

Critical Microbiology Results for Critical Patients

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Disclosures

- I have received Government Research Funding from NIH, AHRQ, CDC, and CTSI
- I have served as a consultant for Achaogen, Allergan, Cempra, Science 37, Theravance, and Thermo Fisher Scientific
- I lead antimicrobial stewardship initiatives in Skilled Nursing Facilities, Expert Stewardship, INC.
- I developed the presentation and the opinions expressed are my own

Objectives

- Discuss a challenging case from a clinical and laboratory perspective
- Evaluate testing options for rapid identification of resistant infections
- Discuss changing epidemiology of *Candida* infections
- Discuss the need for ongoing breakpoint updates

Estimates of HAIs in U.S. Acute Care Hospitals (2011)

Infection Site	Estimated Number
Surgical Site Infections (from any inpatient surgery)	157,500
Pneumonia	157,500
Gastrointestinal Illness	123,100
Other Types of Infections	118,500
Urinary Tract Infections (UTIs)	93,300
Primary Bloodstream Infections (BSIs)	71,900
Estimated Total Number of Infections in Hospitals	721,800

US Causes of Death

	2013	Deaths
1	Heart Disease	611,000
2	Cancer	584,000
3	Accidents	130,000
4	Stroke	129,000
5	Healthcare Associated Infections	100,000
6	Alzheimer's Disease	83,000

<http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm> Accessed 4/22/2015, rounded to the nearest thousand deaths.

http://www.cdc.gov/HAI/pdfs/hai/infections_deaths.pdf Accessed 4/22/2015.

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



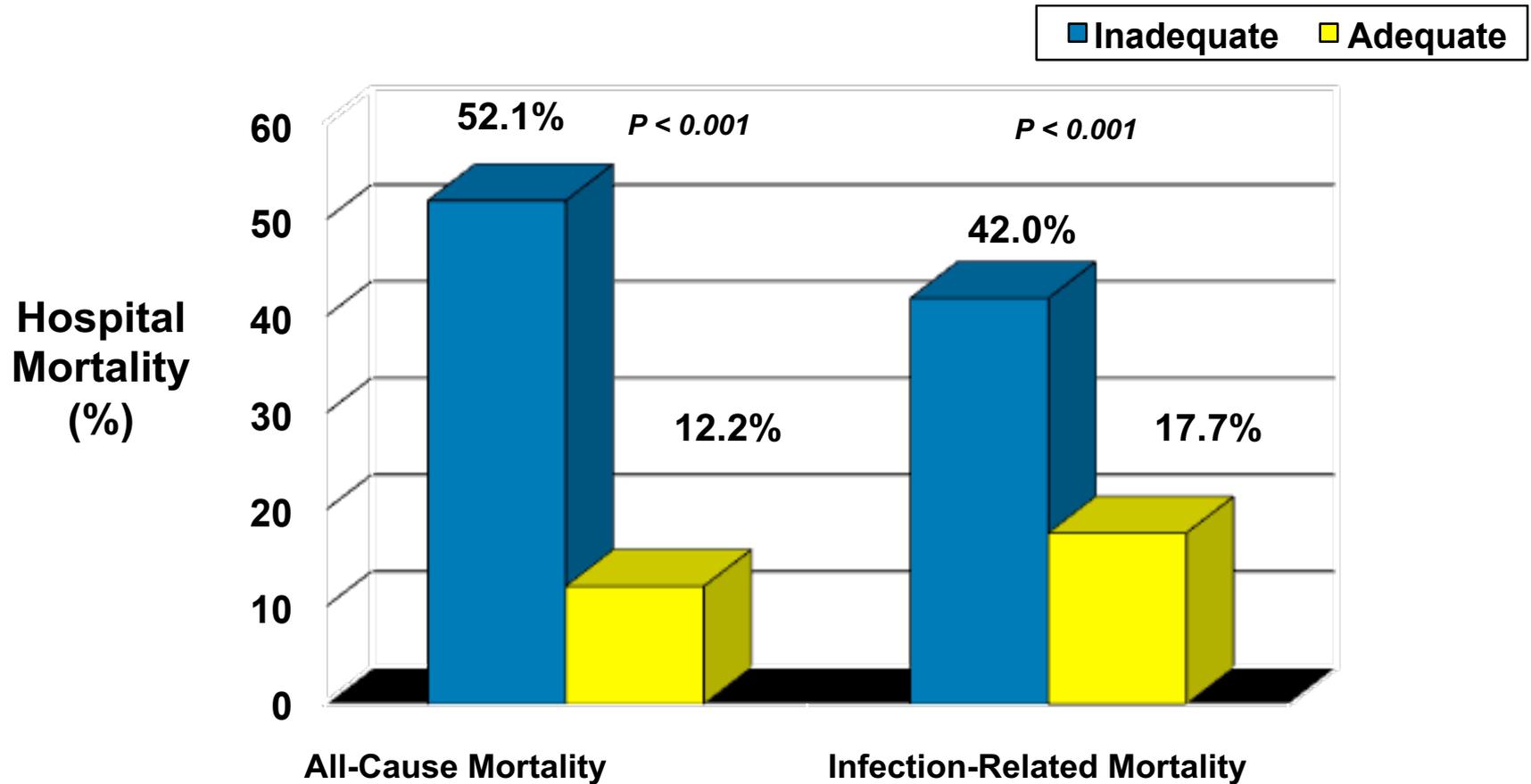
X-Ray Image courtesy of James McKinnell, MD case files
Gram Stain image: CDC Public Health Image Library

Lucy 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

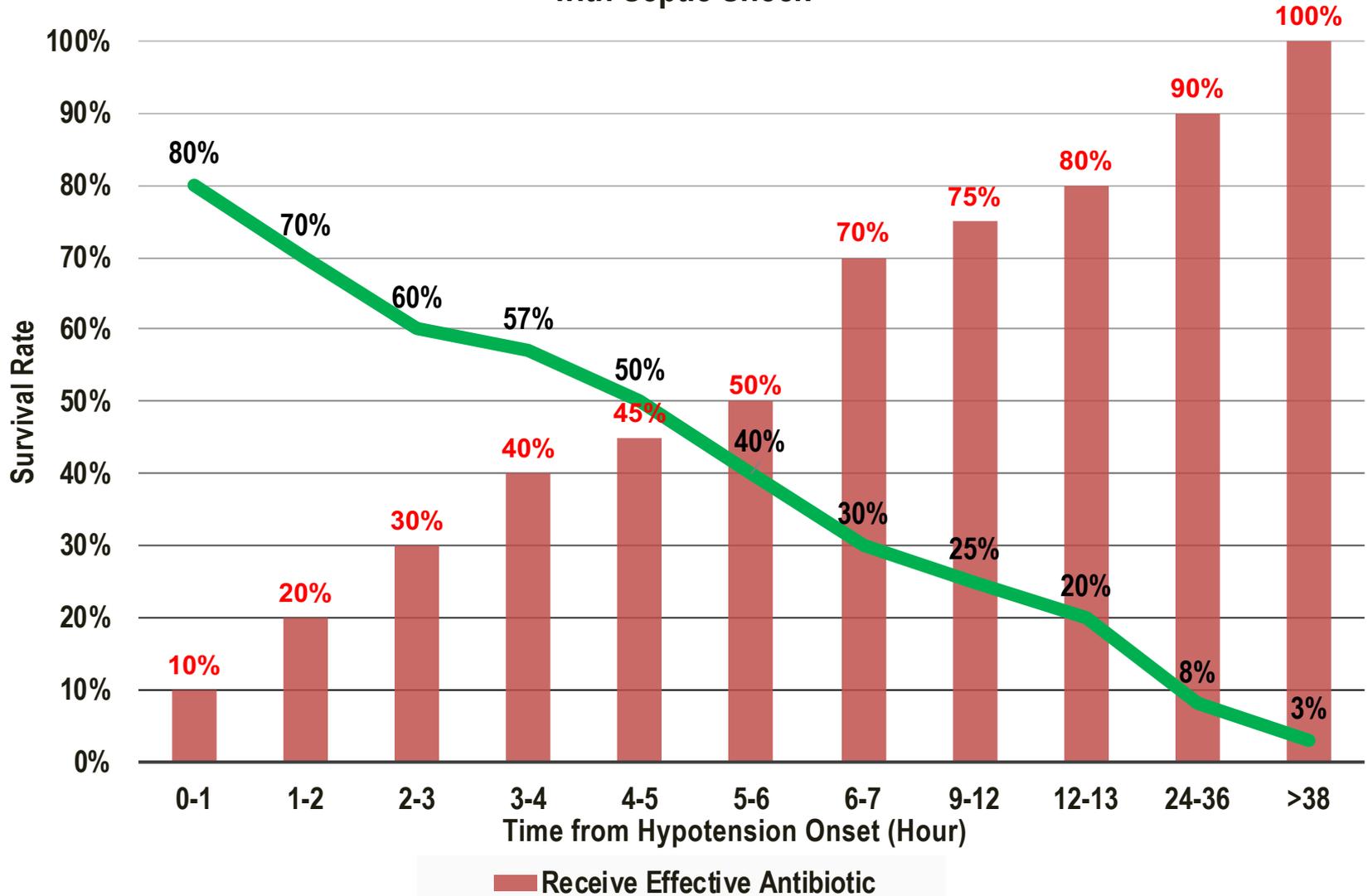


Prospective study (n=2000: 655 with infections)

