The Role of Carbapenemase Testing in Clinical Practice

December 6th, 2022

Presented by Webinar*

*Webinar will be recorded, and a PDF of the slides will be shared with all participants

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Center for Health Care Quality
California Department of Public Health

California Department of PublicHealth

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CPO webinar series

- Sep. 29th, 2022: **Carbapenemase-producing Organisms: Guidance for Reporting and Containment**
  - Hosted by CDPH and Los Angeles County DPH
  - Link to slides (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPO_ReportingAndPreventionWebinar_092922.pdf) and recording (youtu.be/dm4I2ooSA4M?t=79)
- Oct. 27th, 2022 : **Testing for Carbapenemase Production Among Carbapenem-Resistant Organisms: When and How?**
  - Hosted by Janet Hindler at Los Angeles County DPH
  - Link to slides(PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPO_webinar_102722.pdf), recording (youtu.be/I6LPBB9EQ8c), and handout (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CRO_PrimerTests_for_Carbapenemases.pdf)

Presenters

- **Natalie Medvedeva, MD**

  Clinical Assistant Professor

  Stanford University
- **Jeffrey Silvers, MD**

  Medical Director of Pharmacy and Infection Control

  Sutter Healthcare System
- **James A. McKinnell, MD**

  Associate Professor of Medicine, David Geffen School of Medicine

  University of California, Los Angeles

  President, Expert Stewardship

  Newport Beach, California

Objectives

- Discuss the utility of carbapenemase testing for infection prevention and control
- Describe how carbapenemase testing can be used to inform antibiotic prescribing practices
- Understand how local CPO epidemiology can guide empiric treatment decisions

Carbapenem-resistant organisms (CRO)

- Gram-negative bacteria, commonly Enterobacterales (CRE), *Acinetobacter baumannii* (CRAB), *Pseudomonas aeruginosa* (CRPA)
- Non-carbapenemase-producing
  - Resistant due to the presence of porin loss, efflux pumps, etc.
- Carbapenemase-producing
  - Carbapenemase enzymes often plasmid-mediated; transmissible between species
  - Urgent public health threat due to their ability to spread rapidly among patients, especially in the environment or via the hands and clothing of healthcare workers
  - Lab reportable as of September 2022 Title 17 update

Carbapenemase-producing organisms (CPO)

- Carbapenemase enzymes fall into three main categories
  - Class A carbapenemases (e.g., KPC, GES)
  - Class B metallo-β-lactamases (e.g., NDM, VIM)
  - Class D oxacillinases (e.g., OXA-48, OXA-23)

Carbapenemase-producing organisms (CPO)

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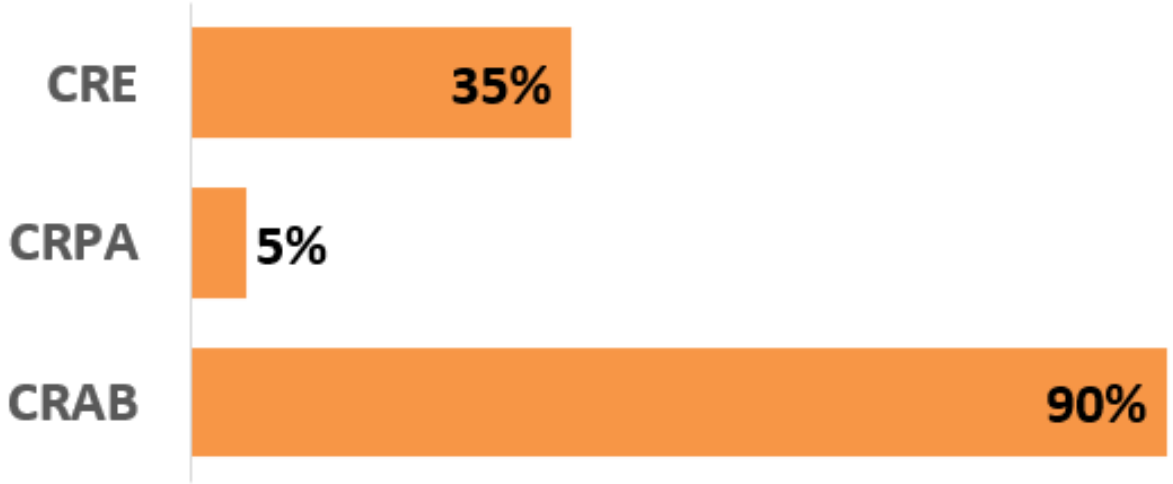
  - *Class D oxacillinases (e.g., OXA-48, OXA-23)*

- Proportion of CRO that produce carbapenemases varies by organism



Source: CDC Antibiotic Resistance & Patient Safety Portal (AR&PSP) AR Lab Network Data (arpsp.cdc.gov/)

CPO and Patient Safety

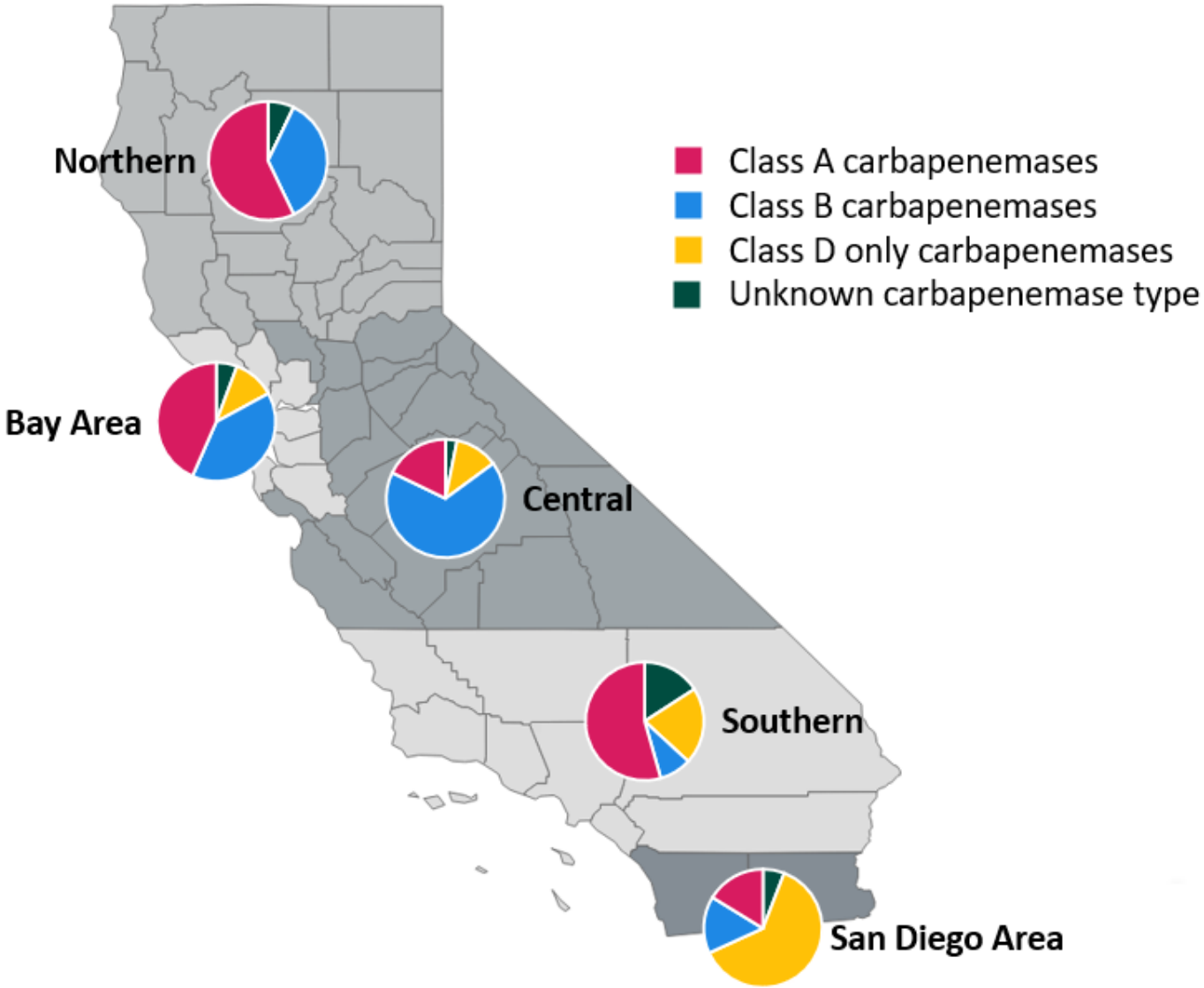
- Knowing a patient's CPO status can improve infection prevention & control
  - Implement Contact Precautions
    - Molecular tests can rapidly detect carbapenemase genetic material days before traditional AST will flag a CRO
  - Identify potential sources of horizontal transmission
    - Epi-linked patients with the same CPO type may indicate the presence of a cluster/outbreak or contaminated device or product
  - Inform patient cohorting strategies
    - Patients with matching carbapenemases can share room/bathroom
  - Promote antimicrobial stewardship (www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/AntimicrobialStewardshipLandingPage.aspx)
    - Right **D**iagnosis, **D**rug, **D**ose, **D**uration, and **D**e-escalation

CRE Treatment Guidelines – IDSA*

Carbapenemase Test	Ertapenem	Meropenem	Recommended Therapy	
			1st line	2nd line
Negative or not done	R	S	Extended infusion meropenem	Ceftazidime-avibactam
Negative or not done	R	R	Ceftazidime-avibactam Imipenem-relebactam Meropenem-vaborbactam	Cefiderocol Tigecycline Eravacycline
Class A (KPC)	-	-	Ceftazidime-avibactam Imipenem-relebactam Meropenem-vaborbactam	Cefiderocol Tigecycline Eravacycline
Class B (NDM, VIM, IMP)	-	-	Ceftazidime-avibactam + Aztreonam Cefiderocol	Tigecycline Eravacycline
Class D (OXA-48-like)	-	-	Ceftazidime-avibactam	Cefiderocol Tigecycline Eravacycline

*For infections outside the urinary tract. Adapted from IDSA Antimicrobial Resistant Treatment Guidance: Gram-Negative Bacterial Infections (PDF) (www.idsociety.org/globalassets/idsa/practice-guidelines/amr-guidance/idsa-amr-guidance.pdf) Slide courtesy of Romney M. Humphries, PhD, D(ABMM), Vanderbilt University Medical Center

Carbapenemase Prevalence by Region, 2020-2022



Carbapenemase Testing

- Two primary methods to detect carbapenemases producers (CP)
  - Phenotypic tests identify carbapenemase production* (CP+ or CP-)
  - Molecular tests detect genes that encode for carbapenemase enzymes
- Carbapenemase testing covered in detail by Dr. Romney Humphries in the 10/27/22 webinar
  - Link to slides (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPO_webinar_102722.pdf), recording (youtu.be/I6LPBB9EQ8c), and handout (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CRO_PrimerTests_for_Carbapenemases.pdf)

*Some phenotypic tests can be used to determine the specific carbapenemase type or Ambler Class

