The Key to Successful Antimicrobial Stewardship: Interdisciplinary Teams

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Objectives

- Explain a challenging case from the perspective of a clinical laboratory
- Evaluate testing options for the rapid identification of resistant infections
- Demonstrate te need for new therapeutics to accompany accurate diagnostics

“Antimicrobial stewardship is defined as a formalized program that provides advice, consent, and institutional guidance on appropriate selection, dosing, route and duration of antimicrobial usage.”

Antimicrobial Stewardship Stakeholders

- ASP Pharmacist
- Pharmacy Director
- Infectious Disease Physician
- Treating Physician (Critical Care Doctor)
- Licensed Nurse
- Laboratory Director
- Laboratory Technician

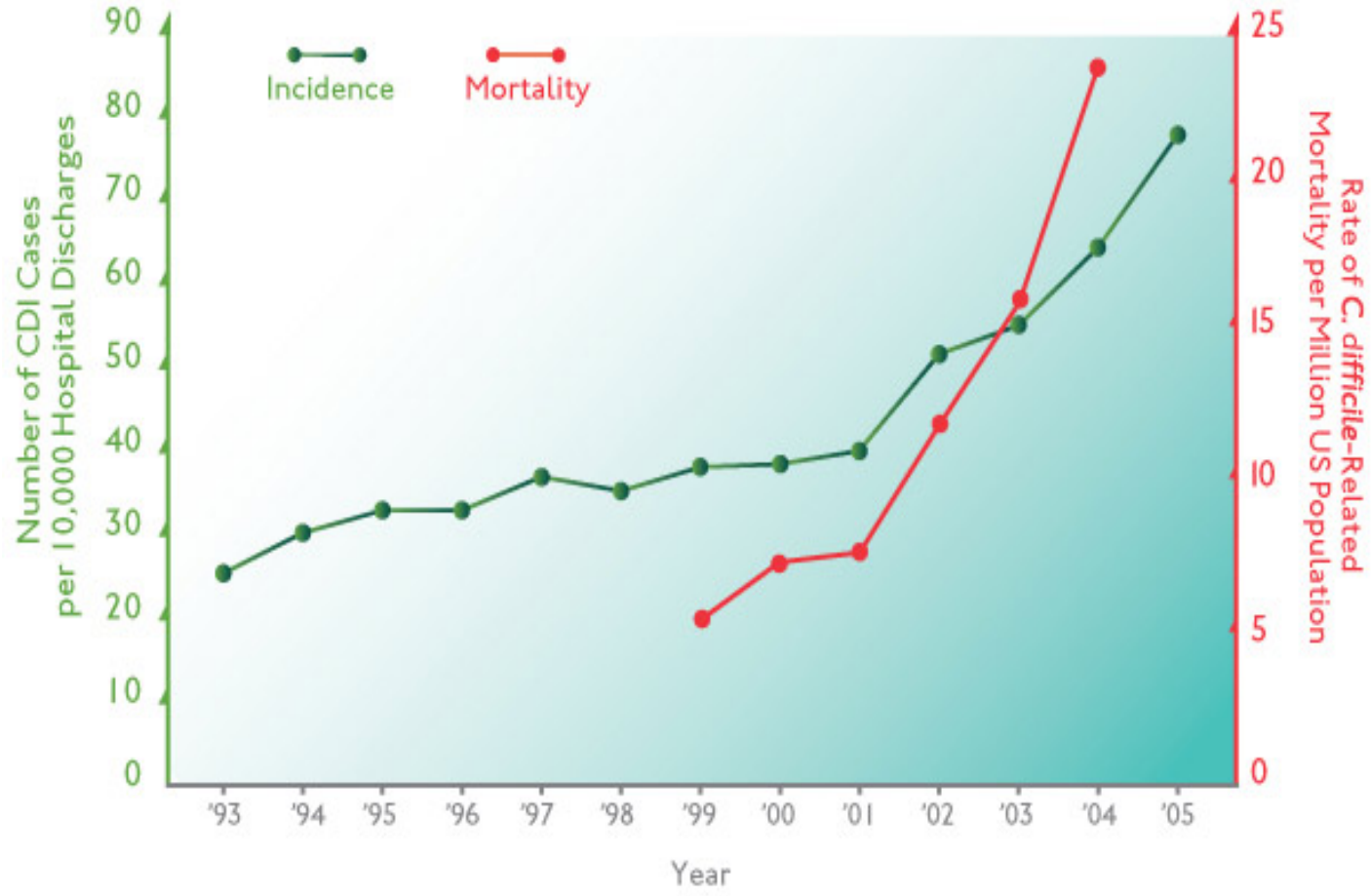
Goals of Antibiotic Stewardship

- Right Drug, Right Patient, Right Time
- Optimize Clinical Outcomes
- Reduce CDI
- Reduce Emergence of Resistance
- Save Money for the Hospital

CDI: Impact

	Number of annual cases	Cost	Number of annual deaths
Hospital-onset, hospital acquired (HO-HA)	165,000	$ 1.3 B	9,000
Community-onset hospital acquired (CO-HA) [4 weeks of hospitalization]	50,000	$ 0.3 B	3,000
Nursing home-onset	263,000	$ 2.2 B	16,500

Increasing US Mortality due to C difficile



* Daneman et al. JAC 66:2856, Dec 2011

CONTACT ISOLATION PRECAUTIONS

Visitors ~ See Nurse before entering

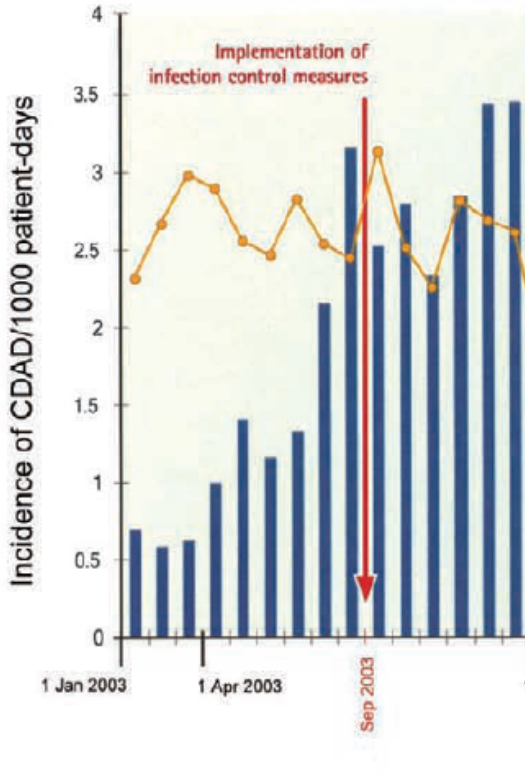
STOP

Clean Hands ~ Gown ~ Gloves

STOP

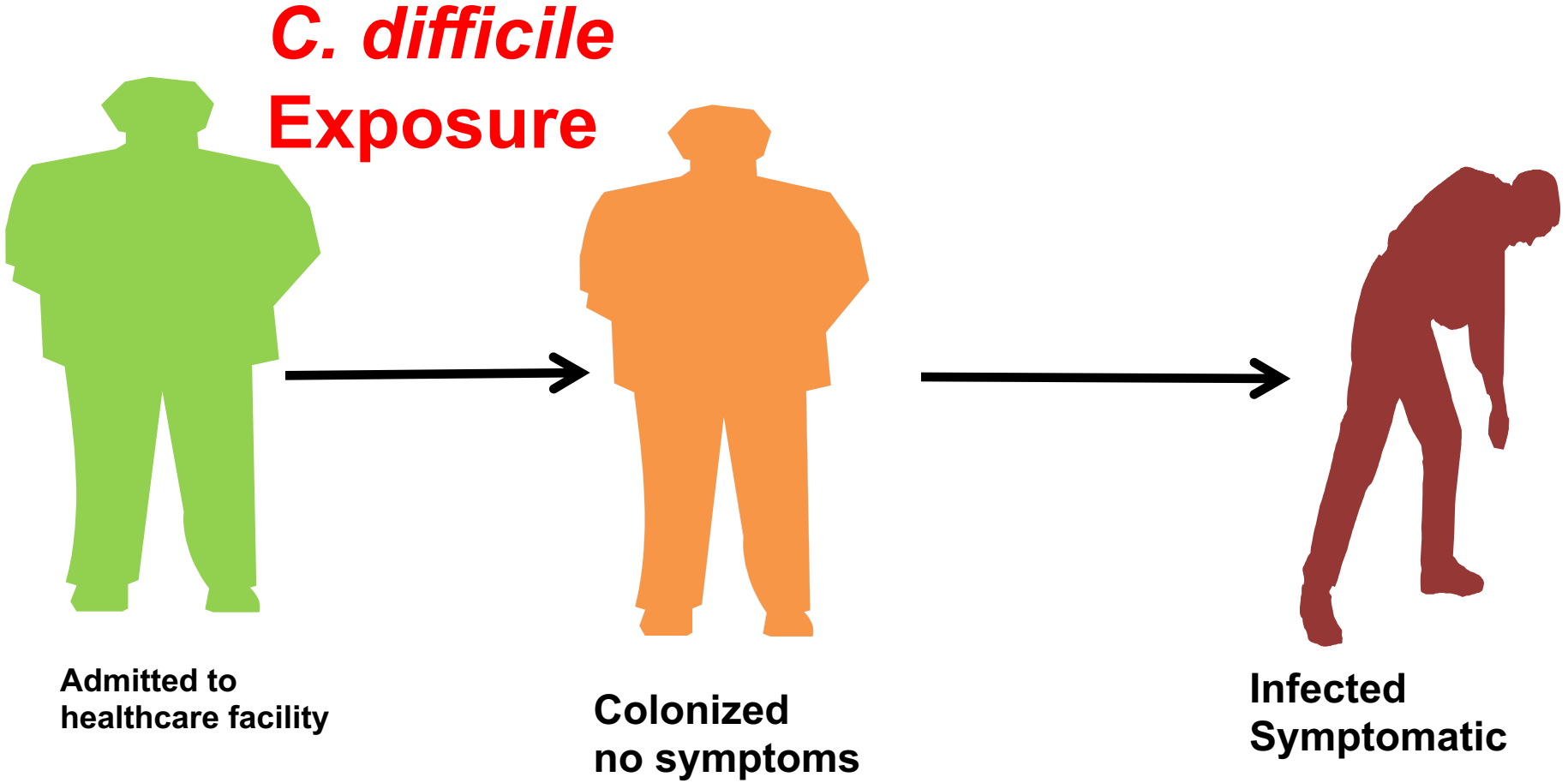
N-95 for High-Hazard Procedures (See other side)

