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Impact of Accelerate Pheno™ System on Management of Gram Negative Bacteremia at an Academic Medical Center

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Medical Director, Quality
Medical Director, Antimicrobial Stewardship Program
Allegheny General Hospital

Objectives

1) Outline Antimicrobial Stewardship Program (ASP) structure, initiatives, outcomes at Allegheny General Hospital (AGH)

2) Describe the clinical utility of rapid susceptibility testing for bacteremia due to gram negative pathogens

3) Define metrics of importance to key stakeholders

4) Outline Accelerate Pheno™ system workflow as part of an ASP gram negative bacteremia clinical management initiative

5) Outline clinical & economic impact of ASP bundled intervention for gram negative bacteremia

Allegheny General Hospital

- Largest of 8 hospitals in the Allegheny Health Network
- 576 bed quaternary care teaching hospital
  - 22,000 admissions/year
  - 427 residents/fellows
    - 100 Internal Medicine residents
- Level 1 trauma center
- 5 Intensive Care Units
  - Trauma
  - Medical
  - Neurosurgical
  - Coronary
  - Surgical

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AGH ASP Team Members

- **4 dedicated ID/ASP clinical pharmacy specialists**
  - 3 at AGH
  - 1 at West Penn Hospital

- **3 ID physicians**
  - 0.5 FTE each

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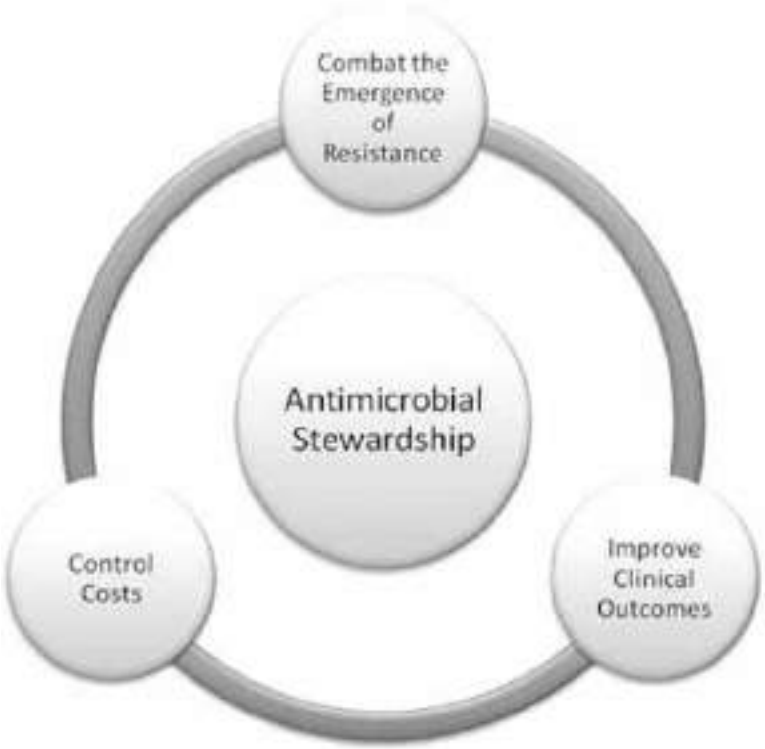
What is Antimicrobial Stewardship

- Multifaceted approach aimed at achieving goals:
  - combating emergence of resistance
  - improving patient outcomes
  - controlling healthcare cost

★ By improving/optimizing antimicrobial utilization



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Lawrence KL et al. Am J Respir Crit Care Med 2009

AGH ASP Strategies

GOAL: To assist care providers to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use

(toxicity, emergence of resistance, selection of pathogenic organisms)

Created Tiers for Antimicrobials

- Prior authorization and mandatory ID consultations for Tier 1 agents
- Prospective audit with real-time intervention and feedback for Tier 2 agents

Disease-Based Initiatives

- Clinical decision making algorithms for high-yield disease states
- Prospective audit with real-time intervention and feedback
- Incorporate biomarkers and rapid diagnostics

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Tier 1 Agents: Prior Authorization *

- Linezolid
- Daptomycin
- Quinopristin/dalfopristin
- Ceftaroline
- Tigecycline
- Ertapenem
- Meropenem
- Amikacin

- Streptomycin
- Aztreonam
- Colistin
- Fosfomycin
- Voriconazole
- Micafungin
- Amphotericin B
- Non-formulary antimicrobials

* Requires ID consultation if continued

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Tier 2 Agents: Prospective Audit

- Ciprofloxacin
- Levofloxacin
- Ceftriaxone
- Cefepime
- Piperacillin/tazobactam
- Clindamycin

- Monday - Friday: ASP team member reviews the charts of all pts receiving Tier 2 agents for appropriateness

