COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN

Automated Susceptibility Testing to Optimize Patient Outcomes

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Learning Objectives

- Describe the impact of effective stewardship practices on mortality and how collaboration between the microbiology lab and stewardship team can improve metrics
- Review the impact of effective stewardship practices in cases of sepsis and septic shock
- Demonstrate the need for new therapeutics to accompany accurate diagnostics

Overview

- Antibiotic stewardship and microbiology
- Priorities in selecting automated systems
- Considerations in susceptibility testing and reporting

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

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

Daily Patient-Care Activities

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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

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

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

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Intervention Group

Rapid Organism ID via MALDI-TOF

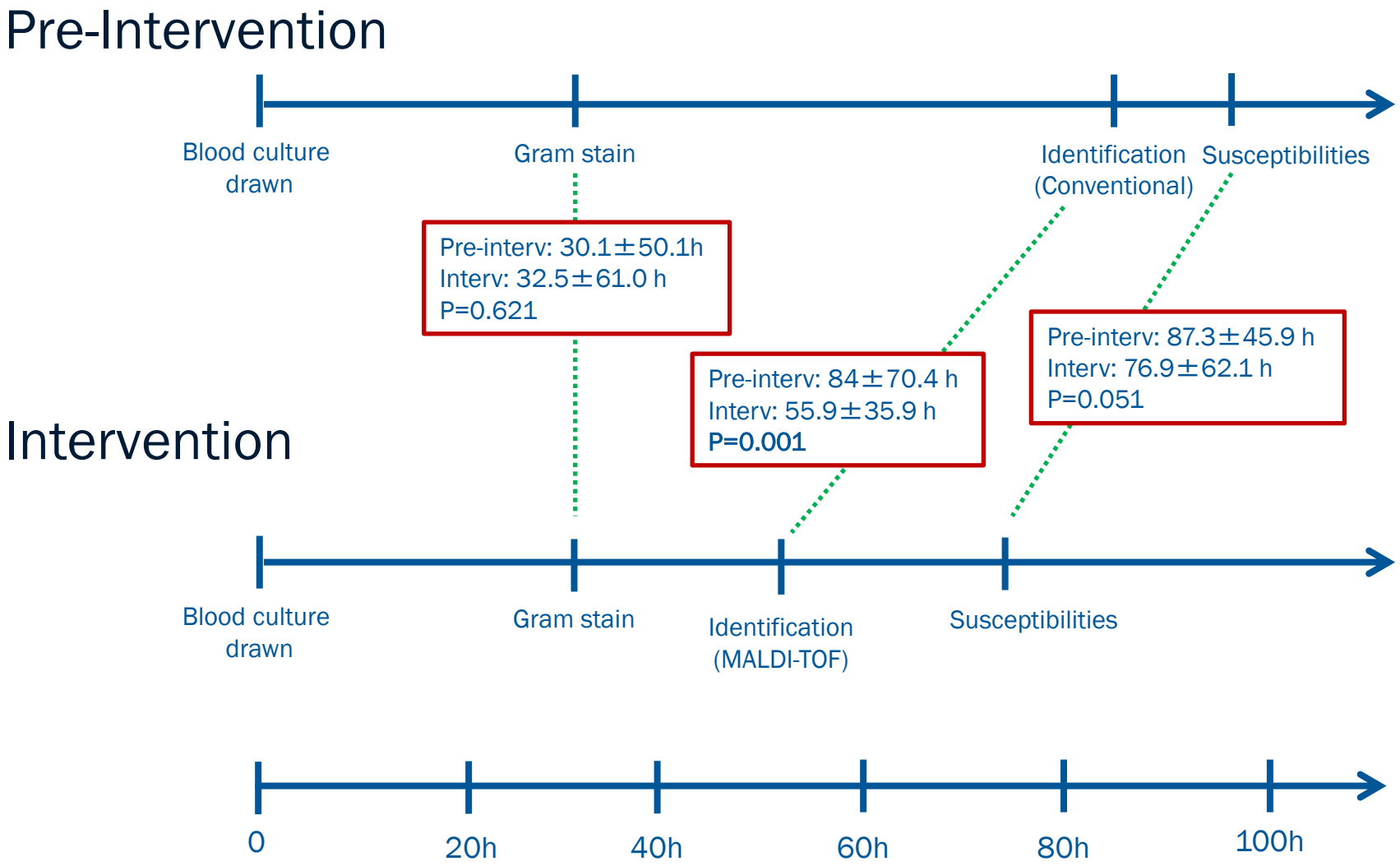
PLUS

Real-time Stewardship Intervention

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

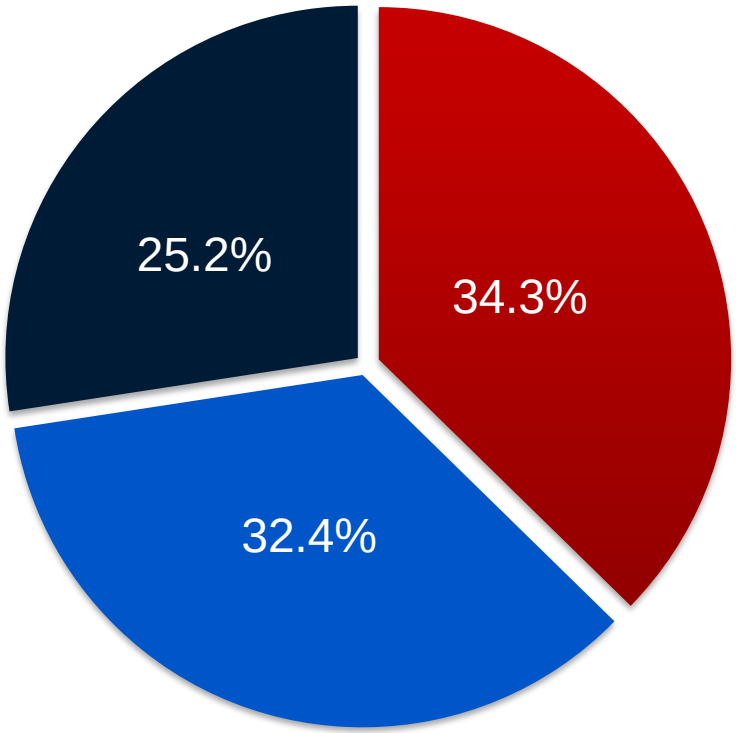
- Positive Gram stain
- Organism identification
- Susceptibility results