25% of patients received inadequate treatment

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

Survival Rates and Time to Effective Antimicrobial Treatment among Patients with Septic Shock



Rank order of Pathogens Causing VAP

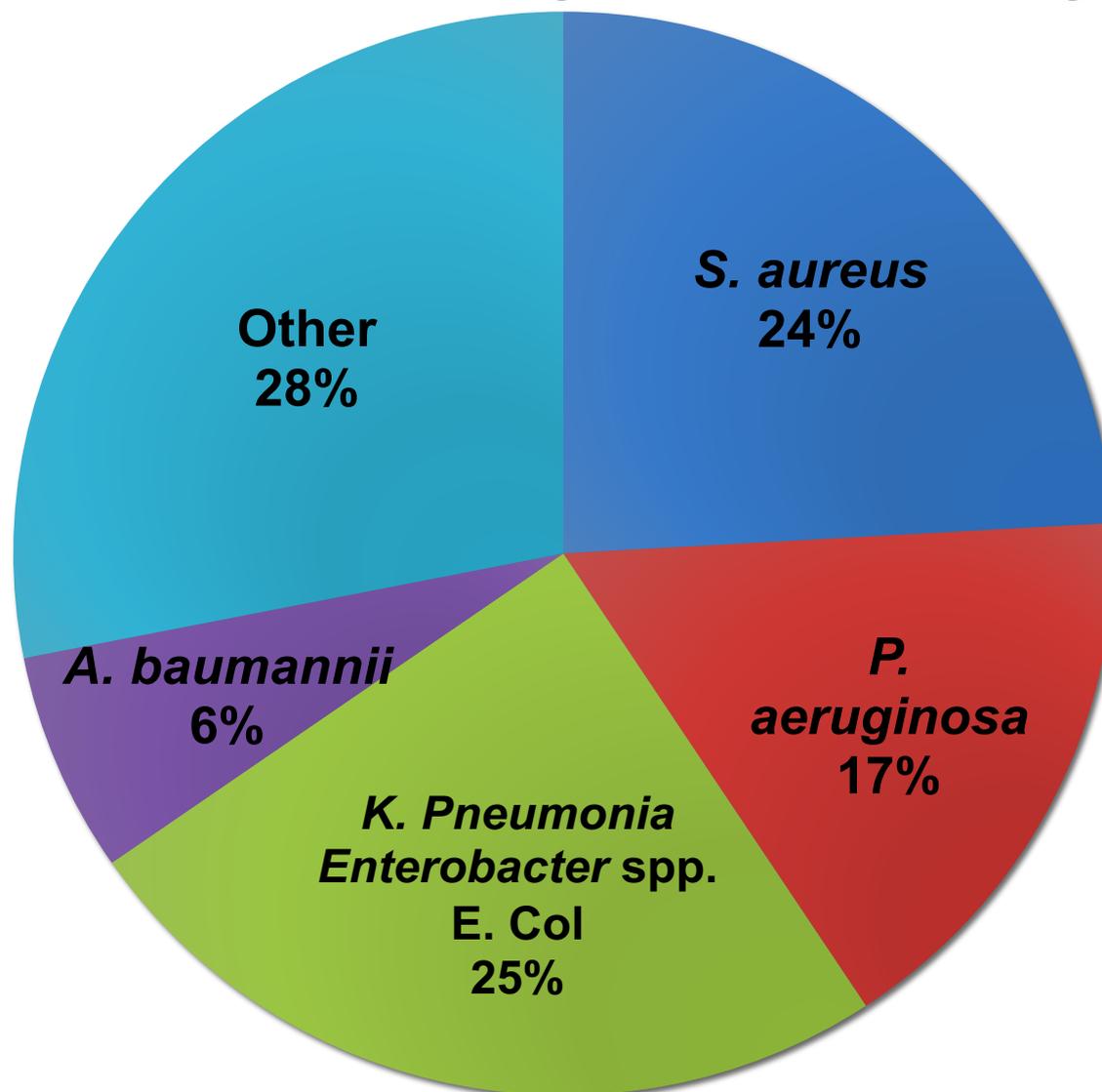


Table 2. Adults (>21 y.o.) Gram-negative Bacteria – Non-Urine Isolates, % Susceptible

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

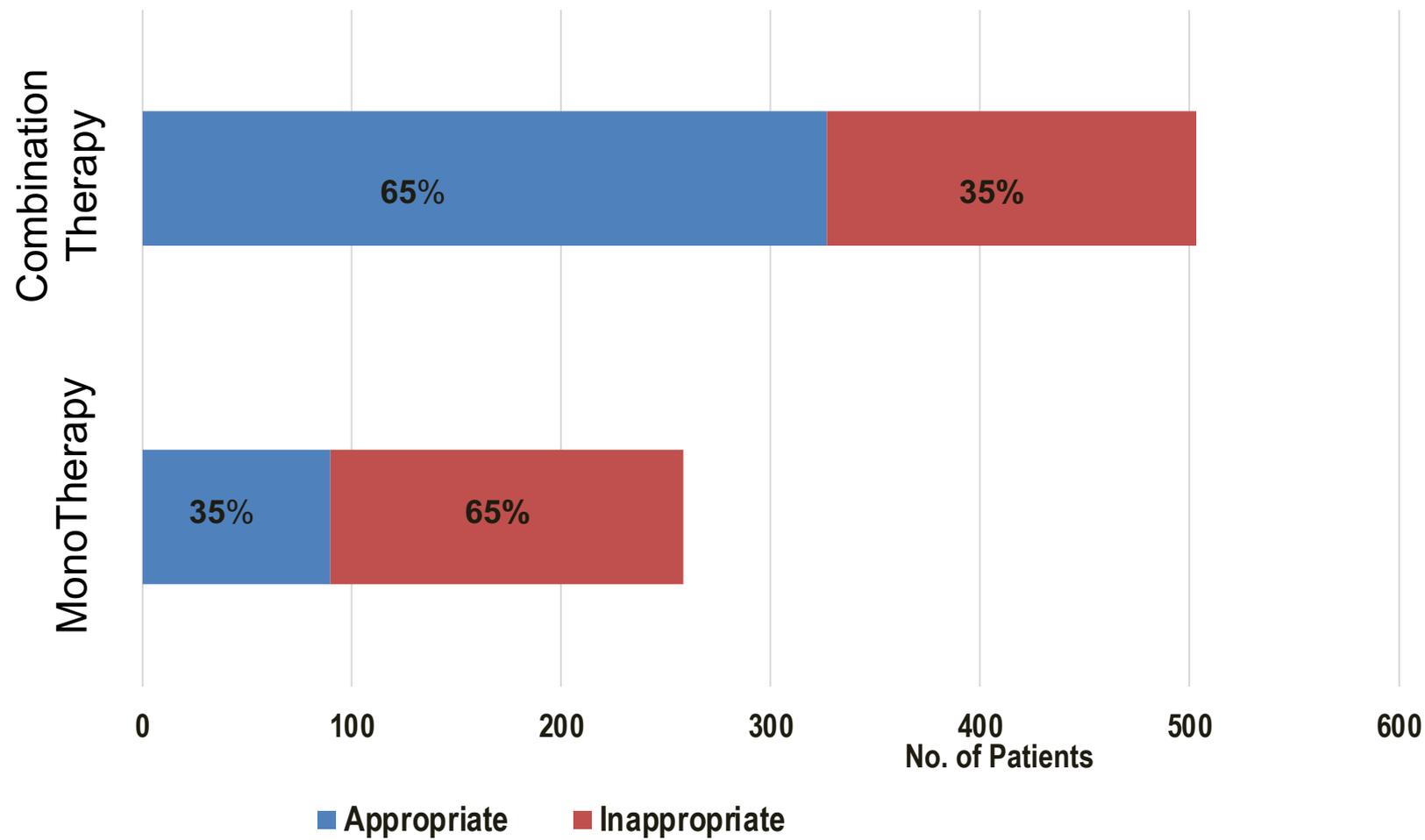
¹ Cefotaxime and ceftriaxone have comparable activity against *Enterobacteriaceae*.