Carbapenemase Testing

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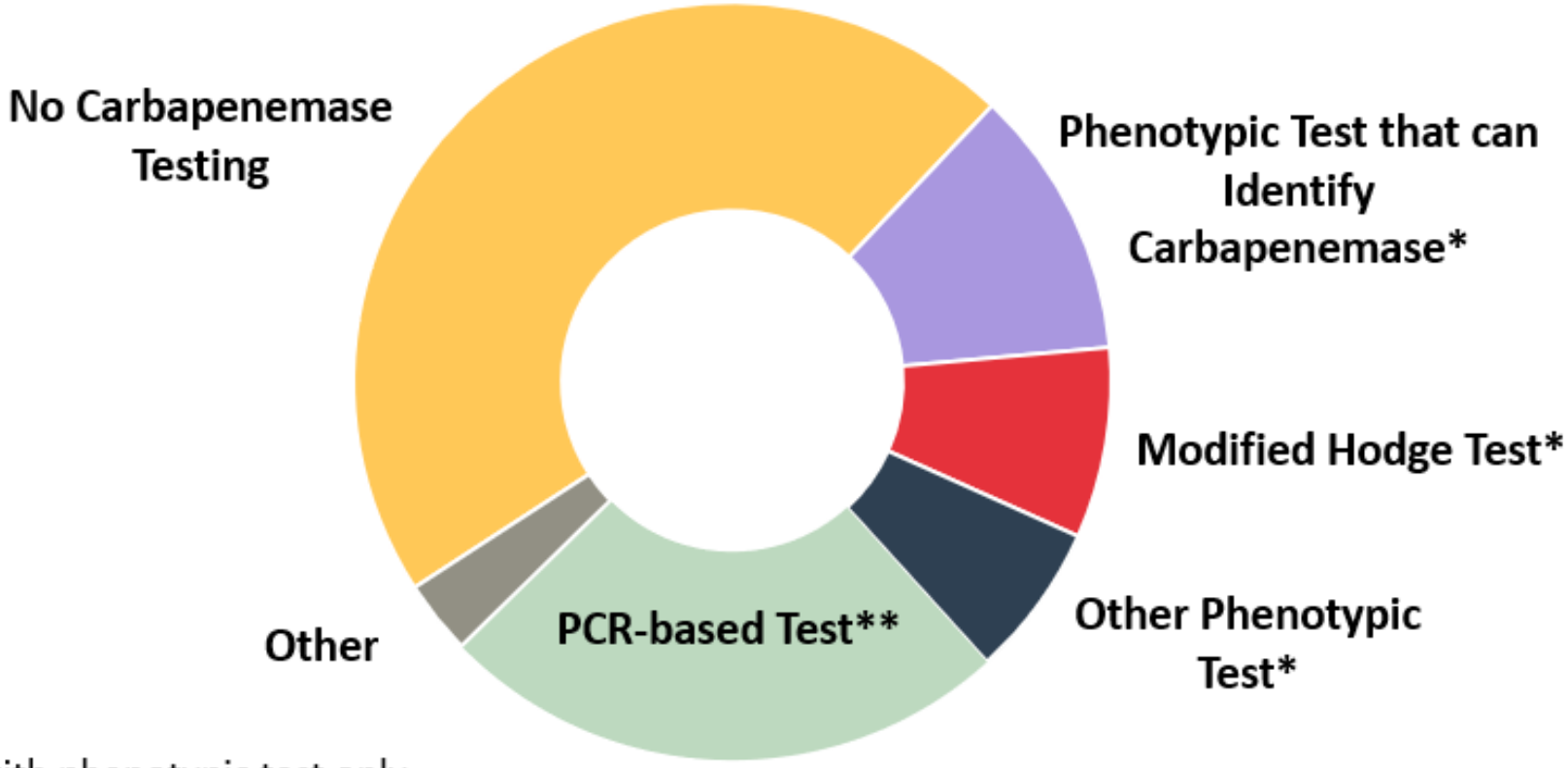
    → **Many public health labs in California perform phenotypic and molecular carbapenemase testing; contact your local health department to learn more about submission criteria**

*Some phenotypic tests can be used to determine the specific carbapenemase type or Ambler Class

Access to Carbapenemase Testing Among 380 Short Stay & Long-Term Acute Care Hospitals, NHSN 2021



*Facilities report using a lab with phenotypic test only
**Facilities report using a lab with PCR and/or a commercial molecular test

Source: NHSN Annual Survey, 2021 (PDF) (www.cdc.gov/nhsn/forms/57.103_pshospsurv_blank.pdf)

Carbapenemase Testing Recommendations

- Patient characteristics
  - Patients at high risk of acquiring a CPO, see CDPH CRE Quicksheet (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CRE_QuicksheetOct2019.pdf)
- Microbiological characteristics
  - Any CRE identified using old carbapenem breakpoints*
  - Isolates from sterile sites (e.g., blood)
  - Pan-nonsusceptible Gram-negative bacteria (I or R to all antibiotics tested)
  - *A. baumannii* resistant to >1 carbapenem
  - *P. aeruginosa* resistant to >1 carbapenem and either I or R to cefepime, ceftazidime, or ceftolozane-tazobactam

*CLSI: When Should Clinical Microbiology Laboratories Perform Carbapenemase Detection Tests? (PDF) (clsi.org/media/2046/burning-question-when-should-clinical-microbiology-laboratories-perform-carbapenemase-detection-tests.pdf)

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Carbapenemase testing: A clinical experience

Natalie Medvedeva, MD
Clinical Assistant Professor
Stanford University

Resistance Mechanisms

- Bacteria harbor diverse and often greater than one mechanism of resistance

- **Enzyme-mediated:**
  - **Beta-lactamases, including carbapenemases:** enzymes which mediate antibiotic inactivation

Many carbapenemases are mediated by genes located on **mobile genetic elements → transferrable between bacteria**

- Other mechanisms:
  - Efflux pumps
  - Porin mutations
  - Target site modification

Bacteria can harbor more than 1 mechanism!

NDM		Positive
OXA-48-LIKE		Positive

CDC Definitions

- CDC's 2015 definition for CRE changed to have higher **sensitivity** for detection
- Carbapenemase identification via molecular testing then allows for enhanced **specificity** of detection

2012 CRE Definition:
- Nonsusceptibility to imipenem, meropenem or doripenem
- AND resistance to all third-generation cephalosporins

→

2015 CRE Definition:
- Resistance to **any** carbapenem

Case #1: A 36-year-old female presents with a post-surgical wound which grows:

Susceptibility

	Enterobacter cloacae complex MIC (Preliminary)	
Amikacin	<=2 ug/mL	Susceptible *
Amoxicillin/Clavulanic Acid	>=32 ug/mL	Resistant
ASP InBasket trigger	100 ug/mL	Don't Send *
Cefoxitin	>=64 ug/mL	Resistant
Ceftazidime	16 ug/mL	Resistant
Ceftriaxone	>=64 ug/mL	Resistant
Ciprofloxacin	<=0.25 ug/mL	Susceptible 1
Ertapenem	4 ug/mL	Resistant *
Gentamicin	<=1 ug/mL	Susceptible
Levofloxacin	<=0.12 ug/mL	Susceptible
Meropenem	<=0.25 ug/mL	Susceptible *
Piperacillin/Tazobactam	32 ug/mL	Intermediate
Tetracycline	4 ug/mL	Susceptible
Tobramycin	<=1 ug/mL	Susceptible
Trimethoprim/Sulfamethoxazole.	<=20 ug/mL	Susceptible

Case #1: A 36-year-old female presents with a post-surgical wound which grows the following

Carbapenemase not detected

CRE but not CPO

Susceptibility

	Enterobacter cloacae complex MIC (Preliminary)	
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Amoxicillin/Clavulanic Acid	>=32 ug/mL	Resistant
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Tobramycin	<=1 ug/mL	Susceptible
Trimethoprim/Sulfamethoxazole.	<=20 ug/mL	Susceptible

Case #2: 54 year-old male presents with fever and hypotension. Blood cultures grow:

Susceptibility

	Escherichia coli MIC	
Amikacin	>32 mcg/mL	Resistant
Amox + clavulanate	>16 mcg/mL	Resistant
Amp/sulbactam	>16 mcg/mL	Resistant
Ampicillin	>16 mcg/mL	Resistant
Aztreonam	>16 mcg/mL	Resistant [1]
Cefazolin	>16 mcg/mL	Resistant [2]
Cefepime	>16 mcg/mL	Resistant [3]
Cefotax/clavulanate	>4 mcg/mL *	
Cefotaxime	>32 mcg/mL	Resistant *
Cefoxitin	>16 mcg/mL	Resistant [4]
Ceftazidime	>16 mcg/mL	Resistant [1]
Ceftriaxone	>32 mcg/mL	Resistant [5]
Cefuroxime	>16 mcg/mL	Resistant [6]
Ciprofloxacin	>2 mcg/mL	Resistant [7]
Ertapenem	>1 mcg/mL	Resistant [5]
Gentamicin	>8 mcg/mL	Resistant
Imipenem	>8 mcg/mL	Resistant [1]
Levofloxacin	2 mcg/mL	Resistant [7]
Meropenem	>8 mcg/mL	Resistant [1]

- Patient is started on **ceftazidime-avibactam**
- Molecular testing results **positive for presence of NDM**
- How do you change management?

Not all **carbapenemases** are the same!
Different spectrum of activity

Similarly, new **beta-lactam/beta-lactamase inhibitors** have their own spectrum of activity

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Treatment of metallocarbapenemases

- Metallocarbapenemases retain susceptibility to **aztreonam**
- But, bacteria can harbor other beta-lactamases which inactive aztreonam (ex. ESBL)
- Avibactam retains activity against these other enzymes

Susceptibility

	Escherichia coli MIC	
Amikacin	>32 mcg/mL	Resistant
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Cefotaxime	>32 mcg/mL	Resistant *
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Ceftazidime	>16 mcg/mL	Resistant [1]

Ceftazidime/avibactam + aztreonam is then one option for treatment

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Cefiderocol

- Siderophore cephalosporin
  - Part of the antibiotic binds iron which enhances uptake into bacterial cell
  - Overcomes resistance mechanisms involving porin mutations and efflux pumps
  - Stable against all classes of carbapenemases, including metallocarbapenemases

- Additional activity against *Acinetobacter* and *Stenotrophomonas maltophilia*

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Type of carbapenemase impacts therapy

Serine carbapenemases

- KPC
  - Ceftazidime-avibactam
  - Meropenem-vaborbactam
  - Imipenem-relebactam
- OXA-48-like:
  - Ceftazidime-avibactam
  - Cefiderocol

Metallocarbapenemases

- NDM
  - Ceftazidime-avibactam + aztreonam
  - Cefiderocol

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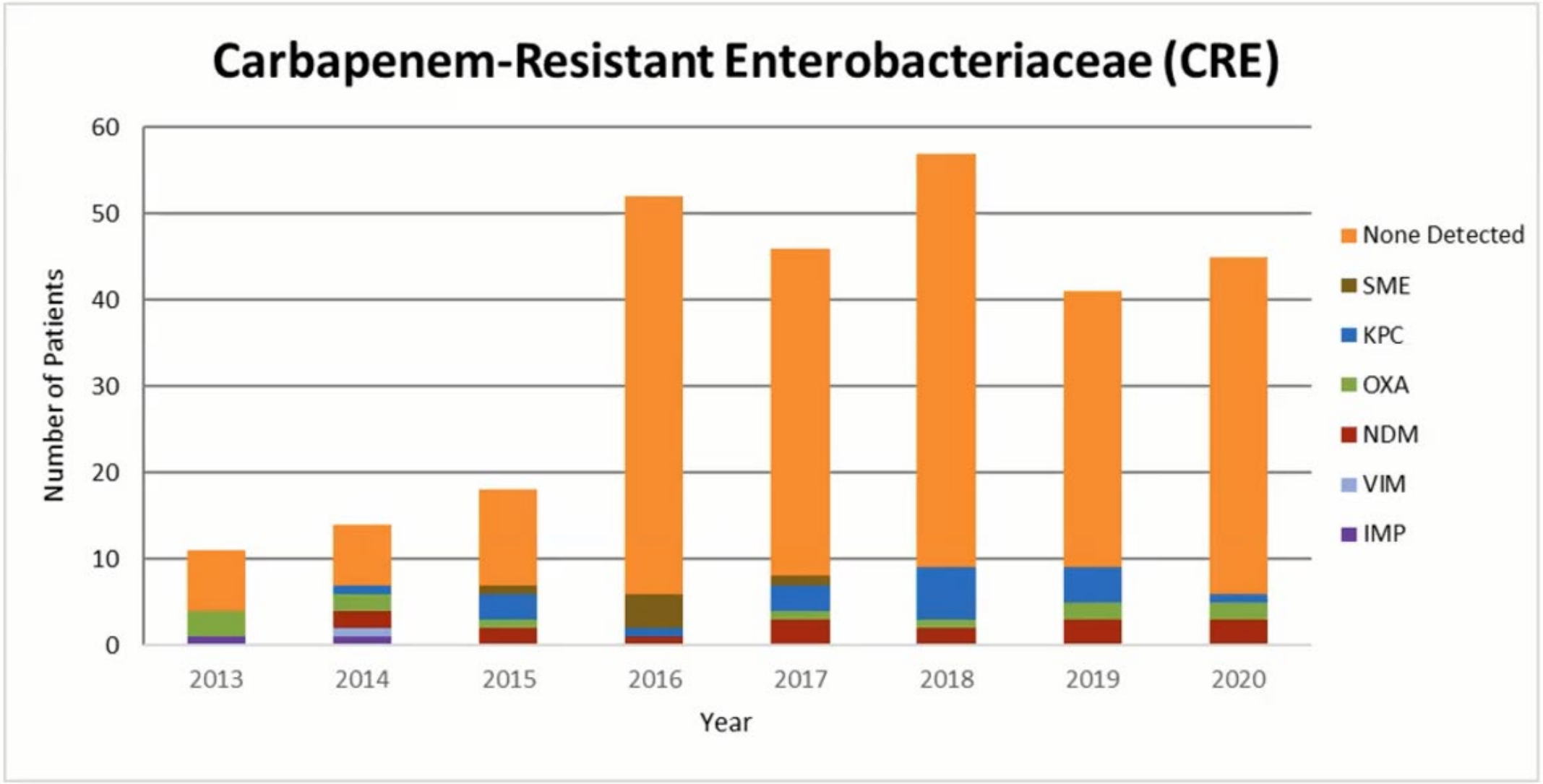
Stanford Experience