Clinical Microbiology Timeline

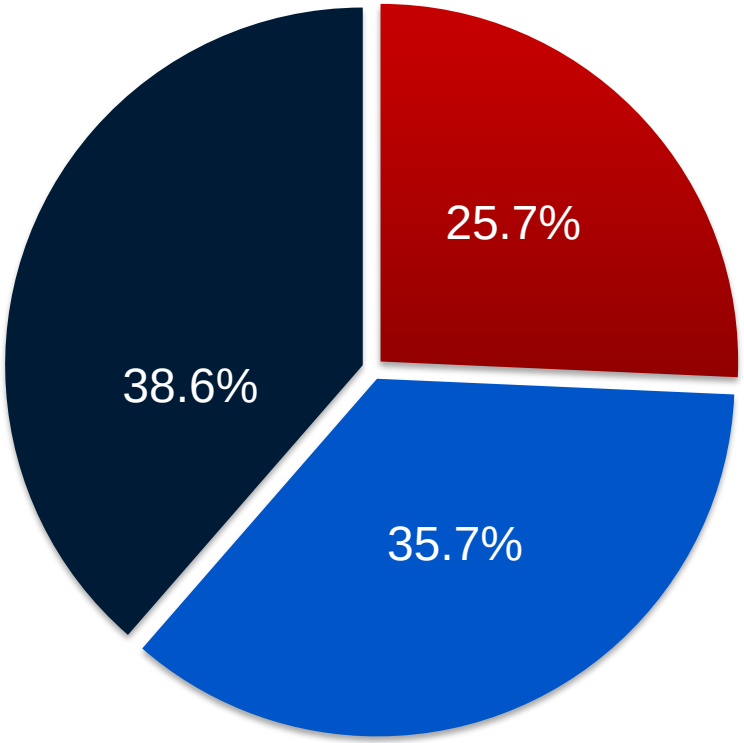


Timing an Characterization of Interventions

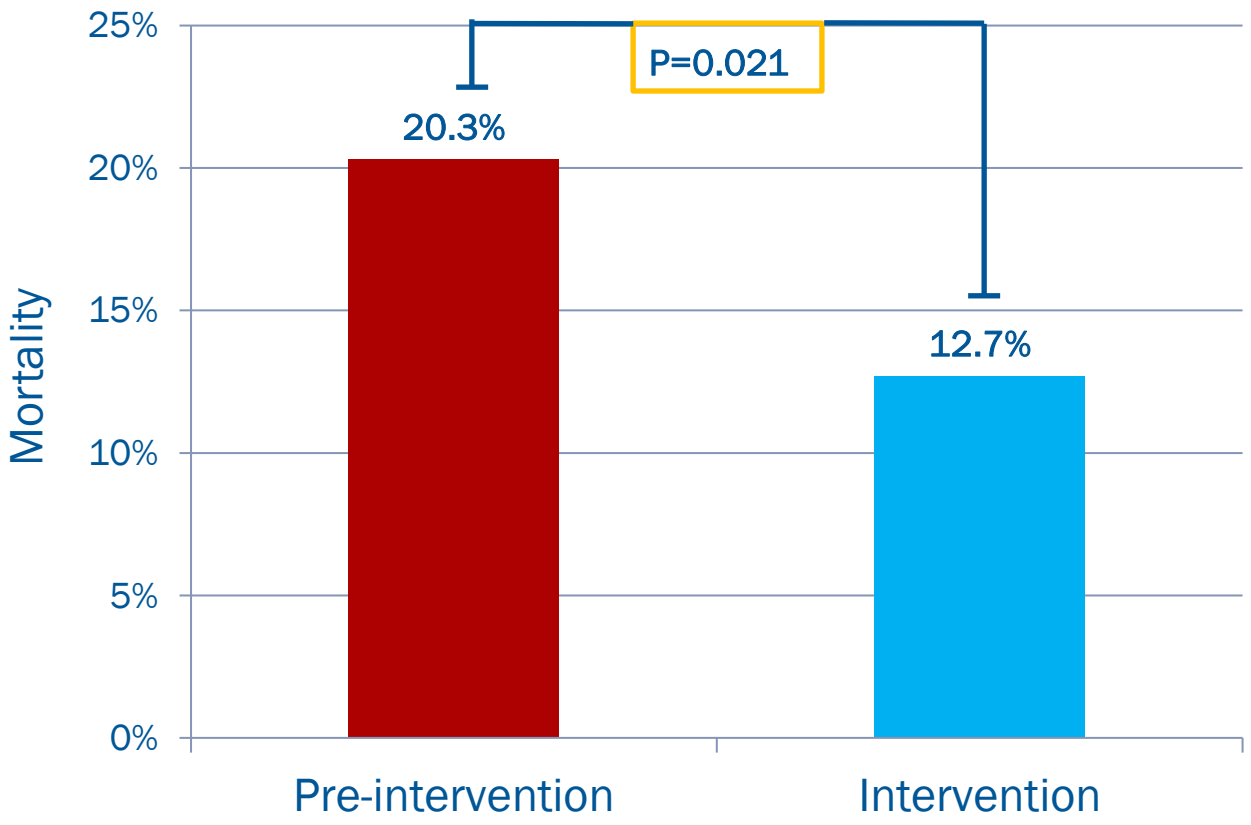
Characterization of Intervention



