practice

# 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)



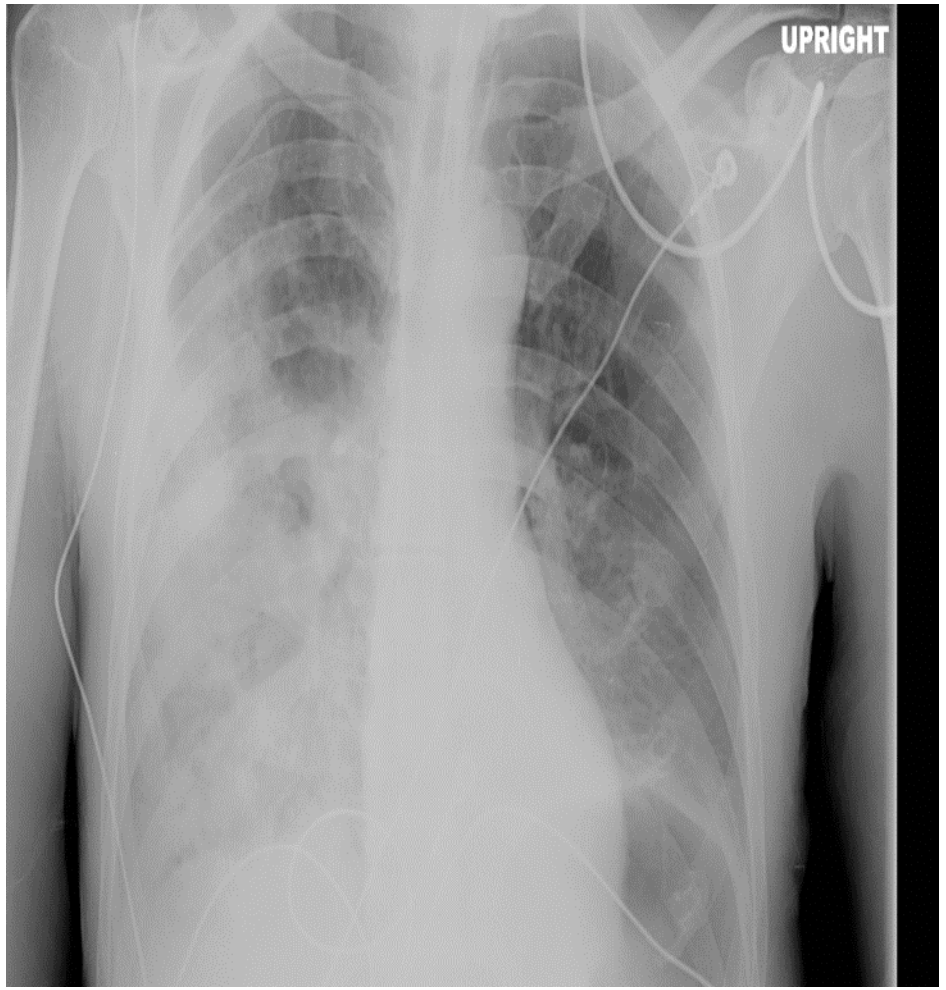
# Lucy: Admission Exam

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

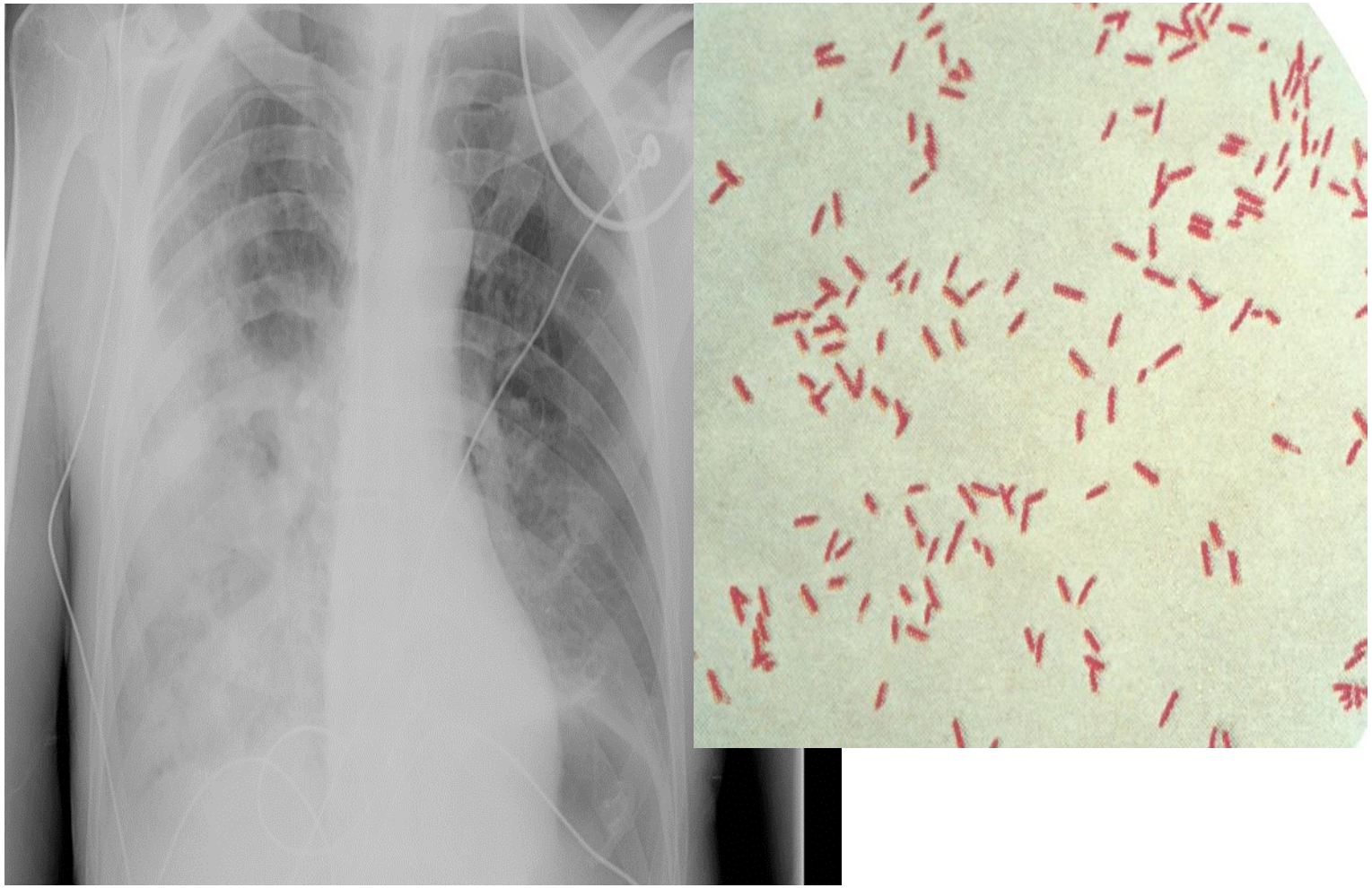
- Intubated, Sedated
- Frail with slight temporal wasting
- JVD was Flat
- Tachycardic, No MRG
- RLL Rhonchi
- Decreased muscle mass
- No Skin Rash