Draconian Infection Control Measures



Valiquette, et al.
Clin Infect Dis. 2007;45:S112-21

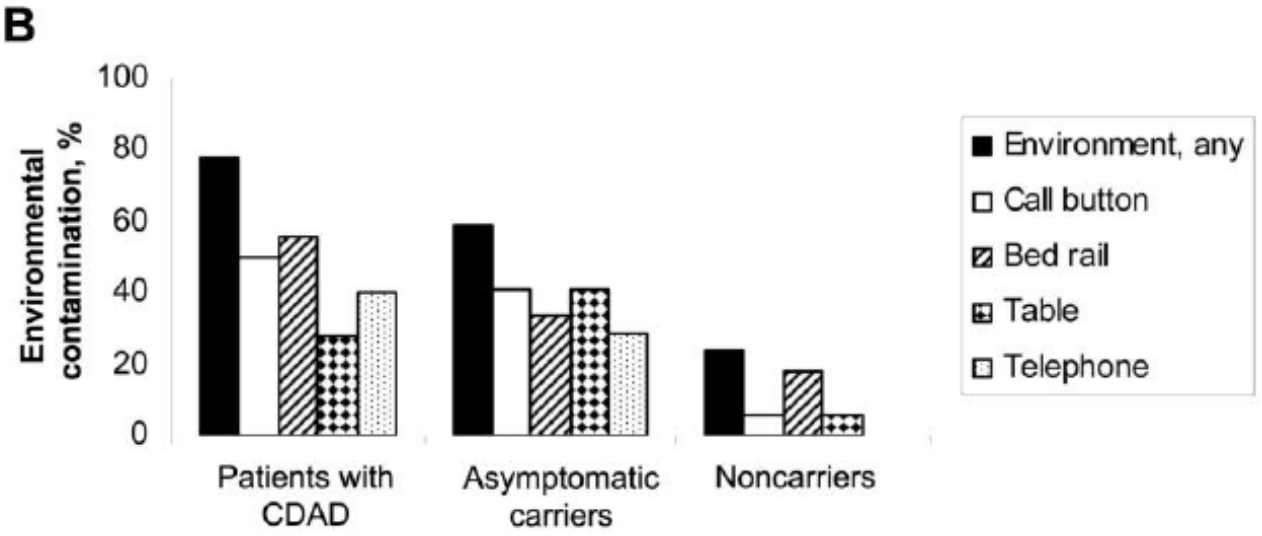
CDI Pathogenesis



Asymptomatic carriers are a potential source for transmission of Clostridium difficile

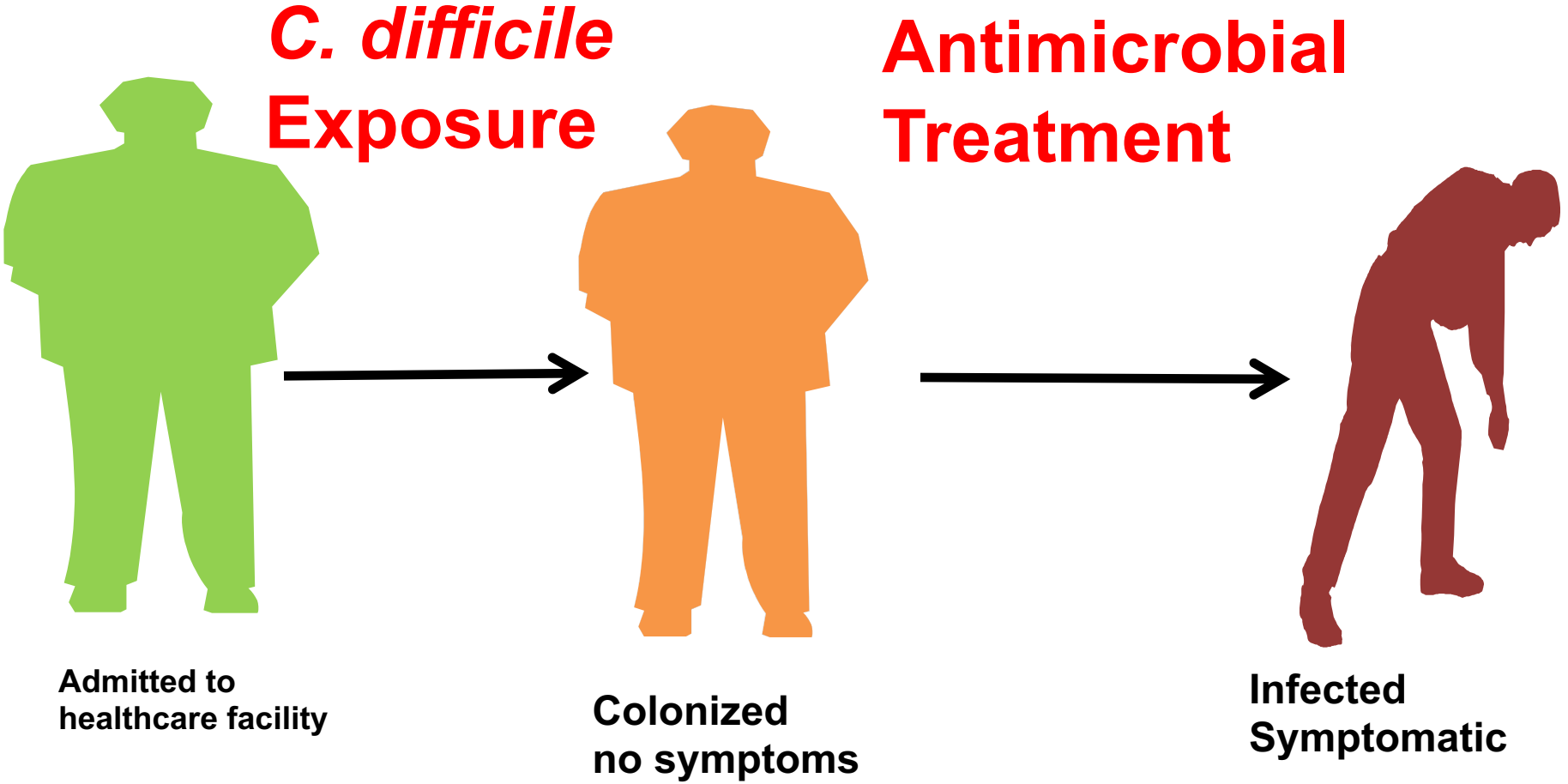
3-month study in LTCF with 73 residents
Five (7%) patients had CDI
35 (51%) were asymptomatic carriers (nine had a prior history of CDI)

Asymptomatic carriers associated with significantly higher rates of skin (61% vs. 19%) and environmental contamination (59% vs. 24%) than non-carriers



Riggs et al Clin Infect Dis 2007 **45**:8, 992-8

CDI Pathogenesis



Antibiotics and CDI

Risk of CDI compared to resident on 1 antibiotic

	Number of ATBs	
2 ATBs	**3-4 ATBs**	**5+ ATBs**
2.5 times higher	3.3 times higher	9.6 times higher

Risk of CDI compared to resident on ATBs for <4 days

	Days of Antibiotic	
4-7 days	**8-18 days**	**>18 days**
1.4 times higher	3 times higher	7.8 times higher

15. Epson,E. Orange County CDI Prevention Collaborative: Antimicrobial Stewardship. CDPH. November 5, 2015. Permission granted for use of this slide by Dr. Erin Epson.
Original slide reference: Stevens,et al. Clin Infect Dis. 2011;53(1):42-48

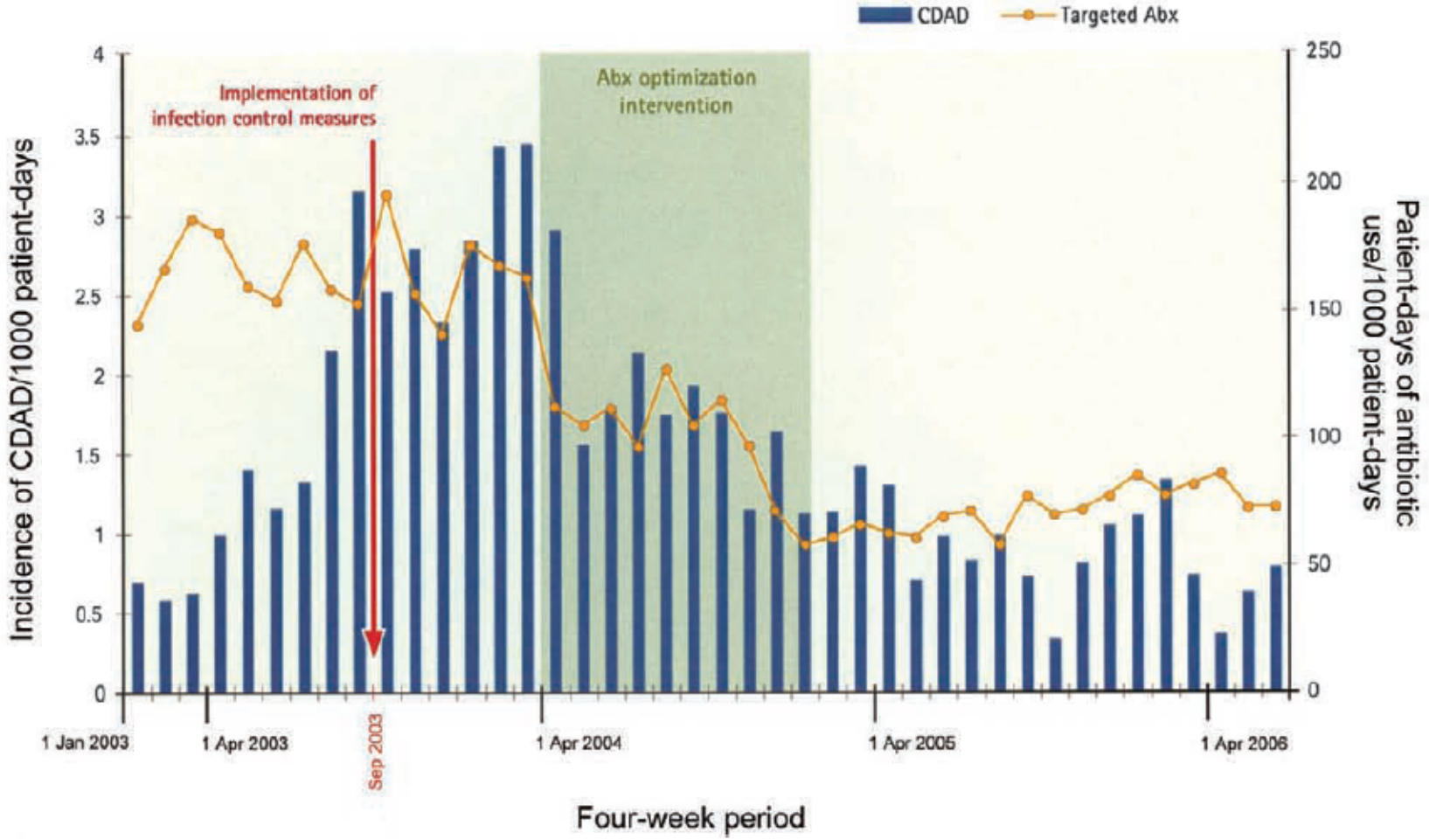
Effects of control interventions on *Clostridium difficile* infection in England: an observational study