- ASP team member contacts the primary team with recommendations for alternative agent if use deemed inappropriate

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Clinical Decision Making Pathways

- Multidisciplinary development of evidence-based practice guidelines

- Incorporate local resistance patterns

- Focus upon high-yield disease processes

- Utilize novel biomarkers and rapid diagnostics

Guidelines and Clinical Pathways

- Skin and soft tissue infections
- Community acquired pneumonia/Acute exacerbated COPD
- Central line associated bloodstream infections (CLABSIs)
- *Clostridium difficile* infections
- *Staphylococcus aureus* bacteremia *(mandatory ID consultation)*
- Febrile neutropenia
- Necrotizing pancreatitis

Other Initiatives

- **Blood Culture reviews**
- **Bug-Drug Mismatches**
- **Beta-Lactam Allergy Assessment Initiative**
- **Antimicrobial Safety & Sustainability Task Force**
  - Lower respiratory tract infections –Procalcitonin guidance
    - CAP/HAP/VAP
    - Acute exacerbated COPD
  - CDI
    - PCR ordering algorithm (diagnostic stewardship)
    - Proton pump inhibitor algorithm
    - Formal review of all HO-CDI cases for opportunities for improvement

Introduction of Rapid Diagnostics

- **Cepheid Xpert®** MRSA/SA Blood Culture
  - ASP team receives real-time alerts with results and contacts primary service with recommendations for management
- **Alere™ PBP2a** for GPCs in clusters for non-blood isolates
- **Biofire® FilmArray®** meningitis/encephalitis panel
- **GenMark's ePlex®** respiratory pathogen panel

ASP team provides clinical decision making algorithms for these disease states and perform prospective audit with real-time intervention and feedback based upon rapid diagnostic results

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Benefits of Expanded ASP Initiatives at AGH

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CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Impact of Procalcitonin Guidance with an Educational Program on Management of Adults Hospitalized with Pneumonia

Thomas L. Walsh, MD,[a,b] Briana E. DiSilvio, MD,[c] Crystal Hammer, MD,[c] Moeezullah Beg, MD,[c] Swati Vishwanathan, MD,[c] Daniel Speredelozzi, MD,[c] Matthew A. Moffa, DO,[a,b] Kurt Hu, MD,[c] Rasha Abdulmassih, MD,[a,b] Jina T. Makadia, MD,[a,b] Rikinder Sandhu, MD,[a,b] Mouhib Naddour, MD,[c] Noreen H. Chan-Tompkins, PharmD BCPS-AQ ID,[d] Tamara L. Trienski, PharmD,[d] Courtney Watson, MPH,[e] Terrence J. Obringer, DO,[f] Jim Kuzyck, MT,[g] Derek N. Bremmer, PharmD, BCPS[b]

Outcome Variable	Pre-intervention (n =152)	Post-intervention (n =232)	P value
Mean length of stay (days)	4.9	3.5	0.006
Mean duration of therapy (days)	9.9	6.0	<0.001
Receipt of 7 days or less of therapy	26.9%	66.4%	<0.001
30-day pneumonia-related re-admissions	7.2%	4.3%	0.26

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Walsh TL et al. Am J Med 2018

Effect of Antimicrobial Stewardship Program Guidance on the Management of Uncomplicated Skin and Soft Tissue Infections in Hospitalized Adults

Thomas L. Walsh, MD; Derek N. Bremmer, PharmD; Matthew A. Moffa, DO; Noreen H. Chan-Tompkins, PharmD; Monika A. Murillo, MD; Lynn Chan, PharmD; Michael J. Burkitt, MD, MPH; Chelsea I. Konopka, PharmD; Courtney Watson, MPH; and Tamara L. Trienski, PharmD

Outcome Variable	Pre-intervention (n = 163)	Post-intervention (n = 165)	P value
Mean length of stay (days)	3.7	2.2	<0.001
Mean duration of therapy (days)	12.6	8.9	<0.001
Gram negative rod therapy	73 (44.8%)	16 (9.7%)	<0.001
Anaerobic therapy	65 (39.9%)	17 (10.3%)	<0.001
Anti-pseudomonal therapy	28 (17.2%)	3 (1.8%)	<0.001
30-day re-admissions	10 (6.3%)	8 (4.9%)	0.64

ASP made recommendations for 125 patients: 96% acceptance rate

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Walsh TL et al. Mayo Clinic Proc Inn Qual Out 2017

Tier 1 & 2 Spend Reduction

Hospital	Year 1 Savings	Year 2 Savings	Year 3 Savings	Total Savings
AGH	$104,505	$180,941	$346,391	$631,837
WPH	$188,212	$261,196	$261,108	$710,516
TOTAL	**$292,717**	**$442,137**	**$607,499**	**$1,342,353**