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

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



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

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 pressures, increased over last 24 hours



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 Carbapenem-Resistant *Pseudomonas aeruginosa* Sepsis.

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



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

Polymyxin Study: AST Methods for Colistin

Broth Microdilution Method

Reference Method – CLSI & EUCAST

Agar Dilution

- Not recommended (CLSI/EUCASST)
- 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.

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)

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.”

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*

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

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]

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.

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

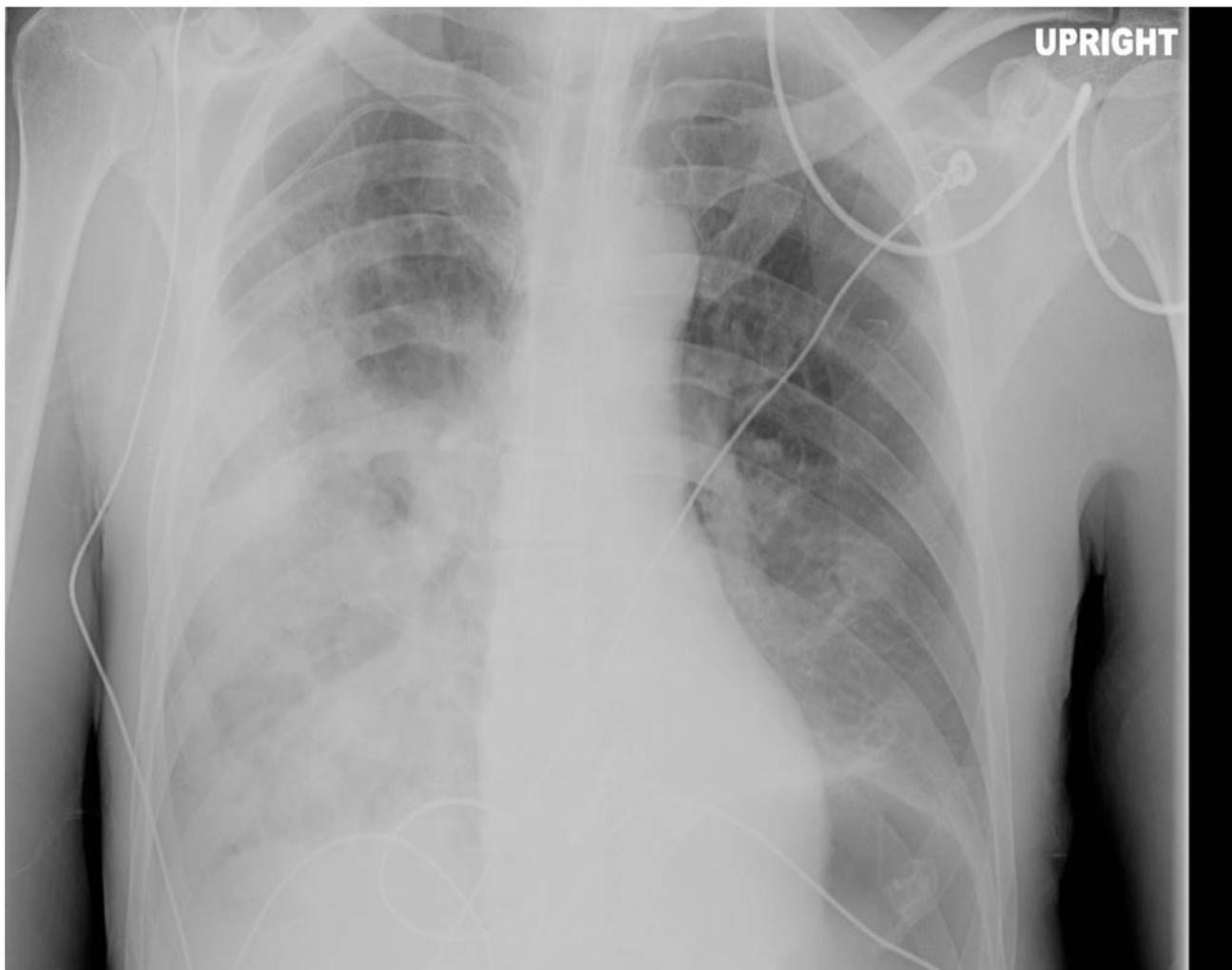
Can you help with my Septic Patient?