Timing of Intervention



Outcomes:
30-day All-cause Mortality

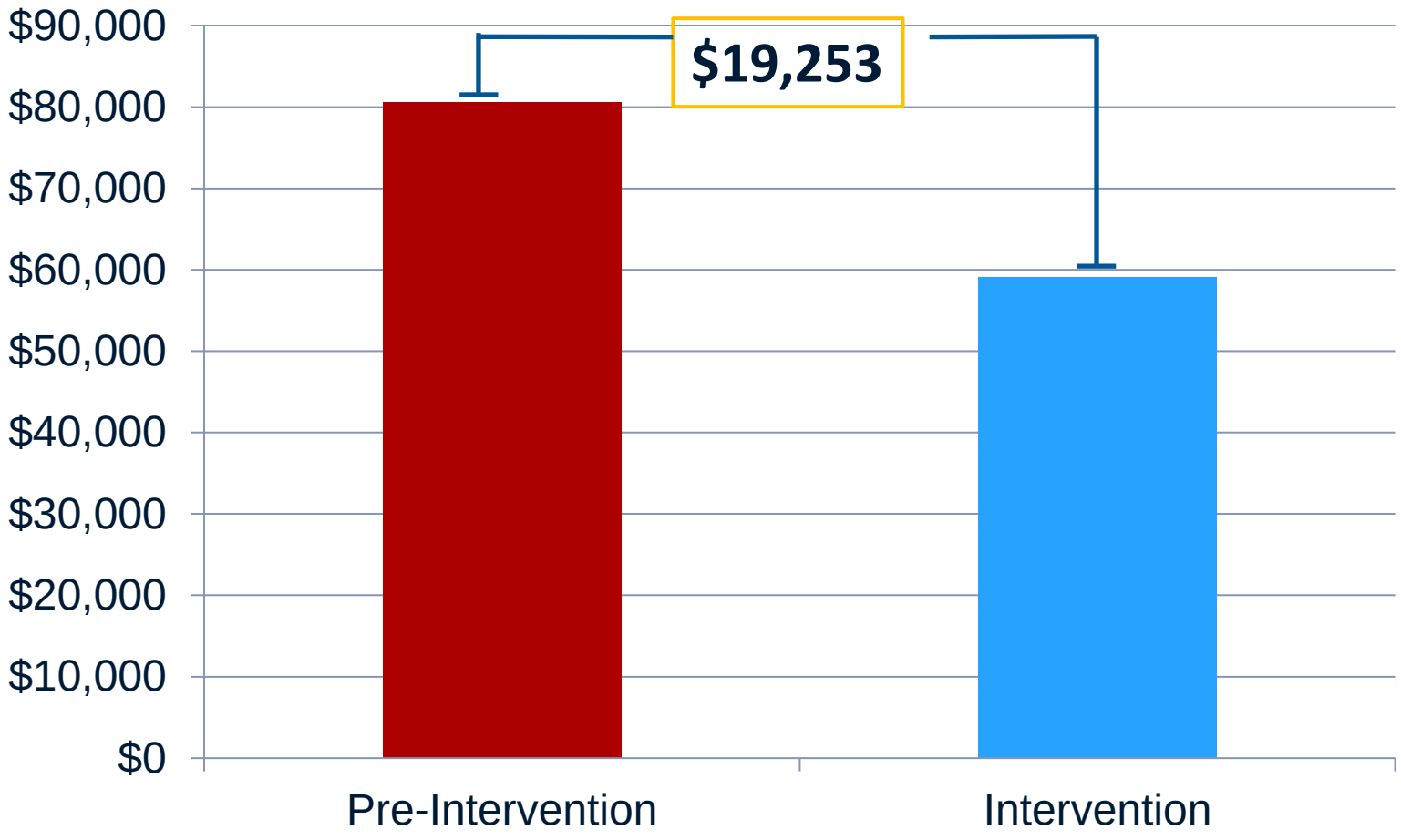


Secondary Outcomes

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

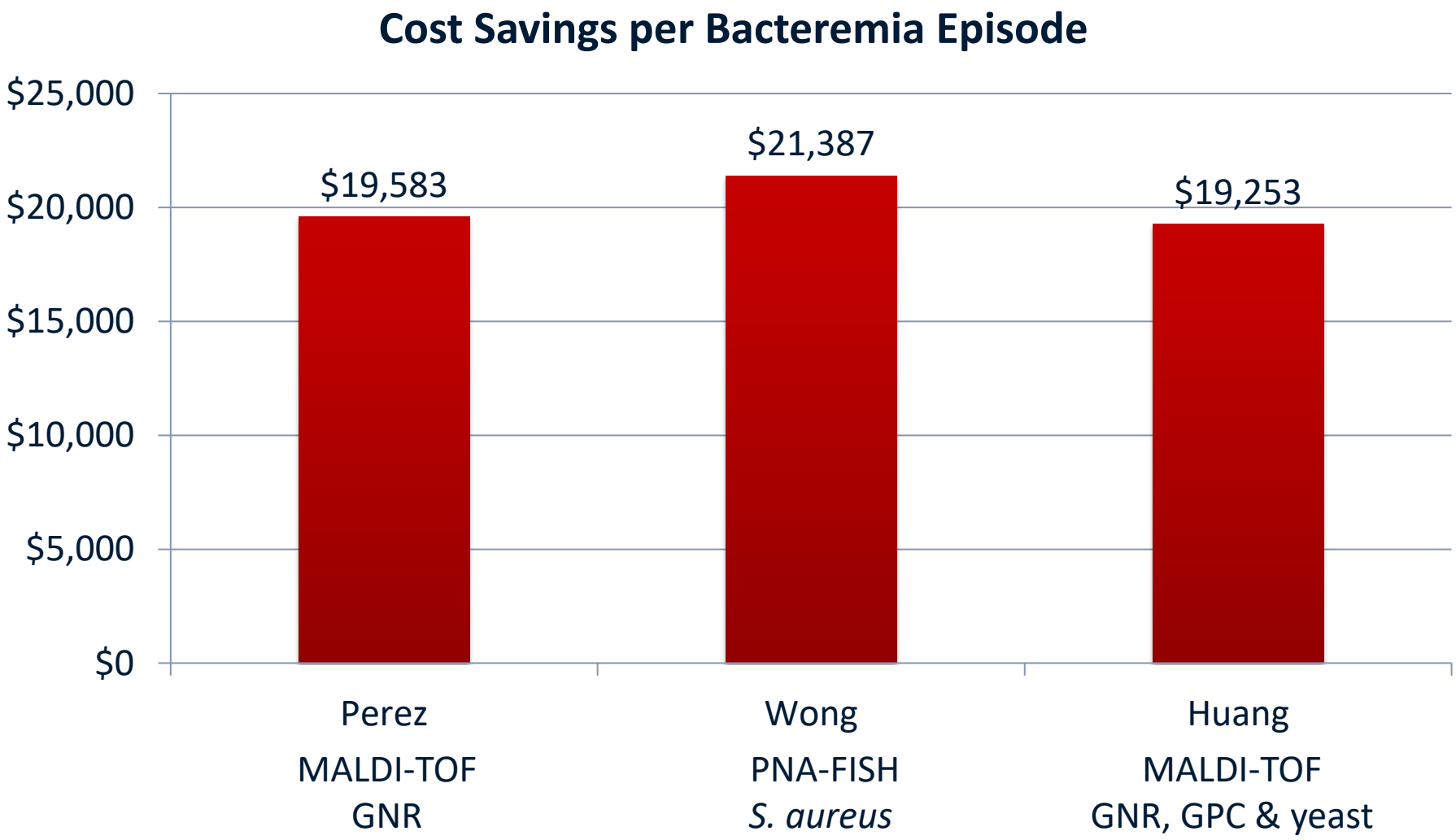