*Kate E Dingle, Xavier Didelot, T Phuong Quan, David W Eyre, Nicole Stoesser, Tanya Golubchik, Rosalind M Harding, Daniel J Wilson, David Griffiths, Alison Vaughan, John M Finney, David H Wyllie, Sarah J Oakley, Warren N Fawley, Jane Freeman, Kirsti Morris, Jessica Martin, Philip Howard, Sherwood Gorbach, Ellie J C Goldstein, Diane M Citron, Susan Hopkins, Russell Hope, Alan P Johnson, Mark H Wilcox, Timothy E A Peto, A Sarah Walker, Derrick W Crook, the Modernising Medical Microbiology Informatics Group**

- Incidence of C. difficle in UK dropped by 80% after 2006
- Decline was due to multiple interventions
- However, Fluoroquinolone reduction is thought to be the primary driver for change

Dingle et al. Lancet ID. 2017

Targeting High-Risk Antibiotics Reduces CDI



Valiquette, et al.
Clin Infect Dis. 2007;45:S112-21

Dr. McKinnell's Notes on Antibiotic Duration

- CAP 7-10
- HAP/VAP 10-14
- Pyelonephritis 10-14
- Cellulitis 7-10
- Bacteremia 14-42

HCAP/VAP
7 DAYS

- **Several RCTs 7-8 days equal to 10-15 days**
- **Reduced emergence of resistance**
- **MRSA and Pseudomonas infections may require longer therapy**

Capellier et al. PLoS One 2012:7:e41290; Chastre et al. JAMA 2003 290:2588-98; Kalil et al. CID 2016 63:e61-e111

Short Course Therapy!!!!

Diagnosis	Short (d)	Long (d)	Result
CAP	3 or 5	7, 8, or 10	Equal
HAP	7	10-15	Equal
VAP	8	15	Equal
Pyelo	7 or 5	14 or 10	Equal
Intra-abd	4	10	Equal
AECB	≤5	≥7	Equal
Cellulitis	5-6	10	Equal
Osteo	42	84	Equal

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

Lucy

65 year old female

transferred from OSH for pneumonia

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

- **2 Weeks ago** Treated in Mexico for pneumonia, prior antimicrobial therapy unknown
- **5 Days ago** admitted to OSH w/ cough, sputum, and SOB. Immediately intubated

Piperacillin-tazobactam 3.375 gm IV q6Hours

Lucy: Admission Exam

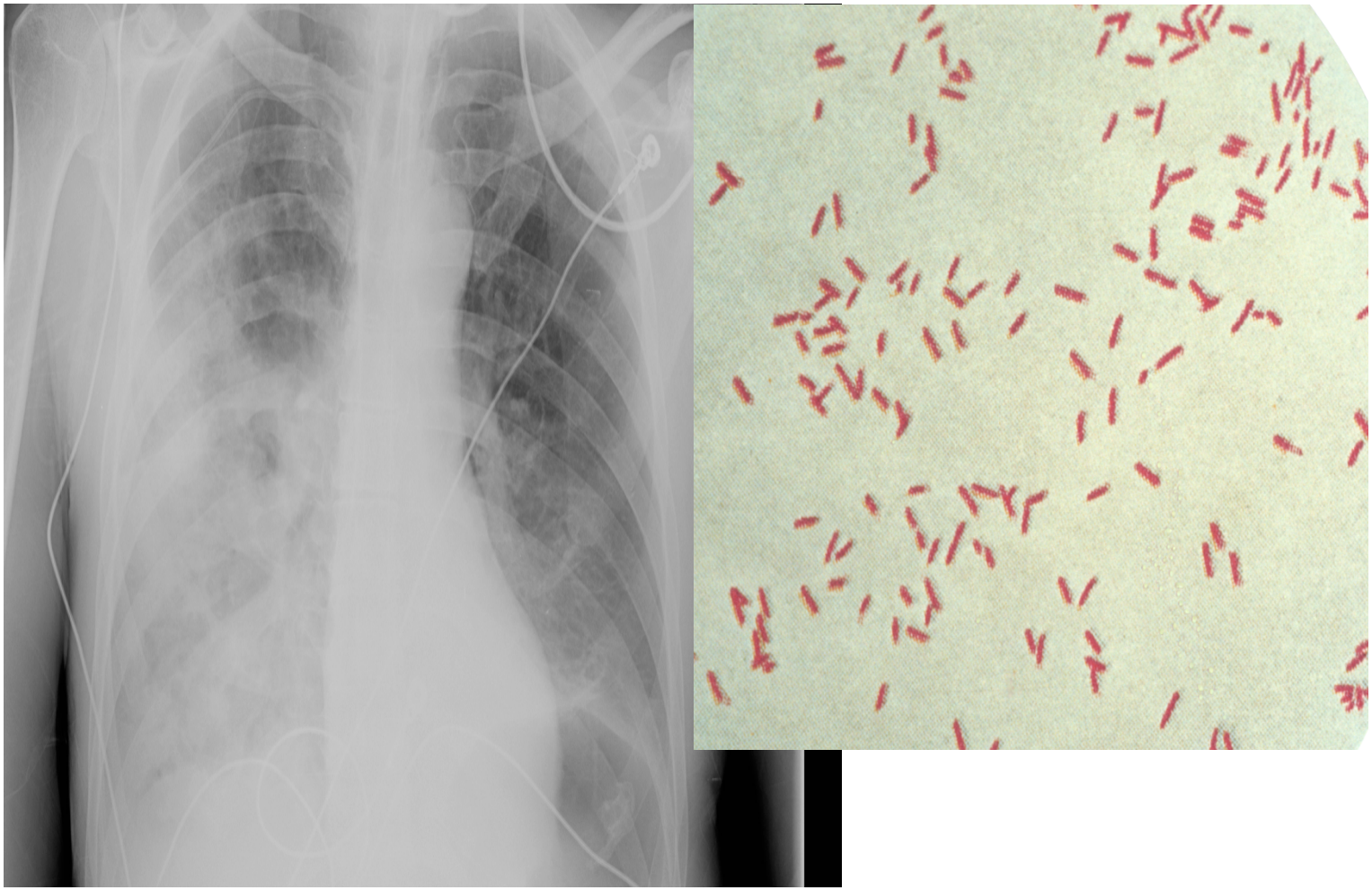
T: 101.2 RR: 22 BP: 104/62 HR: 125 FiO2: 92%