- 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

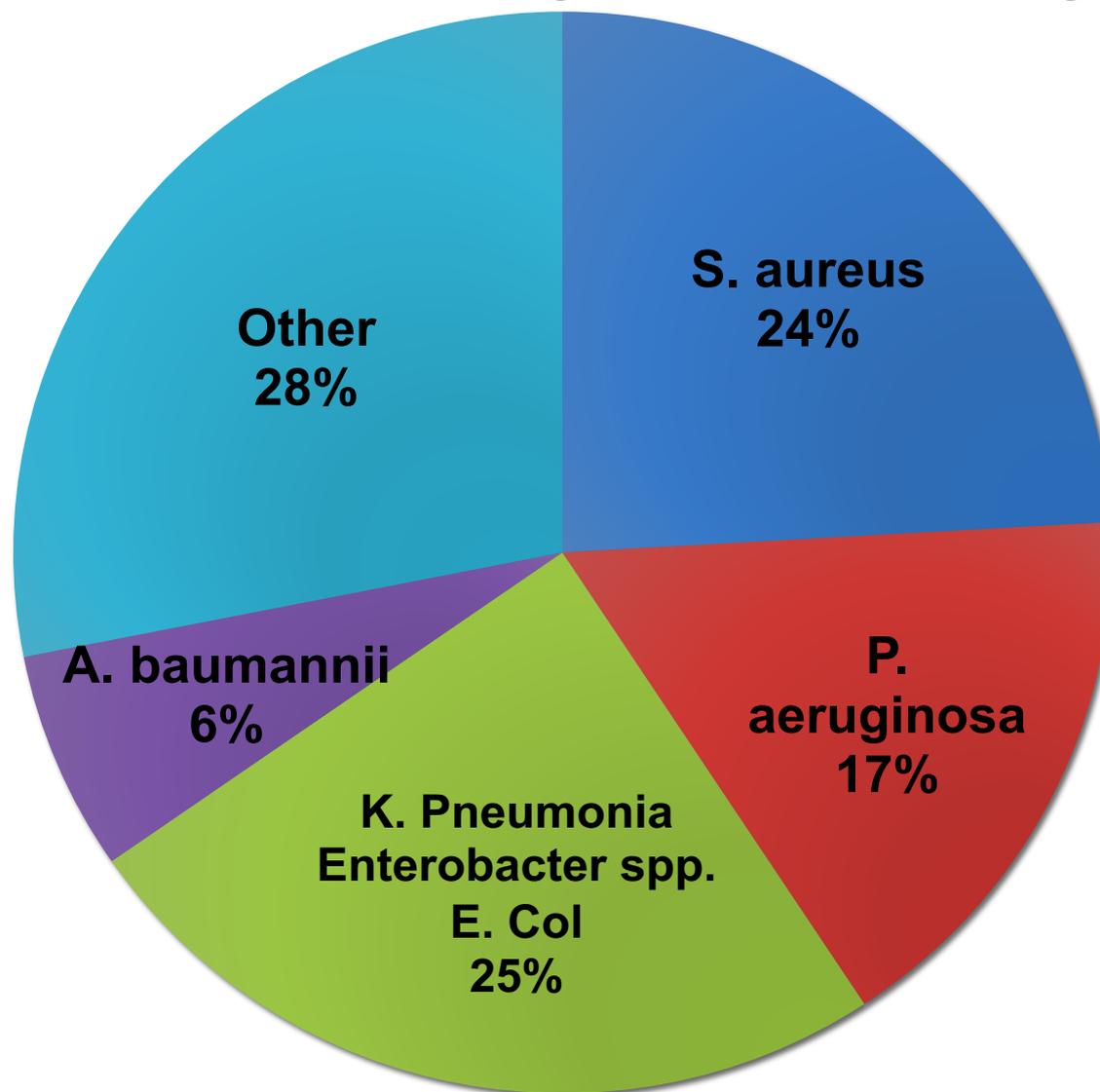
RLL Pneumonia



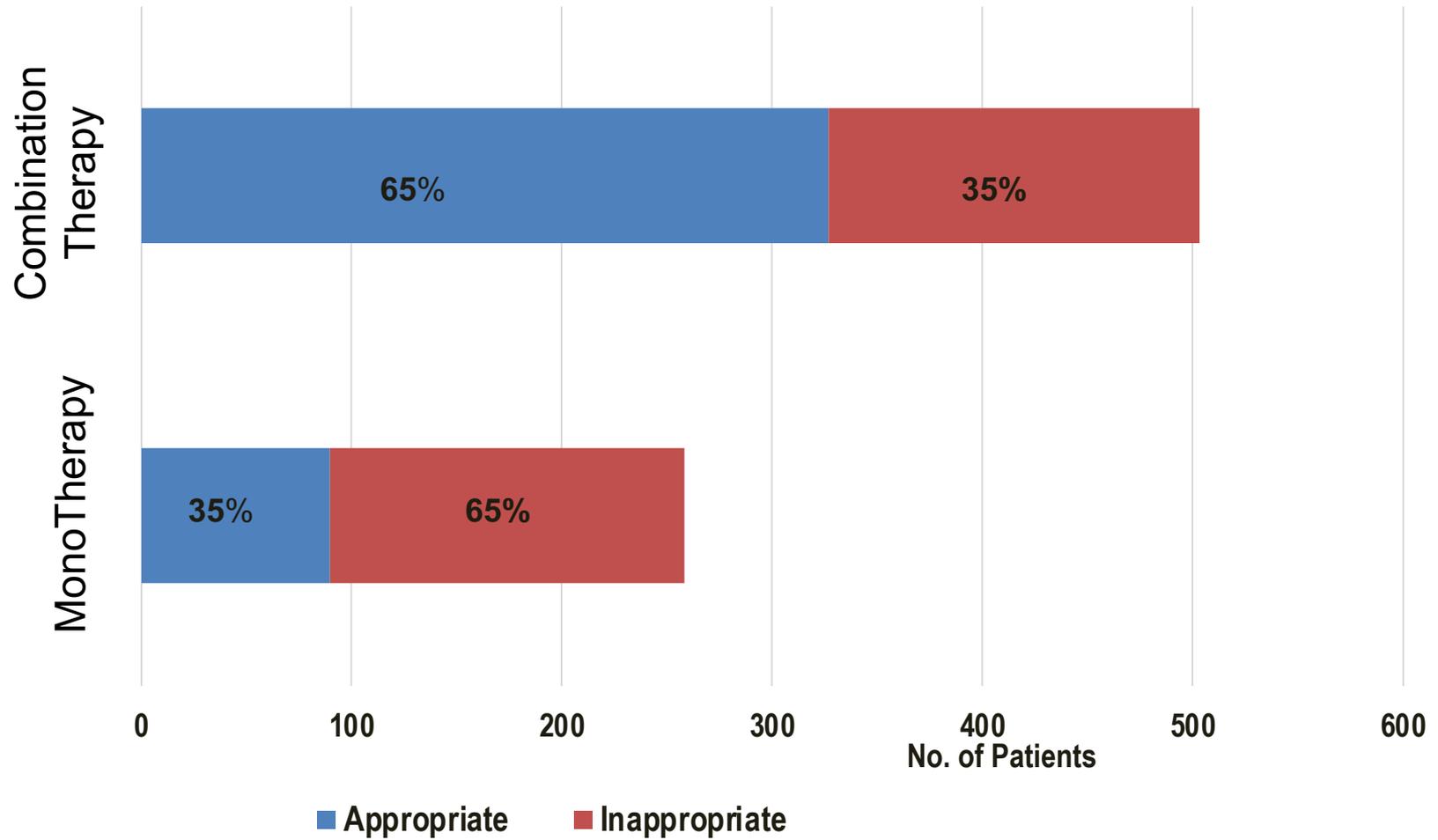
Review of Today's Culture data

- Outside hospital blood cultures: gram-negative rods
- Outside hospital: urine culture positive for “Yeast”

Rank order of Pathogens Causing VAP



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



GNR: Meropenem/Gentamicin

The Power of Rapid Identification

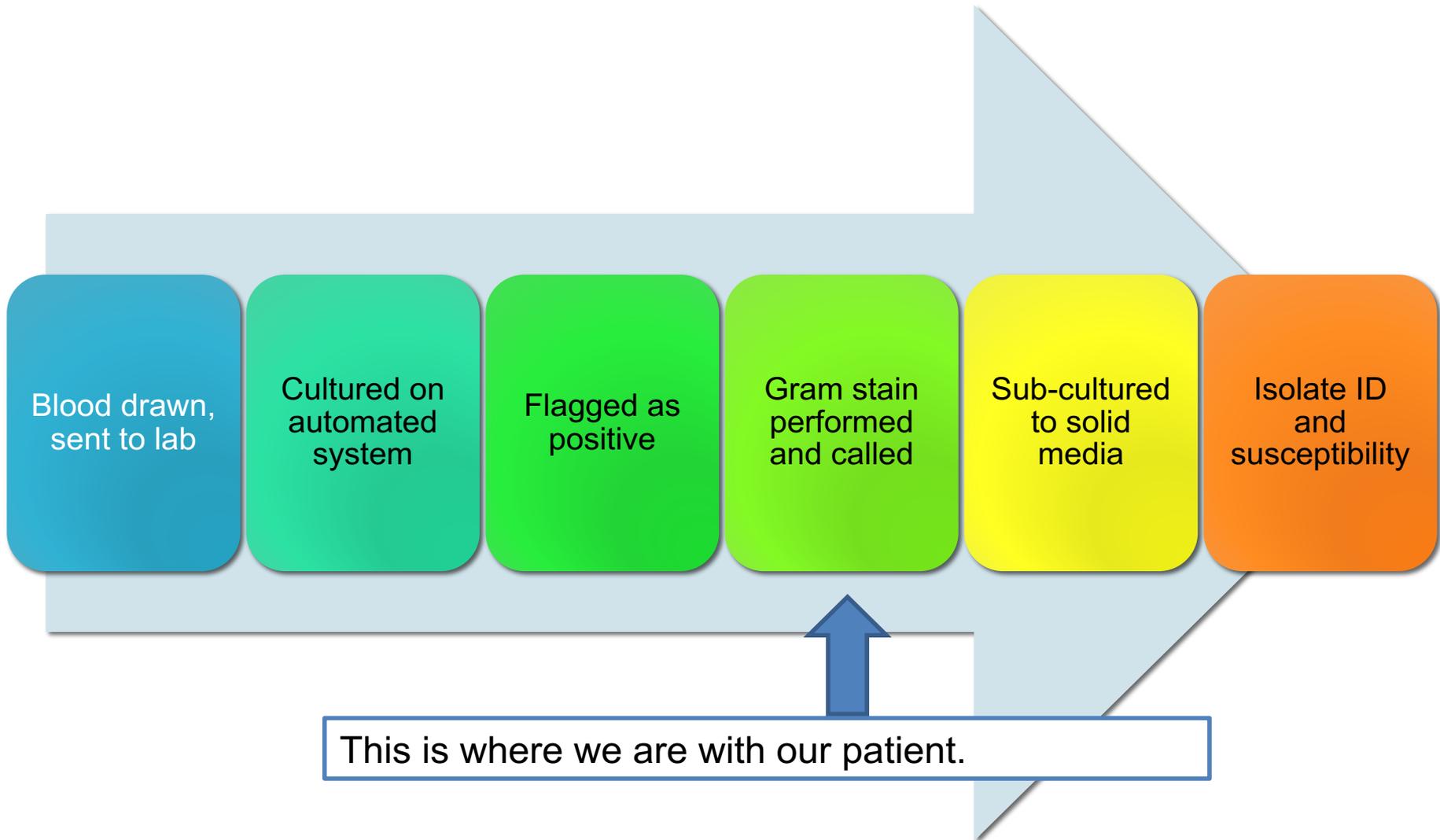


Table 2. RRUMC: Adults (>21 y.o.) Gram-negative Bacteria – Non-Urine Isolates, % Susceptible

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<i>Proteus mirabilis</i>	117	74	87	99	34	95	97	92	99	—	99	99	87	93	71	70	R
<i>Serratia marcescens</i>	99	R	R	98	R	99	— ⁴	— ⁴	99	97	99	99	99	99	93	99	R
<i>Acinetobacter baumannii</i>	49	R	69	49	R	63	61	—	R	74	74	74	65	69	63	67	94
<i>Pseudomonas aeruginosa</i>	498	R	R	87	R	89	90	R	R	80	86	86	92	96	78	R	99
<i>Stenotrophomonas maltophilia</i>	53	R	R	R	R	—	32	R	R	R	—	—	—	R	—	94	45
<i>Burkholderia cepacia complex</i>	12 ⁵	R	R	R	R	R	42	R	R	R	42	R	R	R	58	92	R

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

² R = intrinsic resistance.