Clinical Outcome	Pre-Interv (n=256)	Interv (n=245)	P-value
Time to clinical response (days)	3.97	2.5	<0.001
Time to microbiological cure (days)	3.32	3.27	0.928
Length of hospitalization (days)	21.03	16.73	0.054
Length of ICU stay (days)	16.58	9.15	0.012
Recurrence of same BSI (%)	15 (5.9)	5 (2.0)	0.038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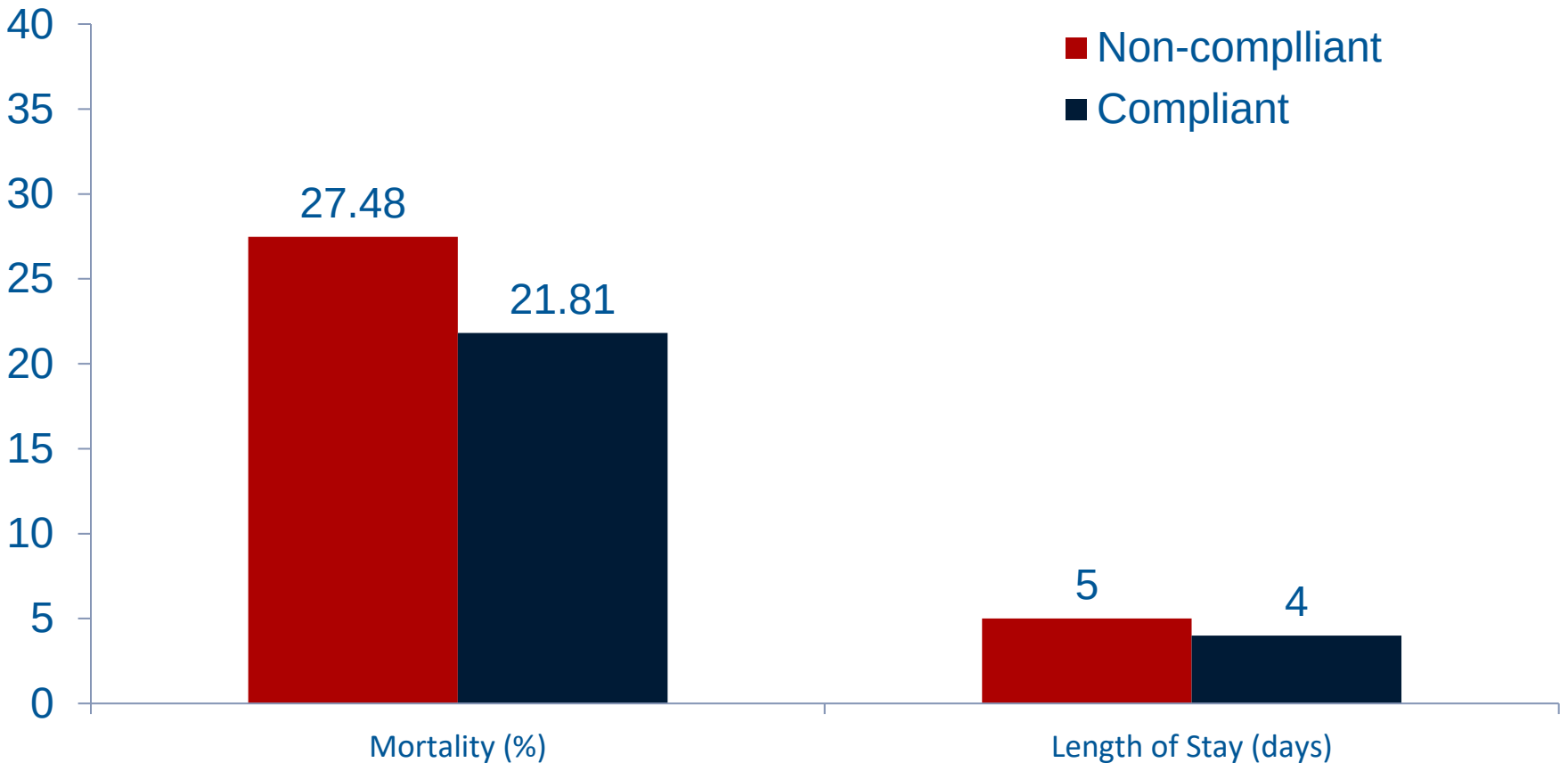
Sepsis Management

