COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN

An Antimicrobial Stewardship Perspective on the Impact of MICs on Patient Outcomes

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Objectives

- Examine the ways in which the focus on antibiotic stewardship is increasing with a view to providing optimal care, and reducing unnecessary antibiotic exposure risk
- Explain how utilization of institutional data can guide empiric therapy for multi-drug-resistant infections
- Discuss the importance of timely and accurate organism identification and susceptibility data in conducting daily antibiotic stewardship activities and treating aggressive, complicated infections
- Describe how effective stewardship can reduce development of resistance and improve patient outcomes

Introduction & Overview

- Provide a stewardship overview, and discuss changes to the national landscape, and priorities
- Discuss the importance of micro lab and accurate MICs to help stewardship programs meet goals/priorities
  - QI work-metrics linked to reimbursement
  - MDRO
  - De-escalation
  - Outcomes programs

What is Antimicrobial Stewardship?

- Prescribe the correct drug, at the correct dose/frequency, at the correct time
- Discontinue unnecessary antimicrobial therapy
- Promote appropriate comprehensive management of infections
- Guide appropriate ordering of labs and reporting of lab results that impact antimicrobial prescribing
- Contribute to initiatives aimed at improving the quality of care and specific metrics related to infection

Movement Away from Fee-for-Service Healthcare Models

- **Increased focus on quality performance measures and patient outcomes**
  - Linked to hospital reimbursement
- **Tracking and public reporting of hospital data**
  - National Quality Forum (NQF)
  - Medicare and Medicaid Services (CMS)
  - Agency for Healthcare Research and Quality (AHRQ)
  - The Joint Commission (TJC)
  - The Leapfrog Group

ID Metrics on Michigan Medicine Executive Dashboard

- **Metrics linked to CMS reimbursement**
  - Sepsis, post-op surgical infections, C. diff, CLABSI, CAUTI
- **Metrics linked to third-party payer & performance**
  - Pneumonia treatment & duration, sepsis, UTI, post-op infections
- **Metrics linked to profit margin**
  - Length of hospitalization, hospital readmissions, antimicrobial cost
- **Stewardship TJC accreditation standards**
  - Antibiotic utilization and resistance in the acute care and ambulatory settings

Daily Patient-Care Activities

Drug-Based Stewardship

- Prior approval
- Criteria restricted

Disease-Based Stewardship

- HIV
- Candidemia
- *S. aureus* bacteremia
- *C. difficile* colitis

Micro-Based Stewardship

- Culture Review
- Multi-drug resistant organisms

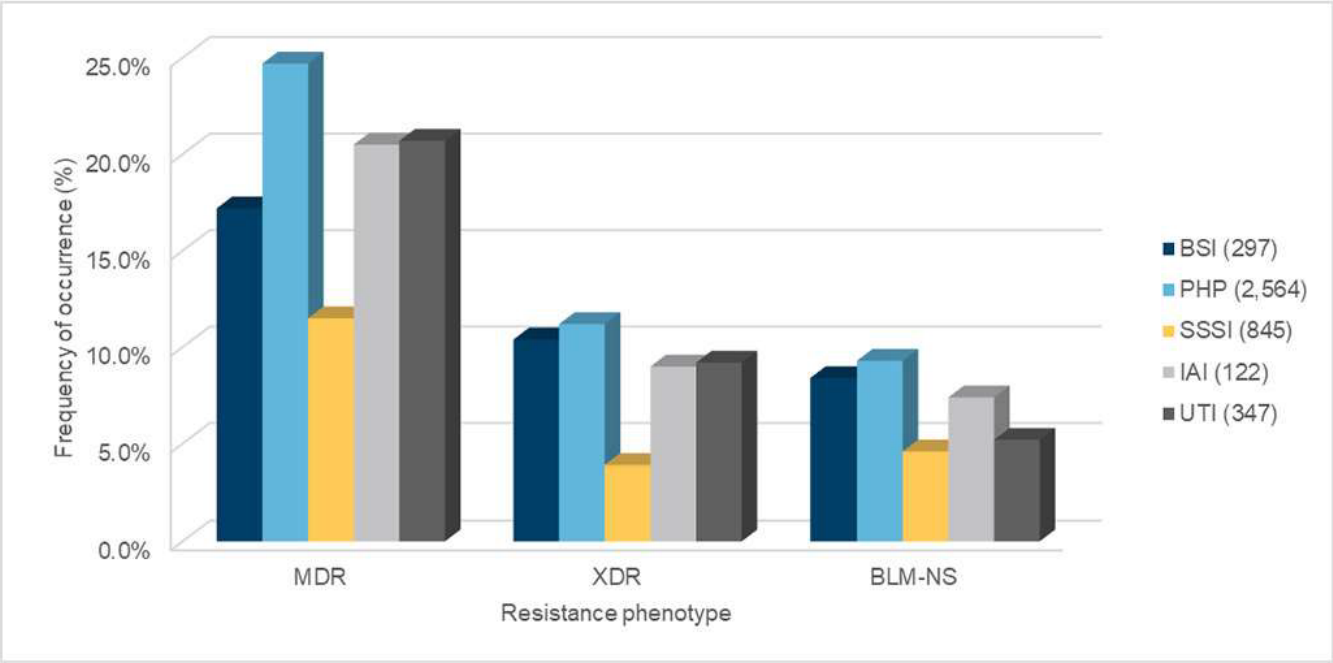
Quality Improvement Activities

- Implement methods to improve management of infectious diseases and antimicrobials
- Improve publicly reported quality performance measures and outcomes measures
- Provide input for various hospital committees

Case: Initial Patient Presentation

- **68 year-old male presents to the ED with respiratory distress, productive cough, and chest pain**
  - PE: Rapid, labored and shallow breathing. Rhales in lower lung
  - PMH: Severe COPD, Dementia, CKD, Malnutrition.
  - SH: Recently hospitalized 3 weeks ago for COPD exacerbation, and currently resides in an extended care facility
  - Micro history: grew Pseudomonas aeruginosa from resp cx
- **Diagnosed with pneumonia**
  - Intubate and admitted to the ICU
  - Blood and sputum cultures are ordered
  - Cefepime, vancomycin and tobramycin are started

Frequency of resistance in *P. aeruginosa* stratified by infection type



MDR = multidrug-resistant
Resistant to ≥ 1 agent in ≥ 3 drug classes

XDR = extensively drug-resistant
Resistant to ≥ 1 agent in all but ≤ 2 drug classes

BLM-NS = β-lactam non-susceptible
Resistant to all beta-lactams tested

BSI = bloodstream infection;
PHP = pneumonia in hospitalized patient;
SSSI = skin and skin structure infection;
IAI = intra-abdominal infection;
UTI = urinary tract infection

Sader HS, et al. *Diagn Microbiol Infect Dis.* 2018;92(1):69-74.

When other options fail

Susceptibility data from clinical *P. aeruginosa* isolates in the U.S. from 2018-2020

- 70.4% representing respiratory isolates

Phenotype	No. (% total)	Antimicrobial agent, % susceptible					
		Cefepime	Piperacillin-tazobactam	Meropenem	Levofloxacin	Ceftazidime-avibactam	Ceftolozane-tazobactam
All	2531 (100)	81.6	77.0	78.3	66.8	**94.4**	**96.4**
MDR	319 (12.6)	12.2	8.8	19.7	18.5	**63.3**	**75.9**
Beta-lactam NS	207 (8.2)	0	0	0	15.9	**50.2**	**73.4**

MDR = multidrug-resistant, resistant to ≥ 1 agent from 3 drug classes

Karlowsky JA, et al. *Antimicrob Agents Chemother.* 2022;66(5):e0018922.