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Case #3

- A 65-year-old has been in the ICU and intubated for 14 days
- He is afebrile, but noted to have increased respiratory secretions. Chest x-ray is normal and unchanged.
- Respiratory culture is sent growing *Klebsiella pneumoniae*, resistant to Meropenem. Gene testing is positive for **KPC**.

- Primary team is asking for treatment options. What are your recommendations?

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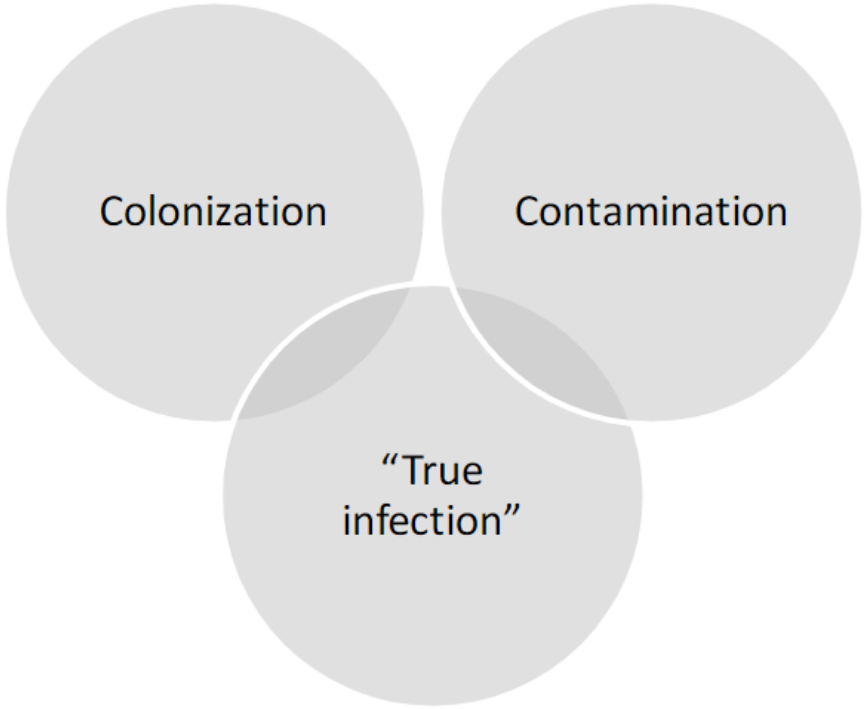
Antimicrobial stewardship: Verify the indication for antibiotics

Even in the setting of MDROs, microbiology results can represent….

Commensal bacteria colonize body sites without causing actual infection



Exogenous microorganisms unintentionally introduced into a clinical specimen

Contact infection prevention, but no antibiotic therapy is needed
Reserve antimicrobials for when they are truly needed!

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Jeffrey Silvers MD

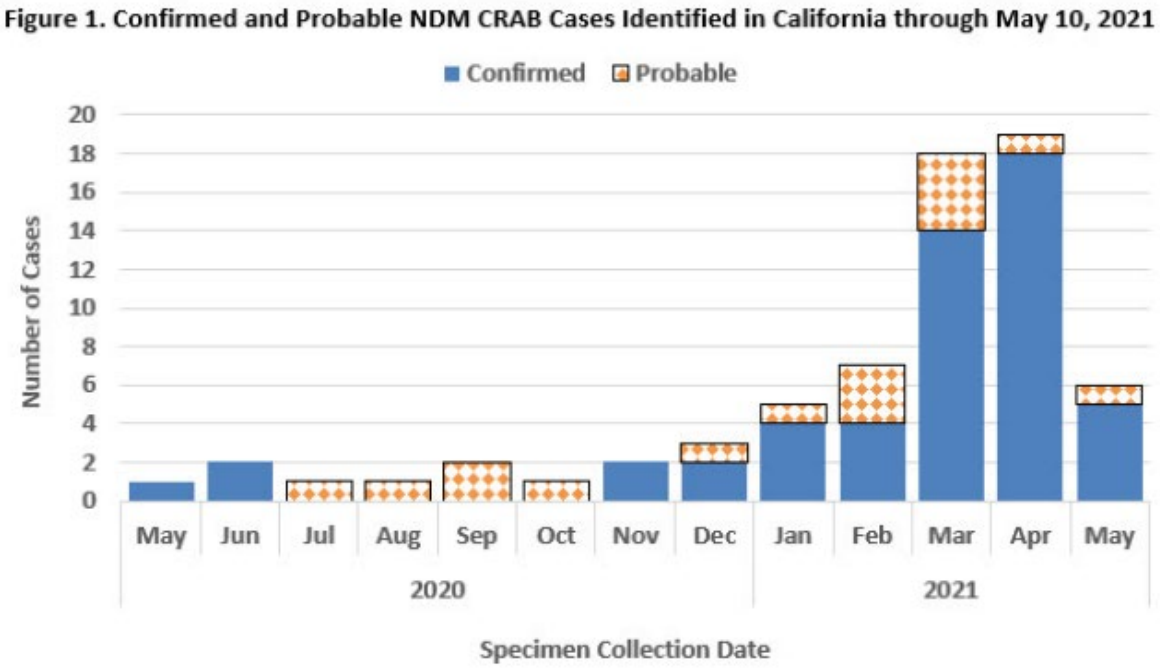
Medical Director of Pharmacy & Infection Control, Sutter Health

Sutter Health

CARBAPENEMASE TESTING FOR INFECTION CONTROL

Sutter Health

[Acinetobacter baumannii CAHAN May 2021](www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CAHAN.aspx)
(www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CAHAN.aspx)



- Regional Outbreak in Northern California involving acute care hospitals, SNF, and LTACH
- 79% OXA-23
- 85% NDM

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CP-CRAB Outbreak Stanislaus County

Most patients were from Stanislaus County

Involved contiguous and non-contiguous counties

Large Sutter Health hospital initially seeing majority of identified patients

Worked with CDPH and LHD on identification and interfacility transfers

Involvement of quality, infection prevention, infectious diseases, risk and pharmacy

Worked with Sutter Health laboratory to establish process for CP testing

CP-CRAB Outbreak Stanislaus County

System-wide screening process established

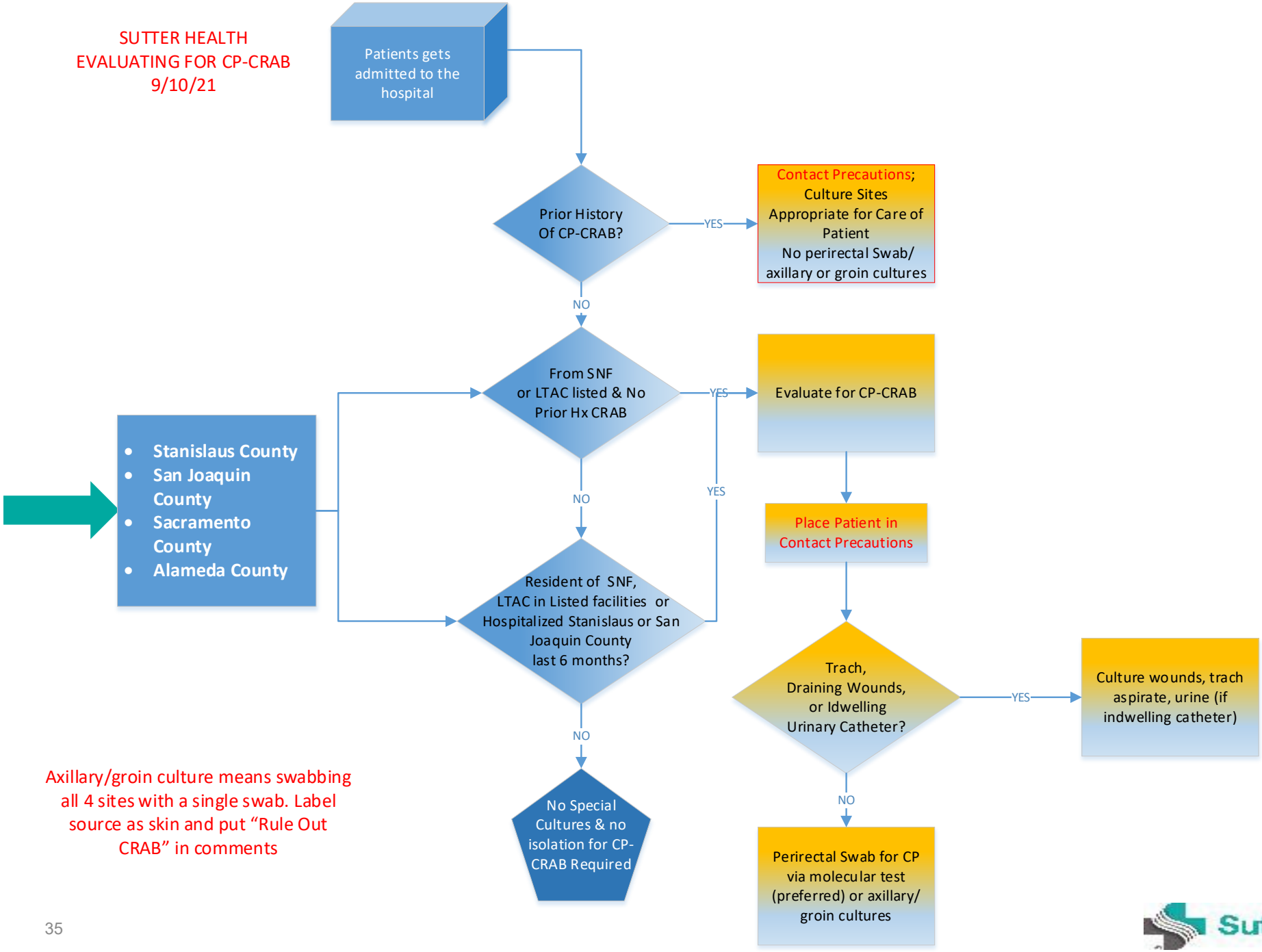
- Identify
- Isolate
- Inform

Patients transferred to counties more than 100 miles away

Many locations were in areas serviced by Sutter Health

Facilities worked with LHD in receiving counties

SUTTER HEALTH
EVALUATING FOR CP-CRAB
9/10/21



Axillary/groin culture means swabbing all 4 sites with a single swab. Label source as skin and put "Rule Out CRAB" in comments

Sutter Health

CP-CRAB Outbreak Stanislaus County

Coordination between CDPH, LHD, and Sutter Health led to control of outbreak.

Major Thank You to everyone that helped.