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

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

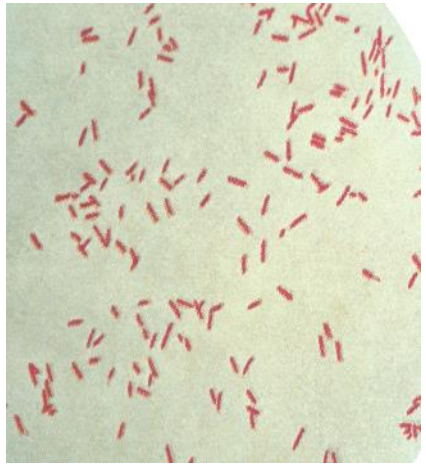


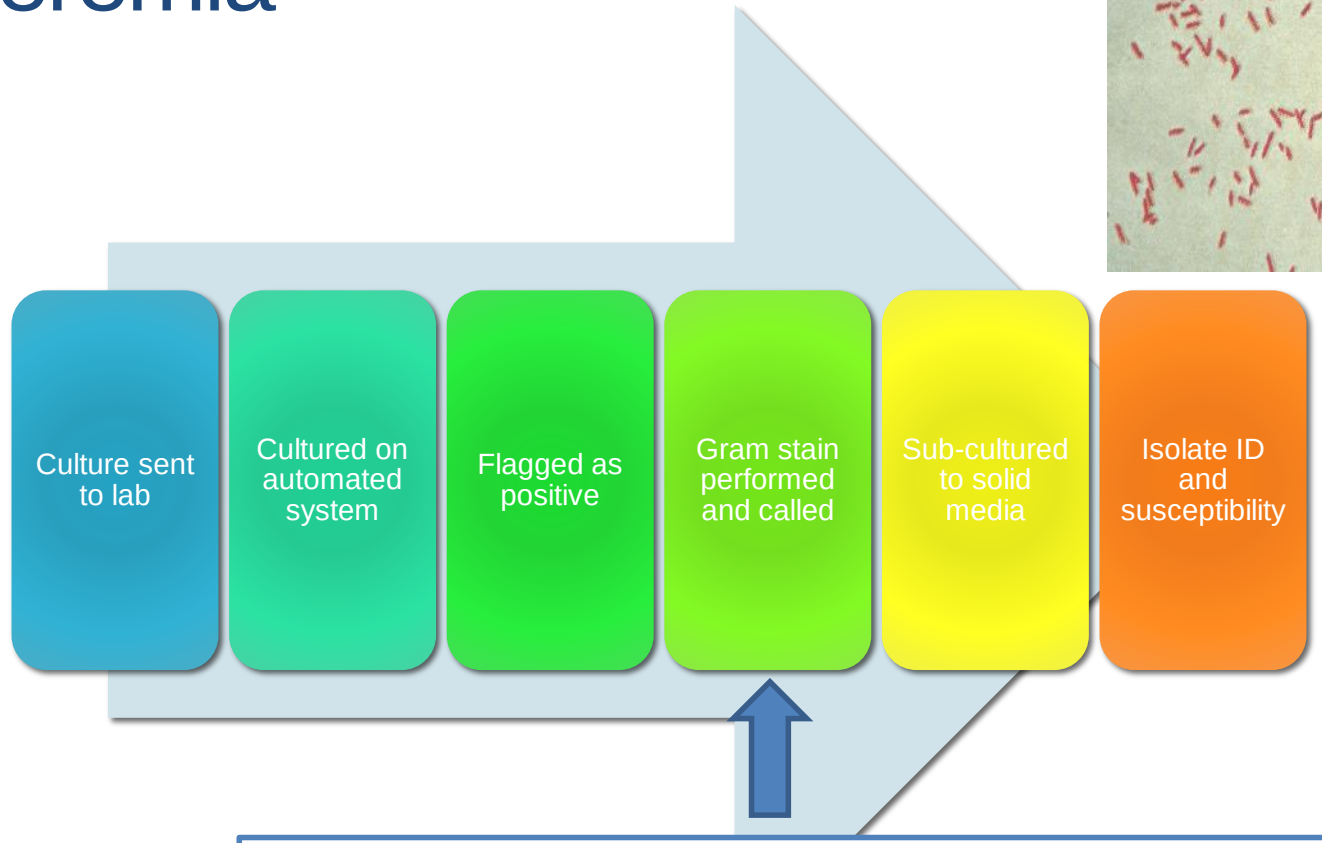
# RLL Pneumonia Gram-Negative Rods



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

# RLL Pneumonia with Bacteremia



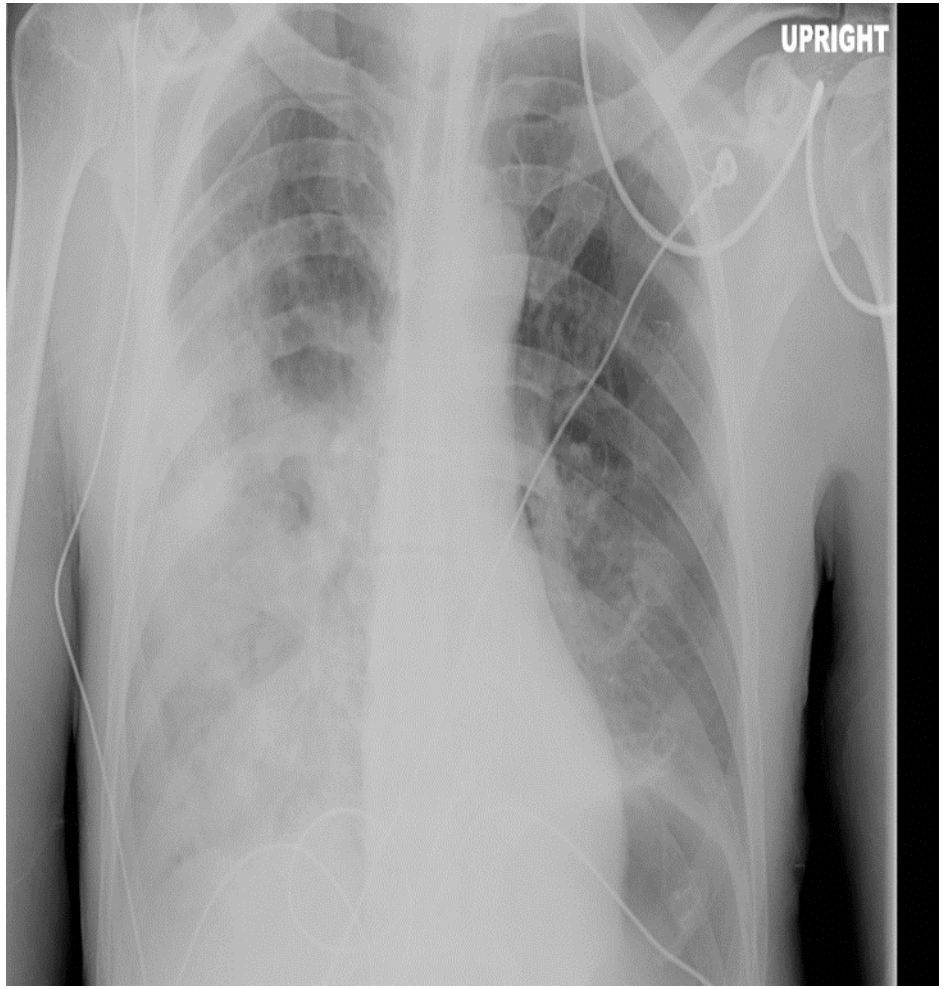



This is where we are with our patient.
We only know we are dealing with a gram negative Rod.

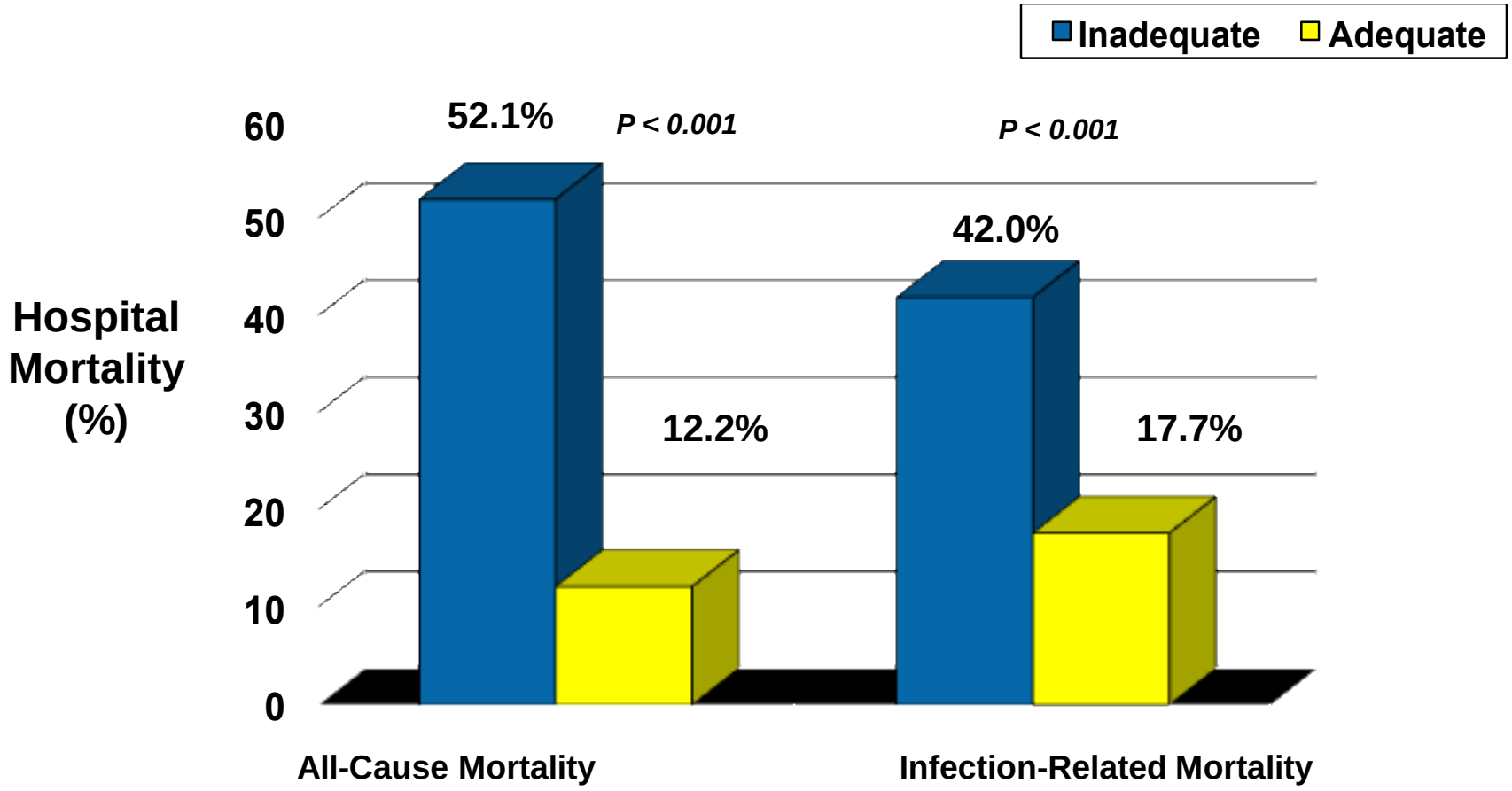
# Lucy: Assessment

- 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.

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

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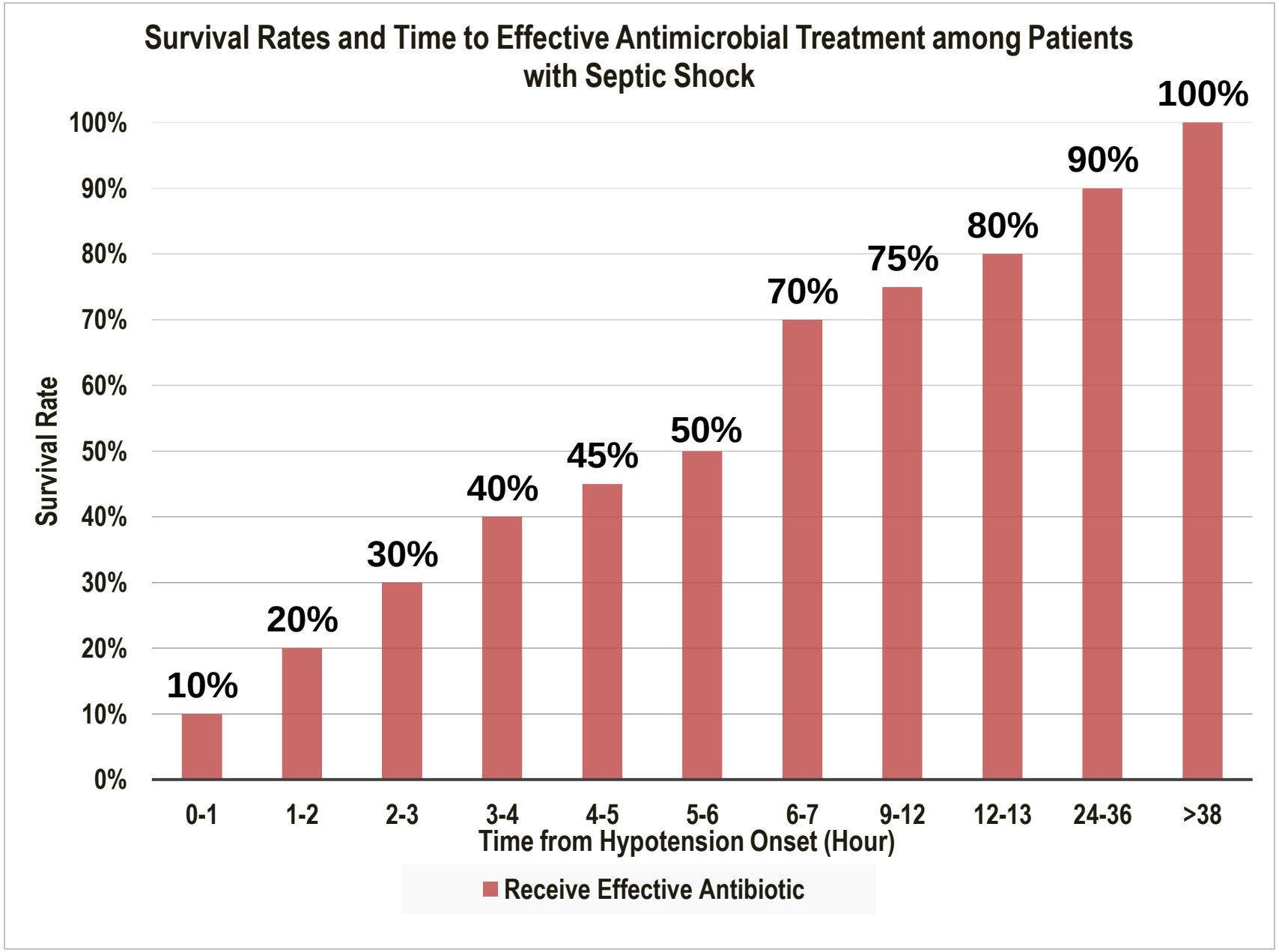


Kumar A, et al. *Crit Care Med* 2006; 1589-1596, Kollef MH., et al. *Chest.* 1999;115:462-474.