What about the bigger picture?

Susceptibility data from hospitalized patients with **additional gram-negative isolates** in the U.S. and Europe from 2020

- 31.8% representing respiratory isolates

Organism	No. isolates	Antimicrobial agent, % susceptible					
		Piperacillin-tazobactam	Meropenem	Levofloxacin	Ceftazidime-avibactam	Ceftolozane-tazobactam	Cefiderocol
Enterobacterales	8047	89.0	97.8	--	99.5	--	**99.8**
P. aeruginosa	2282	78.0	78.1	--	96.4	96.1	**99.6**
Acinetobacter spp.	650	45.8	52.6	--	50.8*	--	**97.7**
S. maltophilia	338	--	--	82.5	16.6*	--	**97.9**

*Susceptibility data for ceftazidime monotherapy

Shortridge D, et al. *Microbiol Spectr.* 2022;10(2):e0271221.

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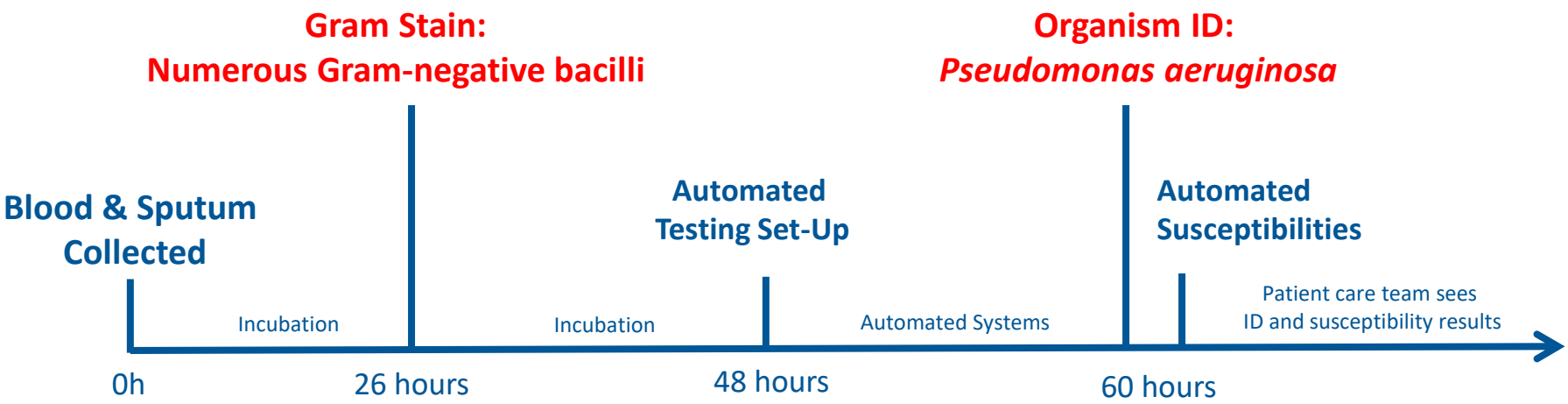
Case: Microbiology Results



Antimicrobial	MIC	Interpretation
Cefepime	>16	R
Ceftazidime	>16	R
Piperacillin/tazobactam	>64	R
Meropenem	>16	R
Ciprofloxacin	>4	R
Tobramycin	>8	R

Case: Next Steps

- **Additional susceptibility requests:**
  - Ceftolozane/tazobactam
  - Ceftazidime/avibactam
  - Meropenem/vaborbactam
  - Imipenem/relabactam
  - Cefiderocol

How much longer would it take to get these MICs and susceptibilities?

Audience Poll Question #1

How much longer would it take to get these MICs and susceptibilities?

A. **No additional time.** Most or all of these antimicrobials are part of a standard Pseudomonas testing procedure
B. **Some additional time is required.** The lab does testing of these antimicrobial for all Pseudomonas via KB, E-test, or other testing methods outside our standard antimicrobial sensitivity workflow
C. **Additional time is needed.** The lab will conduct further antimicrobial testing upon request on case-by-case basis

Efficacy of Ceftolozane/tazobactam Treatment for MDRO *Pseudomonas* Infections

- **Prospective observational study**
  - 205 patients; majority with pneumonia
  - Median APACHE II = 19 and Charlson Comorbidity Index = 4
  - 19% mortality, and 73% clinical and microbiologic success
- **Only 1 factors was associated with survival, microbiologic success and clinical success:**

Initiation of ceftolozane/tazobactam within 4 days of culture	
Survival	5.55 OR (95% CI, 2.14-14.4)
Clinical Success	2.93 OR (95% CI, 1.4-6.1)
Microbiologic Success	2.59 OR (95% CI, 1.24-5.38)

Open Forum Infect Dis. 2018 Oct 31;5(11)

Drive-Home Point #1

- **Having MIC and susceptibility data available for the treatment of MDR Gram-negatives is essential to antimicrobial stewardship**
  - 20-40% of Pseudomonas isolates are resistant to all work-horse beta-lactam
  - ESBL rates vary significantly among geographic regions and rates are increasing

Audience Poll Question #2

Has your lab been involved in quality improvement initiatives linked to hospital financial incentives (sepsis, post-op surgical infections, C.diff, CLABSI, etc)?