- 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

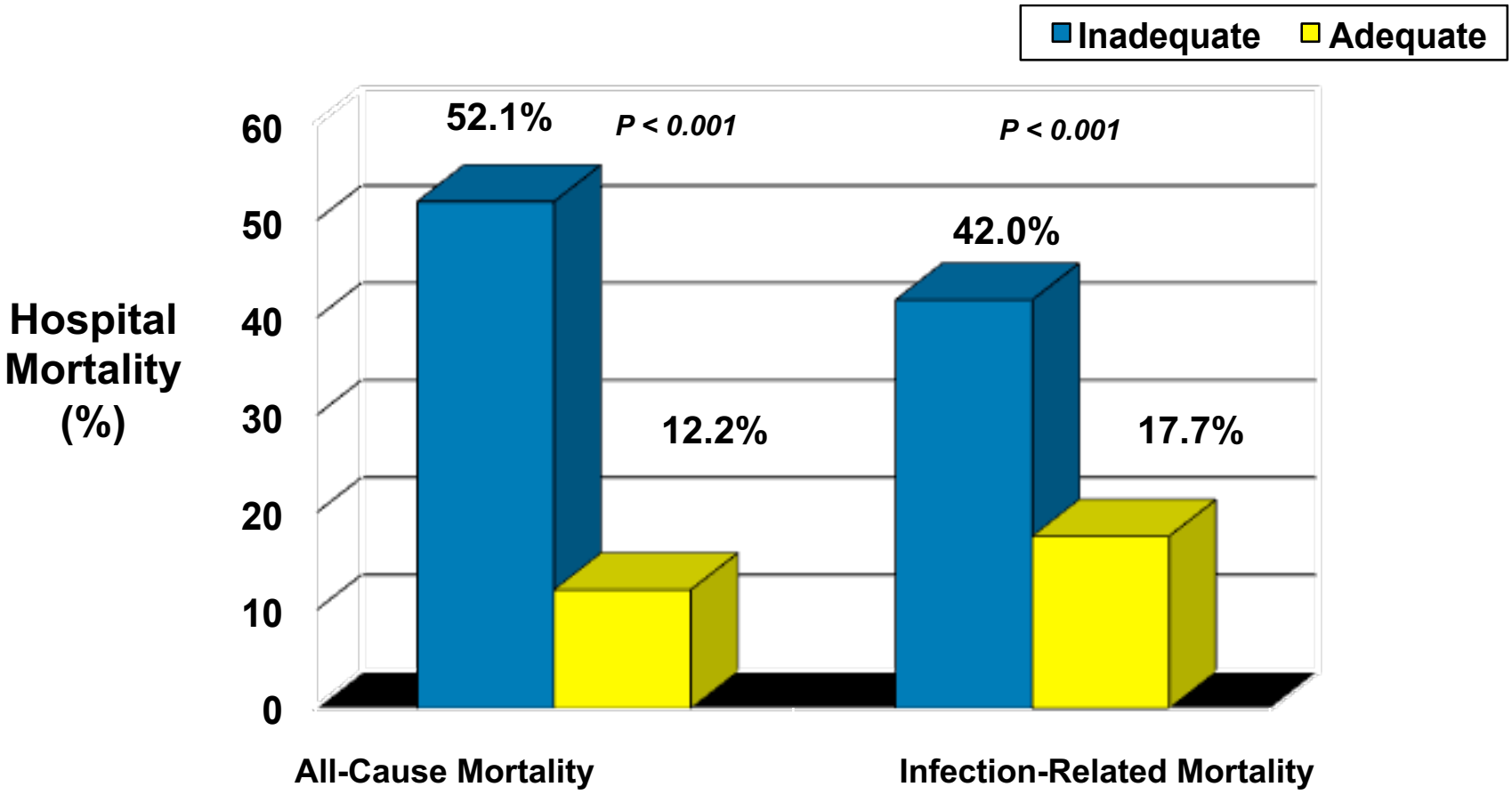


X-Ray Image courtesy of James McKinnell, MD case files
Gram Stain image: CDC Public Health Image Library

Assessment and Plan

- 65 yo with sepsis, RLL pneumonia with Gram-negative rods, respiratory failure, retained organ function on vasopressor therapy.
- RLL pneumonia progressed while on Piperacillin-Tazobactam
- **What Antibiotics Should We Use?**

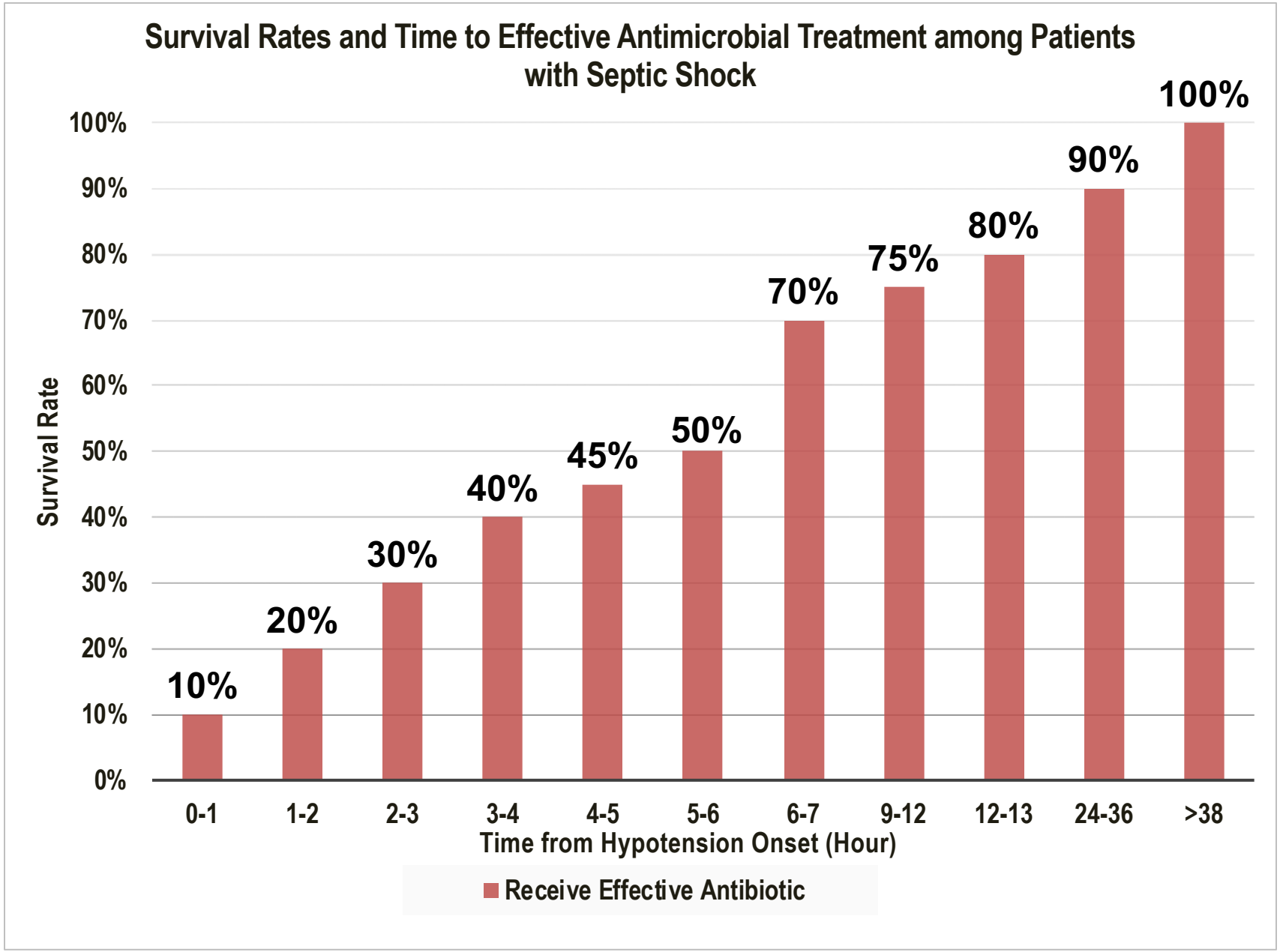
Inadequate antimicrobial therapy associated with higher mortality



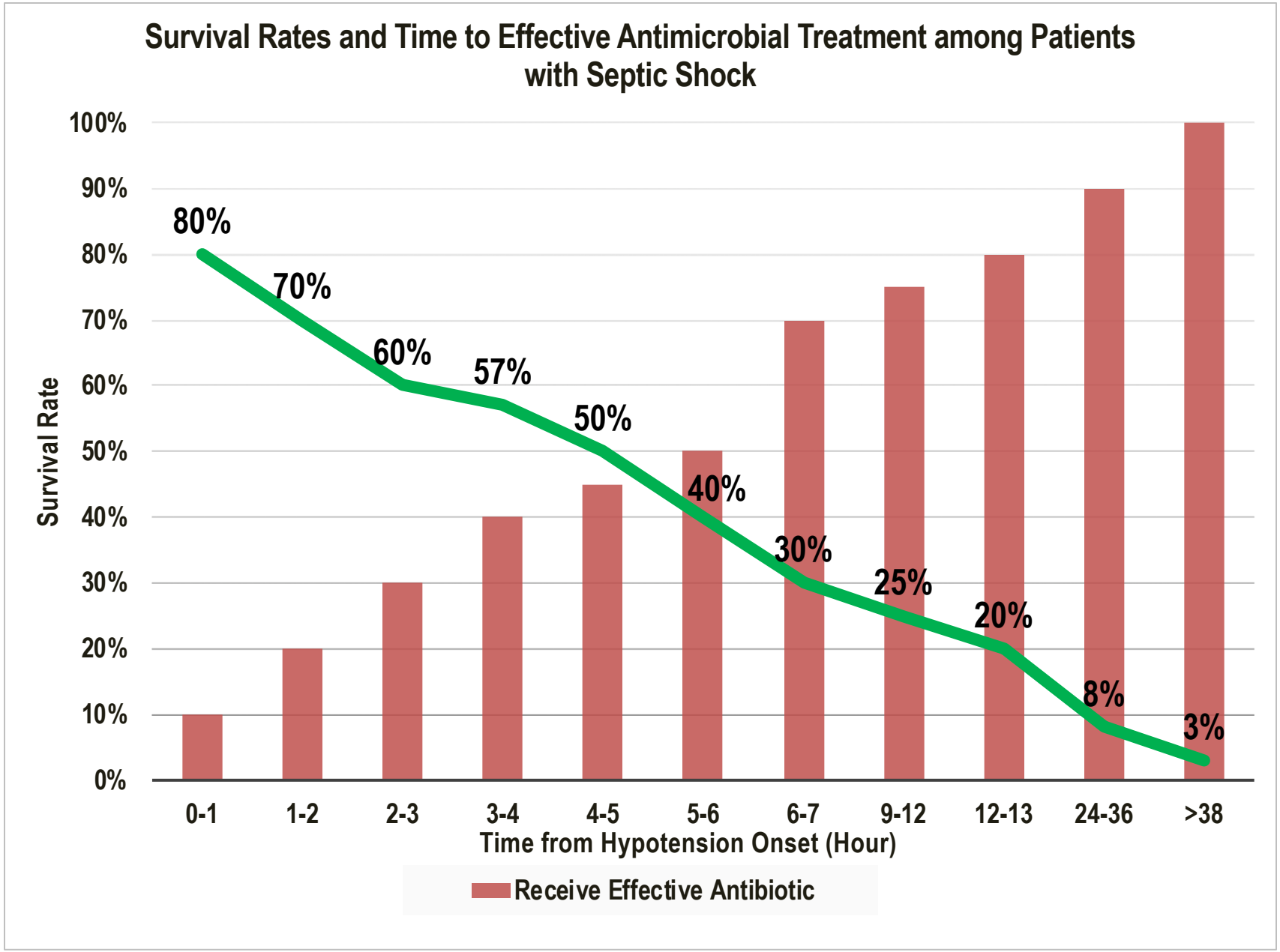
Prospective study (n=2000: 655 with infections)

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.