*Clinical Infectious Diseases*

MAJOR ARTICLE

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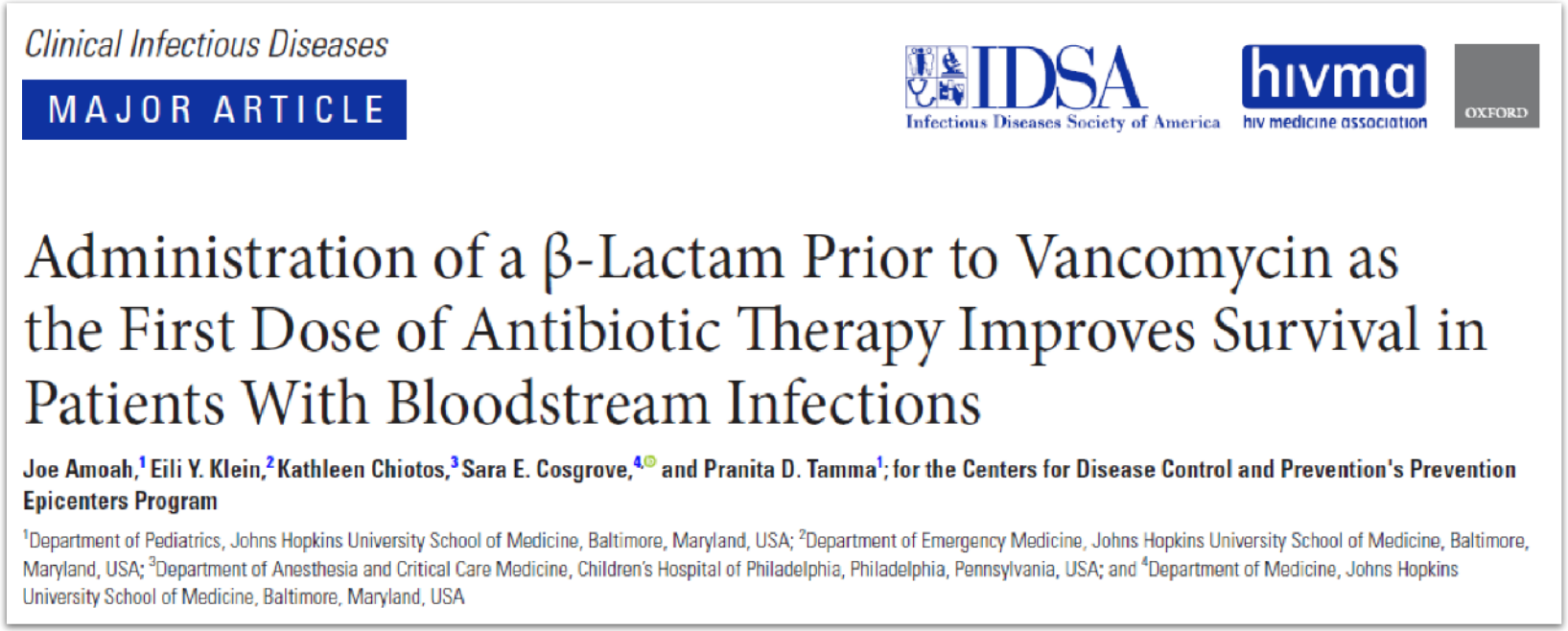
# Administration of a β-Lactam Prior to Vancomycin as the First Dose of Antibiotic Therapy Improves Survival in Patients With Bloodstream Infections

**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**

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

- 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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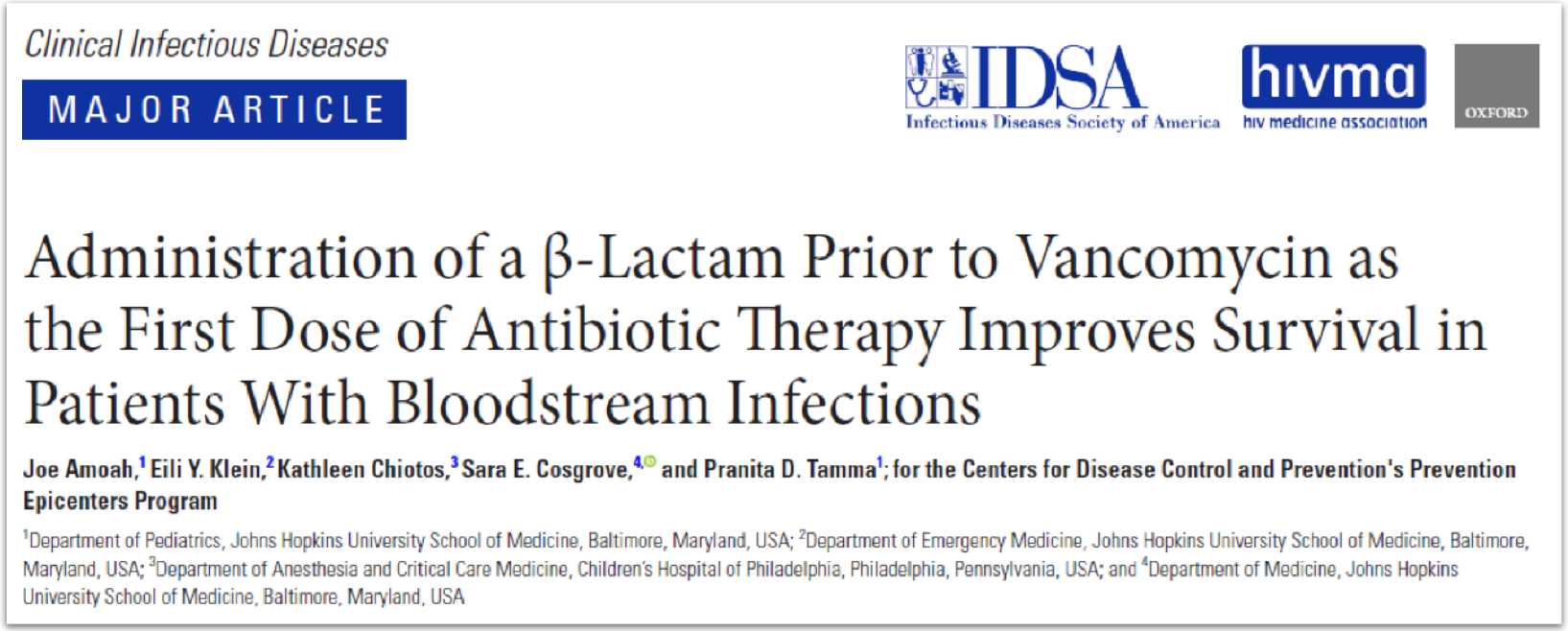

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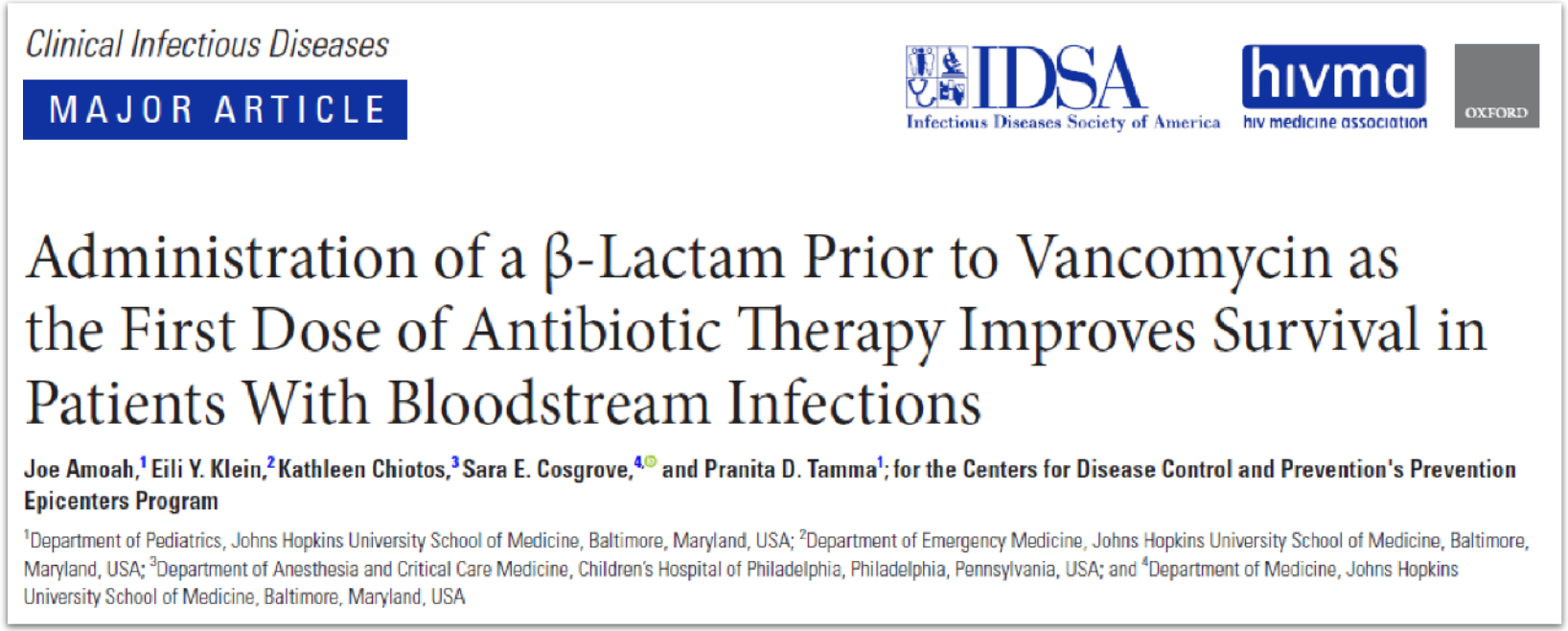
- 2,685 (79.5%) received Beta Lactam First
  - 47.9% Zosyn
  - 42% Cefepime