A. Yes

B. No

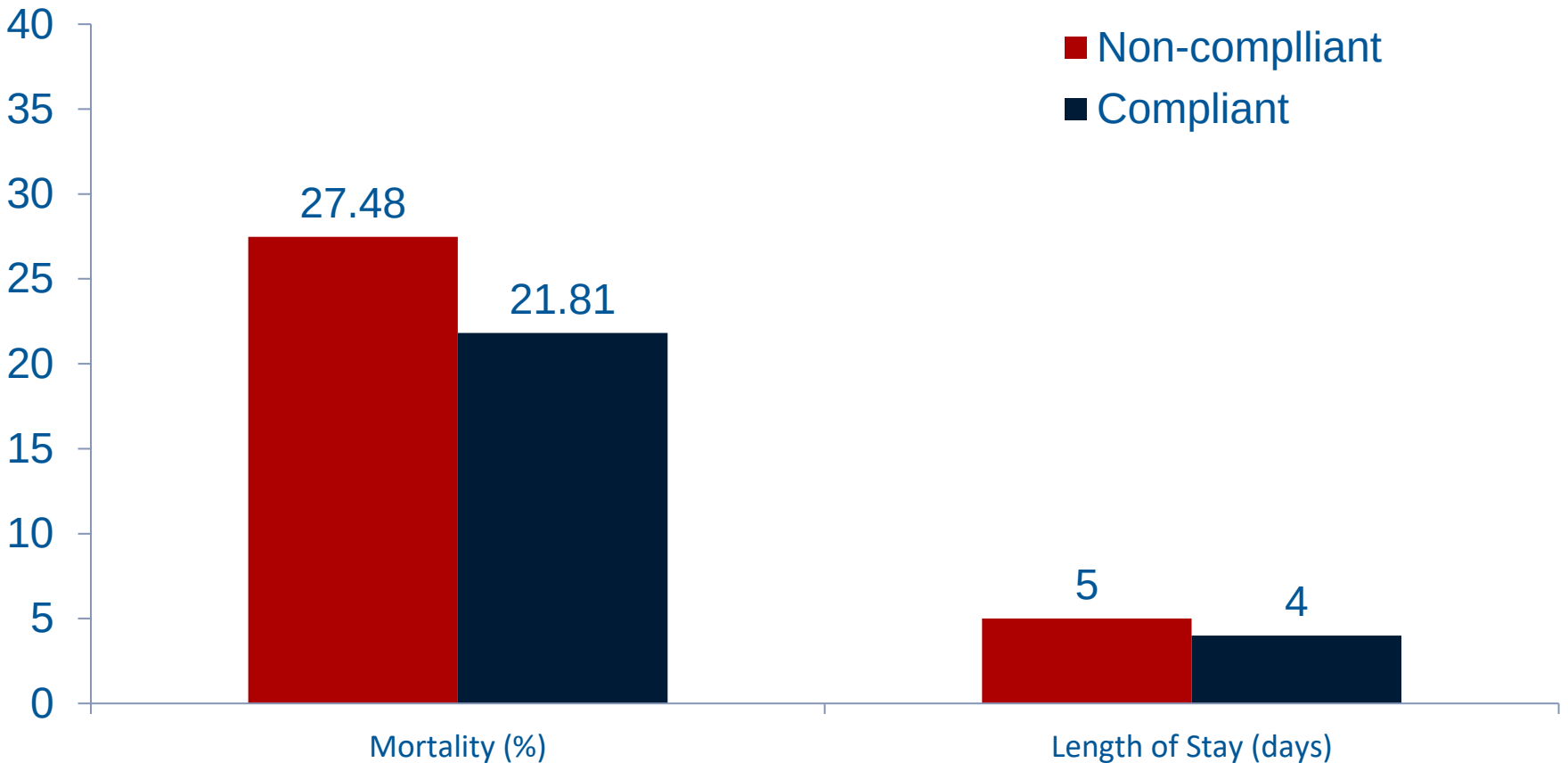
C. Not sure

Sepsis Management

Action	Severe Sepsis		Septic Shock	
	3-hr	6-hr	3-hr	6-hr
Initiate Antibiotics	Yes		Yes	
Blood culture	Yes		Yes	
Initial Lactate	Yes		Yes	
Repeat lactate		Yes*	Yes	
Crystalloid fluids			Yes	
Vasopressor				Yes*
Repeat volume status				Yes*

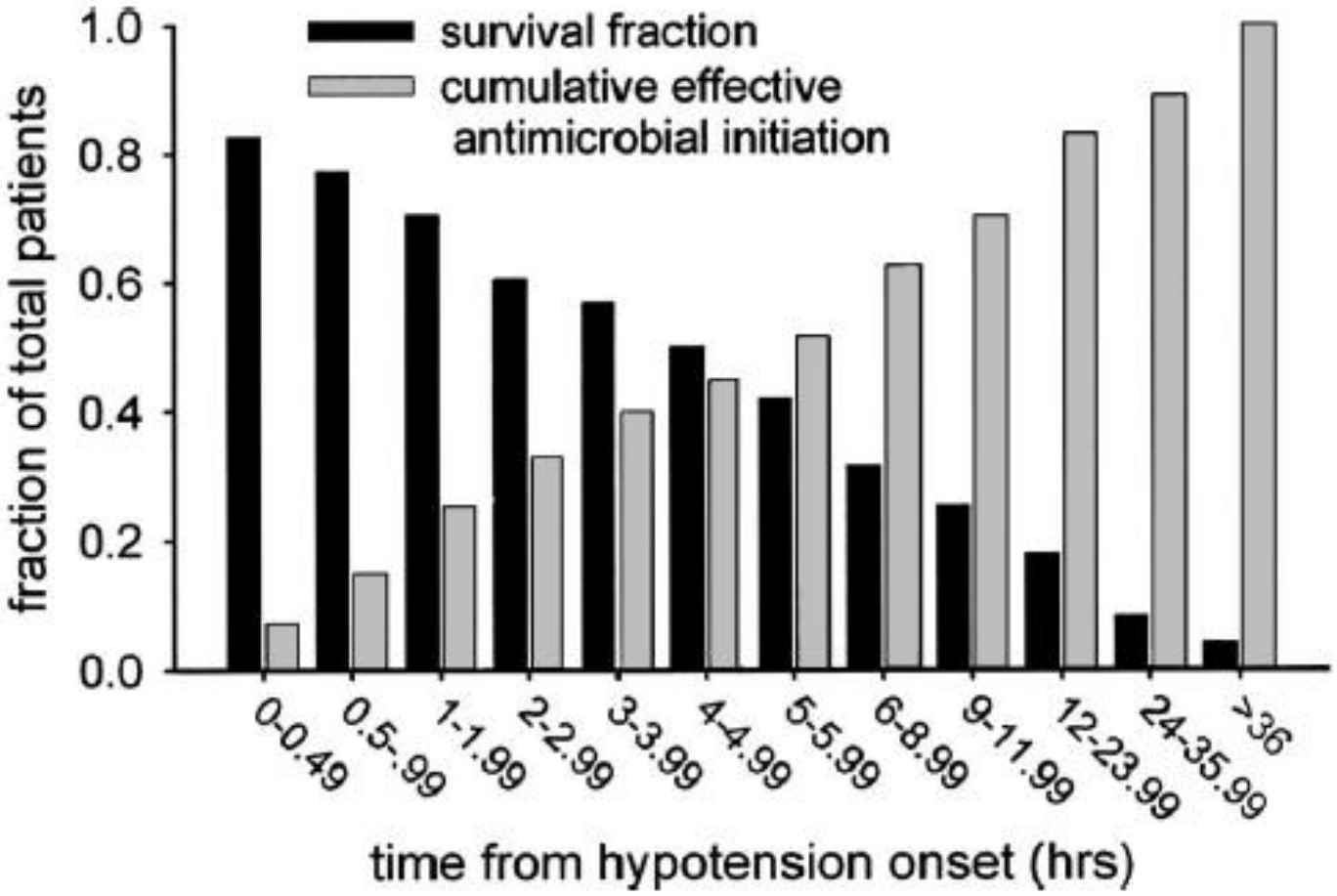
- **Outcome measurements:**
  - **Mortality**
  - **Length of hospitalization**

Compliance with Sepsis Bundle Elements



Chest 2022; 161(2): 392-406

Impact of Delayed Effective Antibiotic Therapy in Septic Shock



Kumar A, et al. Crit Care Med 2006; 34:1589–1596

Rapid Organism Identification plus Real-Time Stewardship Team Review & Intervention