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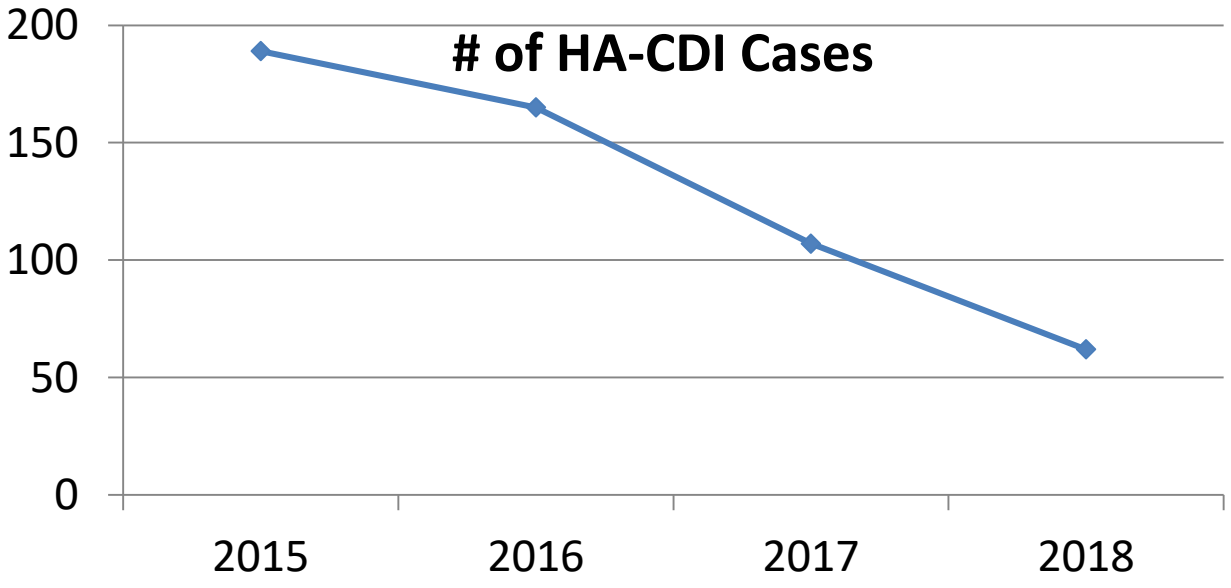
Impact on HA-*Clostridium difficile* rates

- **AGH Hospital-acquired *C. difficile* infections:**
  - **2015:** 189 cases (pre-ASP baseline)
  - **2016:** 165 cases (24 prevented cases x ~$15k per case = $360,000)
  - **2017:** 107 cases (82 prevented cases = $1,230,000)
  - **2018**: 62 cases (136 prevented cases = $1,905,000)



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Opportunities for Improvement

Management of Gram negative bacteremia

Background

- Gram negative bacteria are a predominant cause of bloodstream infections (BSIs) – management complicated by increasing resistance

- Current standard technique for diagnosis and treatment of BSI is via detection of bacteria from automated blood culture systems and subsequent detection of resistance using agar plates and semi-automatic equipment
  - May take 2-4 days, during which time the patient may be receiving inappropriate antibiotic therapy

- **Rapid diagnosis of BSI**: improve patient care & foster effective antimicrobial stewardship by allowing early optimal targeted therapy

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Anderson DJ et al. PLoS One 2014
Henig O et al. Antimicrob Agents Chmother 2018

Plague of Antimicrobial Resistance

"arguably the greatest risk to human health comes in the form of antibiotic-resistant bacteria.

We live in a bacterial world where we will never be able to stay ahead of the mutation curve.

A test of our resilience is how far behind the curve we allow ourselves to fall."