Sutter Health

LOCAL EPIDEMIOLOGY

Know your patient population

- SNF
- LTACH
- Sub-Acute

Any known outbreaks

- Past or Present
- Involvement of health department for mitigation
- Ongoing facility screening

Organisms

- Ambler Class
- Non-CP CRO
- Known Resistance Patterns

Examples of Empiric Therapy

CP Enterobacterales	• Ceftazidime/avibactam • If commonly used in community, consider Imipenem/relebactam or cefiderocol • Add aztreonam if NDM likely

CP-CRAB	• High dose ampicillin/sulbactam plus
	  • Minocycline or tigecycline
	• Cefiderocol plus
	  • high-dose ampicillin/sulbactam, minocycline or tigecycline

Non-CPPA	• Ceftolozane/tazobactam

Prior CPO Does Not Always Mean Cover for a CPO

CPO STEWARDSHIP

Do You Always Need to Cover for a Prior CPO?

If a patient no longer has evidence of a CPO, empiric antibiotics might not need to include coverage for the prior CPO

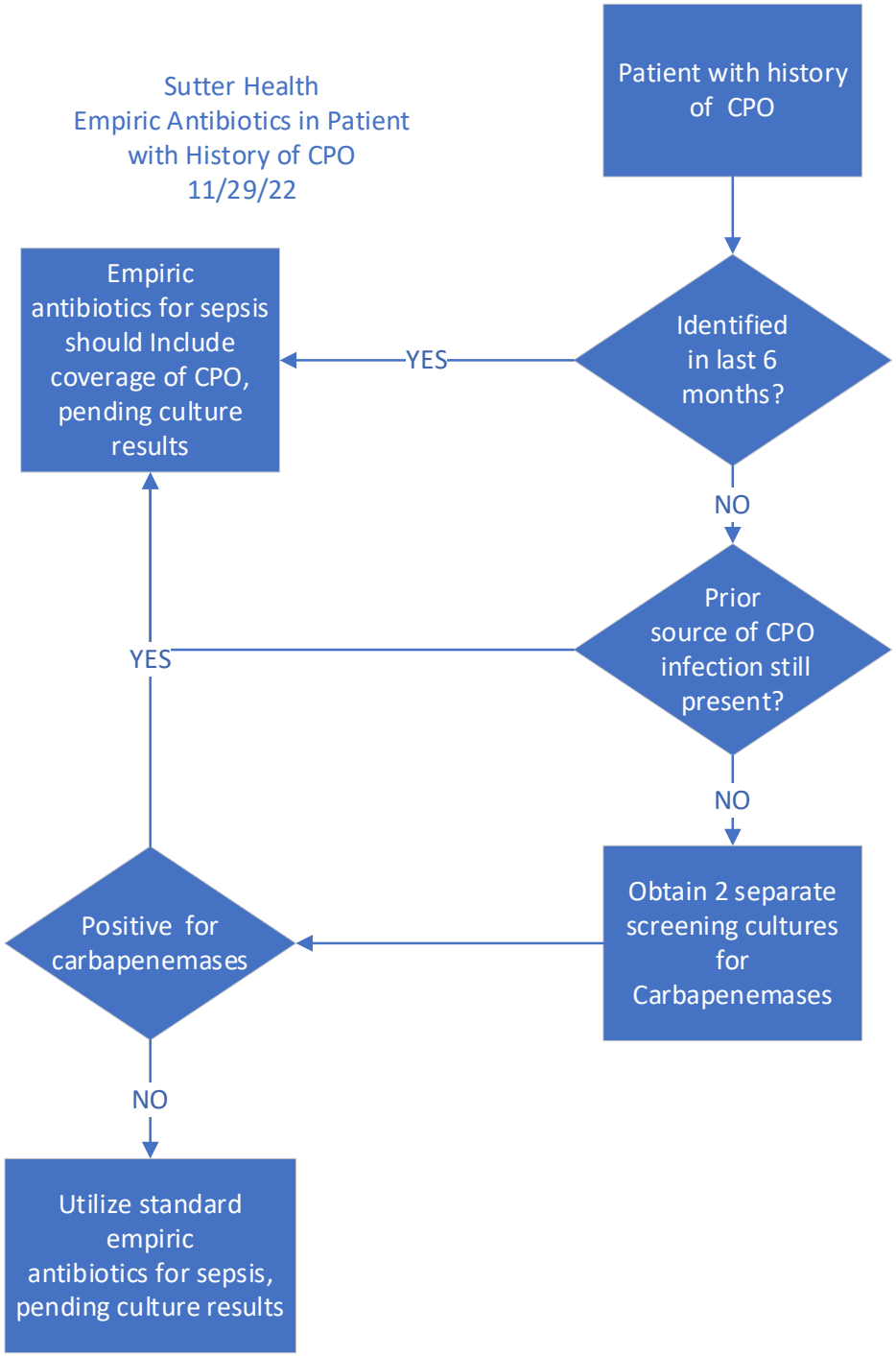
No Specific Written Guidance

Prior CPO identified in prior 6 months

- Treat as CPO still present

More than 6 months use we have an algorithm being developed

Sutter Health
Empiric Antibiotics in Patient with History of CPO
11/29/22



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Value of Carbapenemase Testing in Empiric Antimicrobial Selection

James A. McKinnell, M. D.
Associate Professor of Medicine
Harbor-UCLA Medical Center
David Geffen School of Medicine, UCLA

Infectious Disease Specialist
Milefchik-Rand Medical Group
Torrance Memorial Medical Center

Disclosures

- I have served as a consultant for Thermo Fisher
- I am on the Speaker's Bureau for Abbvie
- I am the president of Expert Stewardship
- The opinions presented here today are my own and do not reflect those of the California Department of Public Health, the Infectious Disease Association of California, or the Orange County Healthcare Association.

Objectives

- Discuss challenging cases from a clinical and laboratory perspective

- Understand how accurate antimicrobial testing and carbapenemase resistance mechanism testing can improve patient outcomes and identify potential cost-saving alternative therapeutic options

Case Presentation

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

Lucy

65 year old female

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

- **2 Months:** Admitted OSH for pneumonia transferred to LTAC, prior antimicrobial therapy unknown
- **2 Weeks:** Transferred to SNF
- **2 Days:** Cough and Sputum
- **2 Hours:** Fever and SOB. Immediately intubated

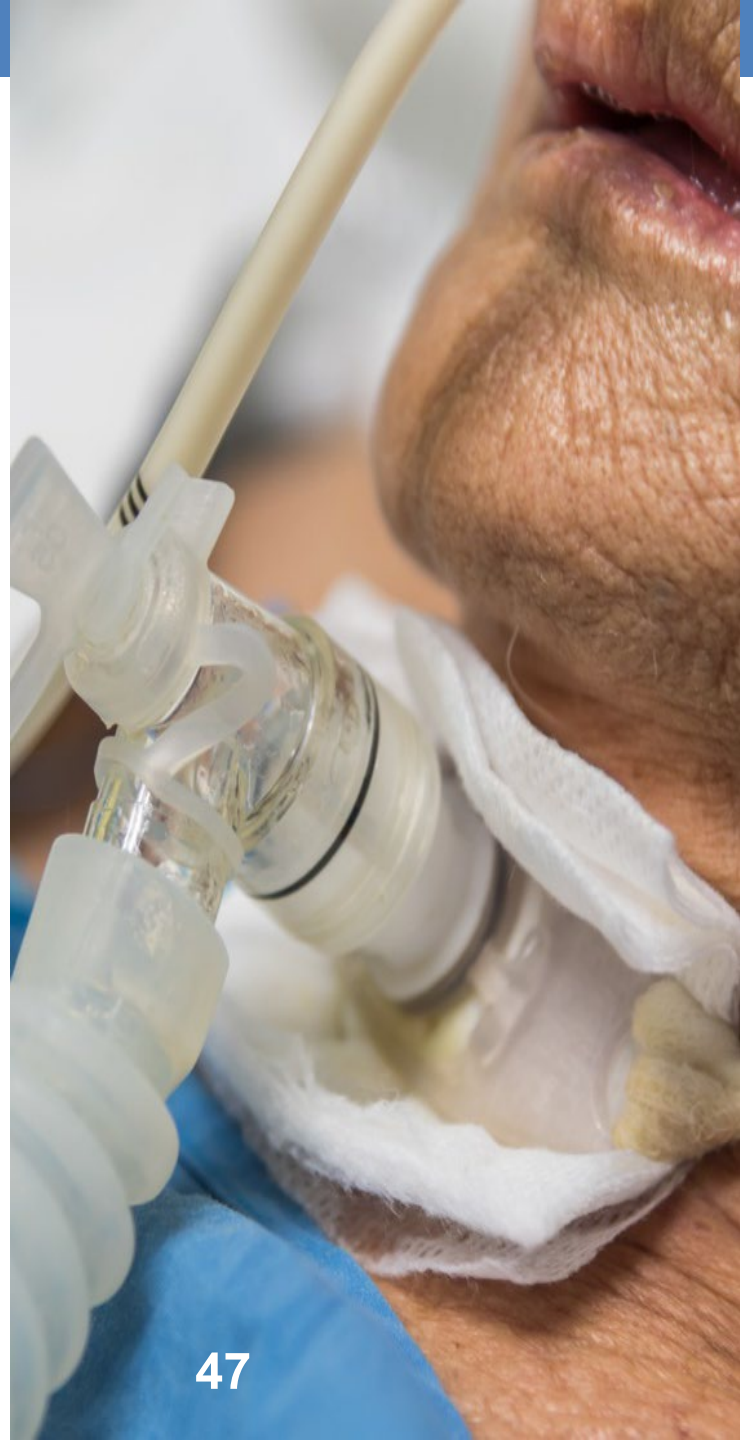
Lucy: Admission Exam

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

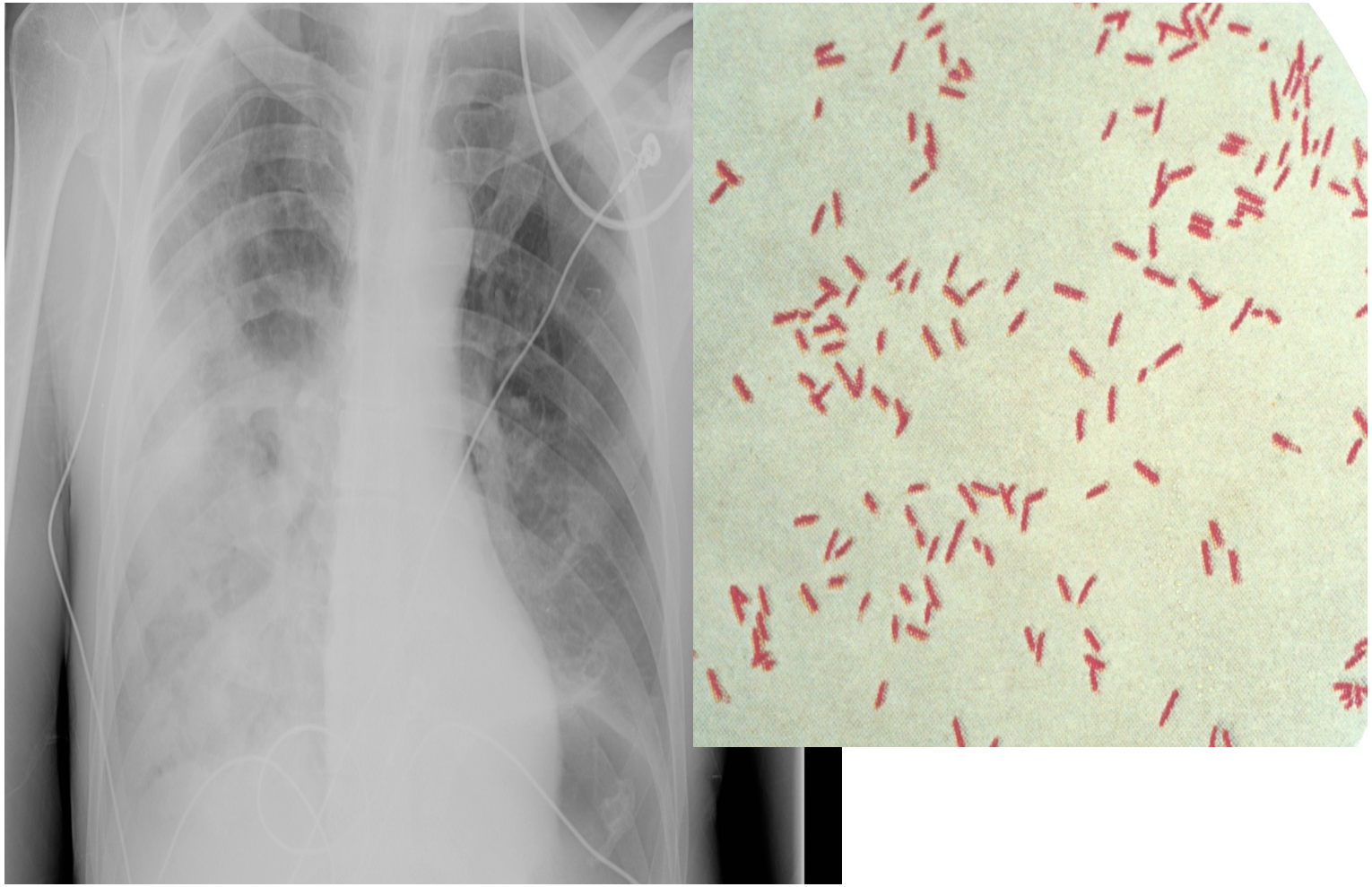
- Intubated, Sedated
- Frail with slight temporal wasting
- JVD was Flat
- Tachycardic, No MRG
- RLL Rhonchi
- Decreased muscle mass
- No Skin Rash