Control Group

Traditional Organism ID

No Real-time Intervention

Intervention Group

Rapid Organism ID via MALDI-TOF

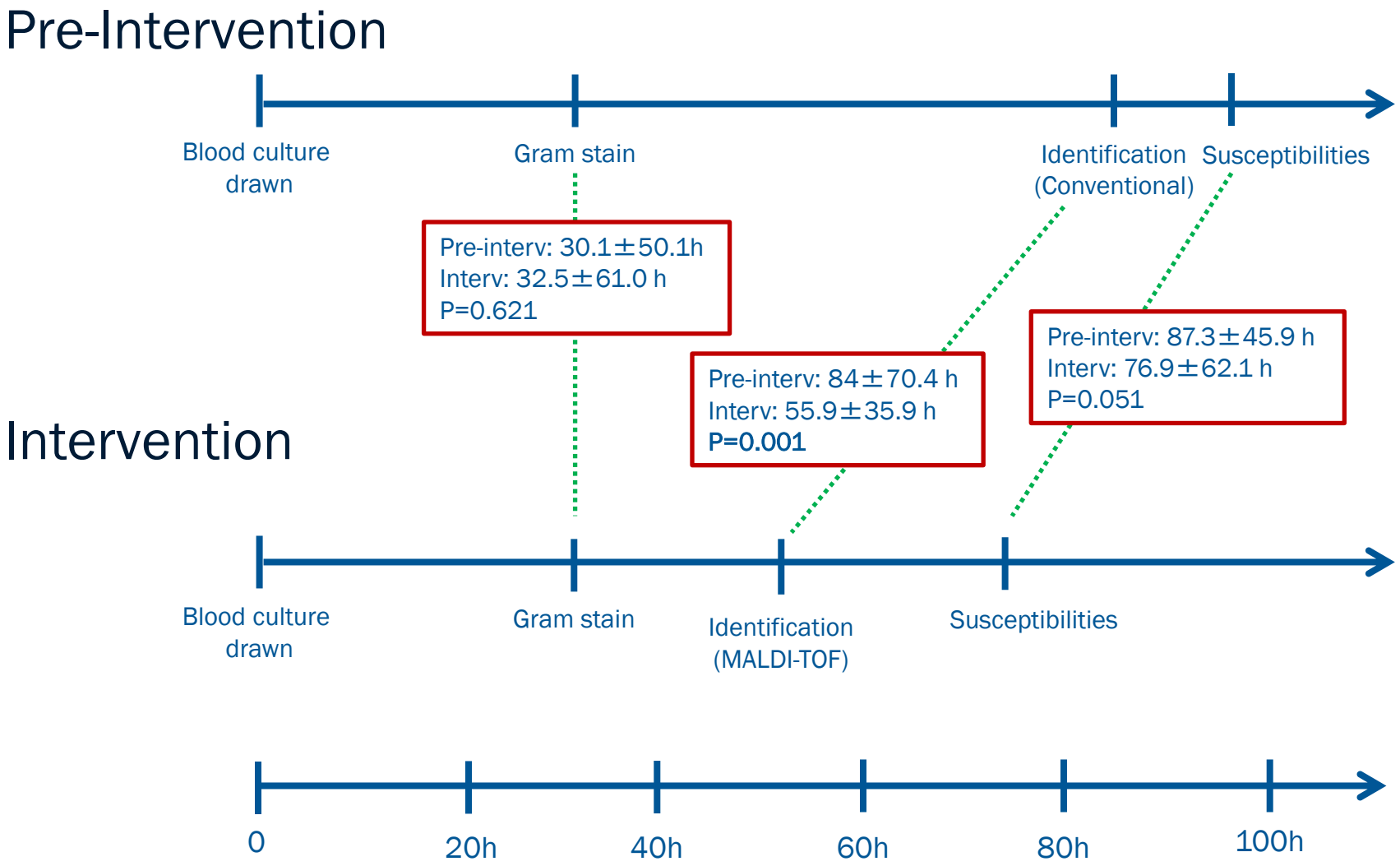
PLUS

Real-time Stewardship Intervention

Implemented an automatic relay system to send 3 real-time alerts to an antimicrobial stewardship pager from 0700-2300:

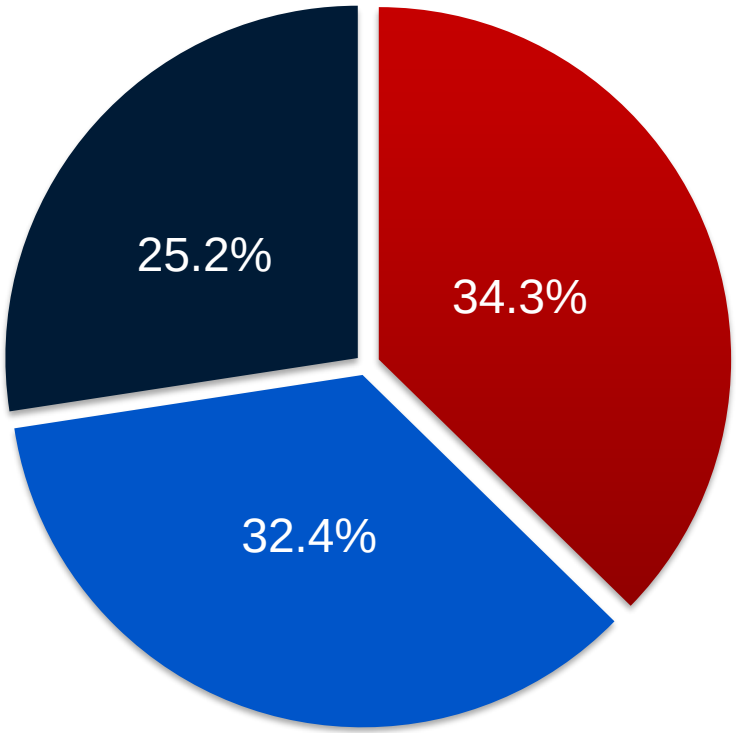
- Positive Gram stain
- Organism identification
- Susceptibility results