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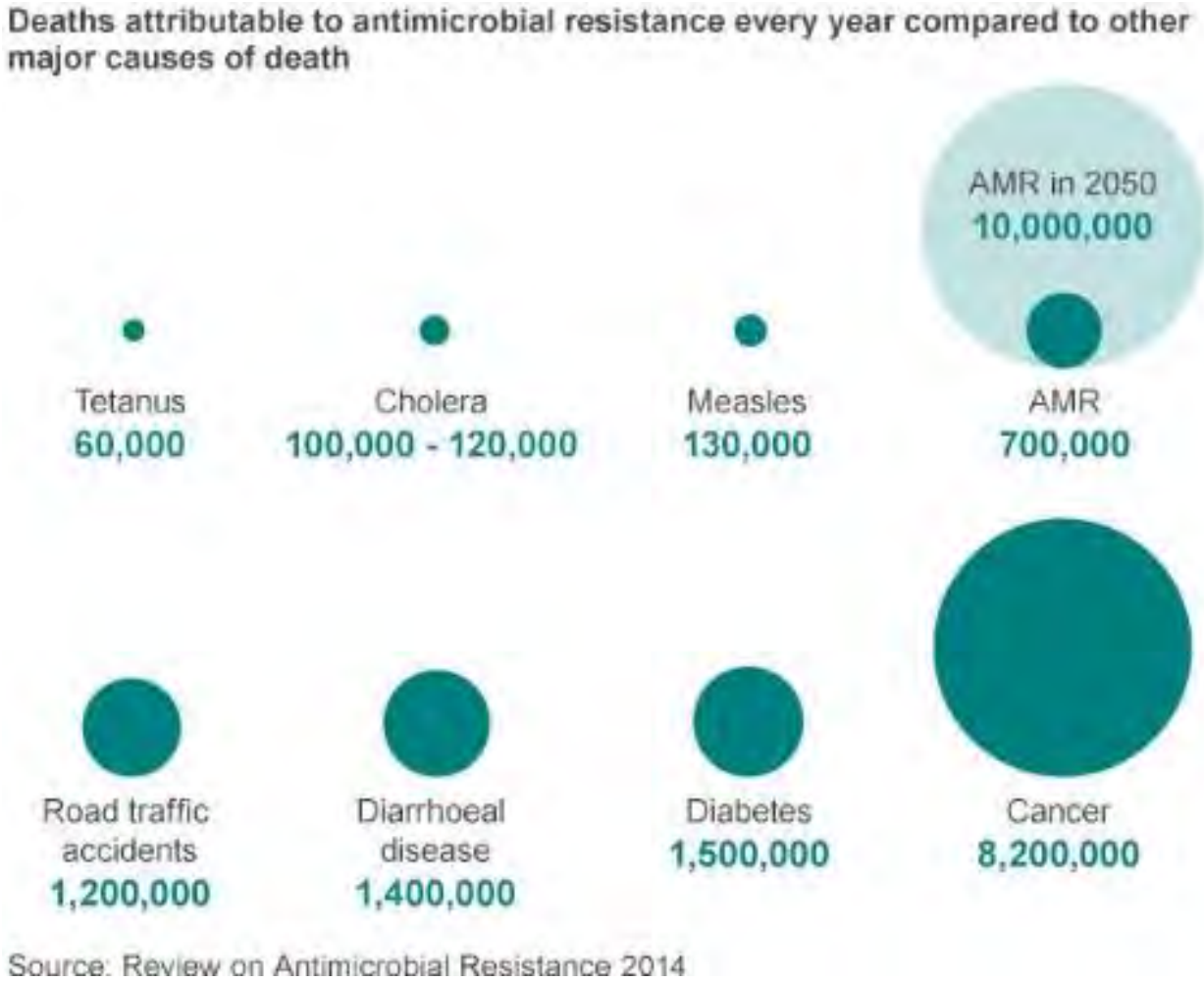
Howell L. World Economic Forum 2013

Plague of Antimicrobial Resistance



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Pitfalls of Unnecessary Therapy

Even abbreviated empiric therapy is potentially harmful

- Among patients who receive anti-pseudomonal β-lactam therapy, every additional day of exposure is associated with an increased risk of new resistance development

- De-escalation from anti-pseudomonal β-lactam therapy in under 48 hours reduces 90-day *C. difficile* infection incidence 3-fold