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

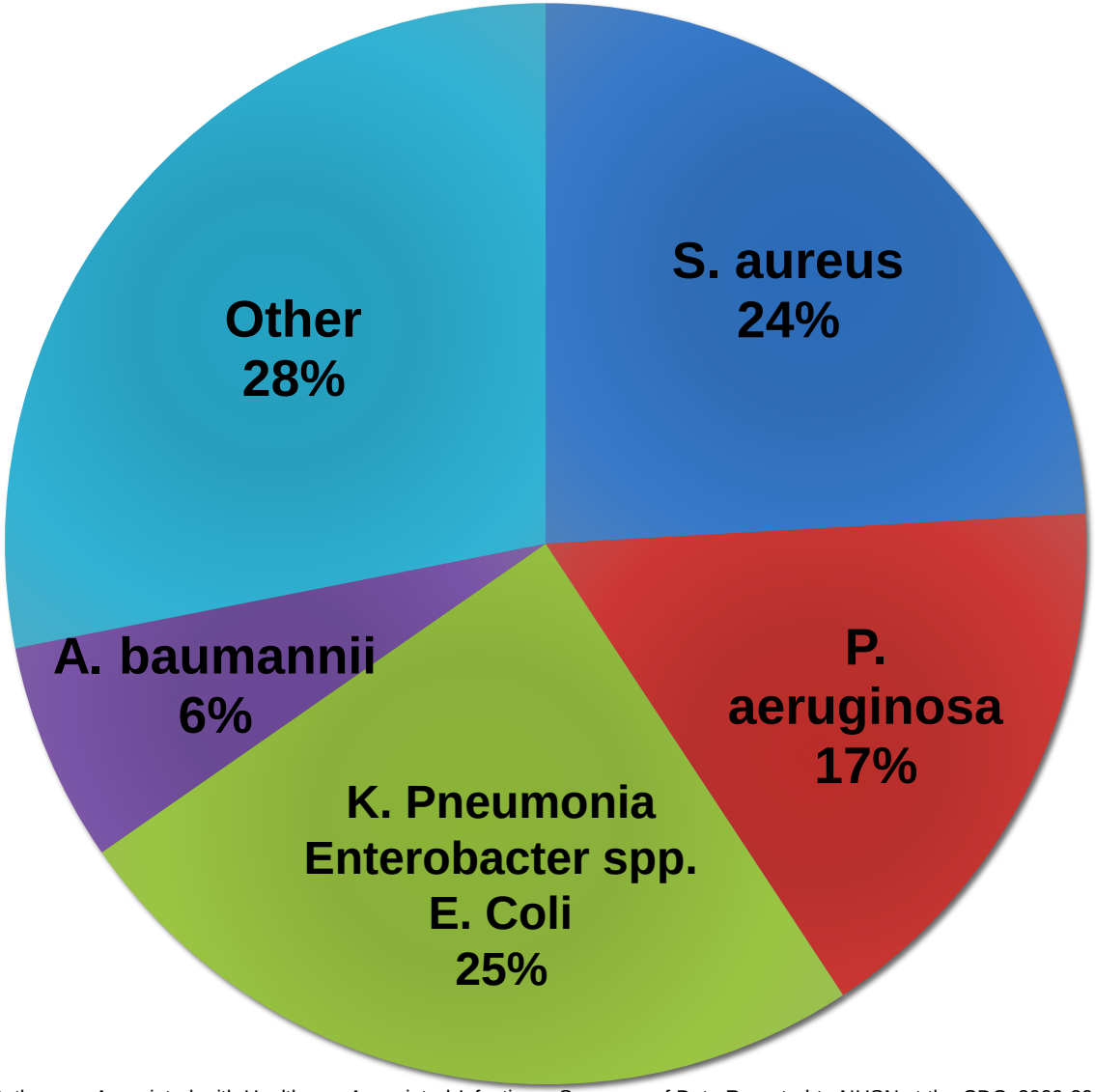
- Beta Lactam First Improved Survival
  - OR 0.48 (0.33-0.69)
  - MRSA 0.93 (0.33-2.62)

# 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 | |
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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 |
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| *Acinetobacter baumannii* | 62 | R | 62 | 53 | R | 58 | 58 | – | R | 62 | 60 | 67 | 60 | 66 | 56 | 60 | 95 |
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| *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 |

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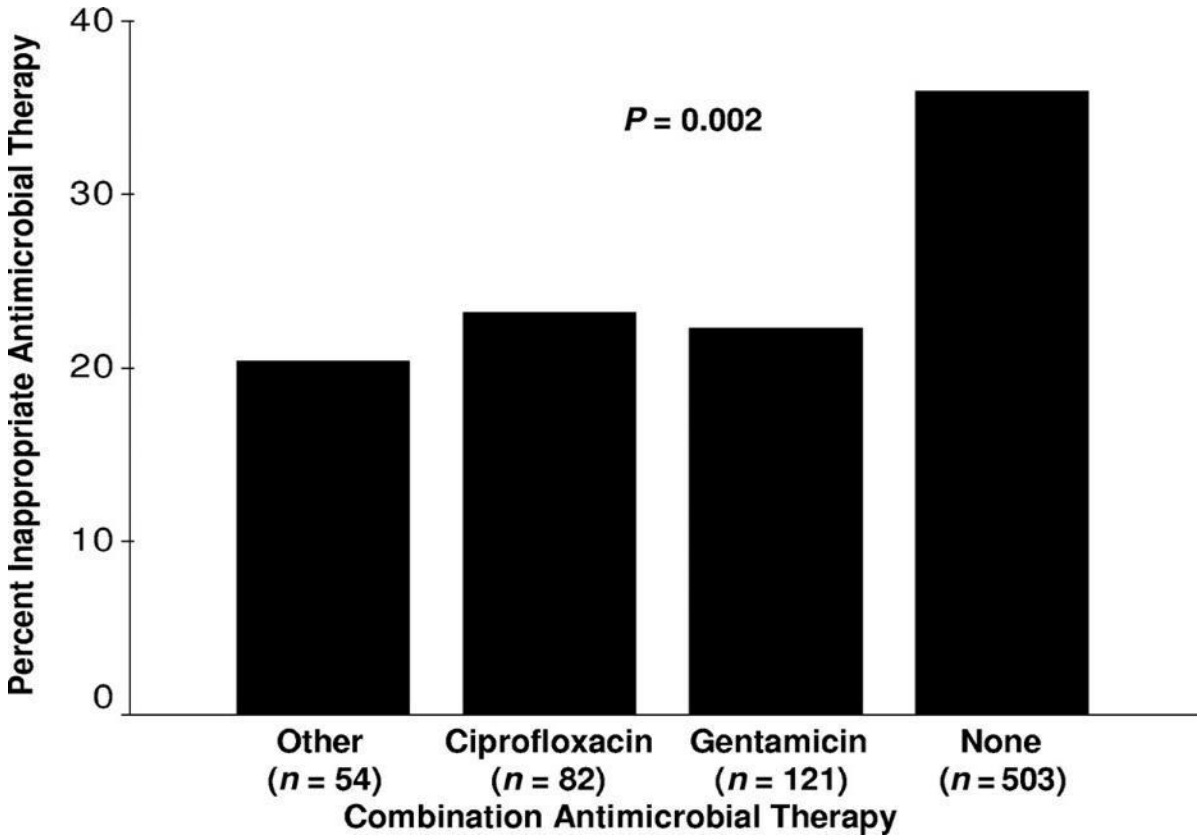
# Empiric combination therapy is associated with higher rates of early, appropriate therapy for patients with sepsis due to Gram-negatives

Retrospective study (n=760)




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

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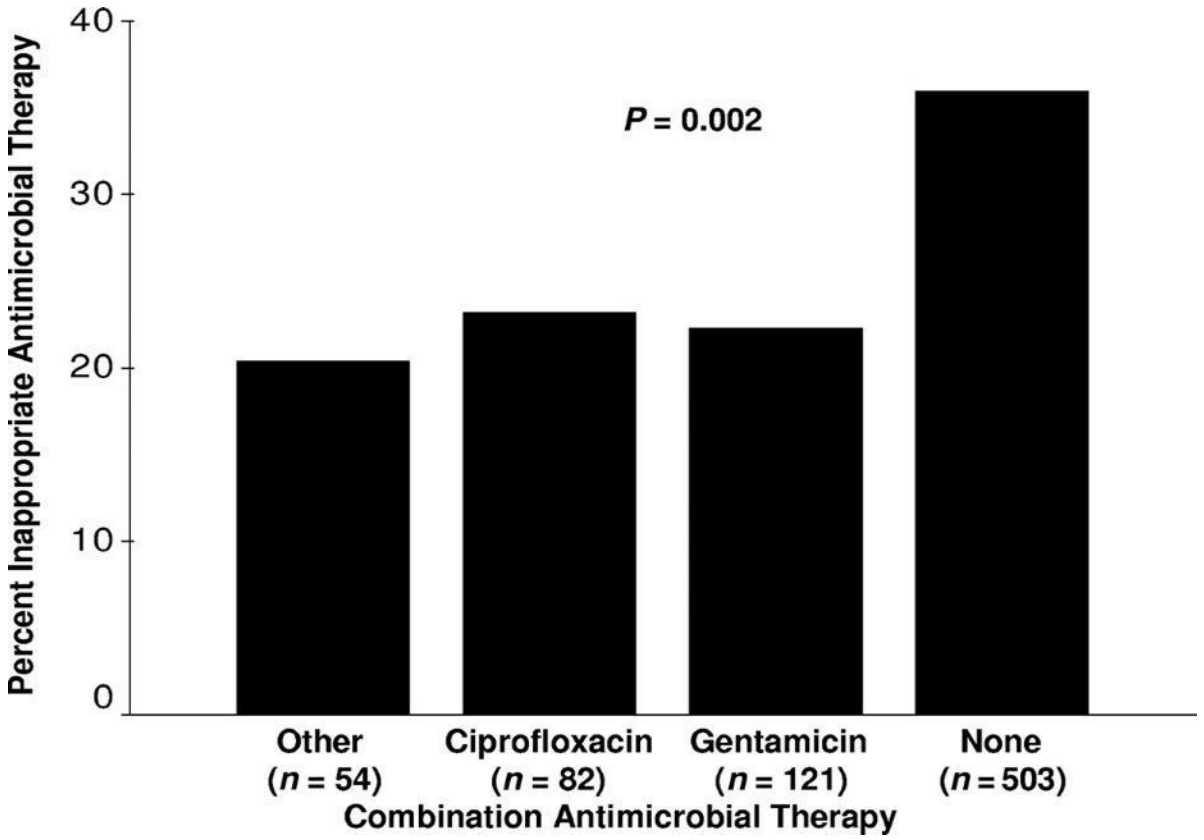


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| *Enterobacter cloacae* | 209 | R | R | 81 | R | 92 | –[4] | –[4] | 89 | 99 | 99 | 99 | 99 | 99 | 98 | 94 | 85 |
| *Escherichia coli* | 752 | 41 | 50 | 94 | 59 | 84 | 83 | 79 | 99 | 99 | 99 | 99 | 82 | 85 | 63 | 60 | 99 |
| *Klebsiella oxytoca* | 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] |
| *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*.