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

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

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

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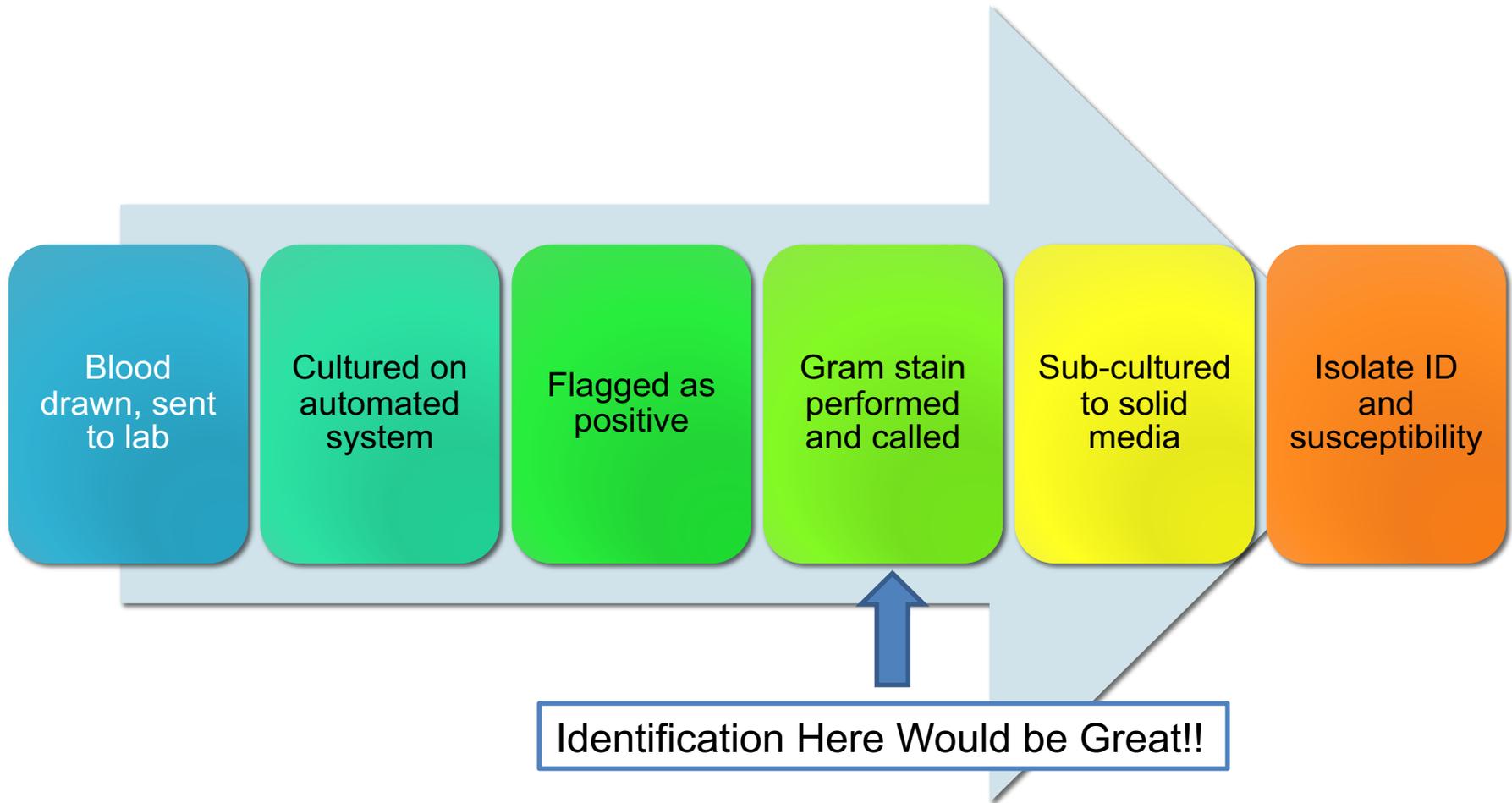
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Hey Micro!!!



GNR: Meropenem/Gentamicin

GP: Vancomycin -> Linezolid

Linezolid for empiric coverage of MRSA pneumonia is controversial. My decision was based on the zephyr trial that suggested improved outcomes with linezolid in treatment of confirmed MRSA pneumonia.

Review of Today's Culture data

- Outside hospital blood cultures: Gram-negative rods
- Outside hospital: **Urine culture positive for "Yeast"**

Should we care about the positive urine culture?