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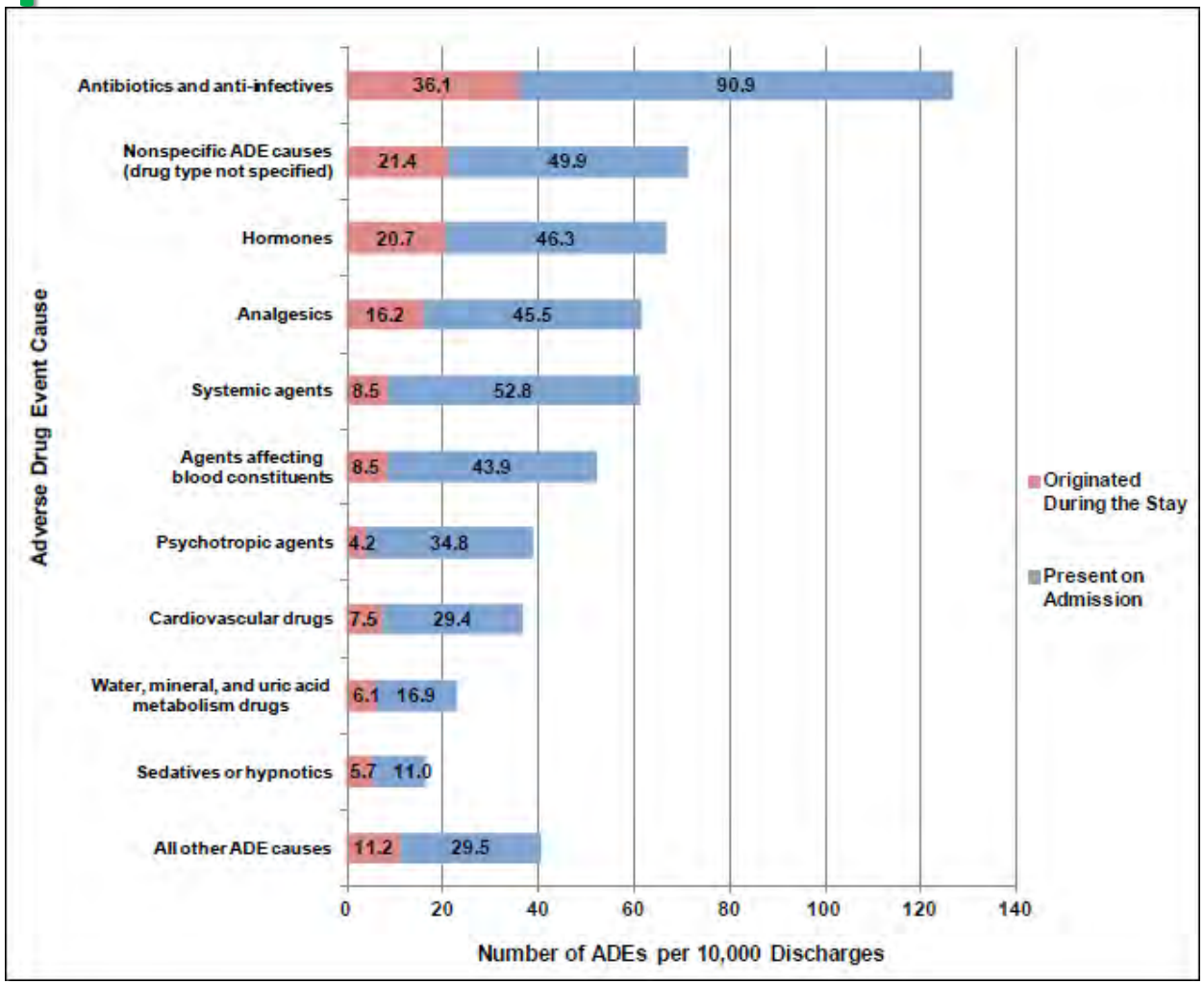
Teshome BF et al. Pharmacotherapy 2018
Seddon MM et al. Clin Infect Dis 2018

Adverse Drug Events (ADE) Causes in Hospitalized Patients

- Data from 32 states
- Antibiotics were most common cause of ADE
- *C. difficile* was the most common antibiotic-associated ADE



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Weiss AJ, et al. Statistical Brief #158, Jul 2013: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb158.jsp
Slide courtesy of Edina Avdic, Pharm.D.

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Timing of Antibiotics in Sepsis