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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] |
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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 |
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| *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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|---|---|---|---|---|
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| Meropenem (87) | 98 | 96 | 97 | 92 |
| Piperacillin-tazobactam (86) | 99 | 97 | 97 | 93 |
| Ciprofloxacin (80) | 98 | 95 | 96 | - |

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1. Percent susceptible for individual drug in parenthesis
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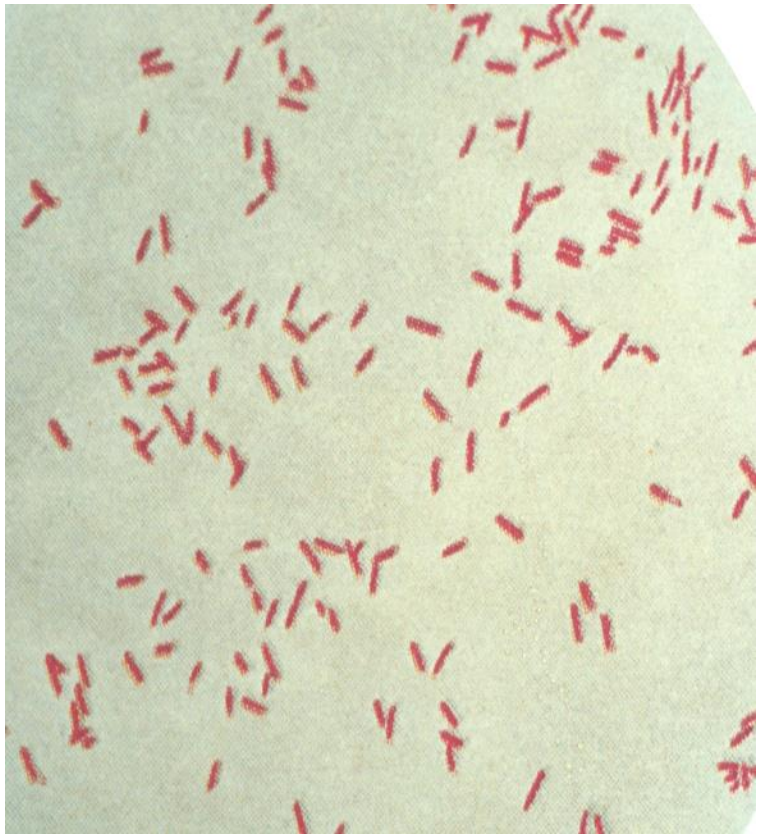
Adapted from antibiogram data source: UCLA Health Infectious Disease

# 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 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

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

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

BACTERIOLOGY

## 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

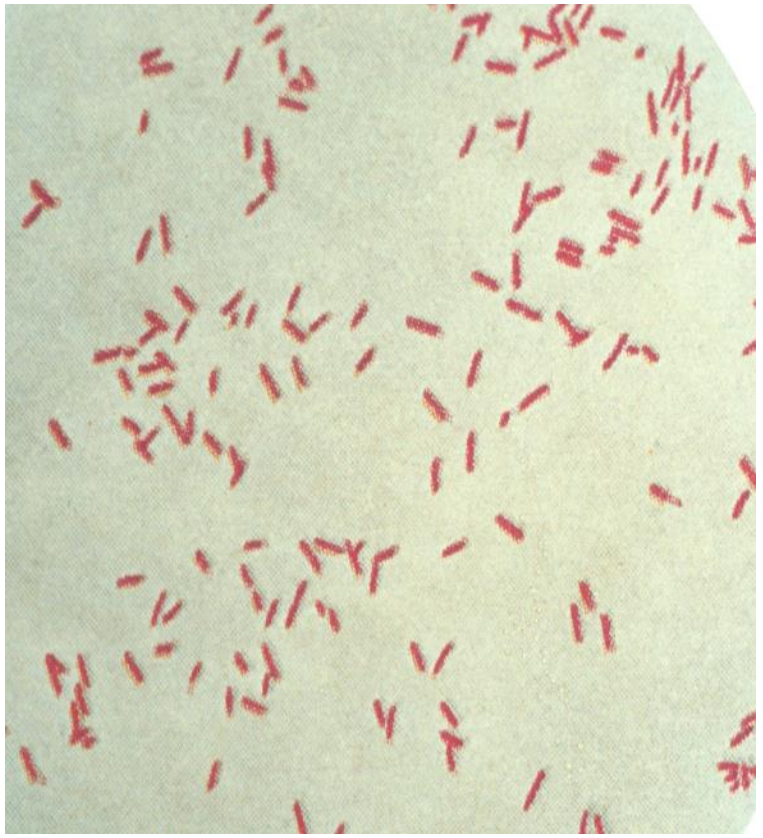
## Risk Factors for Development of Carbapenem Resistance Among Gram-Negative Rods

Stefan E. Richter,[1,2] 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

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

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

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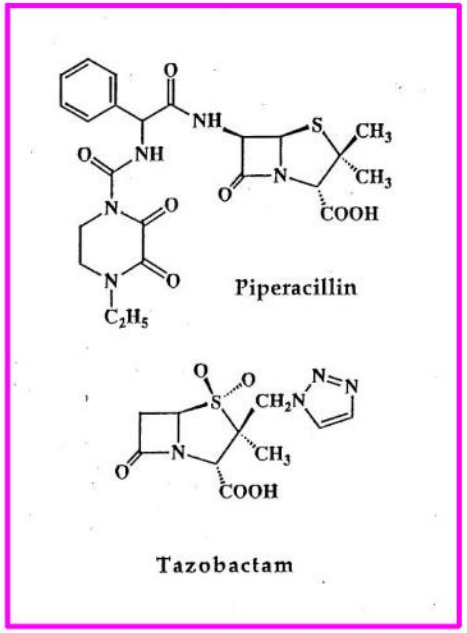
|---|---|
| Cefepime | S-DD (4) |
| Ceftazidime | R |
| Ceftriaxone | R |
| Tobramycin | R |
| Pip/Tazo | S |
| Meropenem | S |
| Tigecycline | R |

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

# Piperacillin-Tazobactam



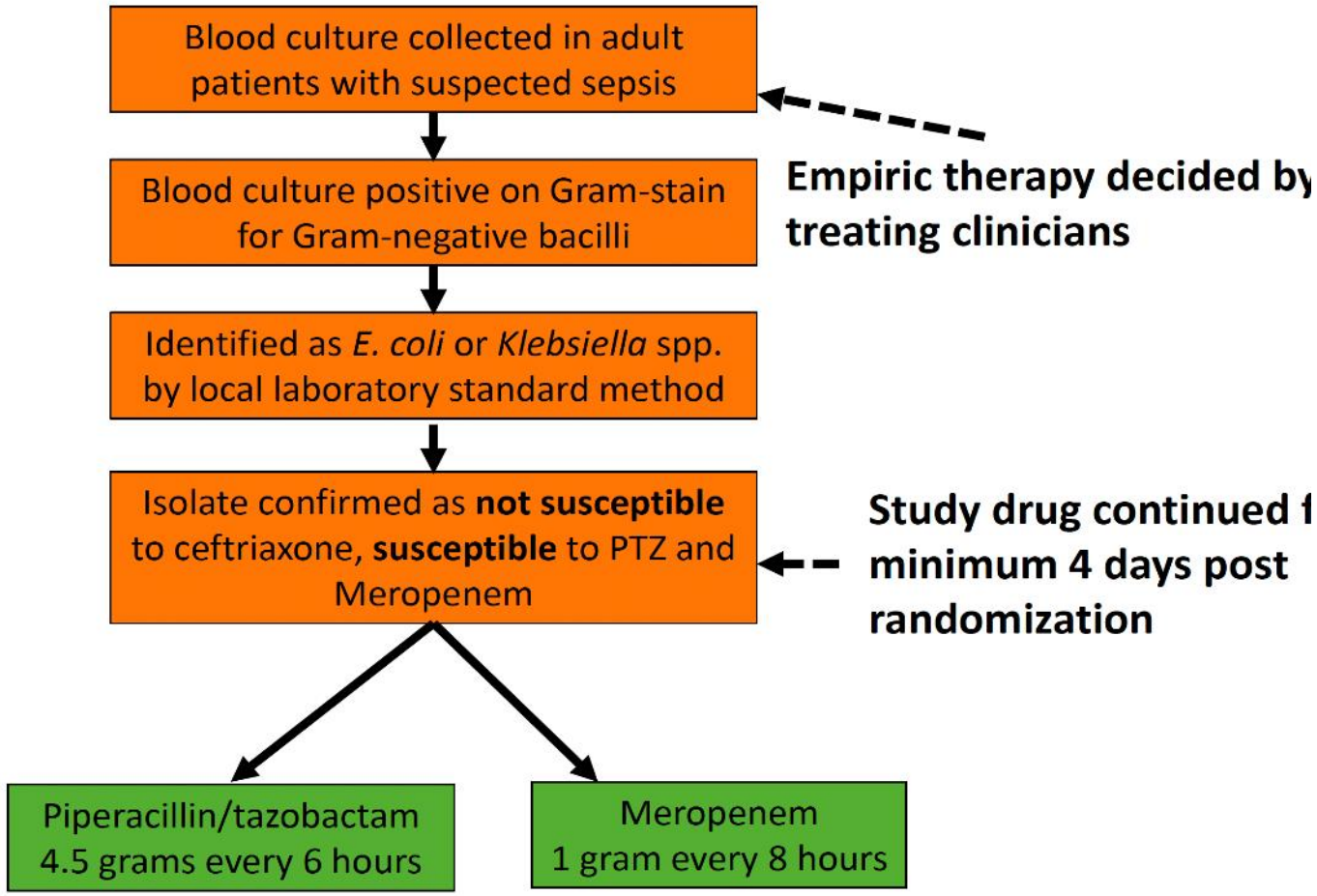

- 1981 - piperacillin approved
- 1993 - piperacillin-tazobactam approved for skin and skin structure and intra-abdominal infections
  - BEFORE ESBLs were wide-spread
  - CLSI never included editing pip-tazo as "R" if ESBL detected, but many do this in practice
- Tazobactam – inhibit activity of ESBLs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