Clinical Infectious Diseases

IDSA GUIDELINE



Infectious Diseases Society of America



hiv medicine association

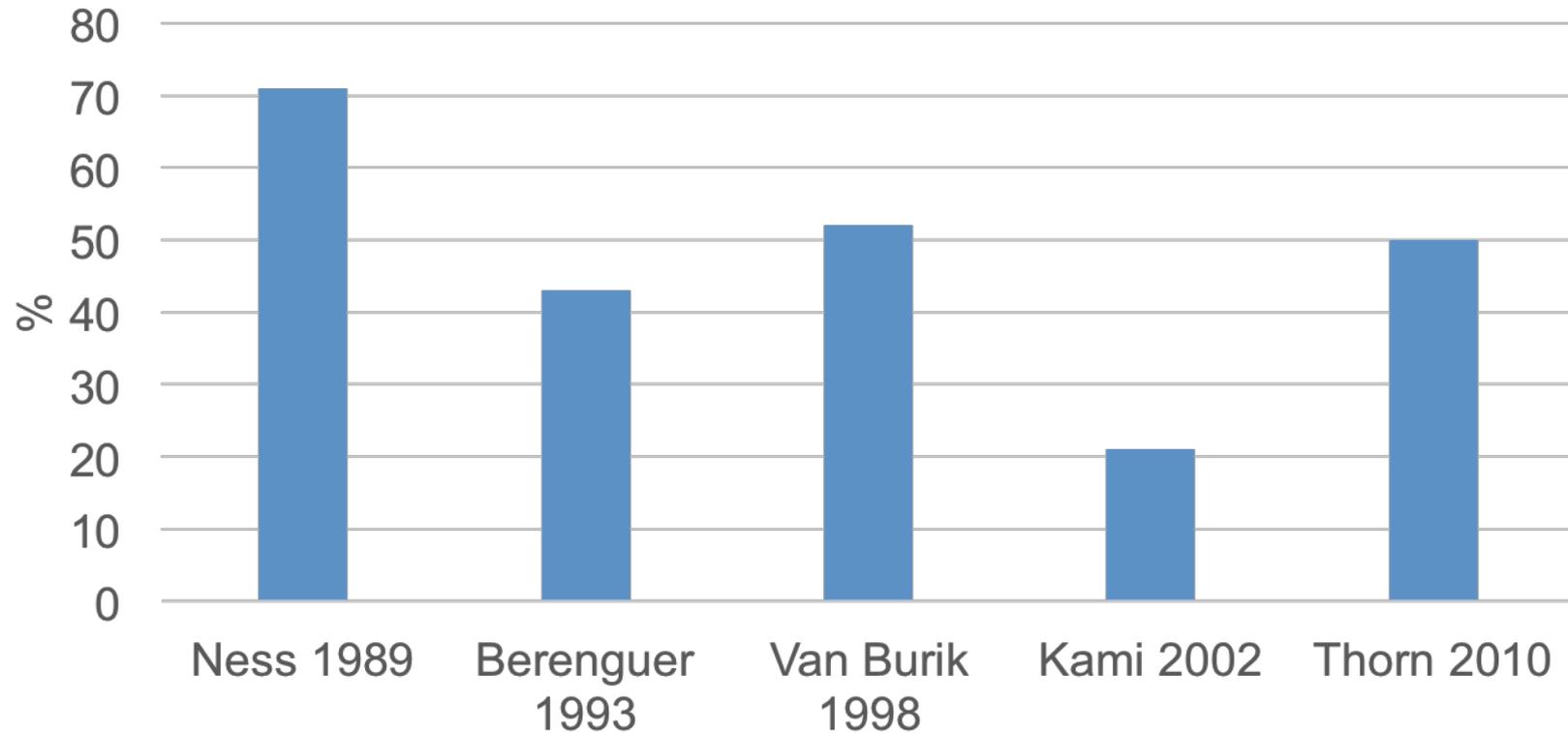


Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,¹ Carol A. Kauffman,² David R. Andes,³ Cornelius J. Clancy,⁴ Kieren A. Marr,⁵ Luis Ostrosky-Zeichner,⁶ Annette C. Reboli,⁷ Mindy G. Schuster,⁸ Jose A. Vazquez,⁹ Thomas J. Walsh,¹⁰ Theoklis E. Zaoutis,¹¹ and Jack D. Sobel¹²

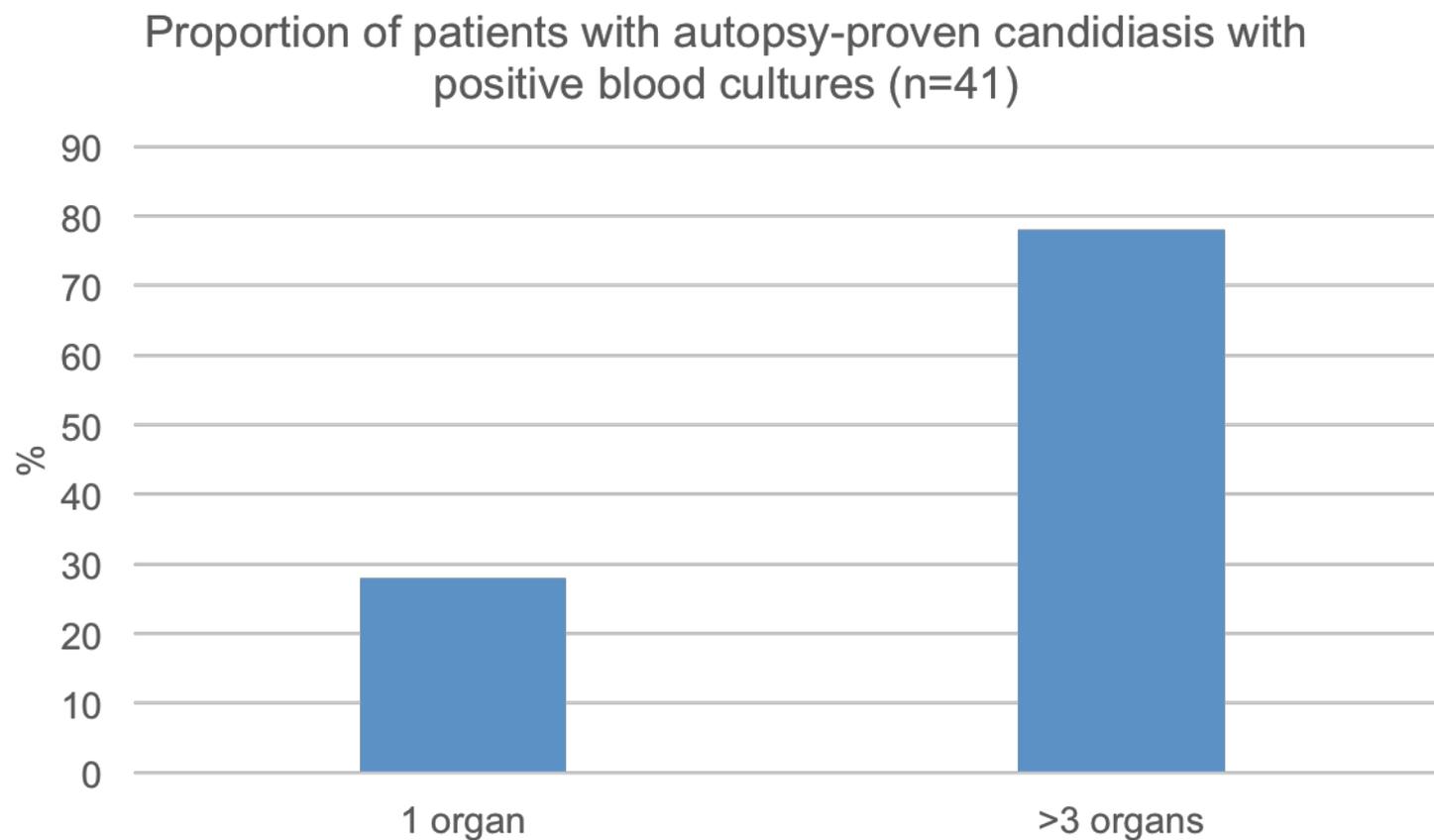
Don't rely on blood cultures to find Candidiasis

Proportion of patients with autopsy-proven candidiasis with positive blood cultures



* CID 2013 56

Too Little, Too Late?



**DMID 1993 17:103-9

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

“Fever in a Patient on Broad Spectrum Antibiotics”

- Candida colonization**
- Severity of illness**
- Exposure to broad-spectrum antibiotics**
- Recent major surgery (especially abdominal surgery)**
- Necrotizing pancreatitis**
- Dialysis**
- Parenteral nutrition**
- Corticosteroids**
- Use of central venous catheters**

Can you help with my Septic Patient?

- MF is a 48 year old male Physician
- No Past Medical History
- Admitted to OSH 3 weeks ago with Ischemic Bowel
- Immediate **Resection of Bowel with Re-Anastamosis**

Can you help with my Septic Patient?

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- Poor Return of GI function on **TPN via PICC line**
- Transferred from the OSH yesterday, doing well on:
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- MF “Crumped” today
- **Febrile**
- Intubated, High Ventilation Requirements
- Multiple Pressors
- **Renal Failure**
- Shock Liver

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,¹ Carol A. Kauffman,² David R. Andes,³ Cornelius J. Clancy,⁴ Kieren A. Marr,⁵ Luis Ostrosky-Zeichner,⁶ Annette C. Reboli,⁷ Mindy G. Schuster,⁸
Jose A. Vazquez,⁹ Thomas J. Walsh,¹⁰ Theoklis E. Zaoutis,¹¹ and Jack D. Sobel¹²