Clinical Microbiology Timeline

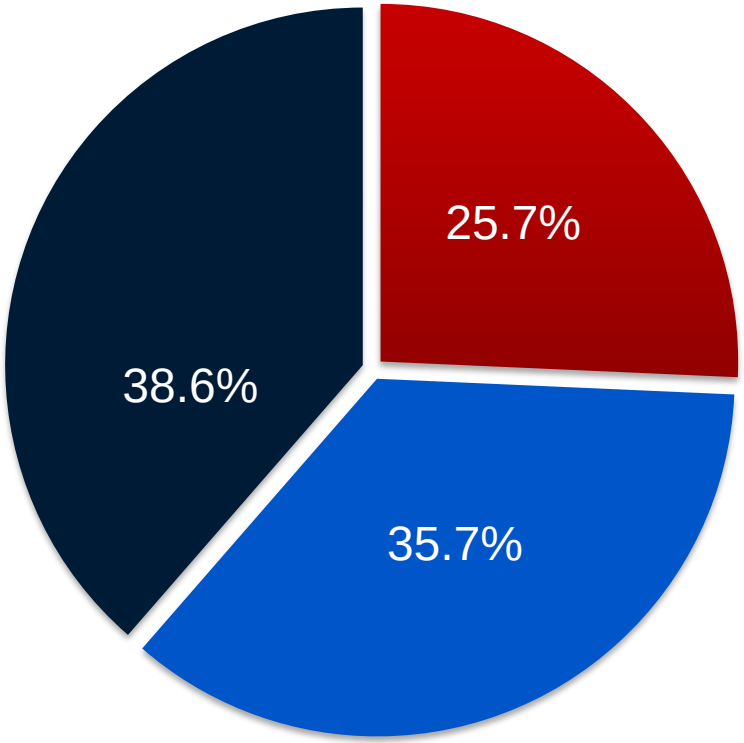


Timing and Characterization of Interventions

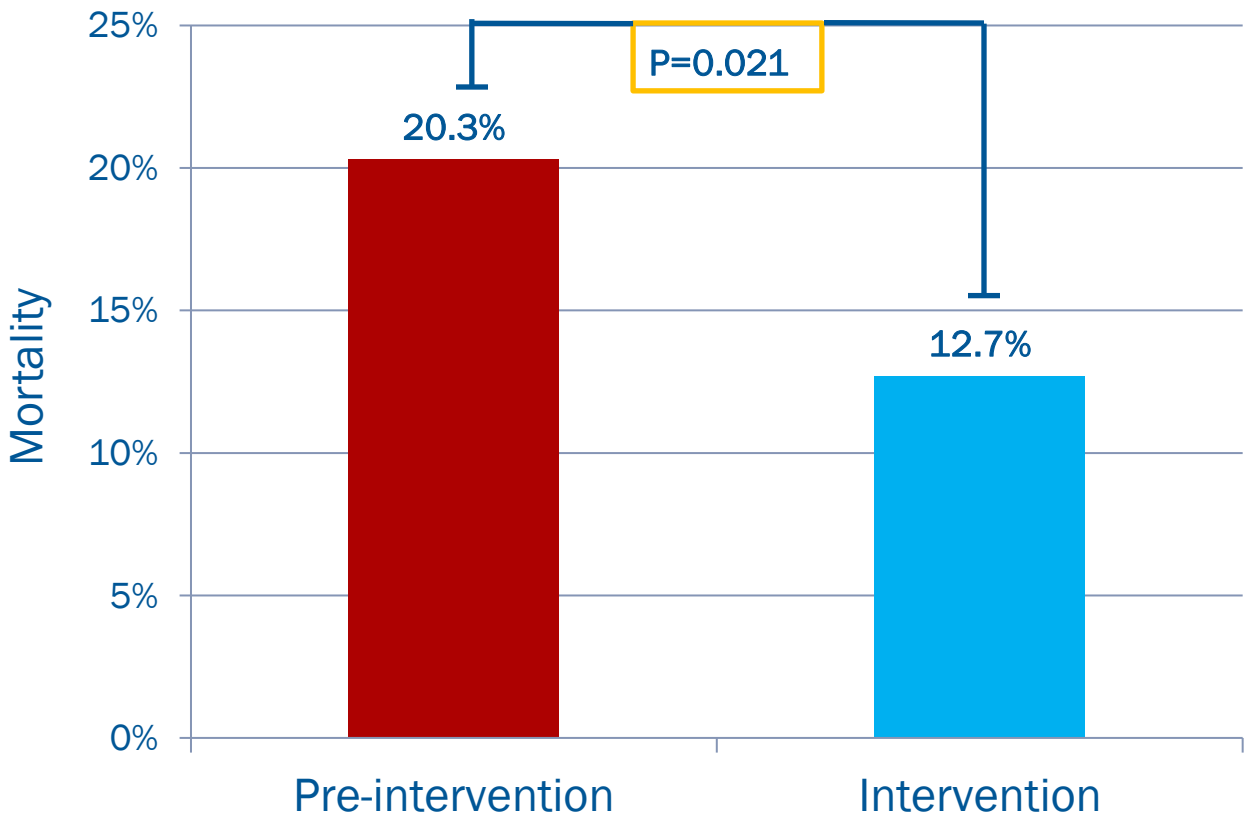
Characterization of Intervention



Timing of Intervention



Outcomes:
30-day All-cause Mortality

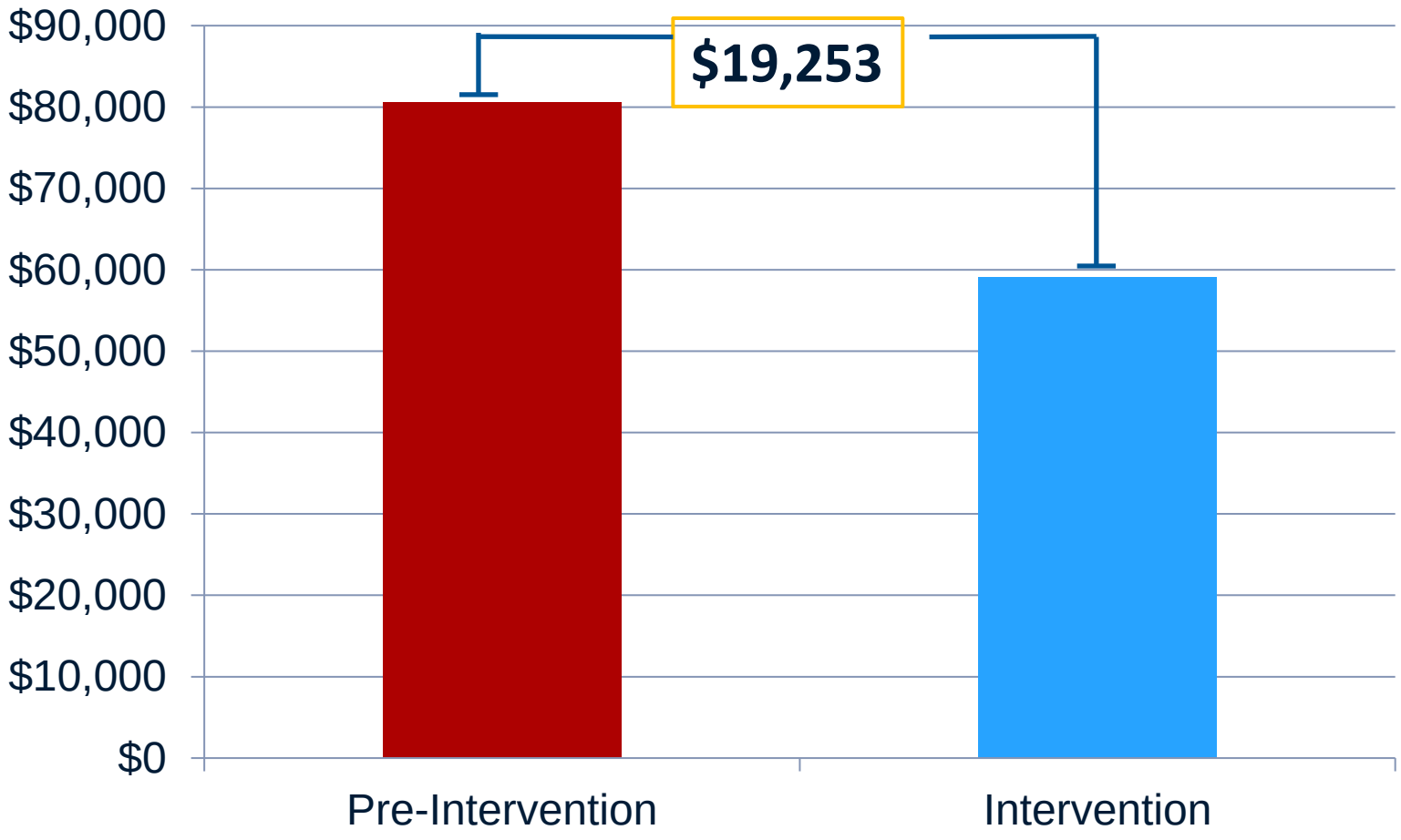


Secondary Outcomes

Therapy-Related Outcome	Pre-Interv (n=256)	Interv (n=245)	P-value
Time to Effective Therapy (hrs)	30.06	20.35	0.021
Time to Optimal Therapy (hrs)	90.34	47.25	<0.001