- **PEEP of 8 cm H2O and 80% FiO2**
- **Currently on norepinephrine at 6 mcg/min**

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



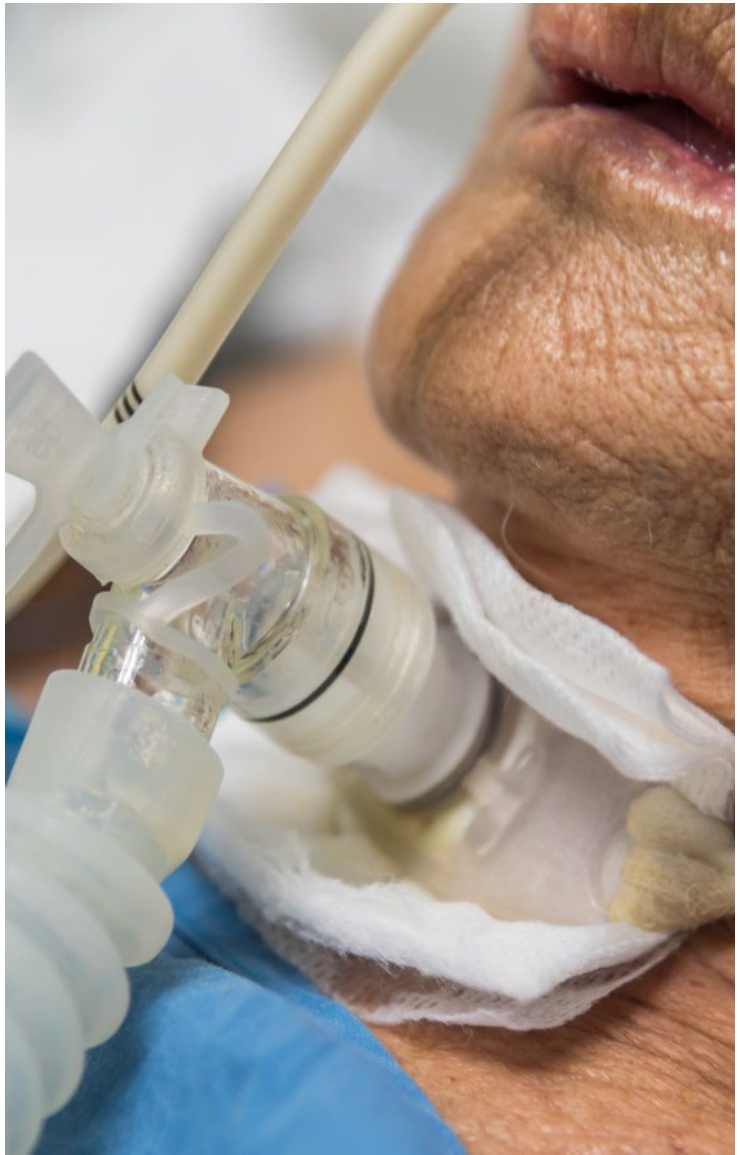
RLL Pneumonia Gram-Negative Rods



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

Lucy Assessment and Plan

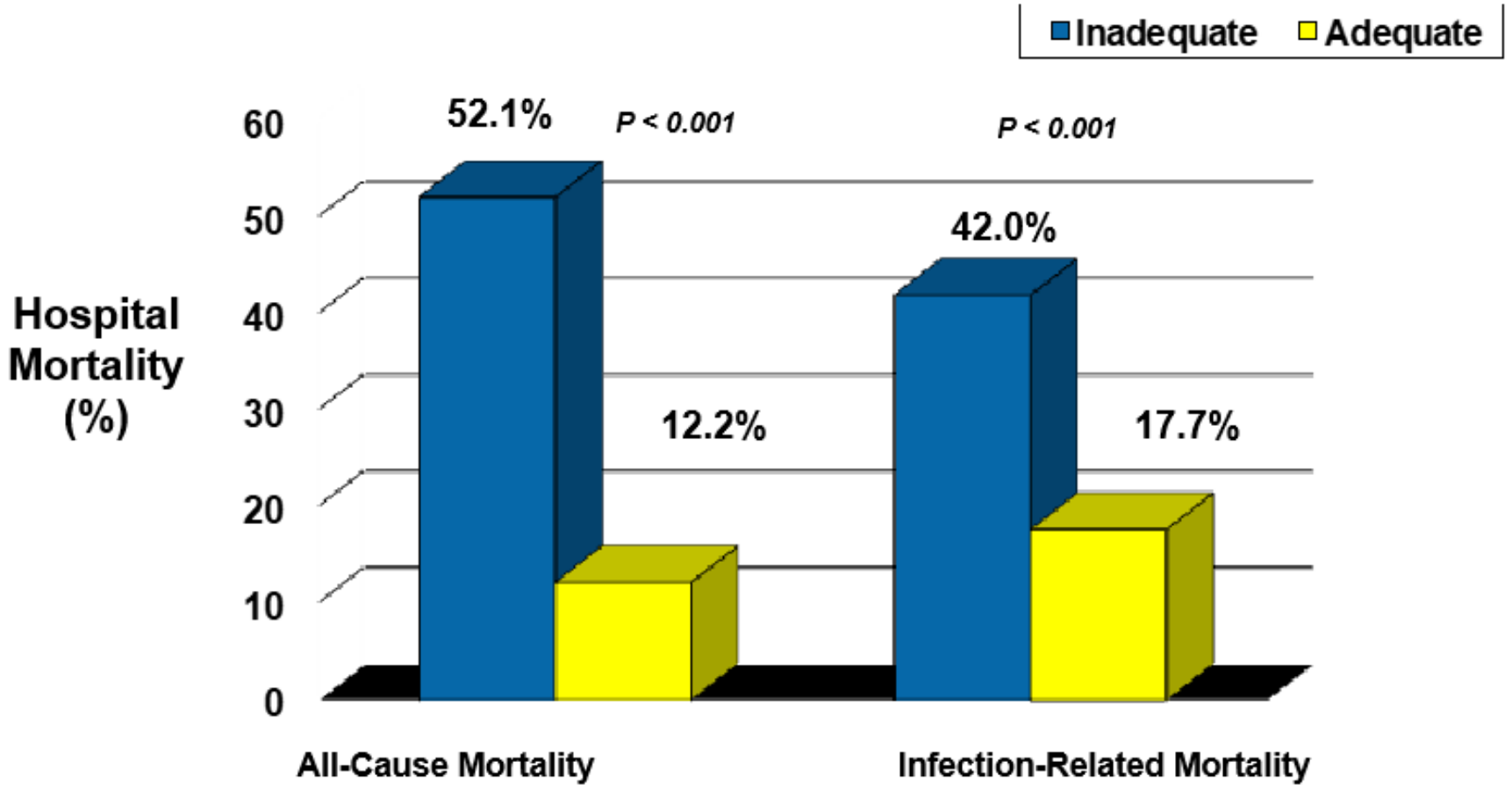
- **What is this clinical syndrome?**



Lucy Assessment and Plan

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

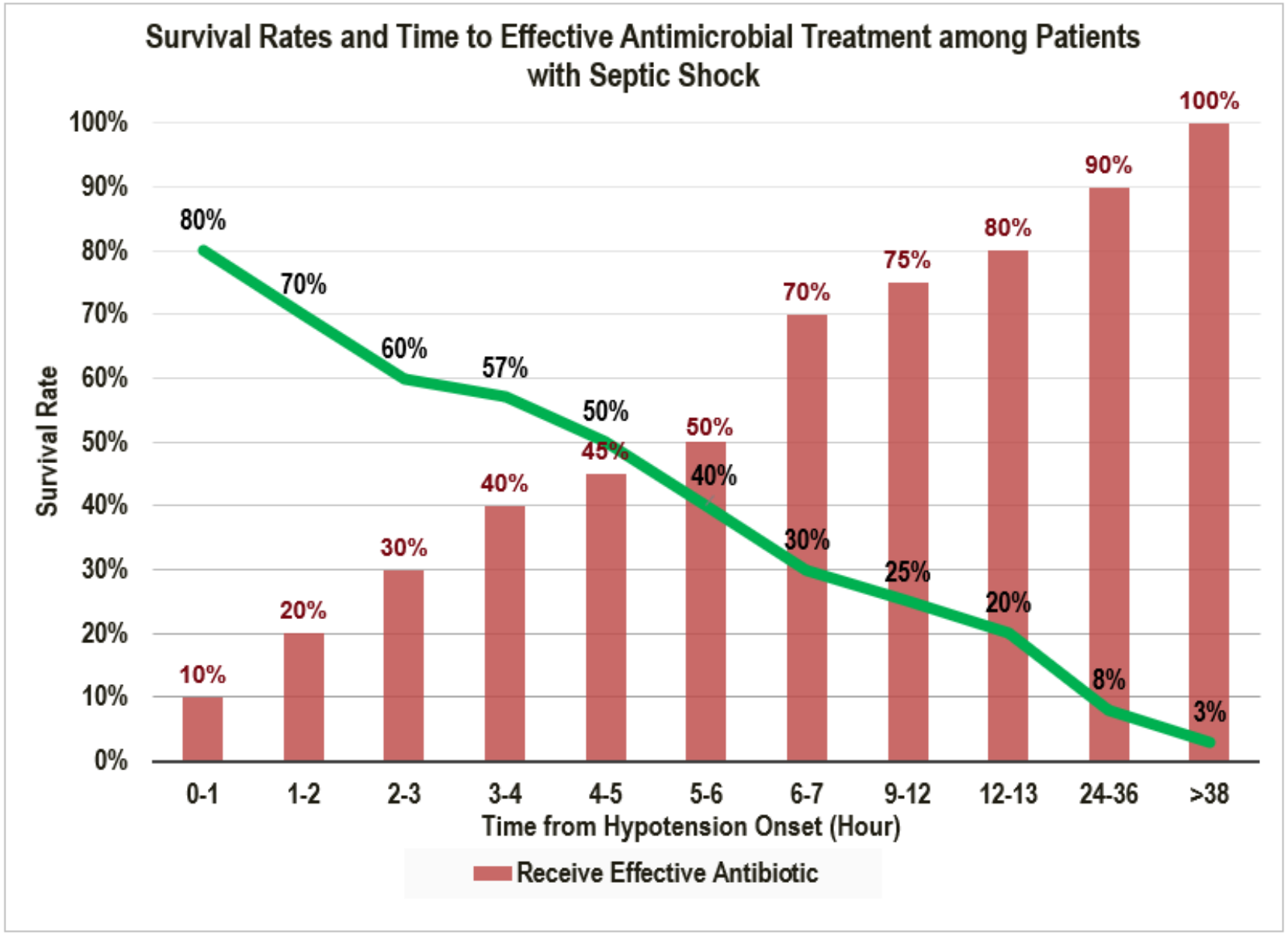
Inadequate antimicrobial therapy associated with higher mortality



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.