Presumptive treatment of occult candidemia for non-neutropenic patients

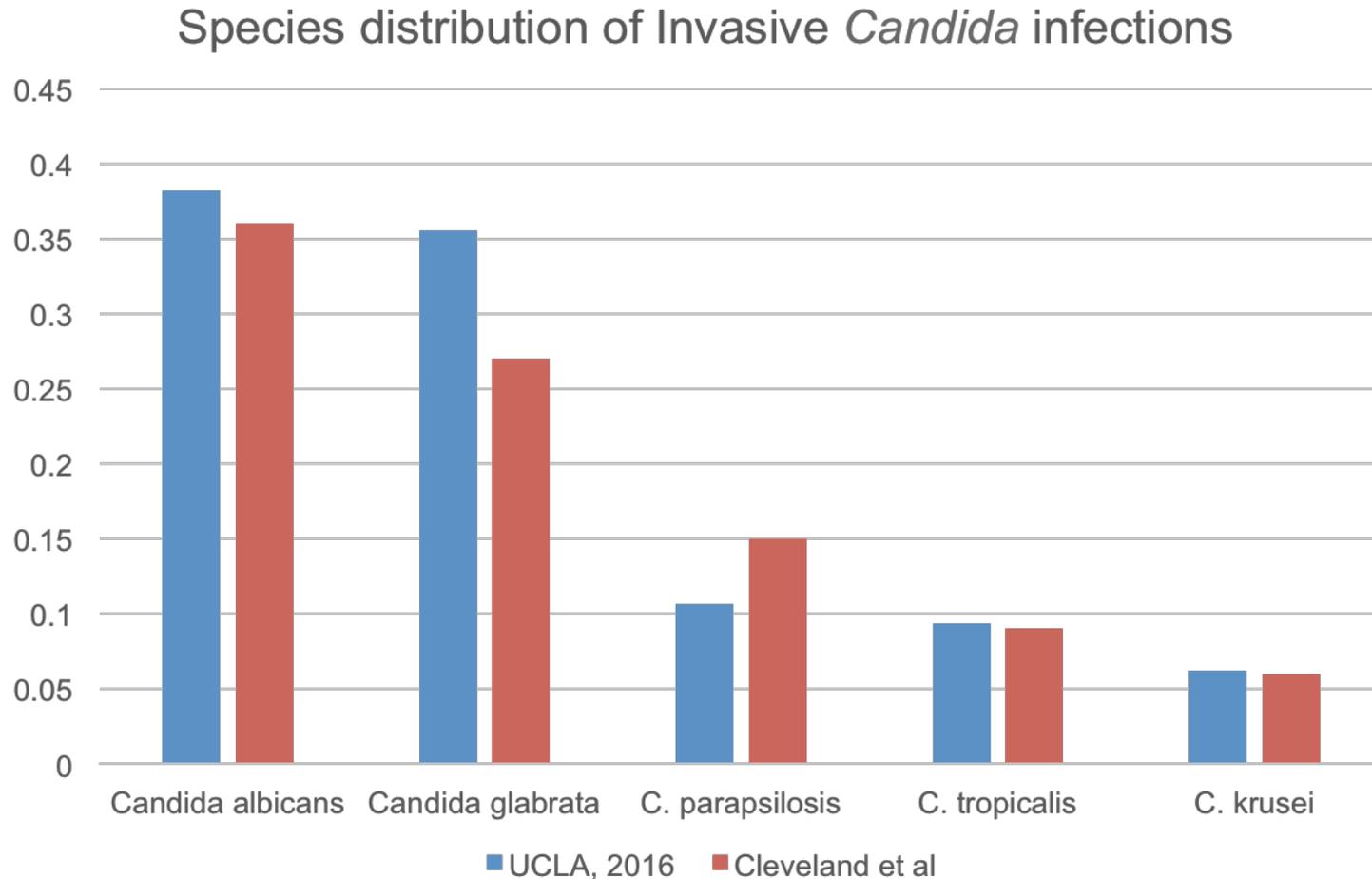
- **Candida colonization**
- **Severity of illness**
- **Exposure to broad-spectrum antibiotics**
- **Recent major surgery (especially abdominal surgery)**
- **Necrotizing pancreatitis**
- **Dialysis**
- **Parenteral nutrition**
- **Corticosteroids**
- **Use of central venous catheters**

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Presumptive treatment based on risk factors

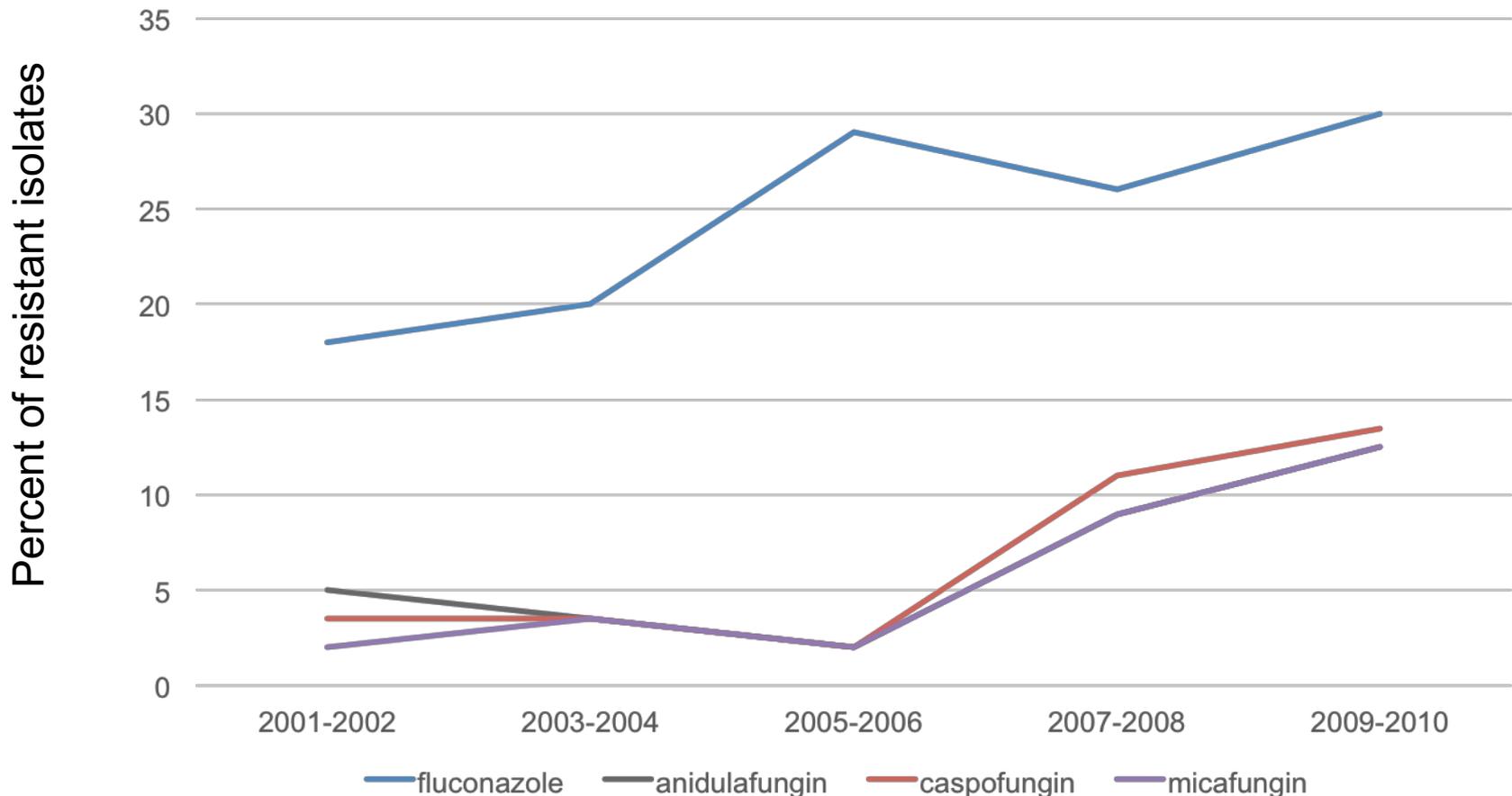
Critical patients should receive an Echinocandin.

Changing epidemiology of *Candida*



Fungal Resistance in *Candida* infections

Resistant *C. glabrata* Blood Stream Infections



Hey Micro!!!

- Can you identify the yeast in the urine?
 - Community urine culture probably not critical
 - In ICU patient, can be very important!
- Can you give me susceptibilities?
 - In-house versus reference laboratory

GNR: Meropenem/Gentamicin

GP: Linezolid

AF: Anidulafungin

1 Day After Consult

- MF still on ventilator with sputum production
- Still febrile on vasopressors
- AST/ALT slightly improved
- Still on dialysis
- Sputum cultures from lab growing *Klebsiella pneumoniae*

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 pressures, 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

Why the discrepancy?

- OSH using old breakpoints, local hospital uses current breakpoints!