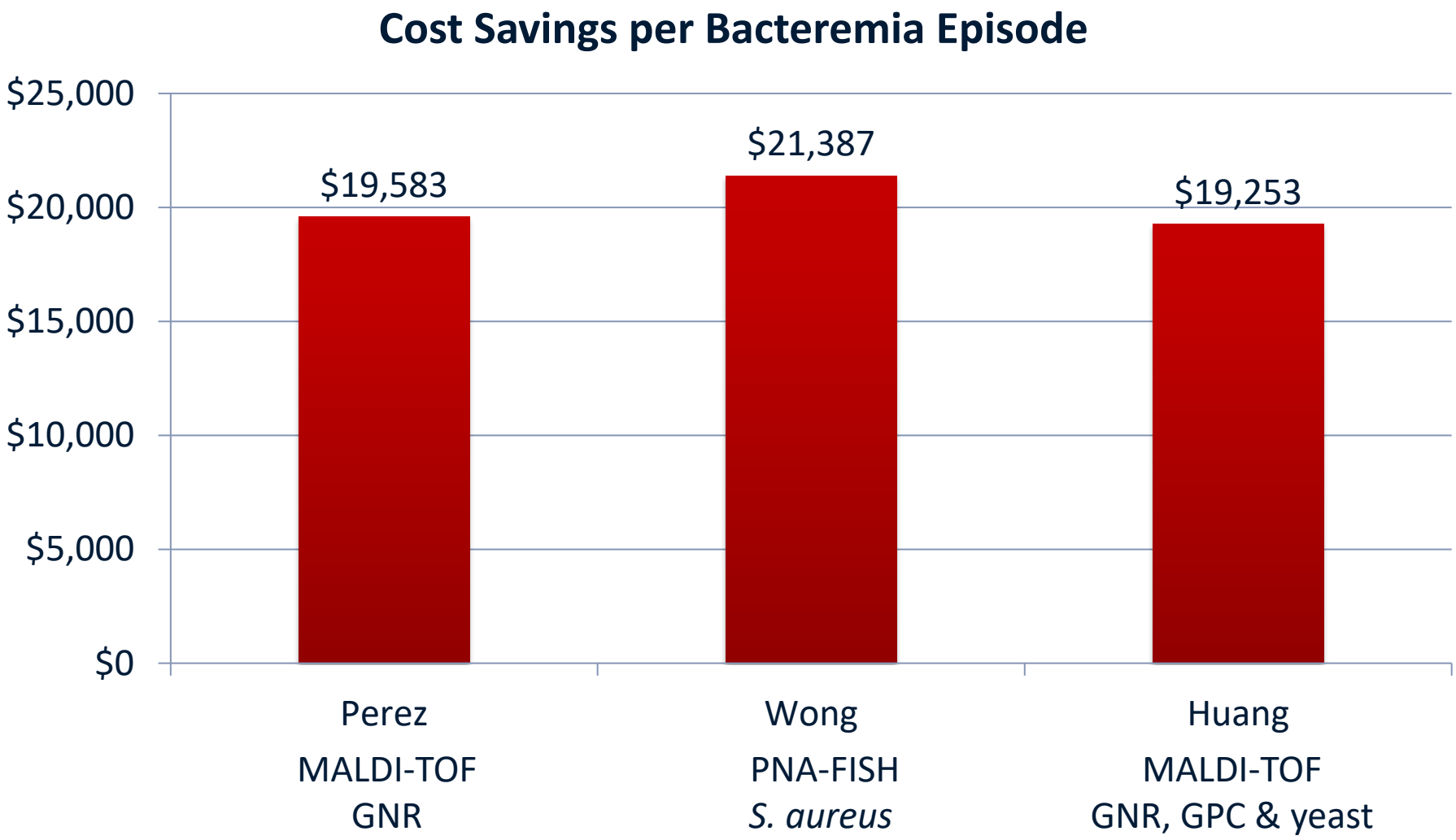
Clinical Outcome	Pre-Interv (n=256)	Interv (n=245)	P-value
Time to clinical response (days)	3.97	2.5	<0.001
Time to microbiological cure (days)	3.32	3.27	0.928
Length of hospitalization (days)	21.03	16.73	0.054
Length of ICU stay (days)	16.58	9.15	0.012
Recurrence of same BSI (%)	15 (5.9)	5 (2.0)	0.038
30-day Readmission with same BSI (%)	9 (3.5)	4 (1.6)	0.262

Total Cost per Bacteremic Episode



Total Cost Saving for 3-month Intervention Period: $4.8 million

Reduction in Total Hospital Costs with Rapid Diagnostic Testing plus Real-time Culture Review



Microbiology-Stewardship Collaboration

Study	RDT/pathogen(s)	Study Design	Outcomes
Forrest, 2006	PNA-FISH *Candida spp.*	Pre/post-intervention: RDT + AST	ID of *C. albicans* 3 days earlier (9.5h vs 44h), ↓ antifungal costs by $1,978/patient
Forrest, 2008	PNA-FISH Enterococcus spp.	Pre/post-intervention: RDT + AST	↓ mortality (45% vs 35%), ↓ time to appropriate abx (1.3 vs 3.1 days)
Ly, 2008	PNA-FISH *S. aureus* vs GPCs	RDT and pre/post AST	↓ mortality (17% vs 8%), ↓ inappropriate abx use by 2.5 days*, trend towards ↓ LOS and cost
Carver, 2008	RT-PCR *mecA* (MRSA)	mecA gene reporting and pre/post AST	↓ time to optimal abx (64.7h vs 39.9h), ↓ duration of *S. aureus* BSI
Wong, 2010	rPCR *S. aureus*	Pre/post intervention: RDT + AST	↓ LOS (21.5d vs 15.3d)
Perez, 2013	*MALDI-TOF GNRs*	Pre/post intervention: RDT + AST	↓ LOS (11.9d vs 9.3d), Trend towards ↓mortality (10.7 vs 5.6%)
Huang, 2013	*MALDI-TOF All Pathogens*	Pre/post intervention: RDT + AST	↓ 30d mortality (20.3 vs 12.7%), ↓ LOS (21 vs 16.7d)

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Drive-Home Point #2

- Microbiology participation in multidisciplinary Quality Improvement initiatives is essential to optimize outcomes
- A business case can be made for incorporating technology that improves timely and accurate results into quality improvement

Identifying Resistance Mechanisms

- Antimicrobial stewardship programs frequently provide treatment recommendations
- Accurate MICs and susceptibilities are essential in making treatment decisions on a case-by-case basis
- Part of the decision-making process should include evaluating MICs, susceptibilities and understanding relationship across the antibiotic panel

Common Pseudomonas Resistance Mechanisms

	Effect of Resistance Mechanism on susceptibility		
Antibiotic	**AmpC hyperproduction**	**MexAB upregulation**	**OprD down-regulation**
Piperacillin-tazobactam	Elevated MICs, but usually resistance	Elevated MICs, or resistance	No Impact on MIC
Cefepime	Elevated MICs, resistance possible	Elevated MICs, or resistance	No Impact on MIC
Ceftazidime	Resistance (usually)	Elevated MICs, or resistance	No Impact on MIC
Aztreonam	Resistance (usually)	Elevated MICs, or resistance	No Impact on MIC
Imipenem	Elevated MICs, but susceptibility retained	No Impact on MIC	Resistance usually seen
Meropenem	No Impact on MIC	Elevated MICs (alone unlikely to cause resistance)	Elevated MICs (alone unlikely to cause resistance)

Example #1 Pseudomonas Susceptibility MexAB upregulation

Antibiotic	**MIC**	**Interpretation**
Piperacillin-tazobactam	16	S
Cefepime	4	S
Ceftazidime	4	S
Aztreonam	1	S
Imipenem	0.25	S
Meropenem	1	S

Example #2 Pseudomonas Susceptibility AmpC Hyperproduction

Antibiotic	**MIC**	**Interpretation**
Piperacillin-tazobactam	16	S
Cefepime	2	S
Ceftazidime	32	R
Aztreonam	16	R
Imipenem	2	S
Meropenem	0.25	S