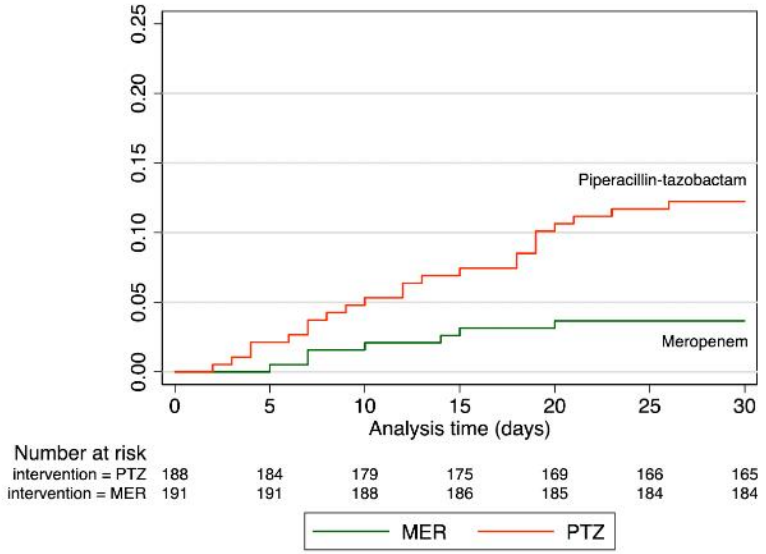



Harris PNA, et al. JAMA. 2018;320:984-994

# 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



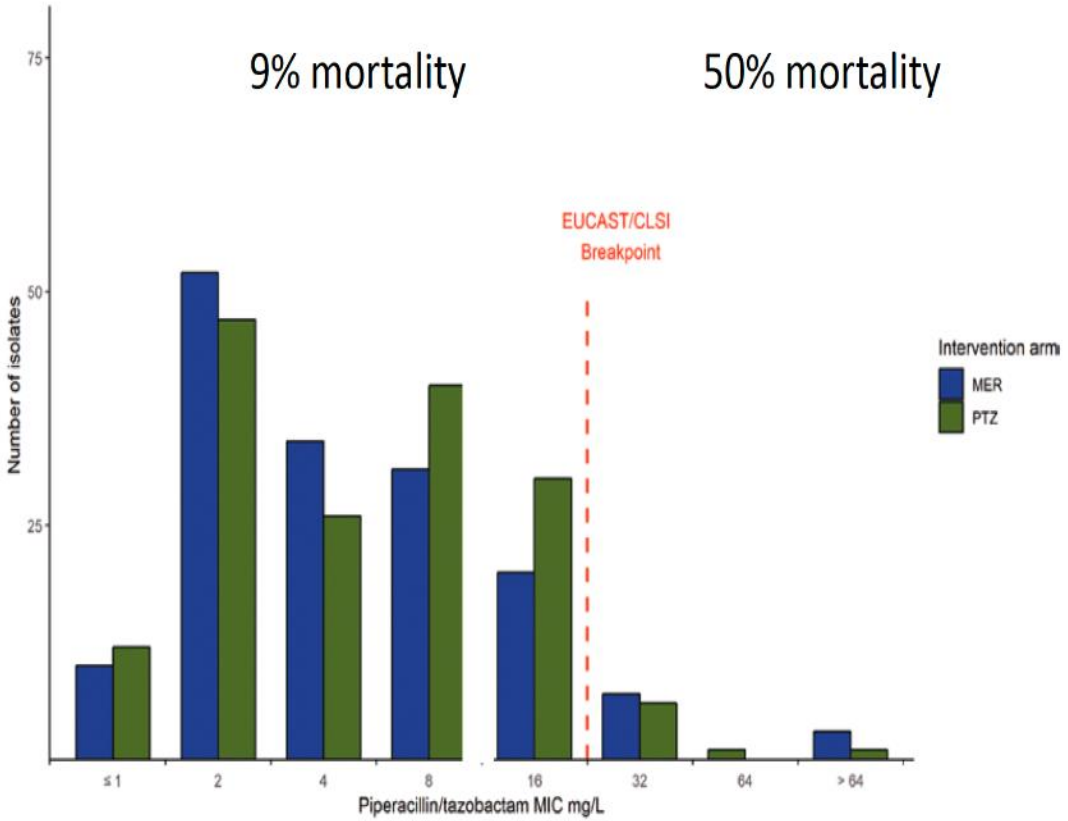

| | Mortality 30 days n/total (%) | | Risk difference % (1-sided 97.5% CI)[c] | *P* value for non-inferiority |
|---|---|---|---|---|
| | Piperacillin-tazobactam | Meropenem | | |
| **Primary analysis** | 23/187 (12.3) | 7/191 (3.7) | 8.6 (-∞ to 14.5) | .90 |
| **Per-protocol analysis** | 18/170 (10.6) | 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* |
| $Log_2$(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 |
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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; PMID: 33106863

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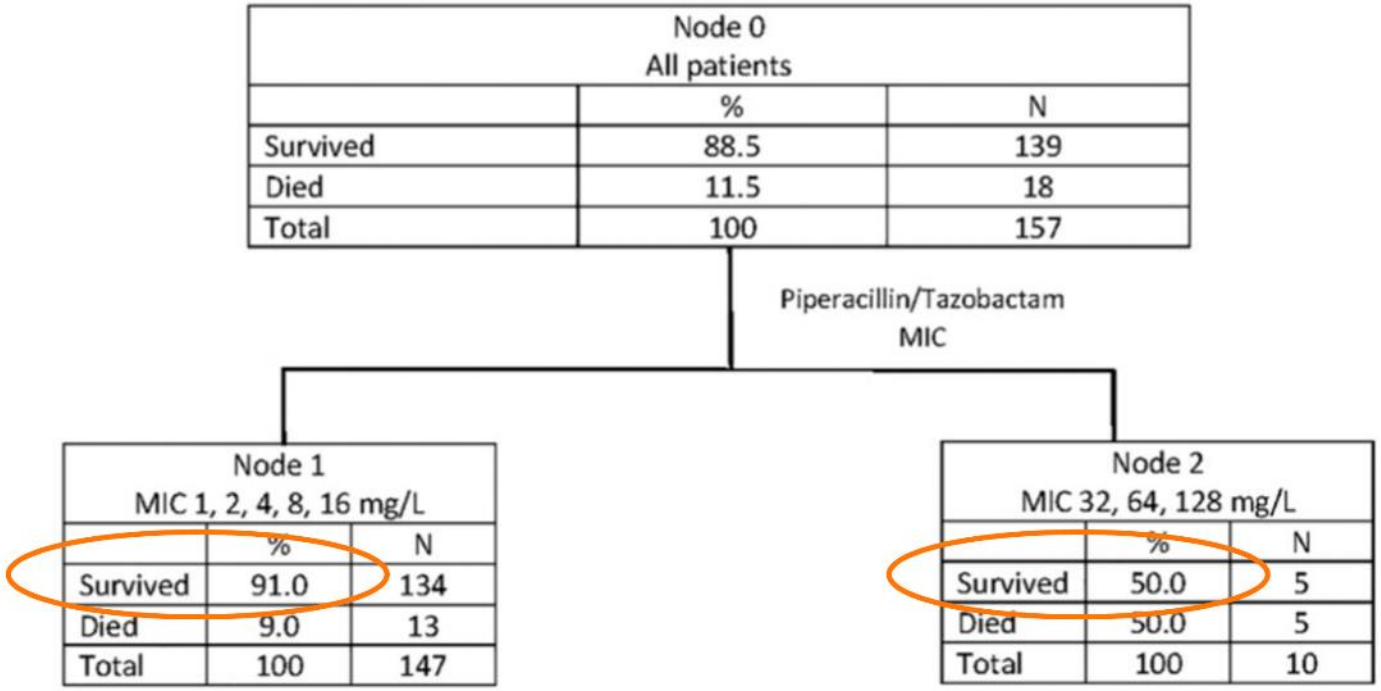


| Node 0<br>All patients | | |
|---|---|---|
| | % | N |
| Survived | 88.5 | 139 |
| Died | 11.5 | 18 |
| Total | 100 | 157 |

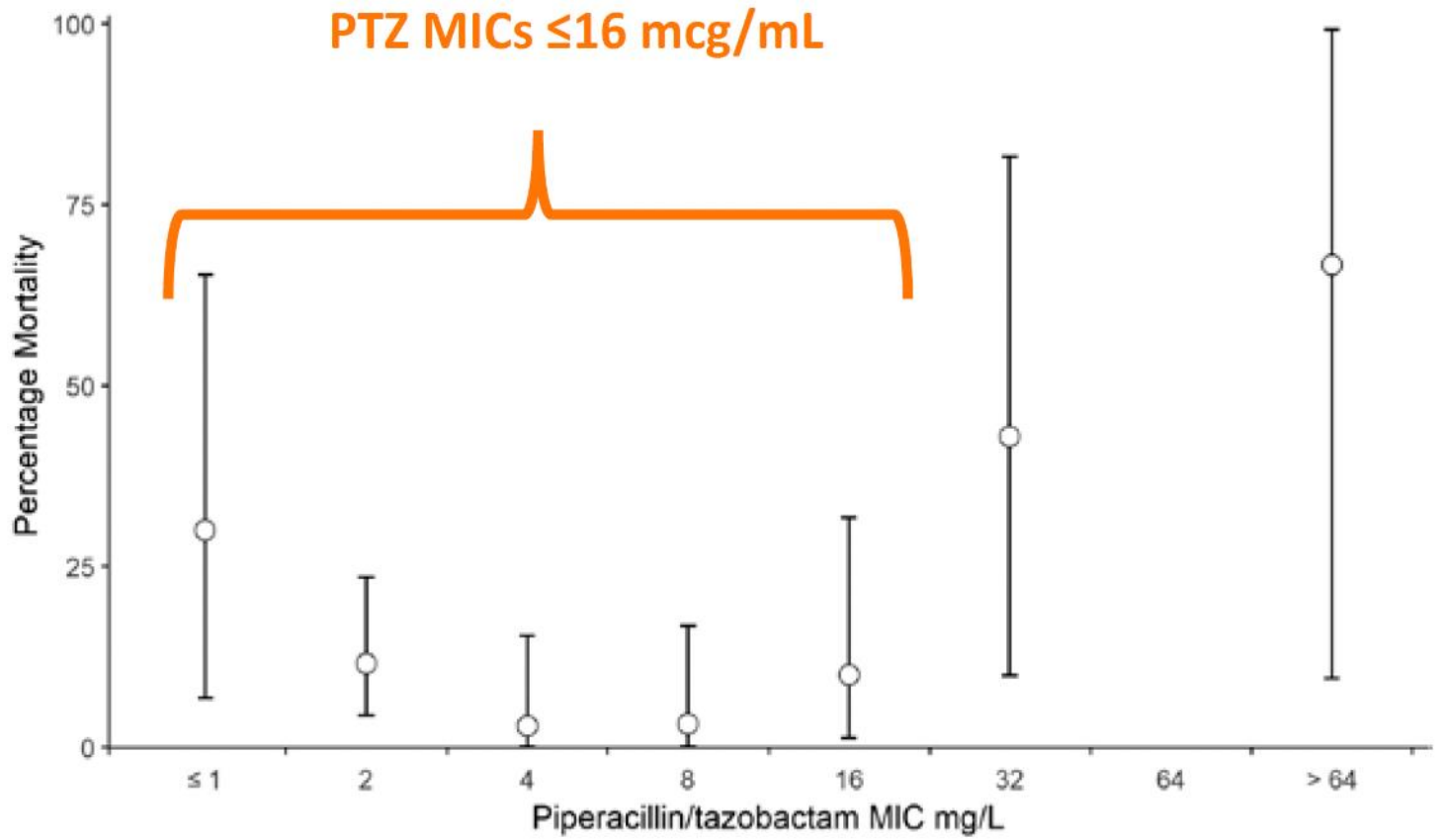
Piperacillin/Tazobactam
MIC

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

| Node 2<br>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

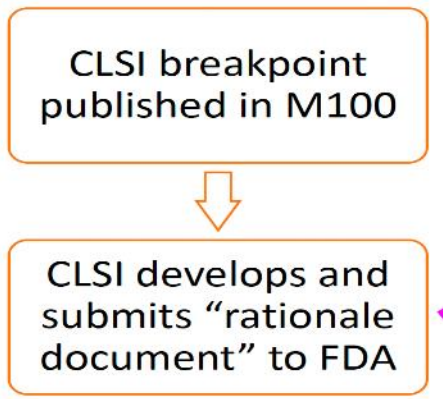
21st Century Cures allows recognition of MANY CLSI breakpoints by FDA…. But not all