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*

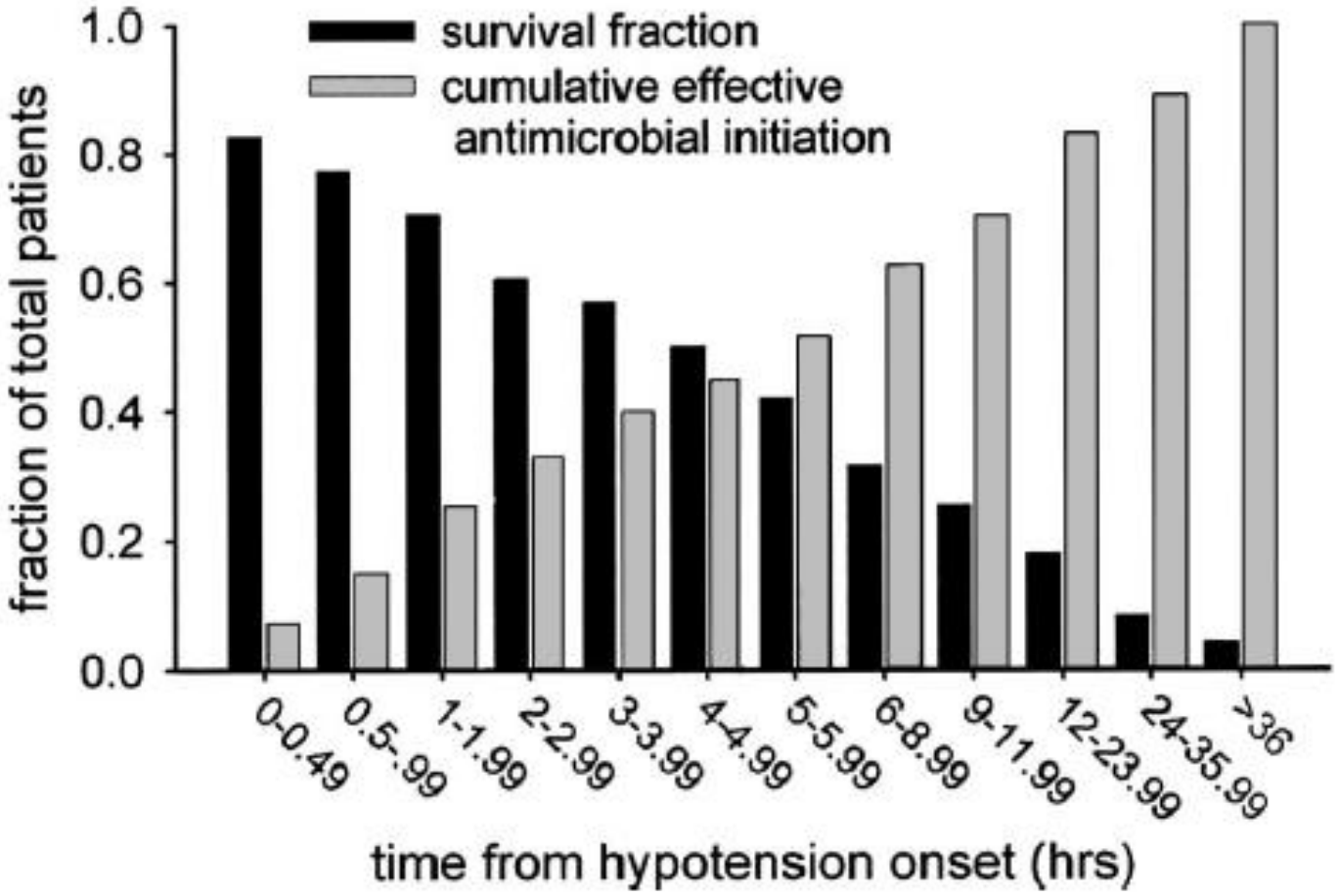
- **Outcome measurements:**
  - **Mortality**
  - **Length of hospitalization**