Beta-Lactams and Escalation of Therapy

Novel BLIs	Ceftazidime/Avibacatam, Ceftolozane/Tazobactam Meropenem/Vaborbactam, Imipenem/Relebactam	**Novel Cephalosporin** Cefiderocol
Carbapenems	Meropenem, Imipenem, Ertapenem	
Traditional Pseudomonal Agents	Piperacillin/Tazobactam, Cefepime, Ceftazidime	
Community Agents	Ceftriaxone, Ampicillin/Sulbactam	

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

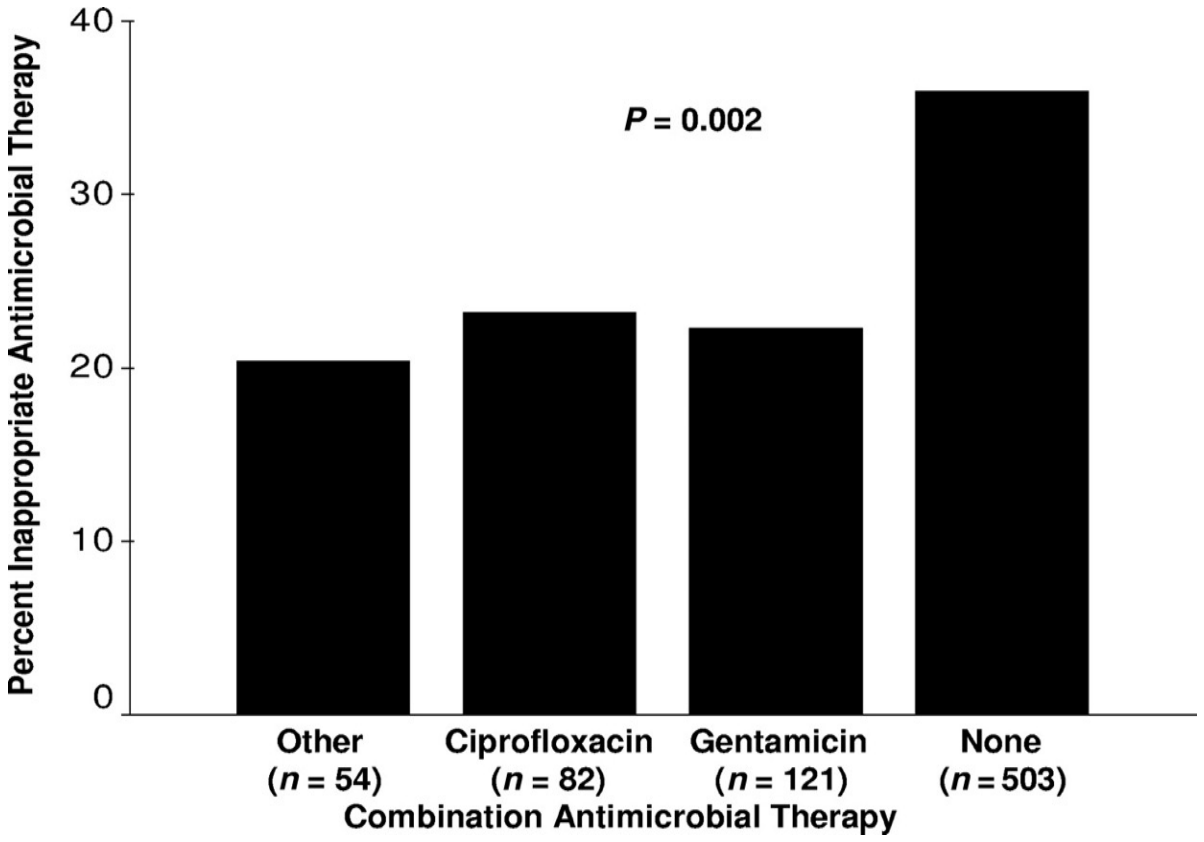
Organism	No. Isolates	Penicillins			Cephalosporins				Carbapenems			Aminoglycosides			Fluoro-quinolone	Other	
		Ampicillin[6]	Ampicillin-Sulbactam[6]	Piperacillin-tazobactam	Cefazolin	Cefepime	Ceftazidime	Ceftriaxone[1]	Ertapenem	Imipenem	Meropenem	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Trimethoprim–sulfamethoxazole	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

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

Adjunctive Agents

AG	Plazomicin, Amikacin, Tobramycin, Gentamicin
FQ	Ciprofloxacin, Levofloxacin, Moxifloxacin
Colistin	Colistin/Polymixin
Tetracycline	Tigecycline, Eravacycline

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

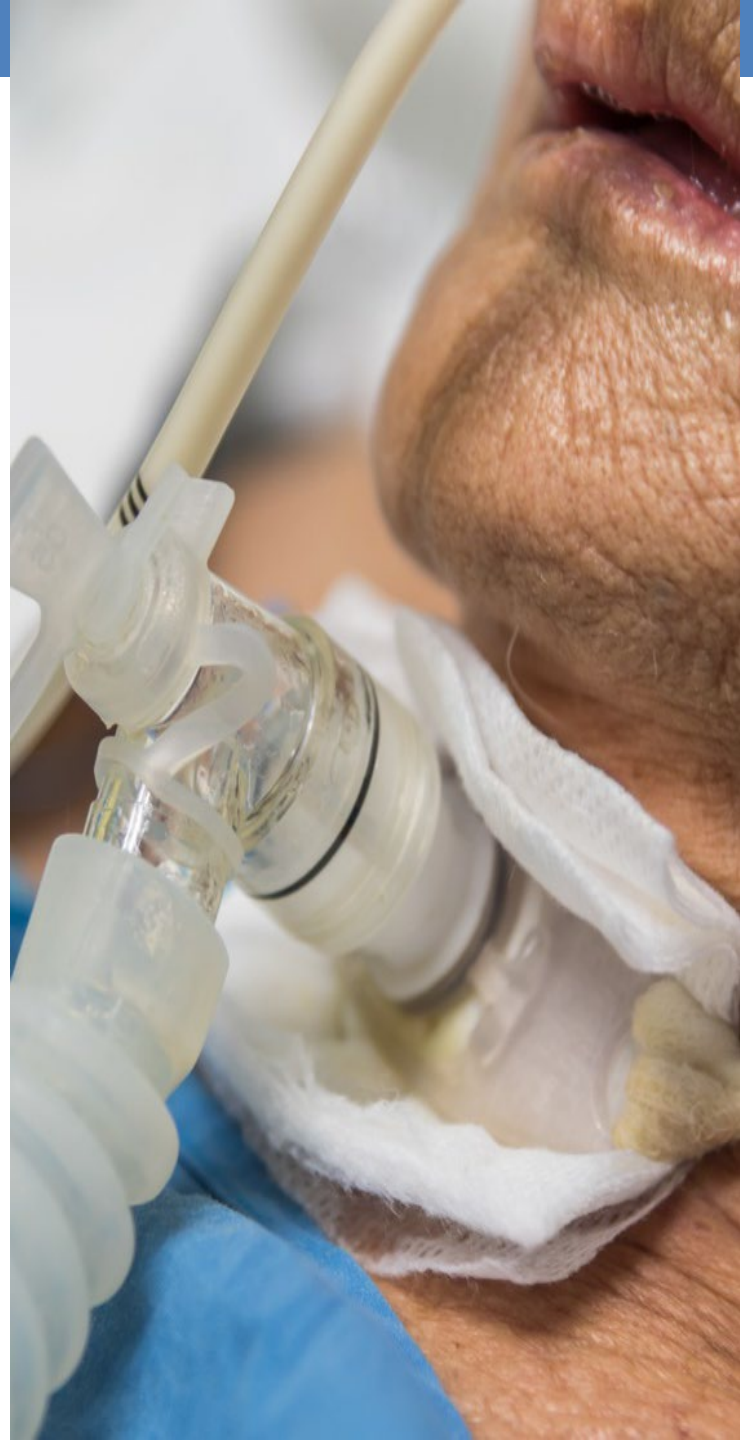
1. Percent susceptible for individual drug in parenthesis
2. Percent susceptible for either or both drugs (eg, %S to amikacin and/or cefepime

Adapted from antibiogram data source: UCLA Health Infectious Disease

GNR: Meropenem/Tobramycin

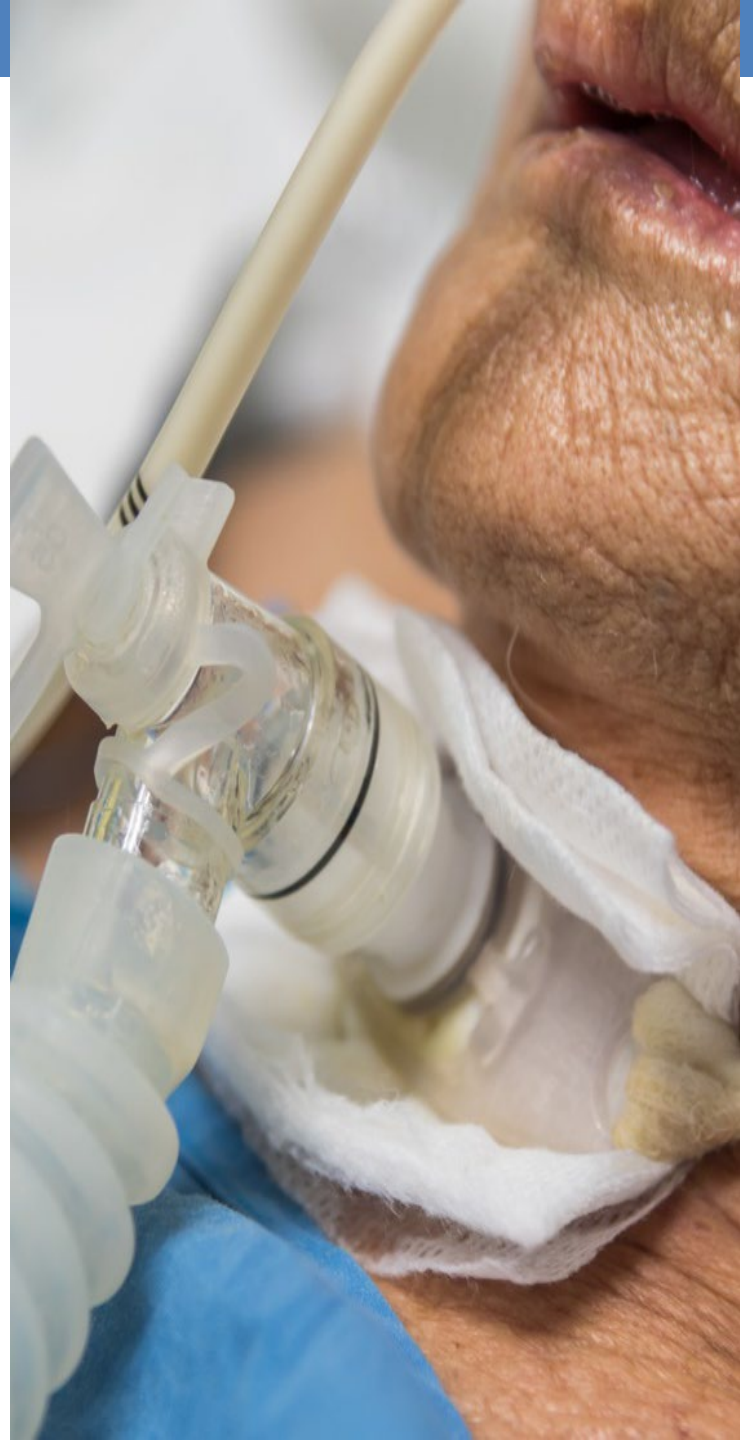
Assessment and Plan

- 65 yo with sepsis, RLL pneumonia, respiratory failure, but retained organ function.
- Meropenem 1 q8 Hours (over 3H)
- Tobramycin 350mg IV q24