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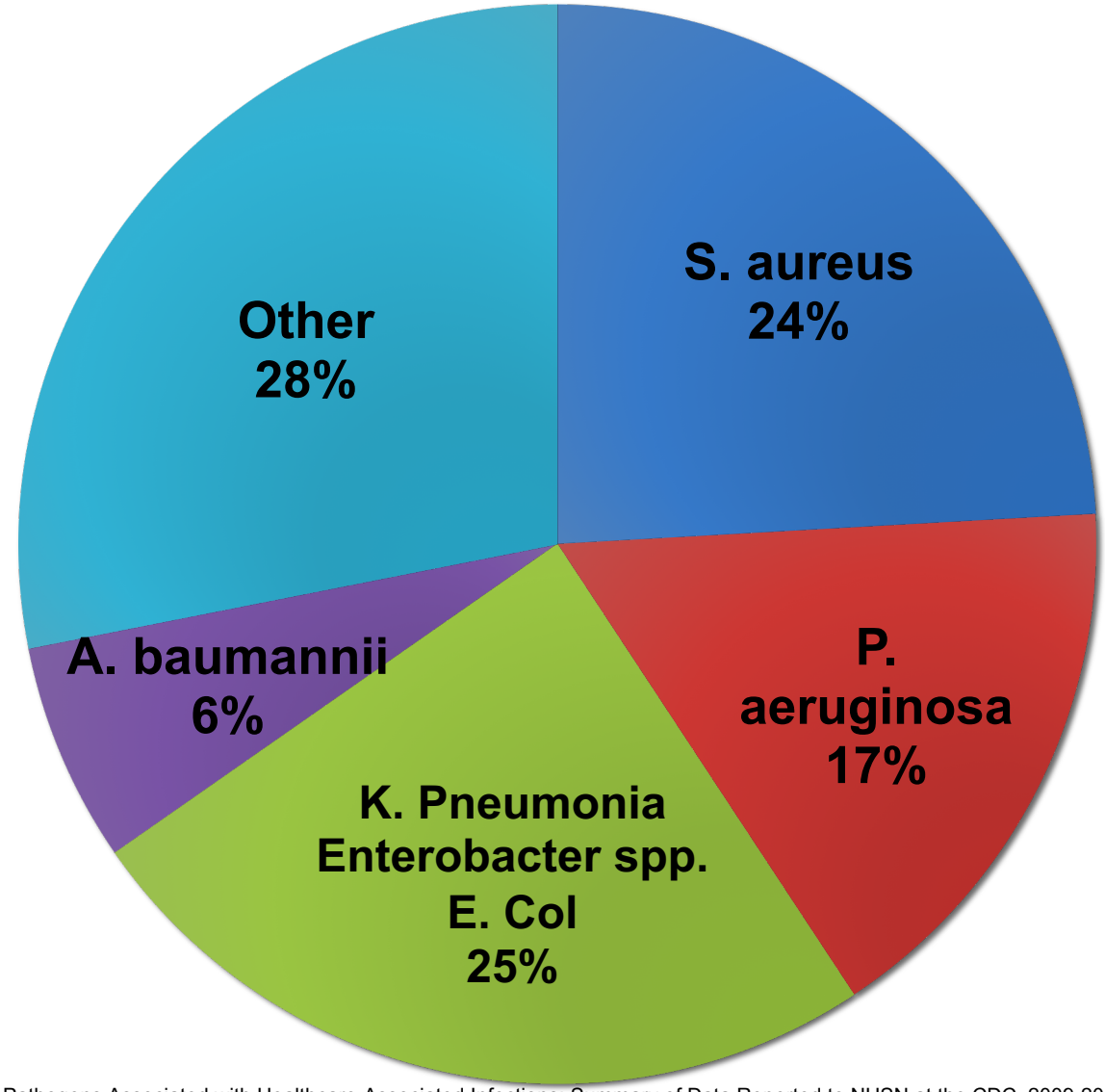
Lucy: Assessment

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

- **What Antibiotics Should We Use?**

Rank order of Pathogens Causing VAP



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

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

Organism	No. Isolates	Penicillins			Cephalosporins				Carbapenems			Aminoglycosides			Fluoro-quinolone	Other	
		Ampicillin[6]	Ampicillin-Sulbactam[6]	Piperacillin-tazobactam	Cefazolin	Cefepime	Ceftazidime	Ceftriaxone[1]	Ertapenem	Imipenem	Meropenem	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Trimethoprim–sulfamethoxazole	Colistin[7]
Citrobacter freundii	37	R[2]	R	76	R	89	–[4]	–[4]	97	99	99	99	89	92	92	81	99
Enterobacter aerogenes	94	R	R	88	R	98	–[4]	–[4]	99	97	99	99	99	99	99	98	98
Enterobacter cloacae	209	R	R	81	R	92	–[4]	–[4]	89	99	99	99	99	99	98	94	85
Escherichia coli	752	41	50	94	69	84	83	79	99	99	99	99	82	85	63	60	99
Klebsiella oxytoca	121	R	64	89	23	95	95	87	98	98	98	99	96	96	94	91	99
Klebsiella pneumoniae	399	R	70	87	71	86	85	84	93	94	94	98	92	88	85	81	97
Morganella morganii	60	R	R	97	R	99	–[4]	–[4]	97	–	98	99	87	98	82	68	R
Proteus mirabilis	197	67	80	99	25	95	97	87	99	–	99	99	90	94	68	67	R
Serratia marcescens	127	R	R	96	R	96	–[4]	–[4]	97	94	96	99	99	96	93	98	R
Acinetobacter baumannii	62	R	62	53	R	58	58	–	R	62	60	67	60	66	56	60	95
Pseudomonas aeruginosa	738	R	R	84	R	88	87	R	R	81	85	96	91	94	78	R	99
Stenotrophomonas maltophilia	84	R	R	R	R	–	30	R	R	R	R	R	R	R	–	99	70
Burkholderia cepacia complex	12[5]	R	R	R	R	R	27	R	R	R	18	R	R	R	36	64	R

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

Antibiogram data source: UCLA Health Infectious Disease

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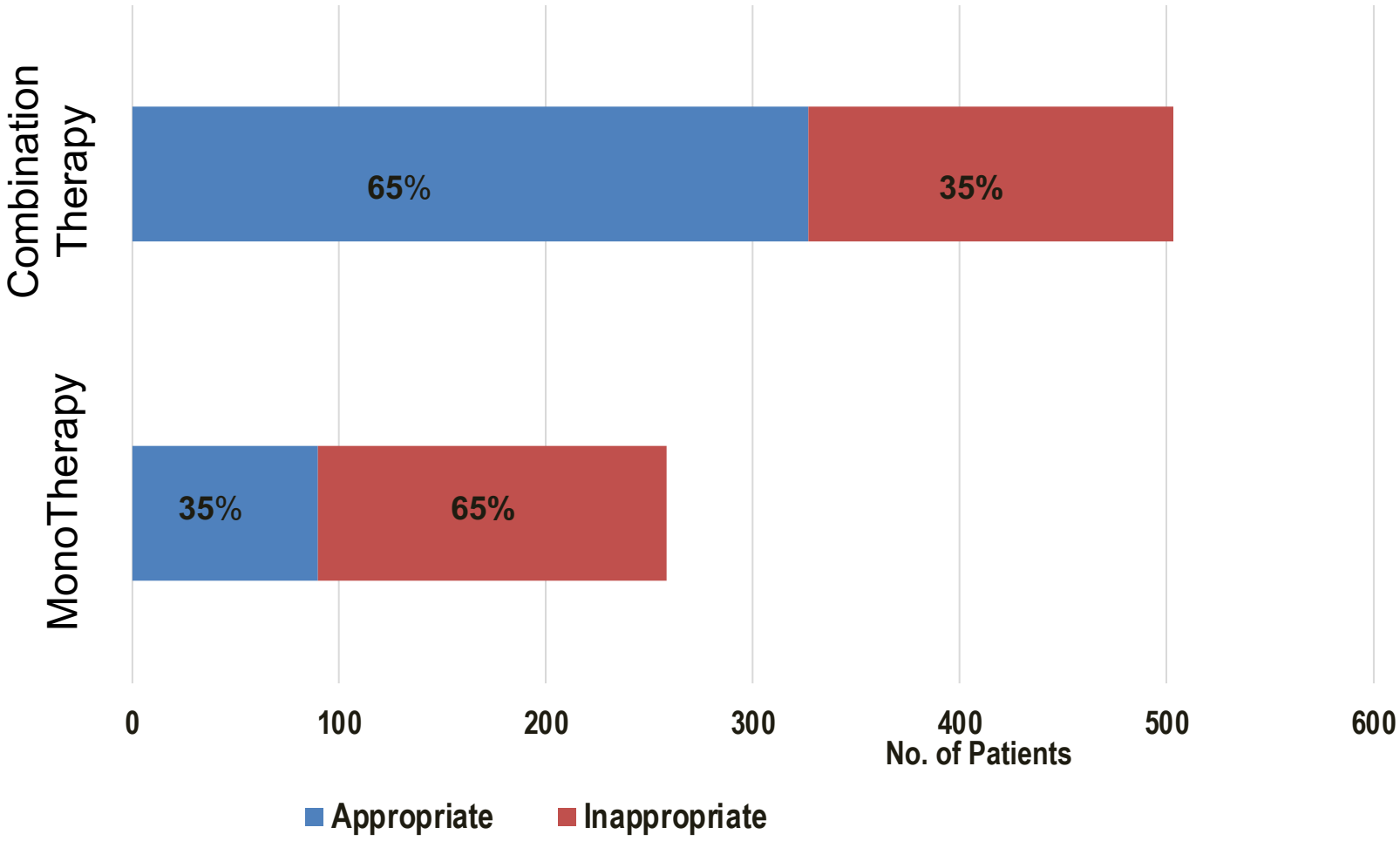
Empiric Combination Therapy Is Associated with Higher Rates of Early, Appropriate Therapy for Patients with Sepsis Due to Gram-negatives



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

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

2 Days After Consult

- Lucy is still on ventilator, 100% O2, high positive ventilatory pressures
- Ongoing sputum production
- Max pressors, increased over last 24 hours

Susceptibility *K. pneumoniae*

Antimicrobial	Susceptibility
Piperacillin/Tazobactam	R
Cefepime	R
Ceftazidime	R
Meropenem	R (MIC-32)
Ciprofloxacin	R
Gentamicin	R
Tobramycin	R
Colistin	S

Laboratory Contribution

Susceptibility *K. pneumoniae*

Antimicrobial	Susceptibility
Piperacillin/Tazobactam	R
Cefepime	R
Ceftazidime	R
Meropenem	R (MIC-32)
Ciprofloxacin	R
Gentamicin	R
Tobramycin	R
Colistin	S

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Polymyxins: Antibacterial Activity, Susceptibility Testing, and Resistance Mechanisms Encoded by Plasmids or Chromosomes

Laurent Poirel, Aurélie Jayol, Patrice Nordmann
April 2017, Clinical Microbiology Reviews Volume 30 Issue 2
https://doi.org/10.1128/CMR.00064-16

Automated Susceptibility Systems Poorly Identify Colistin Resistance

Broth Microdilution Method

Reference Method – CLSI & EUCAST

Agar Dilution

- Not recommended (CLSI/EUCAST)
- Laborious

Disk Diffusion

- Not reliable. Poor agar diffusion.
- High False-Susc. Results. ~35%

Etest (bMX)

- Not reliable.
- High False-Susc. Results of R strains.
- Overcalls MICs of Susc strains.