Example #3 Pseudomonas Susceptibility
MexAB & AmpC Hyperproduction

Antibiotic	**MIC**	**Interpretation**
Piperacillin-tazobactam	64	R
Cefepime	16	R
Ceftazidime	32	R
Aztreonam	16	R
Imipenem	2	S
Meropenem	1	S

Example #4 Pseudomonas Susceptibility
Porin Channel Down Regulation

Antibiotic	**MIC**	**Interpretation**
Piperacillin-tazobactam	4	S
Cefepime	2	S
Ceftazidime	4	S
Aztreonam	1	S
Imipenem	8	R
Meropenem	2	S

Example#5 Pseudomonas Susceptibility
All 3 Major Resistance Mechanisms

Antibiotic	**MIC**	**Interpretation**
Piperacillin-tazobactam	132	R
Cefepime	32	R
Ceftazidime	16	R
Aztreonam	32	R
Imipenem	8	R
Meropenem	8	R
Meropenem/Vaborbactam	8	S
Imipenem/Relabactam	2	S
Ceftolozane/tazobactam	2	S
Ceftazidime/avibactam	2	S

Example#5 Pseudomonas Susceptibility Multiple Mechanisms of Resistance

Antibiotic	**MIC**	**Interpretation**
Piperacillin-tazobactam	132	R
Cefepime	32	R
Ceftazidime	16	R
Aztreonam	32	R
Imipenem	8	R
Meropenem	16	R
Meropenem/Vaborbactam	16	R
Imipenem/Relabactam	4	I
Ceftolozane/tazobactam	8	I
Ceftazidime/avibactam	8	I

Case #2: Patient Presentation

- **85 year-old female presents to primary physician clinic with urinary symptoms: dysuria, frequency and urgency**
  - Her history is significant for recurrent UTIs, CKD, and hypertension. She's currently receiving ciprofloxacin as prophylaxis and has a sulfa allergy

E. coli > 100K CFU/mL	MIC	Interpretation
Ampicillin	>256	R
Nitrofurantoin	8	S
Trimethoprim/sulfamethoxazole	16	S
Ciprofloxacin	>4	R
Ampicillin/sulbactam	>128	R
Cefazolin	>4	I

Case #2: Minimizing Use of Broad Spectrum Antibiotics

Cefazolin: CLSI developed breakpoints for cefazolin to use as a surrogate for oral cephalosporins in urinary isolates

	Susceptible	Intermediate	Resistant
Systemic	MIC ≤ 2 µg/mL	MIC 4 µg/mL	MIC ≥ 8 µg/mL
Urine	MIC ≤ 16 µg/mL	--	MIC ≥ 32 µg/mL

Clinical and Laboratory Standards Institute antimicrobial susceptibility testing standards M100.

UMHS Cephalosporin Data

	% susceptible (3182 total isolates)
Cefazolin (Systemic breakpoint of ≤ 2)	74
Cefazolin (Urine breakpoint of ≤ 16)	94

Component Results

Component
URINE CULTURE (Abnormal)
Klebsiella pneumoniae
Comment:
>100,000 cfu/mL

Susceptibility

	Klebsiella pneumoniae	
	MIC	
Amikacin	<=4 mcg/mL	S
Amoxicillin + Clavulanate	<=8 mcg/mL	S
Ampicillin	>16 mcg/mL	R
Ampicillin + Sulbactam	16 mcg/mL	I
Aztreonam	<=4 mcg/mL	S
Cefazolin	4 mcg/mL	R
Cefepime	<=1 mcg/mL	S
Ceftriaxone	S	
Cefuroxime	16 mcg/mL	I
Cephalexin (cystitis)	S	
Ciprofloxacin	0.12 mcg/mL	S
Ertapenem	<=0.5 mcg/mL	S
Fosfomycin	<=64 mcg/mL	
Gentamicin	<=2 mcg/mL	S
Levofloxacin	<=1 mcg/mL	S
Meropenem	<=1 mcg/mL	S
Nitrofurantoin	<=32 mcg/mL	S
Piperacillin/tazobactam	16 mcg/mL	S
Tobramycin	<=2 mcg/mL	S
Trimethoprim/Sulfa	<=2 mcg/mL	S

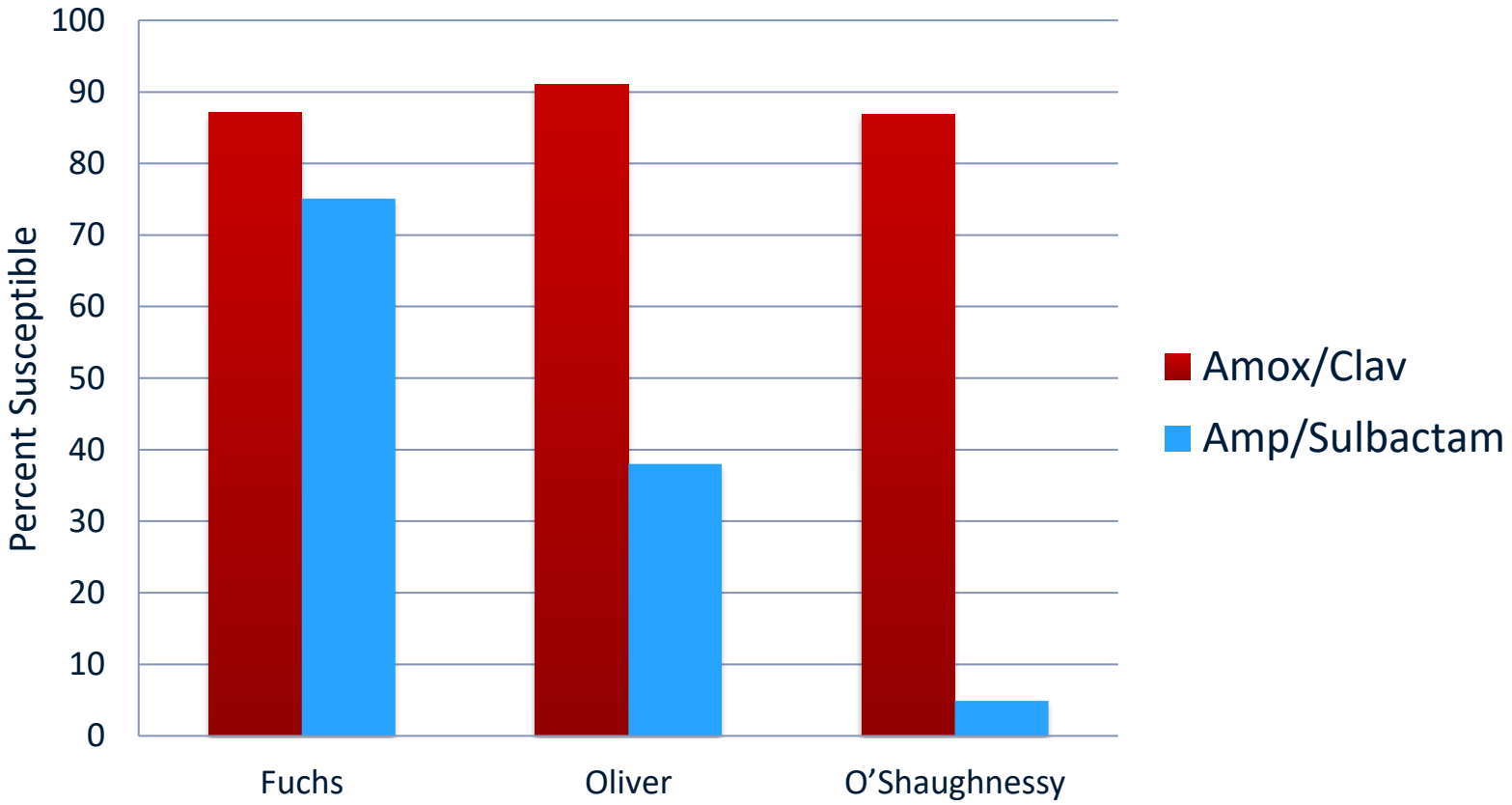
Amoxicillin-clavulanate vs. ampicillin-sulbactam

- Typically, ampicillin-sulbactam susceptibility is tested and amoxicillin-clavulanate susceptibility is inferred
- Clavulanic acid is more active against various TEM and SHV B-lactamases
- Overall **20x** more potent than sulbactam against all tested B-lactamase enzymes

Antimicrob Agents Chemother. 1994 Apr;38(4):767-72.