ID Consult

- Lucy is still on ventilator, oxygenation is stable
- Ongoing sputum production
- Pressor Requirements are Stable



Activity of Older Agents Against CRE from US LTAC Hospitals (January 2014 to March 2015)

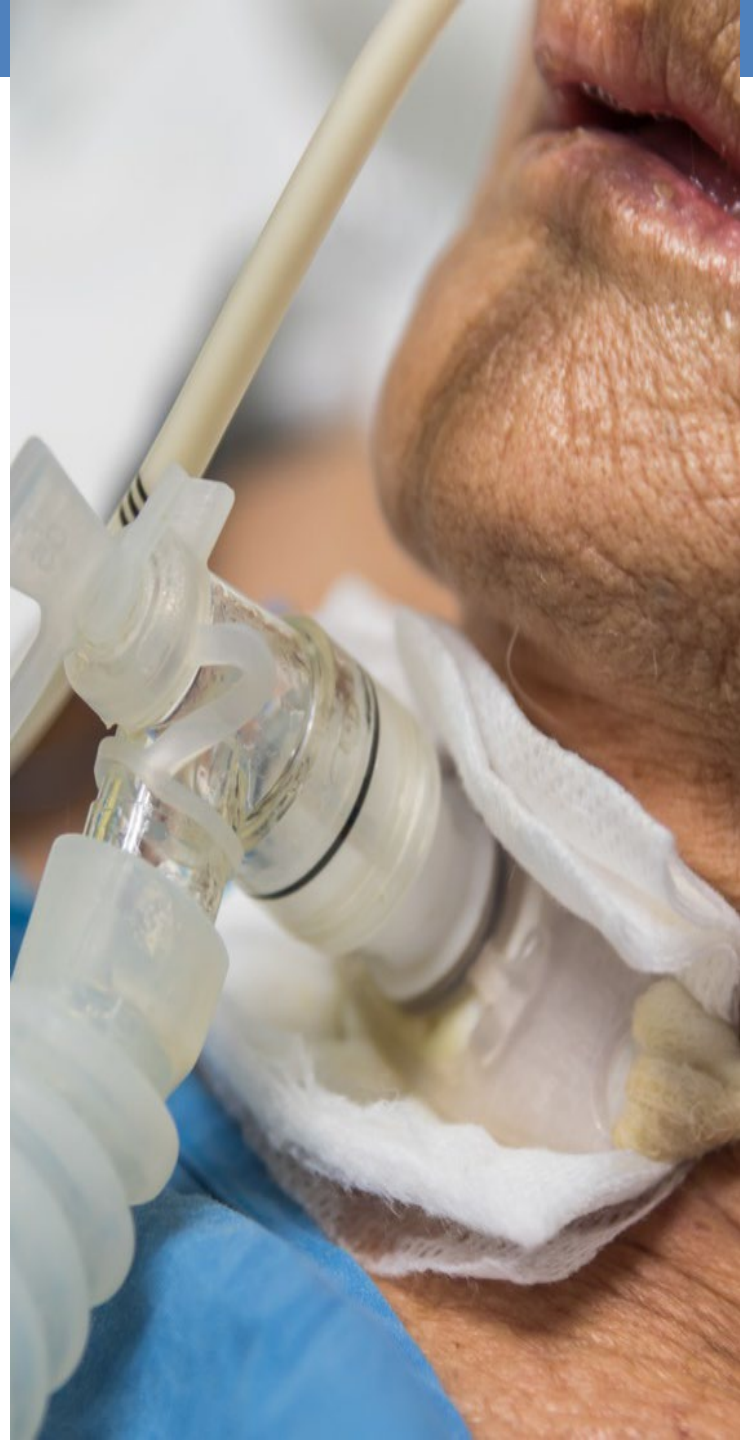
Antibiotic	*Klebsiella pneumoniae* isolates tested (N)	Non-susceptible	
		n	%
Ciprofloxacin	630	620	98%
Levofloxacin	713	701	98%
Gentamicin or tobramycin	630	619	98%
Amikacin	885	587	66%
Colistin or polymyxin B	690	111	16%
Tigecycline	439	26	6%

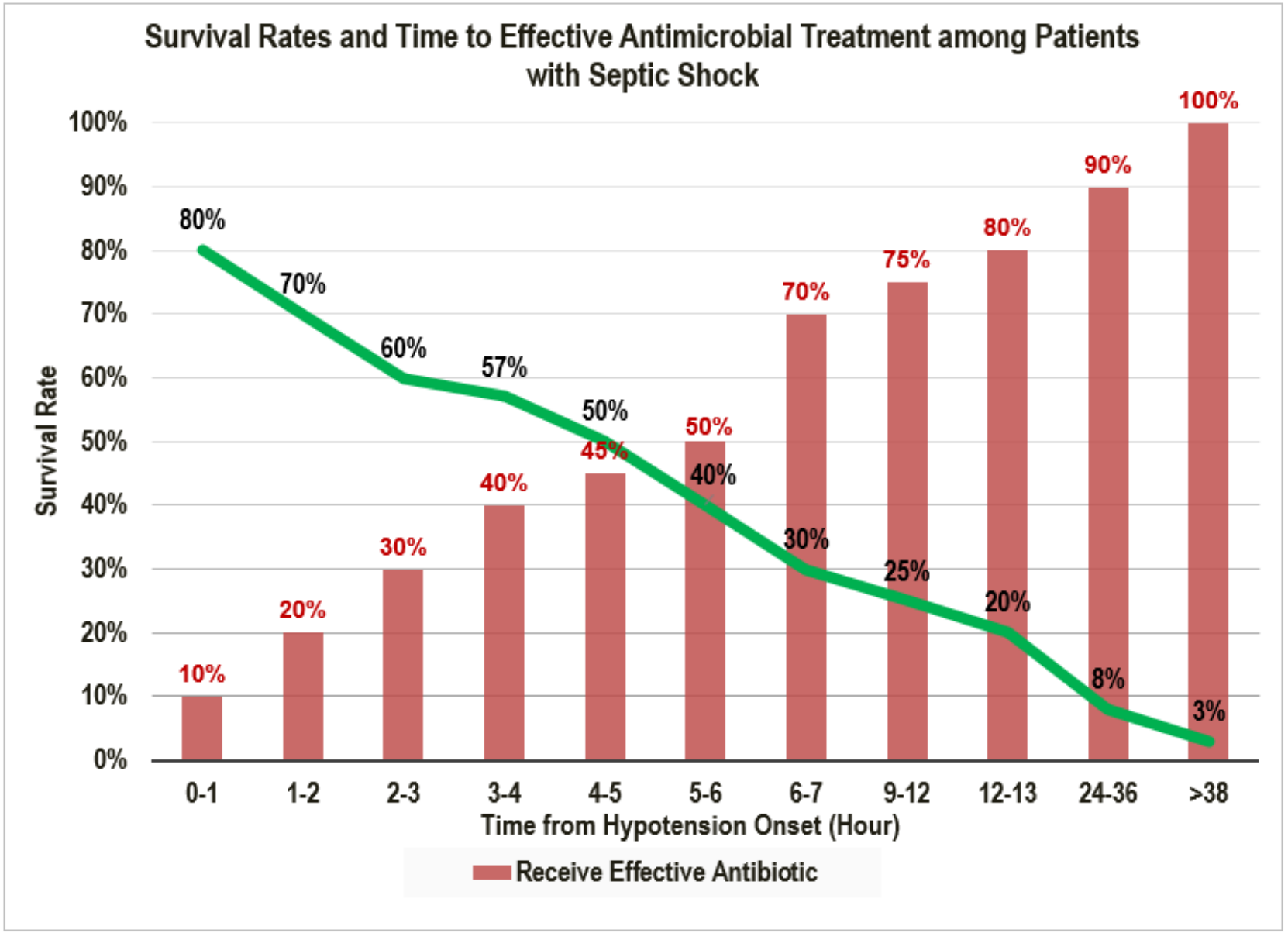
Han, J et al. CID, 2017.

GNR: Meropenem/~~Tobramycin~~

ID Consult

- Lucy is still on ventilator, oxygenation is stable
- Ongoing sputum production
- Pressor Requirements are Stable
- **Now What?**





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

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Amikacin	885	587	66%
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Tigecycline	439	26	6%

Tigecycline has a black box warning from FDA for increased mortality in severe infections!!

Han, J et al. CID, 2017.

Clinical Infectious Diseases

MAJOR ARTICLE

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

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[6] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2]; for the Antibacterial Resistance Leadership Group

- Ceftazidime-Avibactam 9% Mortality
- Colistin 32% Mortality
- “Uniform Superiority of Ceftazidime-Avibactam”
- **LIMITATION: Small <140 patients Observational Study**

Evidence to improve the treatment of infections caused by carbapenem-resistant Gram-negative bacteria

- "The high patient mortality rate (44% at 28 days)… is sobering – considering that infection with bacteria susceptible to colistin was a criterion for inclusion and that colistin dosing was carefully controlled – but is not surprising."
- "…low Charlson and SOFA scores…"
- "…colistin, either as monotherapy or combined with a carbapenem, is not that effective."

Perez F, Bonomo RA. *Lancet Infect Dis.* 2018 Apr;18(4):358-360. doi: 10.1016/S1473-3099(18)30112-9. Epub 2018 Feb 16.

Beta-Lactams and Escalation of Therapy

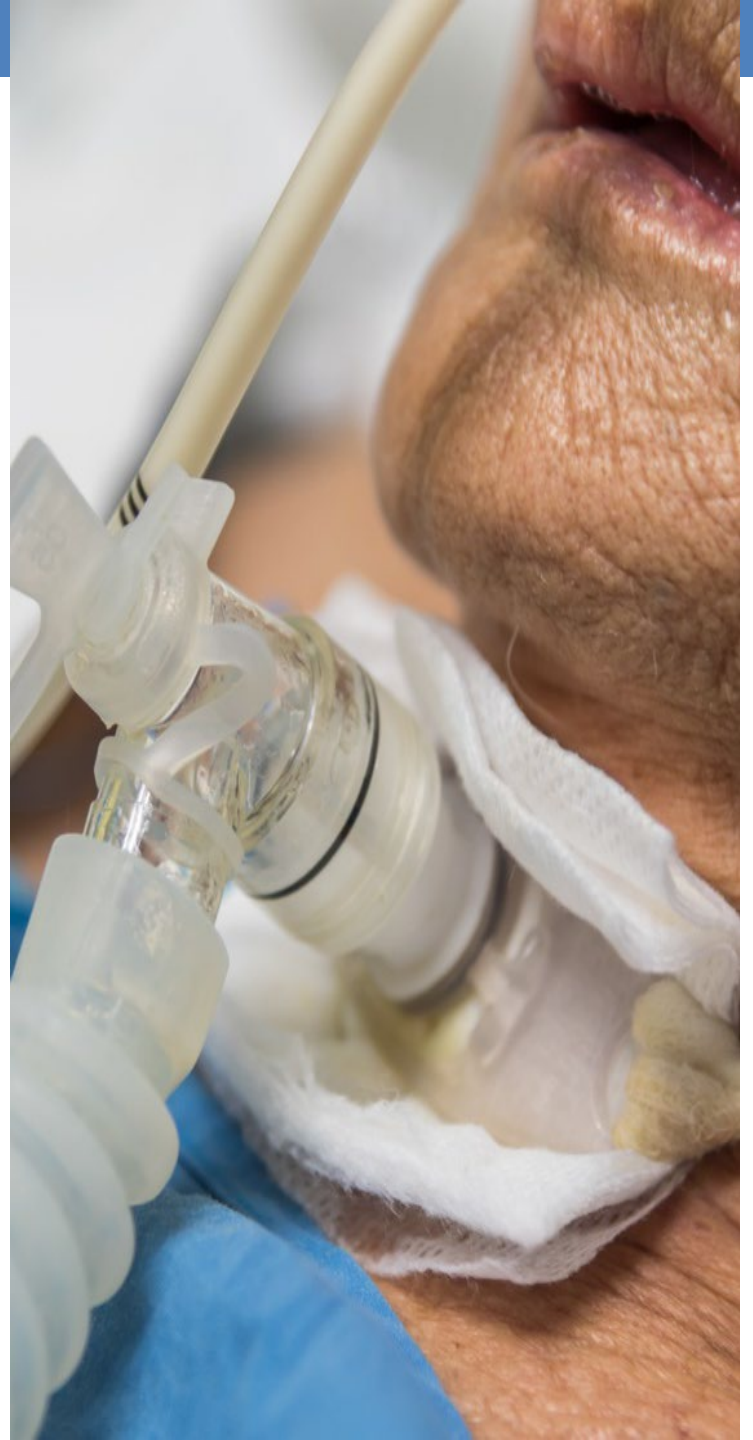
Novel BLIs	Ceftazidime/Avibacatam, Ceftolozane/Tazobactam Meropenem/Vaborbactam, Imipenem/Relebactam	**Novel Cephalosporin** Cefiderocol
Carbapenems	~~Meropenem, Imipenem, Ertapenem~~	
Traditional Pseudomonal Agents	~~Piperacillin/Tazobactam, Cefepime, Ceftazidime~~	
Community Agents	~~Ceftriaxone, Ampicillin/Sulbactam~~	