Vitek2 (bMX)

- Low Sensitivity for resistant strains.
- Not reliable for heteroresistance.
- Europe Field Notification - DNR

Phoenix (BD)

- High False-Susc. Results. ~15%
- Low detection of Colistin heteroresist.

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Microscan (Beckman)

87%
Categorical Agreement
(*Acinetobacter spp.*)

2 MIC Concentrations (2 & 4ug/ml)

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Microscan (Beckman)

87%
Categorical Agreement
(*Acinetobacter spp.*)

2 MIC Concentrations (2 & 4ug/ml)

Sensititre (TFS)

96%
Categorical Agreement

Zero False Susceptibility Results

Concentrations (0.12-128 µg/ml)

Be Honest about Your Information!

Susceptibility *K. pneumoniae*

Antimicrobial	Susceptibility
Piperacillin/Tazobactam	R
Cefepime	R
Ceftazidime	R
Meropenem	R (MIC-32)
Ciprofloxacin	R
Gentamicin	R
Tobramycin	R
Colistin	?

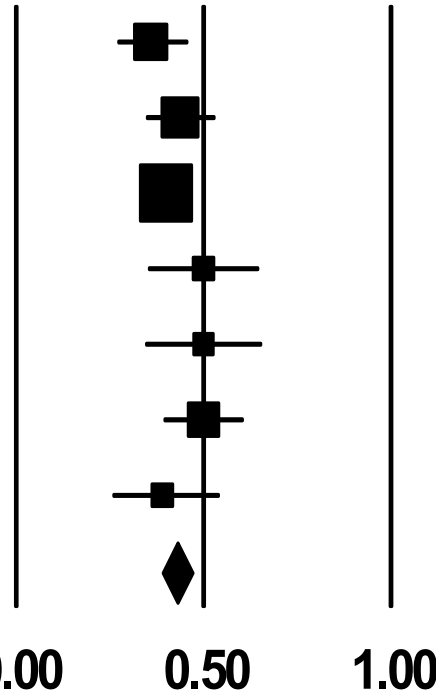
So, now what?

Susceptibility *K. pneumoniae*

Antimicrobial	Susceptibility
Piperacillin/Tazobactam	R
Cefepime	R
Ceftazidime	R
Meropenem	R (MIC-32)
Ciprofloxacin	R
Gentamicin	R
Tobramycin	R
Colistin	?

CRE BSI Nearly 50% All Cause Mortality

Study	Death N	Cases N	Mortality Rate	95% CI	Mortality Rate (95% CI)
Girometti	33	92	0.36	0.27-0.46	
Hussein	45	103	0.44	0.35-0.53	
Daikos	82	205	0.40	0.34-0.47	
Navarro-San Fran.	20	40	0.50	0.35-0.65	
Balkan	18	36	0.50	0.34-0.66	
De Oliveira	39	78	0.50	0.39-0.61	
Qureshi	16	41	0.39	0.26-0.55	
Meta-Analysis	253	595	0.43	0.39-0.47	



All-cause mortality for bloodstream infections (pooled sources) due to CRE at 1 month is 43% (95% CI, 39-47%)

Traditional Therapy Approaches

- High Dose Prolonged Infusion Carbapenem
  - Needs MIC <8
- Tigecycline
  - Black box from FDA on severe infections
- Colistin/Polymixin
  - Nephrotoxicity and difficult to dose
- Fluoroquinolones
  - Black box from FDA due to side effects, widespread resistance
- Classic Aminoglycosides
  - Widespread resistance

Novel Treatment Options

CRE

Novel BL/BLI

- Ceftaz-Avibactam
- Mero-Vaborbactam
- Imipenem-Relebactam

Novel Aminoglycoside

- Plazomicin

Antimicrobial Stewardship Stakeholders

- **ASP Pharmacist**
- **Pharmacy Director**

Novel Agents may be >$1,000 per day!

- **Infectious Disease Physician**
- **Treating Physician (Critical Care Doctor)**

Novel Agent may be best option!!!

- Licensed Nurse
- Laboratory Director
- Laboratory Technician

Two Forms of Carbapenem-Resistant Enterobacteriaceae

Carbapenemase producing (CP-CRE)

Sub-type
KPC, TEM, SHV, CTX-M
NDM, IMP, VIM
OXAs

Non-carbapenemase producing (Non-CP-CRE)

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

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

Ceftazidime-Avibactam

- FDA approved indications: cUTI, cIAI, nosocomial/ventilator pneumonia
- The avibactam is the game-changer
- Ability to inhibit KPC, OXA-48 type, and AmpC inhibition
- No metallo-beta-lactamase inhibition
- Marked improvement in MDR *P. aeruginosa* activity over ceftaz alone

Torres A, et al. *Lancet Infect Dis* 2018. http://dx.doi.org/10.1016/S1473-3099(17)30747-8.

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

CRACKLE

- 38 Patients Ceftazidime-Avibactam, 99 with Colistin
- Mortality 9% versus 32%

Meropenem-Vaborbactam

- FDA approved indications: cUTI
- Vaborbactam is the game-changer
- Ability to inhibit Class A (SHV, TEM, CTX-M, KPC) and Class C (Amp-C)
- No metallo-beta-lactamase inhibition
- Not likely reliable against *P. aeruginosa* compared to meropenem alone

Zhanel GG, et al. *Drugs* 2018.

Infect Dis Ther (2018) 7:439–455
https://doi.org/10.1007/s40121-018-0214-1

ORIGINAL RESEARCH

Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial

Richard G. Wunderink · Evangelos J. Giamarellos-Bourboulis · Galia Rahav · Amy J. Mathers · Matteo Bassetti · Jose Vazquez · Oliver A. Cornely · Joseph Solomkin · Tanaya Bhowmick · Jihad Bishara · George L. Daikos · Tim Felton · Maria Jose Lopez Furst · Eun Jeong Kwak · Francesco Menichetti · Ilana Oren · Elizabeth L. Alexander · David Griffith · Olga Lomovskaya · Jeffery Loutit · Shu Zhang · Michael N. Dudley · Keith S. Kaye

TANGO II

- 28 Patients Meropenem-vaborbactam, 15 with BAT
- Mortality 18% versus 33%

Imipenem/cilastin-Relebactam

- FDA approved indications: cUTI, cIAI
- Relebactam is the game-changer
- Ability to inhibit Class A (SHV, TEM, CTX-M, KPC) and Class C (Amp-C)
- No metallo-beta-lactamase inhibition
- Microbiologic activity for *P. aeruginosa* improved over imipenem alone

Zhanel GG, et al. *Drugs* 2018.

Clinical Infectious Diseases
MAJOR ARTICLE

RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections

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RESTORE-IMI

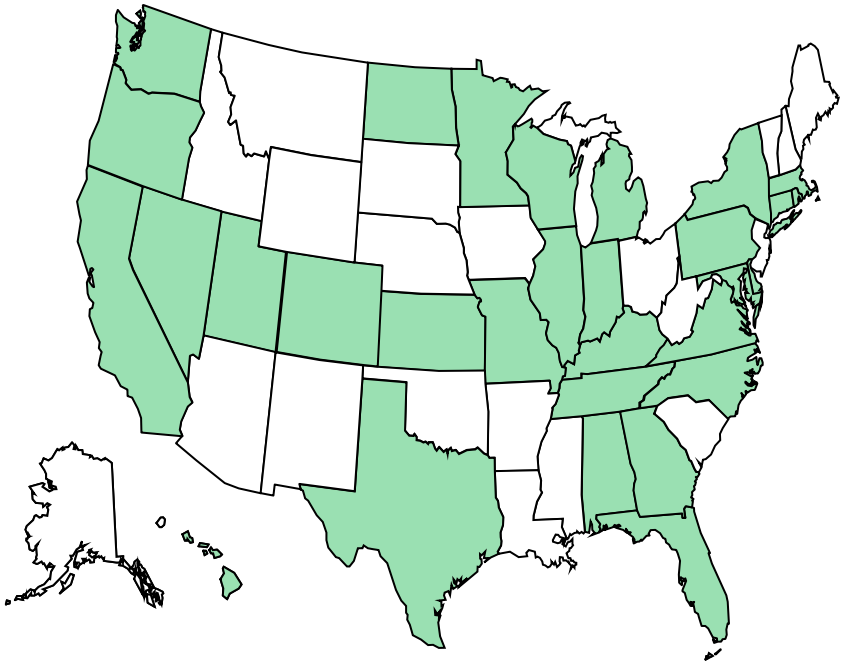
- Randomized trial of HAP/VAP, cIAI, cUTI
- Imi-Rel n=31 compared to colistin+imipenem n=16
- Favorable overall response 71% vs. 70%
- 28 day favorable clinical response 71% vs. 40%
- Nephrotoxicity 10% vs. 56%

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

Non-KPC CRE on the Rise

- Los Angeles 2015-2017
  - 1,000 CRE isolates
  - 20% non-KPC
- Vancouver 2008-2017
  - >3,500 CRE isolates
  - 703 CP organisms
  - 90% non-KPC



Bhaurla, S. et al. LA County Department of Public Health, IDWeek 2017. Hoang, L. BC Center for Disease Control Public Health Laboratory. West Region ARLN EpiTalks Meeting, Sept. 2017.
http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html

Plazomicin

- Next Generation Aminoglycoside
- Not affected by aminoglycoside modifying enzymes (AME)
- Potentially affected by ribosomal methyltransferases and efflux pumps

Zhanel GG, et al. *Drugs* 2018.

Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae

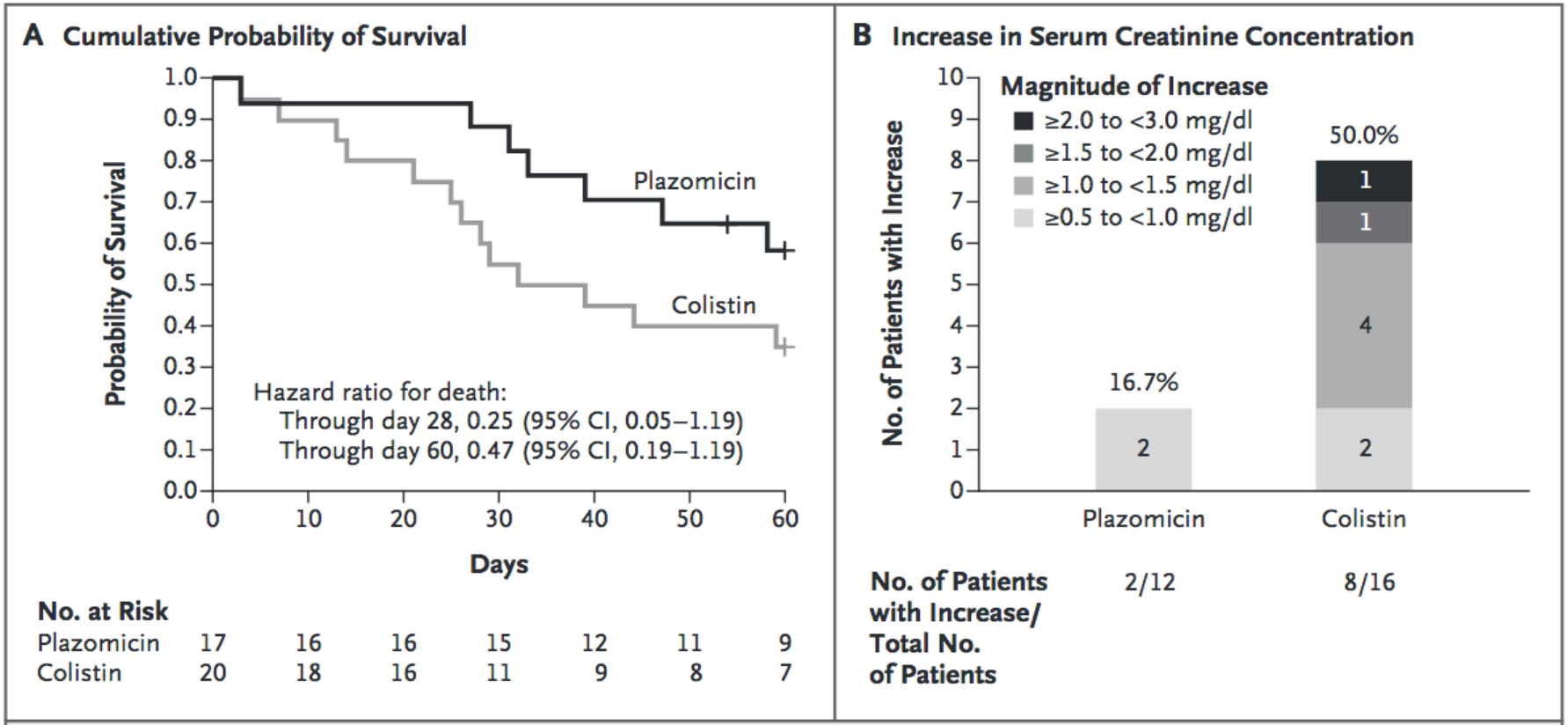


Figure 1. Results of a Definitive Combination-Therapy Regimen with Plazomicin or Colistin for Serious Infections Caused by Carbapenem-Resistant Enterobacteriaceae.

McKinnell et al., NEJM 2019

Novel Agents Should be used for Serious CRE Infections

- Serious Infections – On Vasopressors? Difficult to Ventilate?

- Dual Therapeutic Options with Novel Drugs?

- Dose the Drugs Aggressively for Appropriate Exposure
- Consider MIC in your dosing strategy

- **Bite the Bullet on $$ to Provide Optimal Care**

9 Days After Consult

- Lucy was switched to Ceftaz-Avibactam for hospital day 2-9
- Pressors Stopped on Day 5
- Minimal Vent Settings on Day 9

Antimicrobial RX as Emotional Process

- **ASP Pharmacist**
- **Pharmacy Director**

  Okay --- We are done Treating!!!!

- **Infectious Disease Physician**
- **Treating Physician (Critical Care Doctor)**

  Wait – what --- stop treatment?

- Licensed Nurse
- Laboratory Director
- Laboratory Technician

Serial Procalcitonin Measurement can help wean ID physicians from their ABX addiction

Procalcitonin measurement can be controversial. Stop antibiotics with level <0.5 ng/ml or >80% decrease.

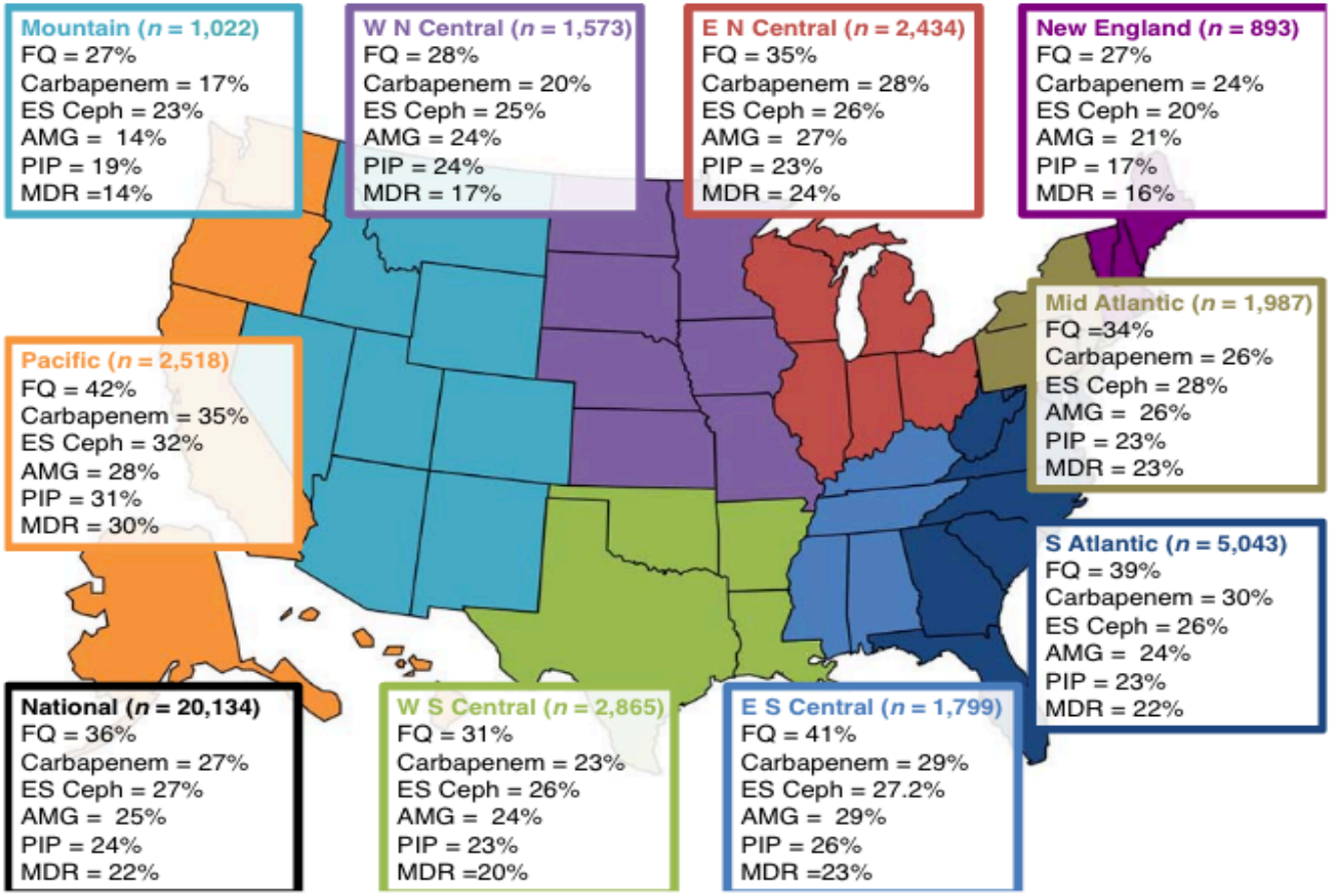
2016 IDSA guidelines recommend clinical criteria alone

2017 European and Latin America guidelines recommend use in selected cases

I favor their use in select cases, particularly to navigate between ASP and clinicians.

Carbapenem Resistant Pseudomonas is a MAJOR Problem.

Carbapenem Resistant Pseudomonas



Appaneal et al., DMID 2018

Susceptibility *Pseudomonas aeruginosa*

Antimicrobial	Susceptibility
Piperacillin/Tazobactam	R
Cefepime	R
Ceftazidime	R
Meropenem	R (MIC-32)
Ciprofloxacin	R
Gentamicin	R
Tobramycin	S
Colistin	S

Aminoglycoside Monotherapy Not Recommended for Pseudomonas

- "Aminoglycoside monotherapy was associated with increased mortality, even after adjusting for confounders…"

Importance of Site of Infection and Antibiotic Selection in the Treatment of Carbepenem-Resistant *Pseudomonas aeruginosa* Sepsis.