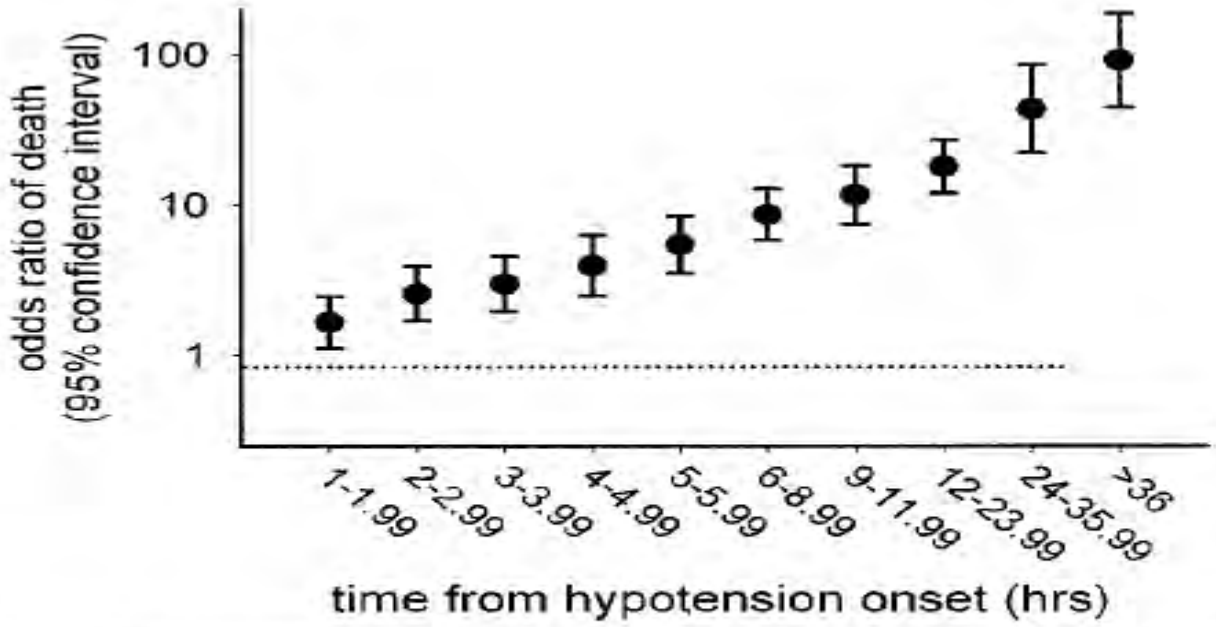

Figure 2. Mortality risk (expressed as adjusted odds ratio of death) with increasing delays in initiation of effective antimicrobial therapy. Bars represent 95% confidence interval. An increased risk of death is already present by the second hour after hypotension onset (compared with the first hour after hypotension). The risk of death continues to climb, though, to >36 hrs after hypotension onset.

- **Each hr of delay in antimicrobial administration was associated decrease in survival of 8%**
- **Time to initiation of effective Abx therapy was the single strongest predictor of outcome**

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

Impact of Inadequate Initial Antimicrobial Therapy on Mortality in ICU Patients with Bloodstream Infections

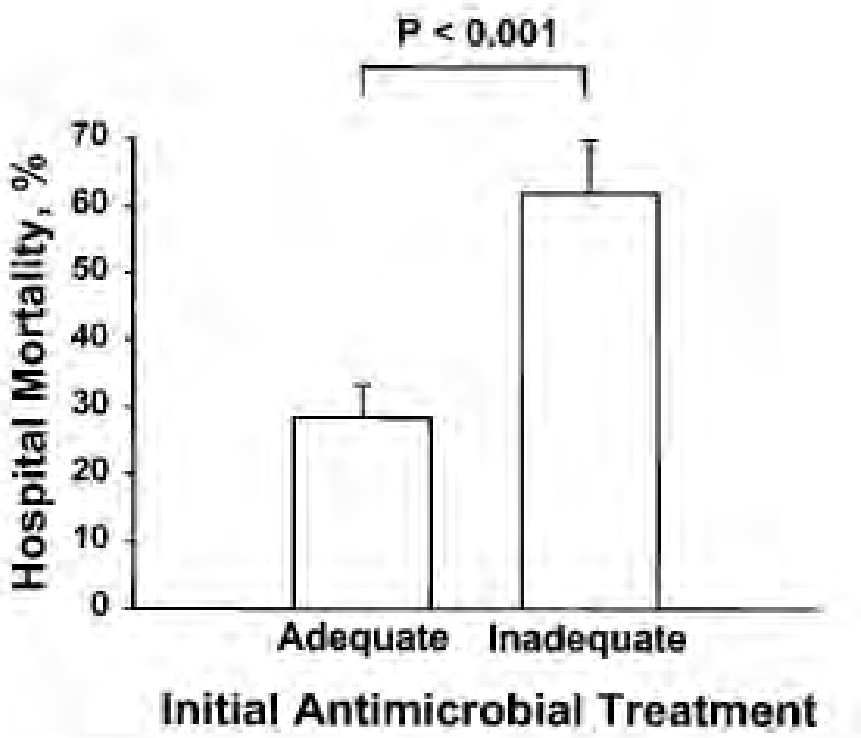

FIGURE 1. Hospital mortality according to the adequacy of the initial antimicrobial treatment prescribed for bloodstream infections. Upper 95% CIs are shown.