Case #2: Minimizing Use of Broad Spectrum Antibiotics

Ampicillin/sulbactam: Oral amoxicilin/clavulanate susceptibility is often inferred from ampicillin/sulbactam



UMHS Amoxicillin-clavulanate vs. Ampicillin-sulbactam

	E. coli % susceptible	*K. oxytoca* % susceptible	*K. pneumoniae* % susceptible
Amoxicillin-clavulanate	**89**	**90**	**95**
Ampicillin-sulbactam	**69**	**58**	**87**

Component Results

Component
URINE CULTURE (Abnormal)
Klebsiella pneumoniae
Comment:
>100,000 cfu/mL

Susceptibility

	Klebsiella pneumoniae	
	MIC	
Amikacin	<=4 mcg/mL	S
Amoxicillin + Clavulanate	<=8 mcg/mL	S
Ampicillin	>32 mcg/mL	R
Ampicillin + Sulbactam	32 mcg/mL	R
Aztreonam	<=4 mcg/mL	S
Cefazolin	<=2 mcg/mL	S
Cefepime	<=1 mcg/mL	S
Ceftriaxone	S	
Cefuroxime	<=4 mcg/mL	S
Ciprofloxacin	<=0.06 mcg/mL	S
Ertapenem	<=0.5 mcg/mL	S
Fosfomycin	<=64 mcg/mL	
Gentamicin	<=2 mcg/mL	S
Levofloxacin	<=1 mcg/mL	S
Meropenem	<=1 mcg/mL	S
Nitrofurantoin	<=32 mcg/mL	S
Piperacillin/tazobactam	<=8 mcg/mL	S
Tobramycin	<=2 mcg/mL	S
Trimethoprim/Sulfa	<=2 mcg/mL	S

UMHS Fosfomycin Susceptibility Data

E. coli urine isolates

Antibiotic	% susceptibility
Fosfomycin	100%
Nitrofurantoin	98%
Ciprofloxacin	83%
Trimethoprim-sulfamethoxazole	80%
Ciprofloxacin	83%
Ampicillin	58%

Comment:
>100,000 cfu/mL

Susceptibility

	Klebsiella pneumoniae	
	MIC	
Amikacin	<=4 mcg/mL	S
Amoxicillin + Clavulanate	<=8 mcg/mL	S
Ampicillin	>16 mcg/mL	R
Ampicillin + Sulbactam	16 mcg/mL	I
Aztreonam	<=4 mcg/mL	S
Cefazolin	4 mcg/mL	S
Cefepime	<=1 mcg/mL	S
Ceftriaxone	S	
Cefuroxime	16 mcg/mL	I
Cephalexin (cystitis)	S	
Ciprofloxacin	0.12 mcg/mL	S
Ertapenem	<=0.5 mcg/mL	S
Fosfomycin	<=64 mcg/mL	
Gentamicin	<=2 mcg/mL	S
Levofloxacin	<=1 mcg/mL	S
Meropenem	<=1 mcg/mL	S
Nitrofurantoin	<=32 mcg/mL	S
Piperacillin/tazobactam	16 mcg/mL	S
Tobramycin	<=2 mcg/mL	S
Trimethoprim/Sulfa	<=2 mcg/mL	S

Susceptibility of Multidrug-Resistant Gram-Negative Urine Isolates to Oral Antibiotics

Antibiotic	% susceptibility (all MDR isolates) n=91
Fosfomycin	94.5
Nitrofurantoin	85.6
Trimethoprim-sulfamethoxazole	40.2
Ciprofloxacin	34.1
Ampicillin	4.2
Antibiotic	**% susceptibility (ESBL confirmed isolates) n=30**
Fosfomycin	96.7
Nitrofurantoin	76.7
Trimethoprim-sulfamethoxazole	43.3
Ciprofloxacin	10
Ampicillin	0

Antimicrob Agents Chemother. 2016 Apr 22;60(5):3138-40.

Drive-Home Point #3

- Accurate antimicrobial MICs and susceptibility are necessary for de-escalation of therapy and promoting the use of narrow-spectrum antibiotics

Audience Participation Question #3

Does your institution have a multi-disciplinary committee that provides input on how microbiology antimicrobial testing should be performed and reported to meet hospital goals?

A. Yes

B. No

C. Not sure

Microbiology-Stewardship Collaboration

- **Microbiology Workgroup Goals**
  - Determine appropriate technologies to optimize patient care
  - Provide information to help understand results and facilitate necessary action
  - Provide timely and accurate pathogen identification and susceptibility
  - Perform targeted screening to detect colonization of MDRO pathogens

Advances in Clinical Microbiology

- **Manual susceptibility testing**
  - Kirby-Bauer, E-test, microbroth, etc.
- **Automated ID and susceptibility systems**
  - Vitek™, Microscan™, Sensititre™, etc.
- **Mass spectrometry**
  - MALDI-TOF
- **Nucleic acid hybridization**
  - PNA-FISH™
- **Nucleic acid amplification**
  - Real-time PCR, Multiplex arrays
- **Magnetic resonance imaging**
  - T2 Biosystems ™
- **Next generation whole genome sequencing**
  - Karius ™

Priorities in Selecting Technology for Organism Identification and Susceptibility Testing

- Produce accurate results
- Optimize workflow
- Enhance susceptibility testing options to help facilitate antibiotic de-escalation AND escalation
- Reduce redundancy
- Meet infection control needs

Stewardship Considerations for Antibiotic Susceptibility Reporting

- **Minimize unnecessary prescribing of antibiotics more likely to promote resistance or cause collateral damage**
  - Carbapenems, 3rd generation cephs, FQs, linezolid, daptomycin, clindamycin, vancomycin
- **Provide options for narrow spectrum antibiotic options for de-escalation for common infections**
  - UTI, SSTI, Pneumonia and Intra-abdominal infections account for over 90% infections causing hospitalization
  - De-escalation to amoxicillin, penicillin, amoxicillin/clavulanate, 1st/2nd gen oral cephalosporins, tetracyclines, fosfomycin, etc
    - Need to provide sufficient dilutions to accommodate urine vs. non-urine isolates and all organisms with different CLSI breakpoints

Summary

- **The role of antibiotic stewardship is increasing, and activities focus on optimizing care, reducing risk for antibiotic resistance, meeting quality metrics, and improving safety**
  - Microbiology participation in multidisciplinary quality improvement initiatives is essential to optimize outcomes
  - A business case can be made for incorporating technology that improves timely and accurate results into quality improvement
  - Having MIC and susceptibility data available for the treatment of MDR Gram-negatives is essential to antimicrobial stewardship

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An Antimicrobial Stewardship Perspective on the Impact of MICs on Patient Outcomes

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