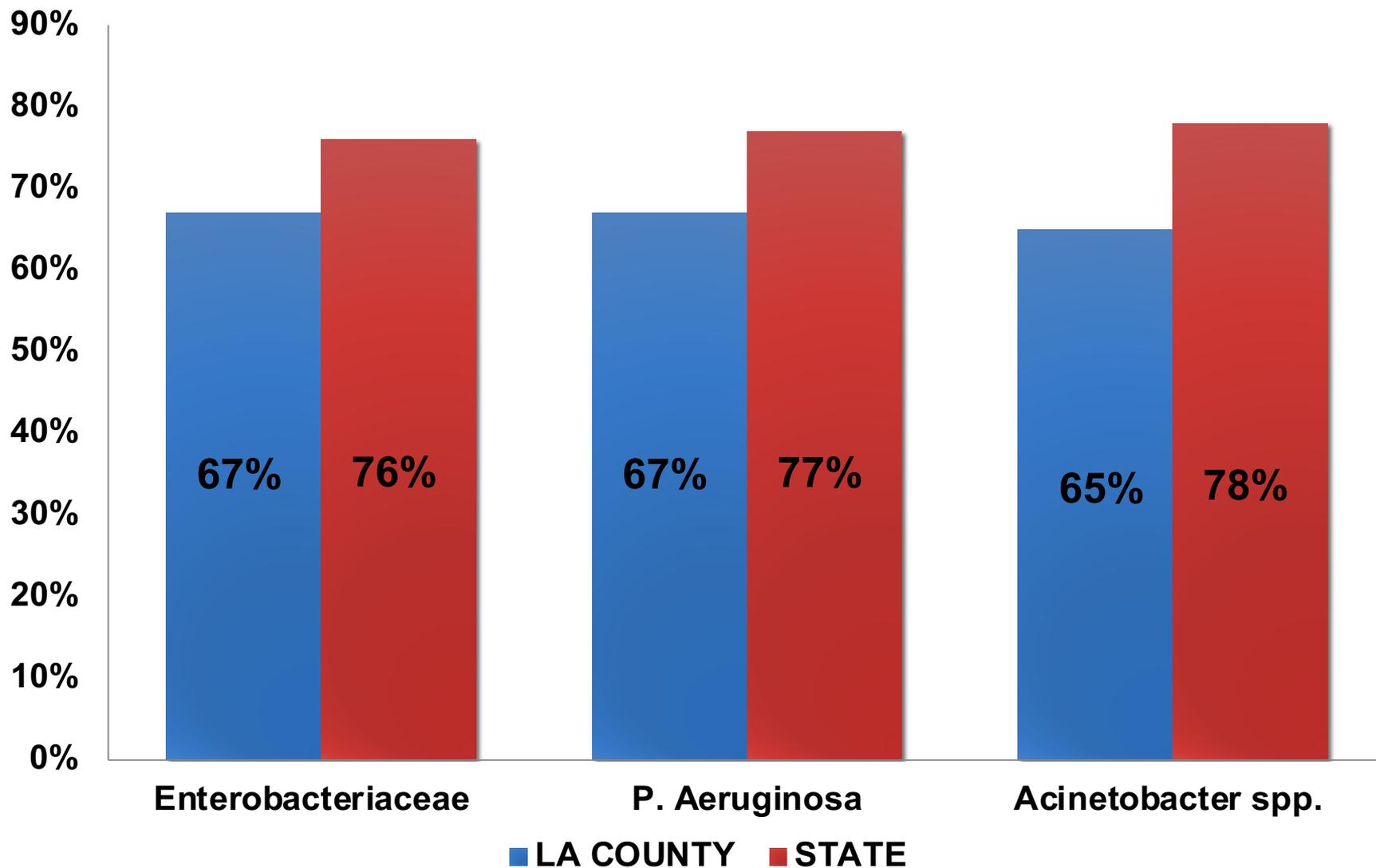
Enterobacteriaceae breakpoints

<u>Antibiotic</u>	<u>Current Breakpoints</u> (M100-S22) MIC (ug/mL)			<u>Previous Breakpoints</u> (M100-S19) MIC (ug/mL)		
	<u>Susceptible</u>	<u>Intermediate</u>	<u>Resistant</u>	<u>Susceptible</u>	<u>Intermediate</u>	<u>Resistant</u>
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.

Use of current CLSI breakpoints



Why would anyone use the old CLSI breakpoints?

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

Not all automated laboratory systems have updated their breakpoints.”

K. pneumoniae final results

Antimicrobial	Susceptibility
Meropenem	R
Meropenem MIC	2

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



Clinical Outcomes of *Enterobacteriaceae* Infections Stratified by Carbapenem MICs

Twisha S. Patel, Jerod L. Nagel

Departments of Pharmacy Services and Clinical Sciences, University of Michigan Health System and College of Pharmacy, Ann Arbor, Michigan, USA

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

Does knowing the MIC matter?

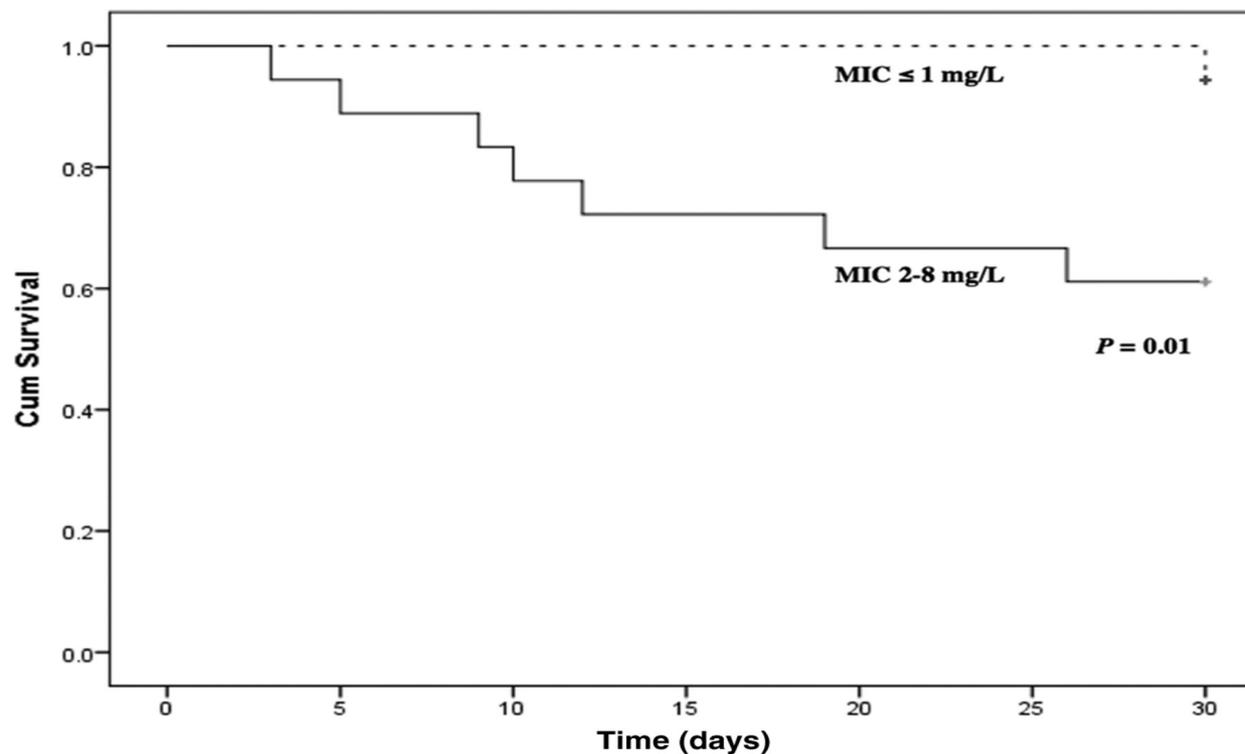


TABLE 3 Clinical outcomes stratified by carbapenem MIC

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

Does knowing the MIC matter?

- Carbapenems are un-reliable when the MIC is ≥ 2 mcg/ml
- Failure of carbapenems at MIC ≥ 2 mcg/ml is largely due to the pharmacokinetics of the drug
- Carbapenems work by time-dependent killing, measured as time above the MIC

GPC: Linezolid

GNR: ~~Meropenem/Gentamicin~~

Ceftazidime-Avibactam

Meropenem

Colistin Inhaled

Other: Anidulafungin

GPC: Linezolid

GNR: ~~Meropenem/Gentamicin~~

Ceftazidime-Avibactam

Plazomicin

~~**Meropenem**~~

~~**Colistin Inhaled**~~

Other: Anidulafungin

8 Days After Consult

- MF still on ventilator, but sputum production nearly resolved
- Afebrile
- Off Pressors
- Still on Dialysis, but urine output improving

Summary

- Dealing with MDRO infections is challenging and complex
- Develop your relationship with the microbiology laboratory to understand your local limitations;
 - Breakpoints
 - Antifungal Drug Testing
 - Rapid Diagnostics
- Critical microbiology results can improve care, particularly for critically ill patients