Compliance with Sepsis Bundle Elements



Chest 2022; 161(2): 392-406

Impact of Delayed Effective Antibiotic Therapy in Septic Shock

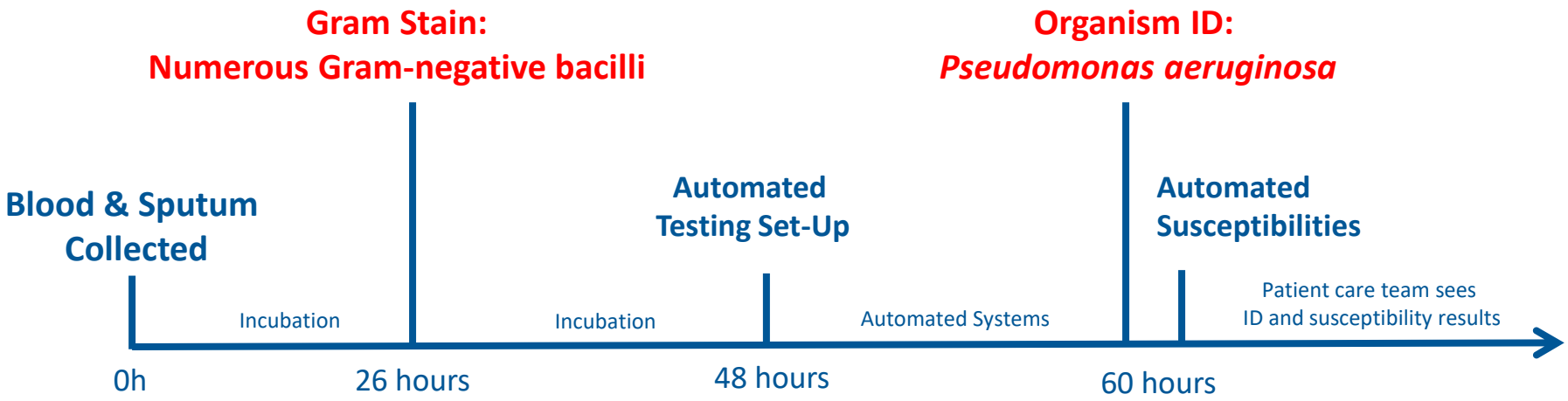


Kumar A, et al. Crit Care Med 2006; 34:1589–1596

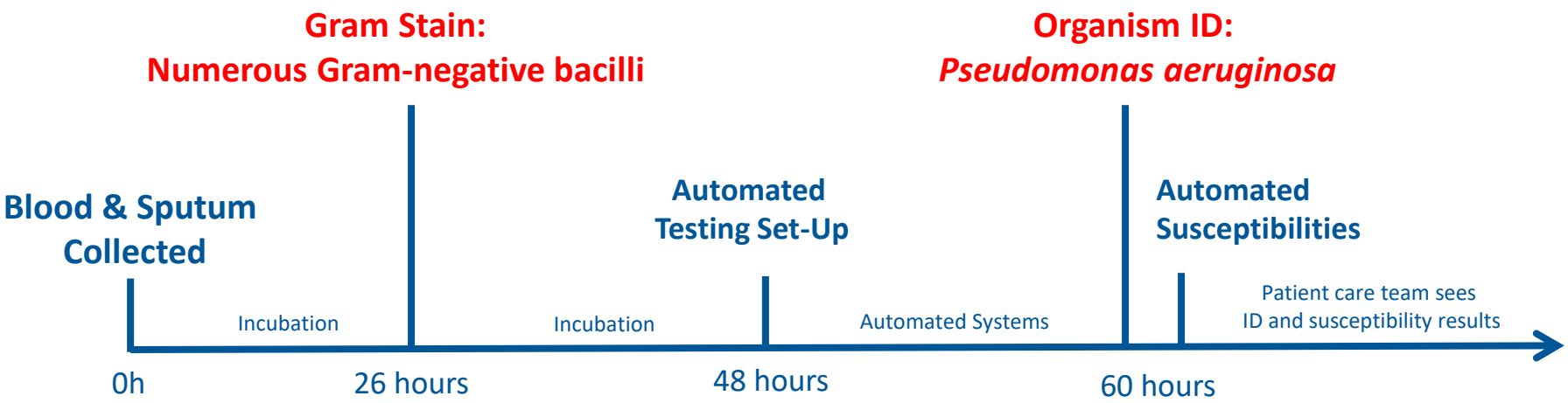
Case: Initial Patient Presentation

- **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
- **Diagnosed with pneumonia**
  - Intubate and admitted to the ICU
  - Blood and sputum cultures are ordered
  - Cefepime, vancomycin and tobramycin are started

Case: Microbiology Results



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

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- **Additional susceptibility requests:**
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  - Ceftazidime/avibactam
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  - Imipenem/relabactam
  - Cefiderocol

How much longer would it take to get these susceptibilities?

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)

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

Produce Accurate Results and Optimize Workflow

- **University of Michigan Microbiology history:**
  - Completely manual system for ID and AST (pre-2007)
  - Implemented automated system for ID and AST (starting 2007)
  - MALDI-TOF for ID (2011), then Verigene (2016)
- **Concerns and limitations of automated system for AST**
  - Limited accuracy of specific bug-drug combinations, which forced us to use alternate methods (microbroth, E-test, KB)
  - AST cards were limited in customizable dilution options, and limited space to report susceptibility for narrow-spectrum agents
  - Timeliness of changes to the cards with new CLSI breakpoints
  - Timeliness of adding new antibiotics to AST cards

Determining Antibiotics for Susceptibility Reporting

- Unfortunately, its very difficult to test all antibiotics likely to be prescribed. Prioritization of which antibiotics are tested is usually necessary
- Sensititre™ offers standardized and customizable panels, including the ability to select antibiotic dilutions
- From a stewardship standpoint, “narrow spectrum” antibiotics will not be utilized unless susceptibility results available
- Also need to balance the need to quickly obtain susceptibility results for multi-drug resistant organisms

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

Stewardship Considerations for Antibiotic Susceptibility Reporting

- **Provide timely and optimal therapy for multi-drug resistant organisms, or therapy that facilitates OPAT (which is commonly with newer antibiotics)**
  - Minimize the need for reflex testing, when organisms is resistant to everything on the standard panel
  - Sufficient delays in testing additional antibiotics can impact patient care
  - Senititre™ frequently offers newer antibiotic on susceptibility panels sooner than competition

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 new 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**

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Tobramycin	<=2 mcg/mL	S
Trimethoprim/Sulfa	<=2 mcg/mL	S