# 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




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

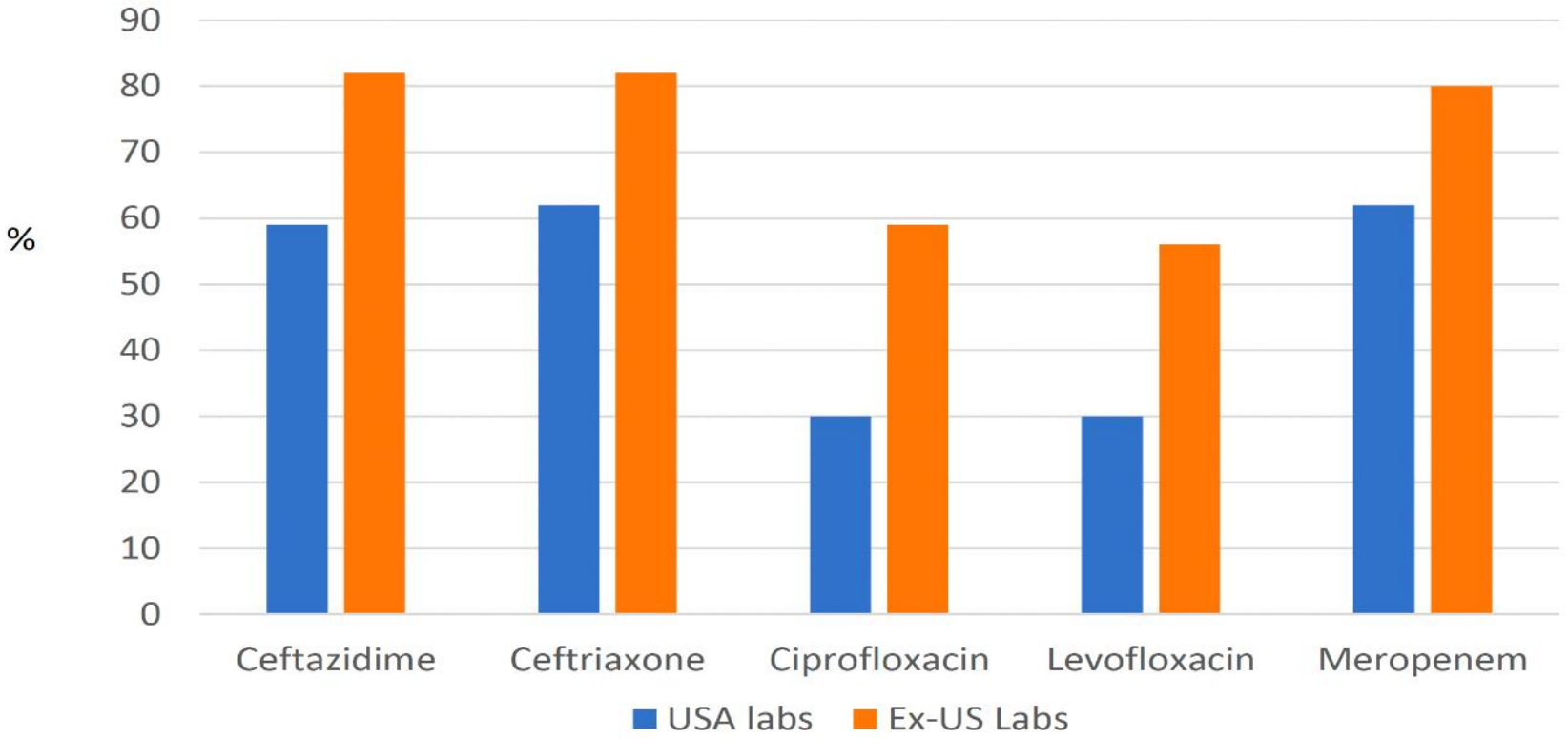
STIC, Susceptibility Test Interpretive Criteria

# 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

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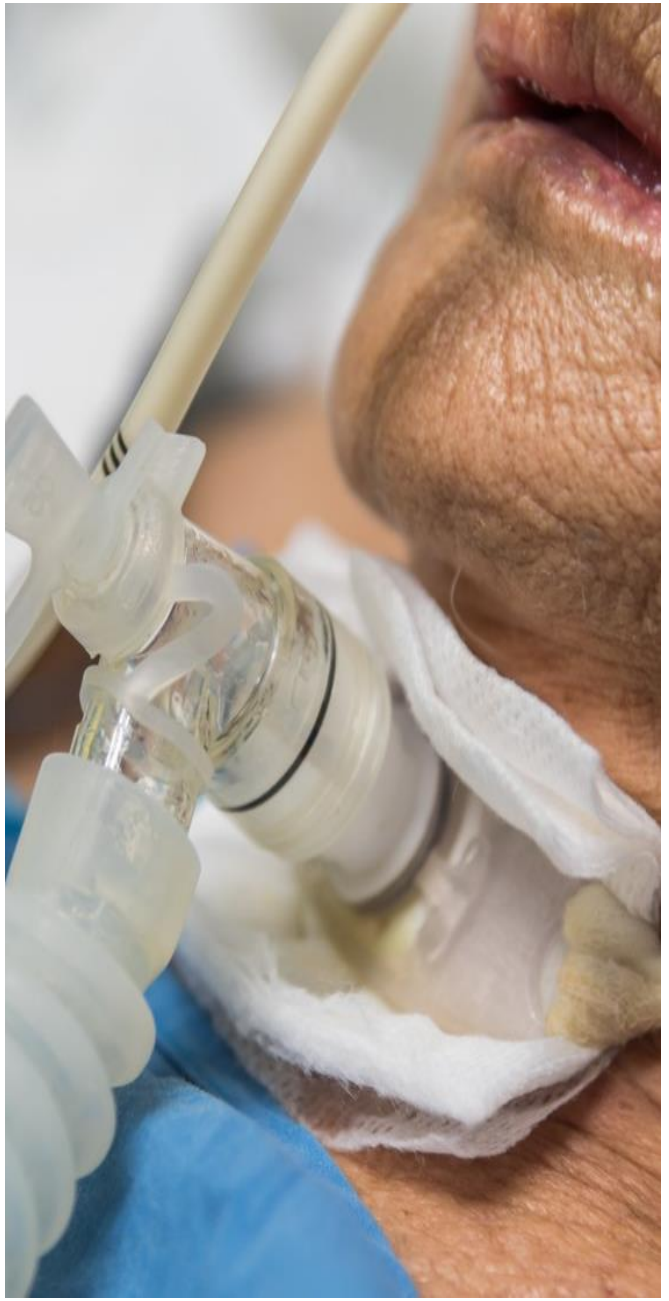
- Save Lives
- LA County Department of Public Health Assisted in Carbapenem Breakpoint Updates for their Hospitals

# 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/

# *A. Baumannii* resistance mechanisms are complicated

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- Porin Loss
- Efflux Pumps (Tet and AdeABC )
- 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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- Sulbactam is also a Beta-Lactam Antibacterial against PBP1 and PBP3 inhibition of *A. baumannii*

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- **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 use ampicillin Sulbactam

# Antibiotic Strategy

- **High Dose Ampicillin-Sulbactam**

# Antibiotic Strategy

- **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

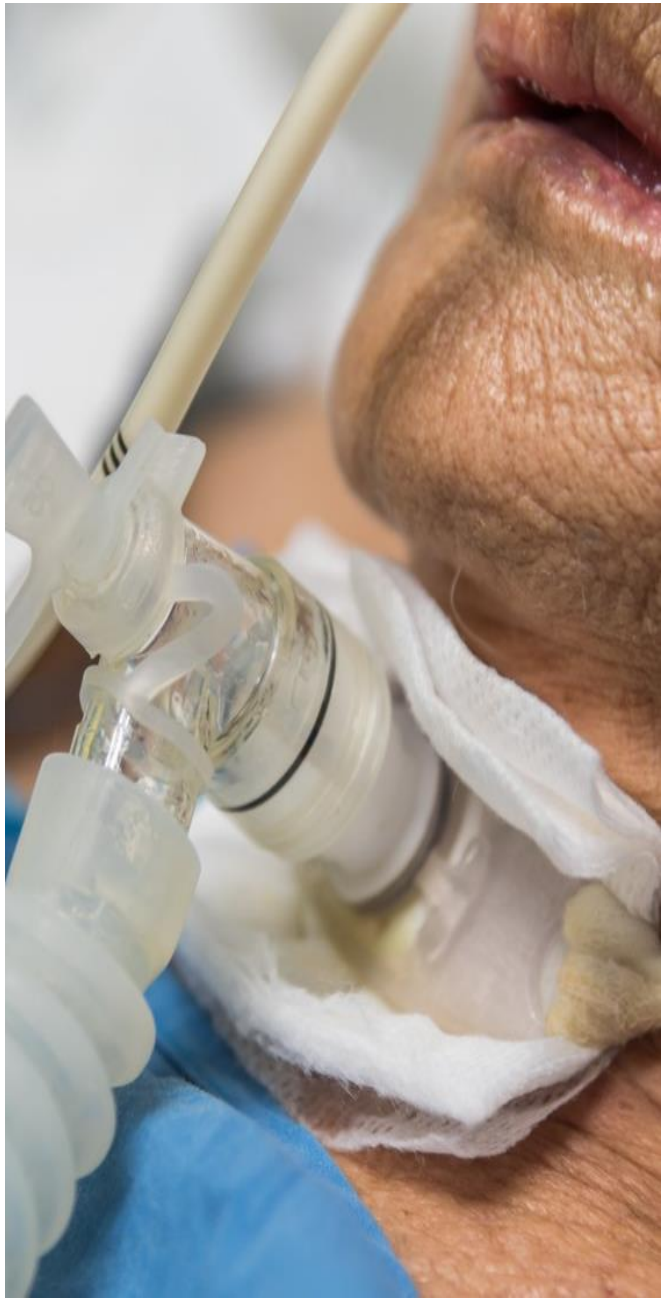
- High Dose Ampicillin-Sulbactam
- TMP/SMX
- Eravacycline
- Did not try Minocycline or Omadacycline
- ~~Cefiderocol~~
- ~~Delafloxacin~~