Adjunctive Agents

AG	Plazomicin, ~~Amikacin, Tobramycin, Gentamicin~~
FQ	~~Ciprofloxacin, Levofloxacin, Moxifloxacin~~
Colistin	~~Colistin/Polymixin~~
Tetracycline	~~Tigecycline,~~ Eravacycline

ID Consult

- Lucy is still on Ventilator, Oxygenation is Stable
- Pressor Requirements are Stable
- **Now What?**
- **Recommendation for Novel BLI or Novel Cephalosporin**
- **$1,000/day!!!**



Two Forms of Carbapenem-Resistant Enterobacteriaceae

Carbapenemase producing (CP-CRE)

Sub-type
KPC
NDM, IMP, VIM
OXA 23, 48

Non-carbapenemase producing (Non-CP-CRE)

Additional mechanism
Porin mutation
Efflux pump
+
Sub-type
AMP-C, ESBL

KPC=*K. pneumoniae* carbapenemase, NDM=New Delhi metallo-betalactamase, IMP=Imipenemase, VIM=Verona integraon-encoded metallo-betalactamase, OXA=oxacilinase

Novel BL/BLI Not Always the Answer

CP-CRE	Sub-type	Novel BL/BLI
Carbapenemase	KPC	YES
Metallo-carbapenemase	NDM, IMP, VIM	NO
Carbapenemase	OXA 23, 48	Variable
Non CP-CRE		
Beta-lactamase + additional mechanisms	AMP-C + ESBL Porin mutation Efflux pump	Variable

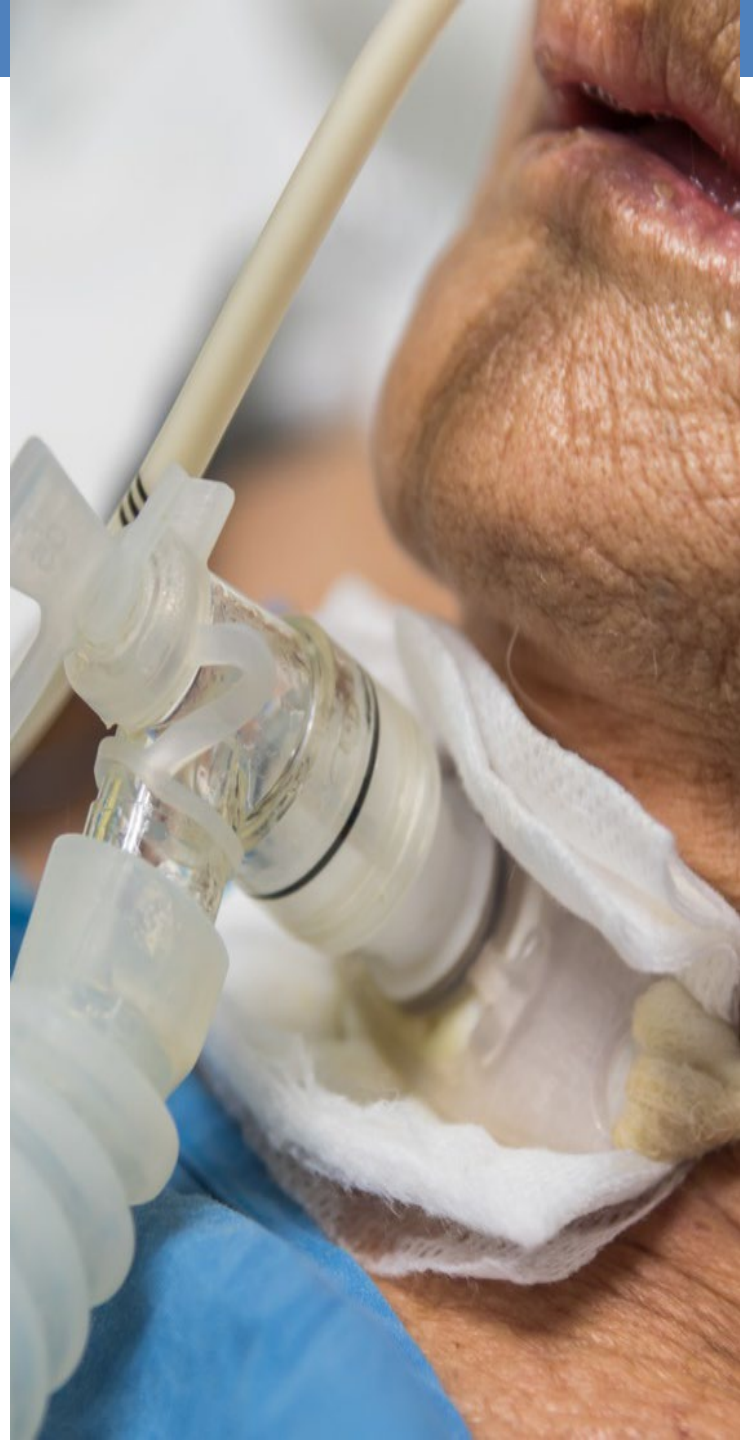
ID Consult

- Lucy is Still on Ventilator, Oxygenation is Stable
- Pressor Requirements are Stable
- **Now What?**

- Cepheid Gene Xpert Carba-R: KPC, NDM, VIM, OXA-48, and IMP not detected

- **Recommendation to Continue Meropenem/Tobramycin**

Note: Cepheid Gene Xpert is what my hospital uses, this is not a specific product endorsement



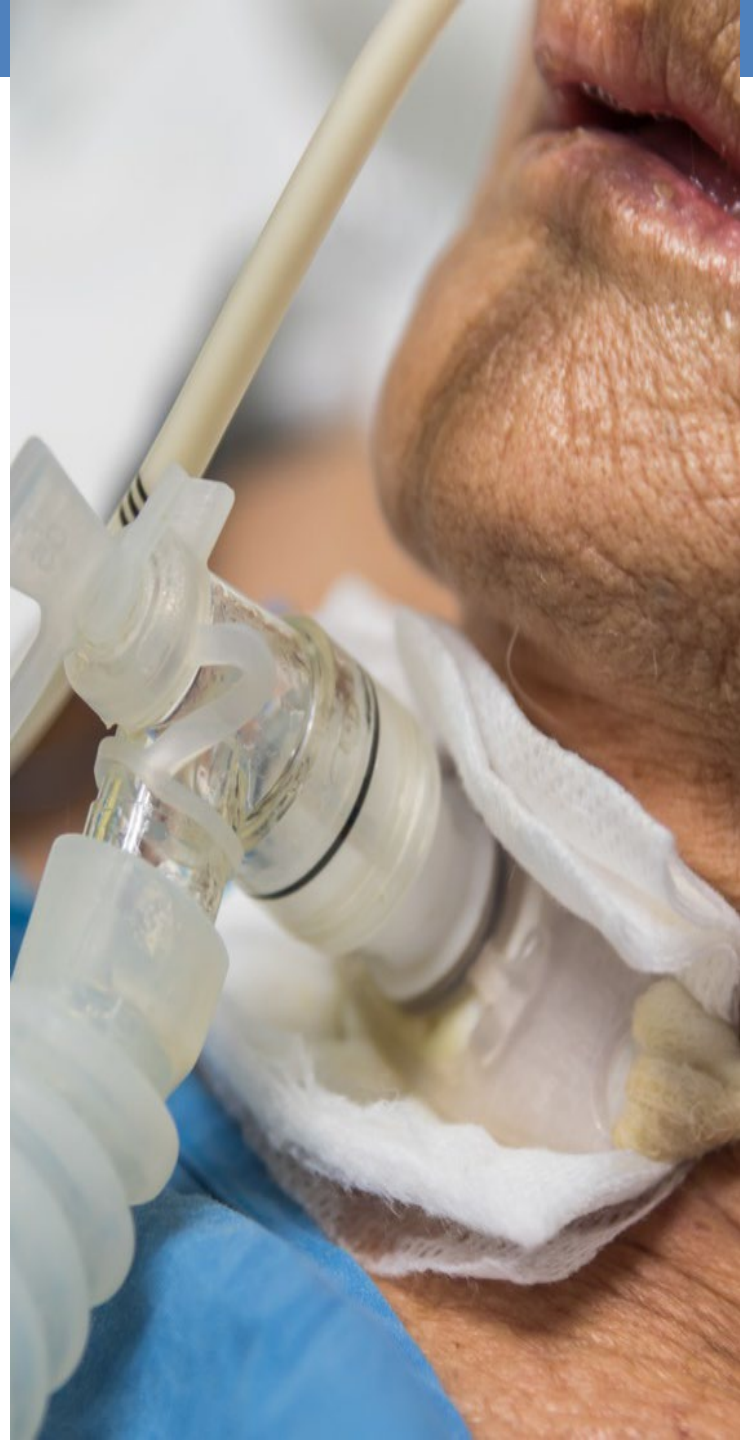
ID Consult

- Lucy is Still on Ventilator, Oxygenation is Stable
- Pressor Requirements are Stable
- **Now What?**

- Cepheid Gene Xpert Carba-R: **KPC detected**

- **Recommendation to Start Expensive Novel Agent**

Note: Cepheid Gene Xpert is what my hospital uses, this is not a specific product endorsement



Empiric Antimicrobial Selection is by nature a partial information game with decisions based on patient's prior antimicrobial exposure, healthcare exposure and risk of death.

If the Microbiology Laboratory can Give Me a Peak at The Next Card, I Will Play My Hand Better.

Summary

- Dealing with MDRO infections is challenging and complex

- Carbapenemase testing can improve care, particularly for critically ill patients, and may have impact on pharmacy budgets

Resources

- CDPH CPO Webpage
  (www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CRE_InfectionPreventionStrategies.aspx)
- CDPH CPO Reporting FAQ (PDF)
  (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPOReportingFAQ.pdf)
- CDPH Algorithm for Prioritizing Carbapenemase Testing (PDF)
  (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPTestingPrioritizationAlgorithm.pdf)
- CDPH CPO and *C. auris* Screening Decision Tree (PDF)
  (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/Tier2_Pathogen_Screening_Decision_Tree_Oct2020.pdf)
- MDL Submission Instructions and Forms
  (www.cdph.ca.gov/Programs/CID/DCDC/Pages/MDLSubmissionInstructionsandForms.aspx)
- MDL Carbapenemase Testing Services FAQ (PDF)
  (www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/MDL_Expanded-Carbapenemase_Testing_FAQ-Sheet.pdf)
- CDPH California Health Alert Network (CAHAN) AR-related Advisories
  (www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CAHAN.aspx)

California Department of PublicHealth

Please enter questions and comments into the Q&A

Email HAI_Program@cdph.ca.gov for more information about CPO and carbapenemase testing resources