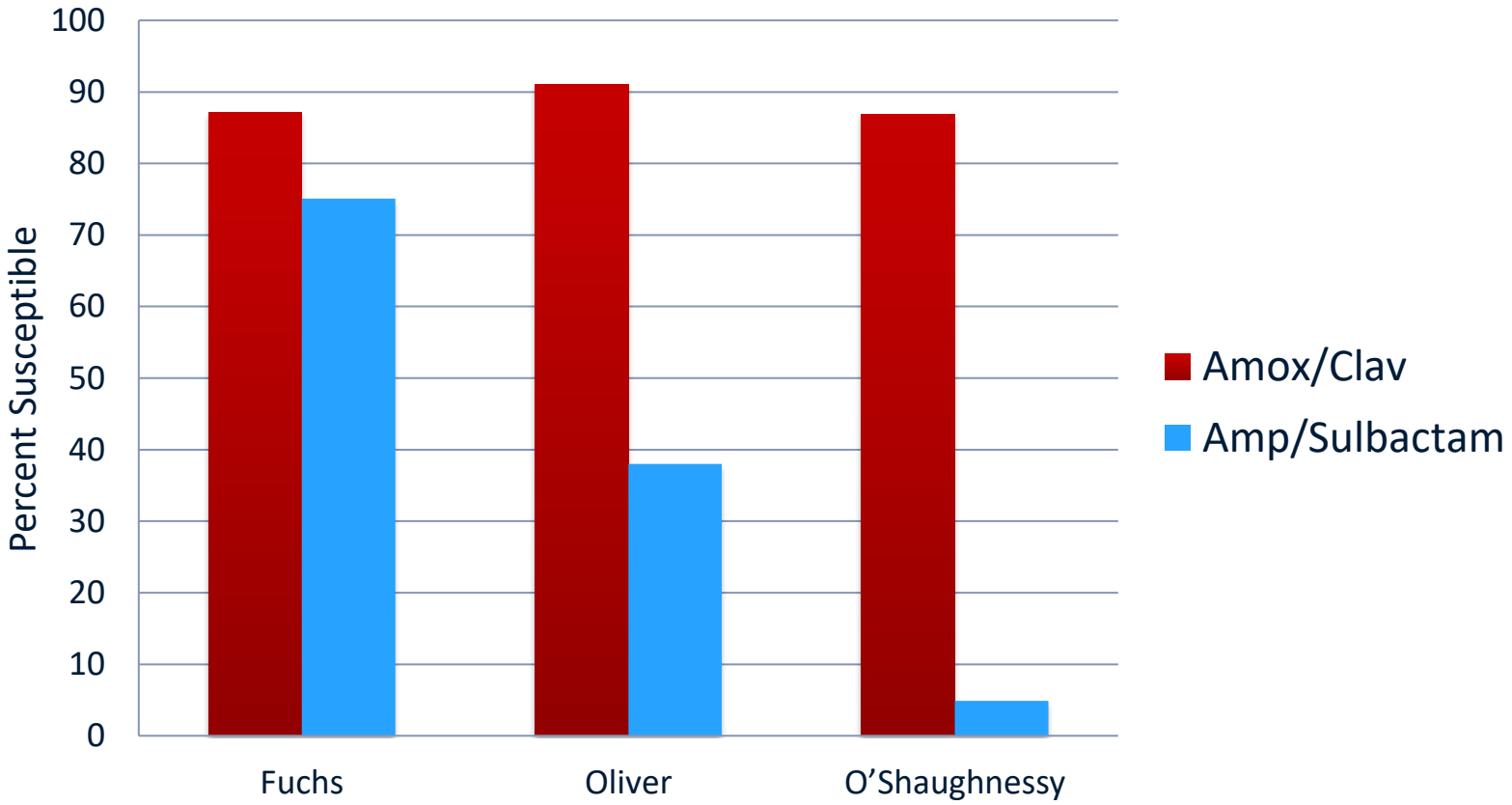
Amoxicillin-clavulanate vs. ampicillin-sulbactam

- 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**

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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
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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%

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Susceptibility

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	MIC	
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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
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Gentamicin	<=2 mcg/mL	S
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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	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.

Utilization of Institutional Data to Guide Empiric MDRO Therapy

- Routine testing of newer antibiotics allows for analysis of populations that would be benefit from empiric therapy
- Example: ceftolozane/tazobactam traditionally preferred for Pseudomonas resistant to piperacillin/tazobactam, cefepime and carbapenems (EBR)
  - Evaluate incidence of ceftolozane/tazobactam resistance in relation to other newer agents for EBR Pseudomonas
  - Identify risk factors for ceftolozane/tazobactam resistance based on institutional patient data

Summary

- The focus on antibiotic stewardship is increasing and will be mandated, with the focus on providing optimal care, and reducing unnecessary antibiotic exposure risk for developing MDR infections
- Obtaining timely and accurate organism identification and susceptibility data is essential in conducting daily antibiotic stewardship activities
- Multidisciplinary collaboration is essential in optimizing patient outcomes

Summary

- **Sensititre™ offers several potential advantages that impact microbiology and stewardship:**
  - Fewer number of “limitations” that force alternate methods to identify an organisms or test susceptibilities, which may cause a delay in appropriate therapy
  - Recently approved antibiotics are available for susceptibility testing significantly sooner
  - Fully customizable panel allow selection of drug AND concentration
  - Changes to panel configurations can be done in a timely manner, and allow compliance with CLSI breakpoint changes

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Automated Susceptibility Testing to Optimize Patient Outcomes

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