Britt et al. *Antimicrob Agents Chemother.* 2018 Mar 27;62(4). pii: e02400-17. Print 2018 Apr.

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.

Ceftolozane-Tazobactam

- **FDA indications:** complicated UTI and complicated intra-abdominal infection
- *P. aeruginosa* activity includes cefepime + pip-tazo + meropenem-resistant strains
- The tazobactam adds almost nothing for *P. aeruginosa* activity
- Current FDA approved dose is 1.5g Q8h. 3.0g Q8h for nosocomial pneumonia – study completed 6/6/2018
- No activity against carbapenemase producing *Enterobacteriaceae*

Clinicaltrials.gov: NCT02070757. Available at: https://clinicaltrials.gov/ct2/show/NCT02070757. Accessed September 13, 2018.
Bulik CC et al. *Antimicrob Agents Chemother* 2010;54:557-559.

Ceftazidime-Avibactam & Ceftolozane-Tazobactam for *P. aeruginosa* Resistant to: Ceftazidime, Meropenem, & Pip-Tazobactam

Cumulative % inhibited at an MIC of:

	#	≤0.25	0.5	1	2	4	8	16	32	>32
Ceftazidime-Avibactam	**330**		**0.3**	**1.5**	**15.2**	**45.1**	**71.8**	**87.9**	93	100
Ceftolozane-Tazobactam	**175**			**12.6**	**39.4**	**68.6**	**85.1**	**89.7**	92	100

Sader HS et al. *Antimicrob Agents Chemother* 2015;59:3656-3659. Table 1
Farrell DJ et al. *Antimicrob Agents Chemother* 2013;57:6305-6310. Table 3

Ceftazidime-Avibactam Versus Ceftolozane-Tazobactam for P. aeruginosa Resistant to: Ceftazidime, Meropenem, & Pip-Tazobactam*

	Number of Isolates	Caz/Avi	C/T
Humphries	105	29%	52.4%
Grupper	103	54%	79%
Sader	47	70.2%	72.3%

*Buehrle et al and Gonzalez et al excluded due to too few isolates for BLR resistance phenotype

Humphries et al. *Antimicrobial agents and chemotherapy.* 2017 Dec 1;61(12):e01858-17.
Grupper et al. *Antimicrob Agents Chemother.* 2017 Sep 22;61(10). pii: e00875-17. doi: 10.1128/AAC.00875-17. Print 2017 Oct.
Sader et al. *J Antimicrob Chemother.* 2018 Jul 27. doi: 10.1093/jac/dky279. [Epub ahead of print]

Activity of Ceftolozane-Tazobactam and Imipenem-Relebactam against *Pseudomonas aeruginosa* Isolates with Common Resistance Mechanisms

Phenotype/resistance mechanism	IMI		IMI/REL		C/T	
	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S
P. aeruginosa, All (n=5,635)[b]	16	68.9	2	90.8	4	90.6
All IMI-S (n=3,884)[c]	2	100	0.5	100	2	98.4
Inferred derepressed AmpC (n=221)	2	100	0.5	100	4	91.0
Inferred upregulated MexAB-OprM (n=111)	1	100	0.5	100	4	95.5
All IMI-NS (n=1,751)	>32	0	>32	70.5	>32	73.2
No acquired β-lactamase (n=1,381)[d]	16	0	4	86.2	4	91.2
Inferred derepressed AmpC, OprD- (n=151)	32	0	4	89.4	8	84.8
ESBL-positive (n=52)	16	0	4	61.5	>32	9.6
Serine carbapenemase-positive (n=76)	>32	0	>32	2.6	>32	9.2
MBL-positive (n=224)	>32	0	>32	1.3	>32	0.9

Young et al. ECCMID 2018

I need to know antimicrobial susceptibility to these novel agents to effectively manage P. aeruginosa resistant to Ceftazidime, Meropenem, and Pip-Tazo.

It's not all the time, but when I need AST data – there is no substitute.

Treatment Options

CRE

Novel BL/BLI

- Ceftaz-Avibactam
- Mero-Vaborbactam
- Imipenem-Relebactam

Novel Aminoglycoside

- Plazomicin

CR-Pseudomonas

Novel BL/BLI

- Ceftaz-Avibactam
- Ceftolozane-Tazobactam
- Imipenem-Relebactam

Can you help with my Septic Patient?

- MF is a 48 year old male physician
- No past medical history
- Admitted 3 weeks ago to an OSH with ischemic bowel
- Immediate resection of bowel with re-anastamosis

Can you help with my Septic Patient?

- Post-operatively develops mild peritonitis
- Poor return of GI function on TPN via PICC line
- Transferred yesterday, doing well on:
  Vancomycin and Piperacillin-Tazobactam

Can you help with my Septic Patient?

- MF “Crumped” today
- Febrile
- Intubated, high ventilation requirements
- Multiple pressors
- New leukocytosis, renal failure, shock liver

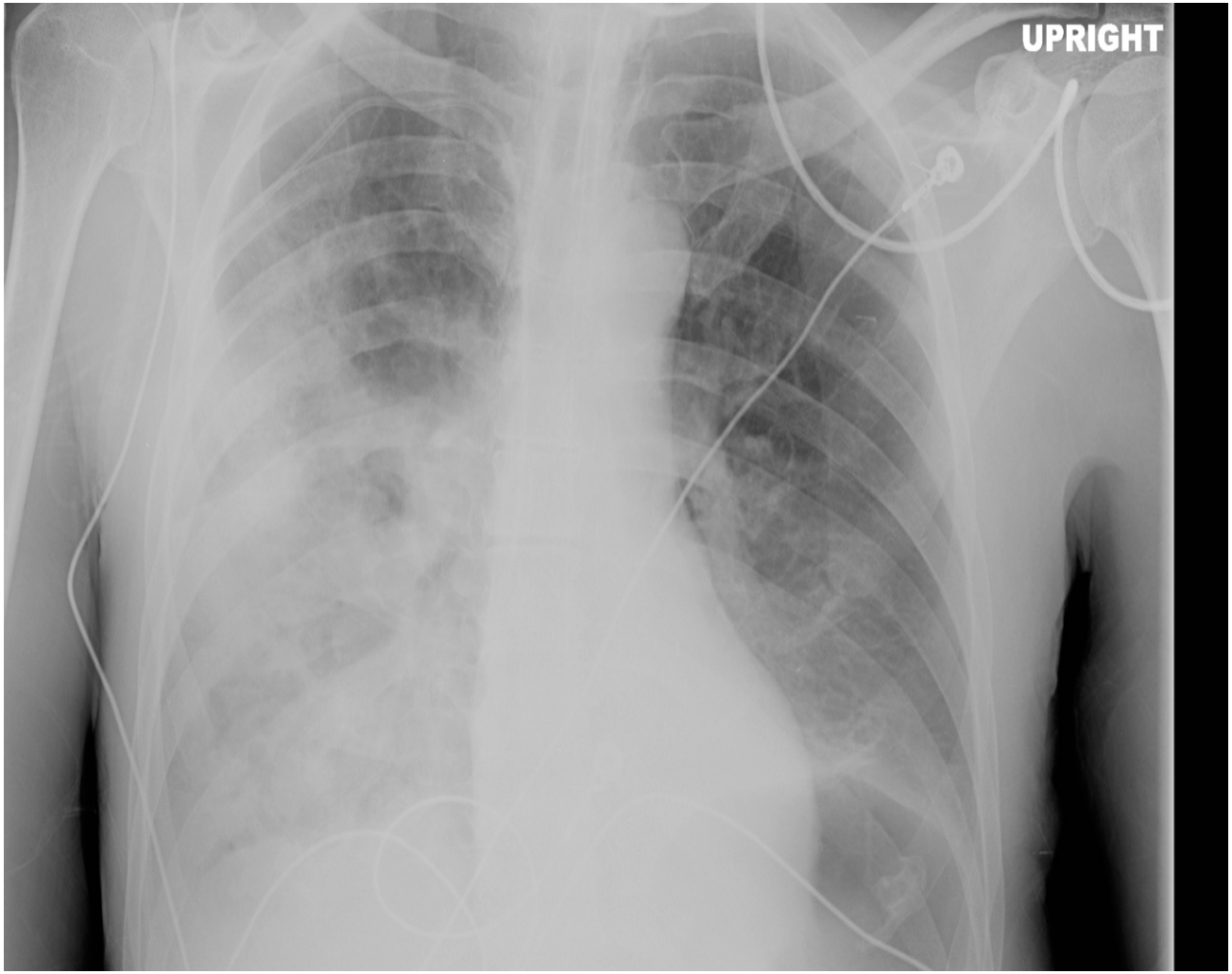
ASSESMENT: FTD

Plan:

1) Find the infection (s)

2) Broad empiric antibiotics

RLL Pneumonia



Review of Today's Culture data

- Outside hospital blood cultures: gram-negative rods

GNR: Meropenem/Gentamicin

K. Pneumoniae from OSH

Antimicrobial	Susceptibility
Ciprofloxacin	R
Pip/Tazobactam	R
Gentamicin	R
TMP-SMX	R
Meropenem	S
Tigecycline	R

2 Days After Consult

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

K. pneumoniae from Local Laboratory

Antimicrobial	Susceptibility
Ciprofloxacin	R
Pip/Tazobactam	R
Gentamicin	R
TMP-SMX	R
Meropenem	R
Tigecycline	R

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

Lodise et al 2018.

Why the discrepancy?

- 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.

Antimicrobial Stewardship Stakeholders

- ASP Pharmacist
- Pharmacy Director

We need correct data!!!

- Infectious Disease Physician
- Treating Physician (Critical Care Doctor)

We need correct data!!!

- Licensed Nurse
- Laboratory Director
- Laboratory Technician

We need resources for all of this testing!!!

Summary

- Dealing with MDRO infections is challenging and complex
- Traditional therapeutic approaches have significant limitations
- Clinicians must be aware of the clinical benefits of novel antimicrobial agents
- Antibiotic Stewardship is designed to get the right drug to the right patient at the right time