Ibraham EH et al. CHEST 2010

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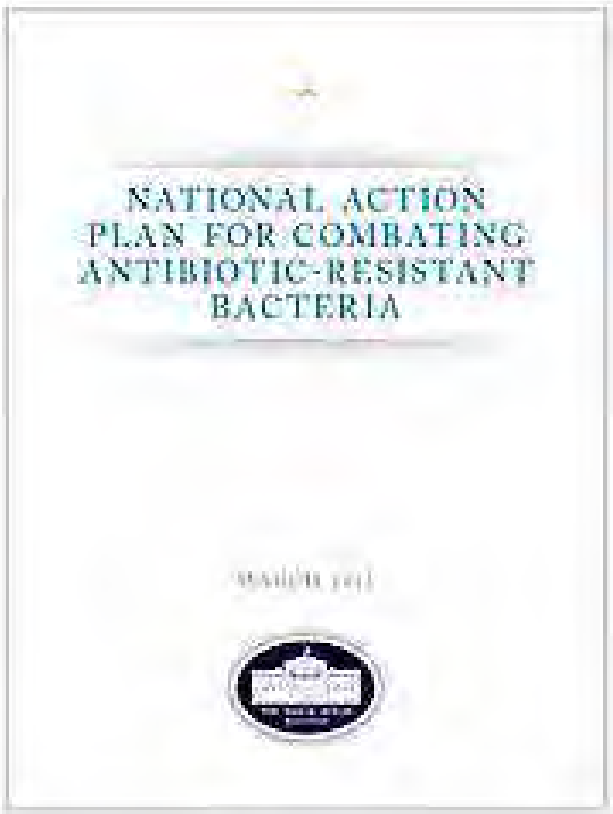
Timing of Antibiotics in Sepsis



- Slow & prevent the spread of AMR bacteria
- Advance development and use of rapid and innovative diagnostic tests for the ID and characterization of AMR bacteria

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Benefits of Rapid Diagnostics

Benefits of Speed

- Reduce time to effective therapy **AND** time to optimal therapy
  - For hemodynamically stable patients
    - Decreased LOS
    - Reduces downstream effects of unnecessarily broad spectrum therapy
      - Antibiotic resistance
      - *C. difficile* infection rates
    - Decrease healthcare costs
  - For critically ill patients
    - Reduce mortality
    - Shorter ICU LOS
    - Improved patient outcomes
    - Improved patient satisfaction

Options for Gram Negative Rapid Diagnostics

- Majority of current rapid technologies focus on rapid ID of pathogen
- Information on susceptibilities not available or limited to a few clinically relevant resistance genes
  - *mecA* for beta-lactam resistance in staphylococci
  - *vanA, vanB* for glycopeptide resistance in enterococci
  - Carbapenemases and a few select ESBL genes for Gram negatives
    - Technologies based on detection of resistance genes only include limited number of resistance markers
    - Detection only indicates possible resistant phenotype to some agents
      - Does not reliably inform on complete susceptibility profile or MIC data

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Ozenci V et al. Journal of Antimicrobial Chemotherapy 2019

Limitations of Most GNR Rapid Diagnostics

- Reporting of a limited number of resistance mechanisms present, numerous others not reported – can be counter-productive
  - May lead to false sense of security that not encountering a resistant pathogen leading to inappropriate early de-escalation
    - Absence of a resistance gene does NOT = pathogen is susceptible
      - Porin mutations
      - Efflux pumps

Examples

- **Rapid diagnostics**: *Pseudomonas aeruginosa* negative for KPC, IMP, VIM, OXA, NDM
  - Lack of carbapenemase does not inform if meropenem susceptible as unable to determine if porin deficiencies present *(major cause of carbapenem-R Pa)*