# 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.

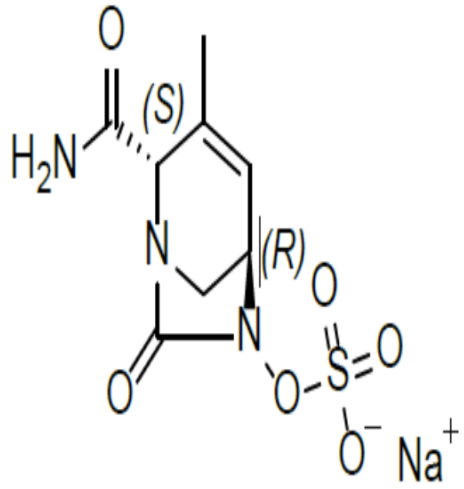
**PMH:** Pulmonary Fibrosis (not on oxygen)

**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

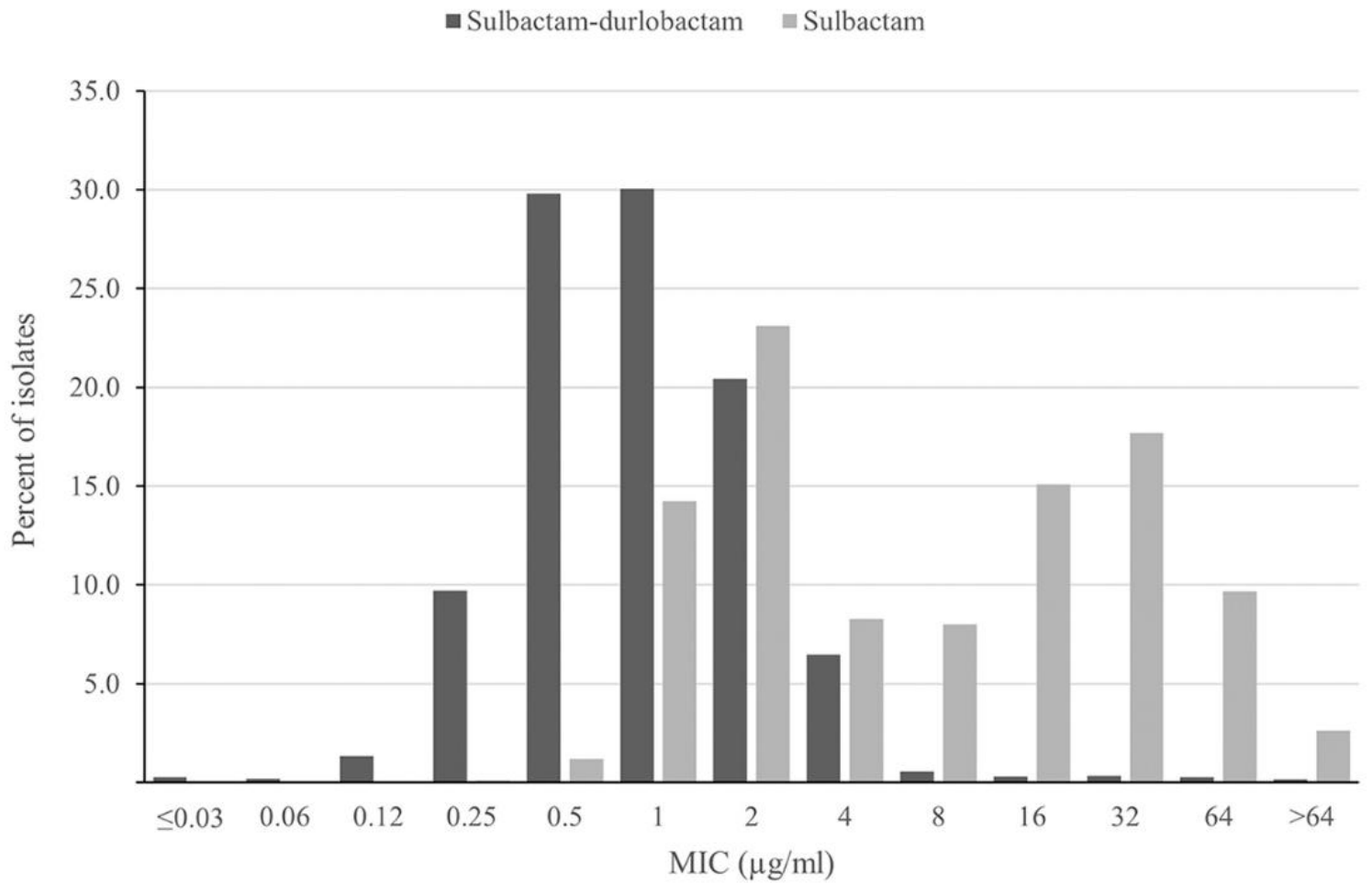
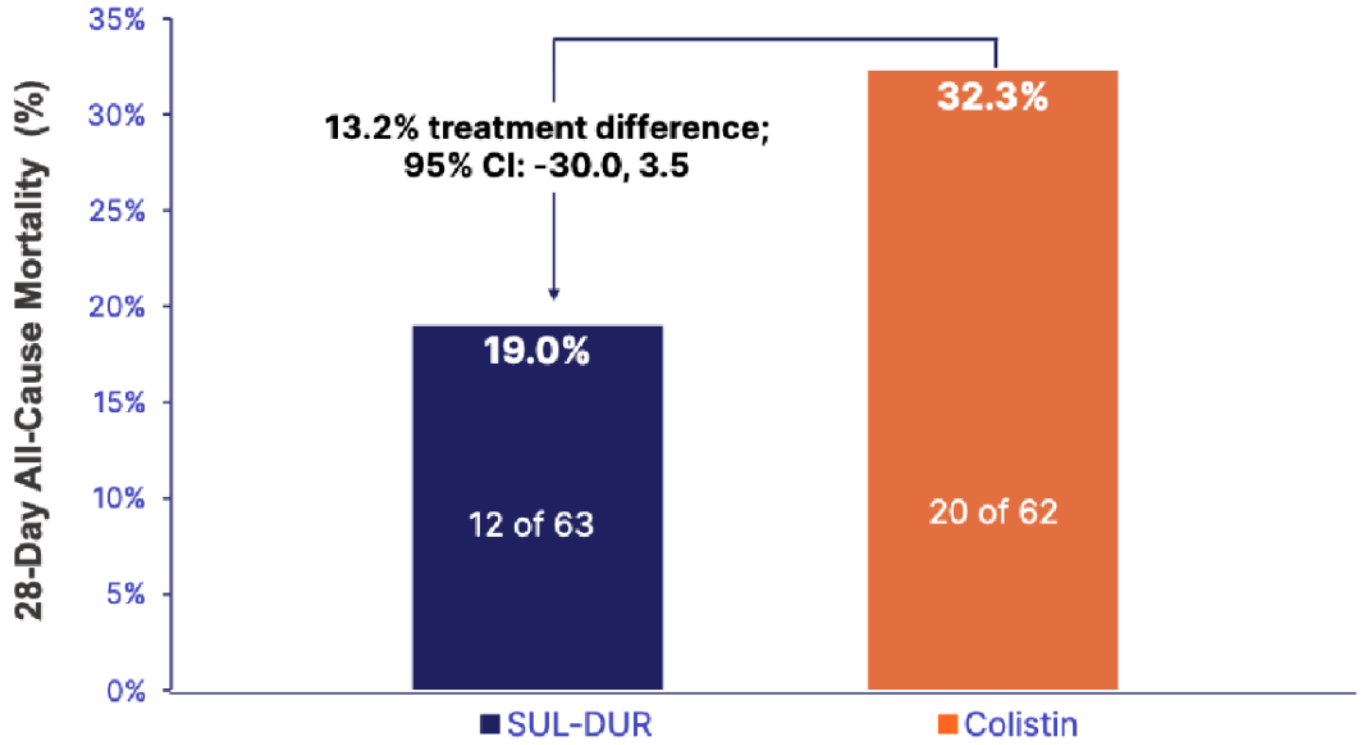



**FIG 1** Sulbactam-durlobactam (black bars) and sulbactam (gray bars) MIC distributions for 5,032 isolates of *Acinetobacter baumannii-calcoaceticus* complex (ABC) species collected globally from 2016 to 2021.

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

**As expected only really active against A. Baumannii**

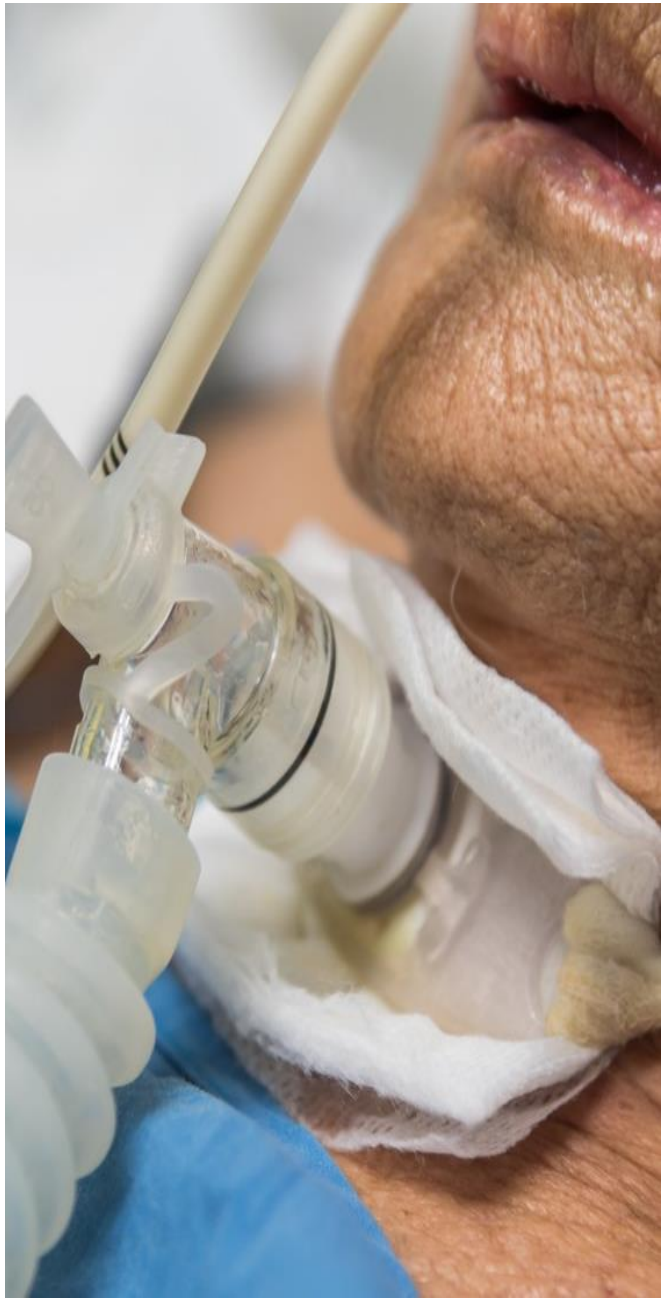



McLeod SM, et al. Id Week 2023

# 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