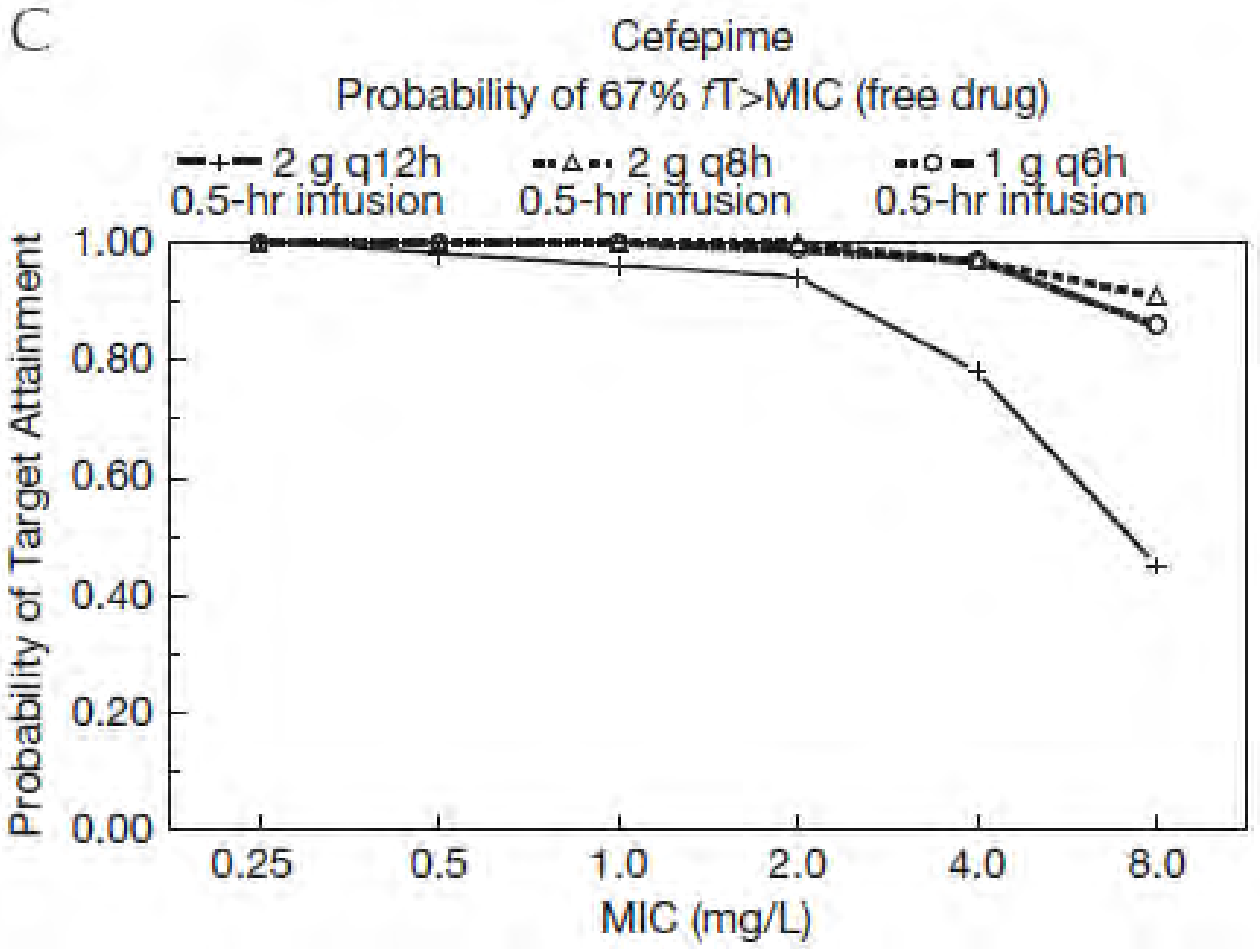
- **Rapid diagnostics:** *Klebsiella pneumoniae* negative for all resistance markers including CTX-M (main ESBL resistance mechanism in our area)
  - Does not report numerous other ESBL resistance mechanisms and can lead to false confidence in de-escalating (> 1800 beta lactamase genes)

Limitations of Most GNR Rapid Diagnostics

- Detection of specific gene target is not necessarily associated with gene expression in vivo – could lead to over-reporting resistance

- Molecular genotypic testing is an adjunct to – does not replace – phenotypic testing
  - Potential to increase costs and labor in a clinical lab

MICs – more than "S", "I", and "R"



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Lodise TP et al. Pharmacotherapy 2006
Tam VH et al. J Antimicrob Chemother 2002

MICs – more than "S", "I", and "R"

- Critically ill patients:
  - Fluctuations in volume/fluid status, renal/hepatic dysfunction and perfusion affect PK/PD and efficacy at site of infection
  - MIC information (rather than just resistance mechanism or "S/I/R" allows for deployment of more sophisticated dosing strategies in complex patients
  - Availability of data early has potential to impact outcomes
  - With movement towards therapeutic drug monitoring (TDM), value of precision medicine by adjusting dosing based upon patient's drug levels and MIC

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Economou CJPet al. Jantimicrob Agents 2017;49:589-594

Hayashi T et al. Int J Antimicrob Agents 2013;41:162-166

Limitations of Most GNR Rapid Diagnostics

- For stable patients, does not provide susceptibility data for oral agents with excellent bioavailability to promote early IV to PO conversion
  - Missed opportunity to optimize definitive therapy for discharge home with PO agents

- By focusing exclusively on genotypic drug resistance, most platforms help clinicians escalate therapy, but are of no help with de-escalation
  - Switching from broad- to narrow-spectrum agent performed more often by ID service than primary team in response to positive blood cultures **(100% vs. 50%; P < 0.001)**
  - De-escalation therapy in severe sepsis and septic shock is safe and associated with significantly lower mortality

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Fluckiger U et al. European Journal of Clinical Microbiology and Infectious Diseases 200;19:493-500

Garnacho-Montero J et al. Intensive Care Med 2014;40:32-40

Accelerate Pheno™

- Fully automated fluorescent in-situ hybridization (FISH) to provide ID within 1.5 hours
- Morphokinetic cellular analysis then used to determine MIC within 7 hours

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Accelerate Pheno™ System

System
- 1-4 module(s)
- Control & Analysis PCs
- Touchscreen monitor

Module
- Automated pipetting robot
- Digital camera
- Custom microscope

Kit
- 48 flow-channel cassette
- Reagent cartridge
- Sample vial

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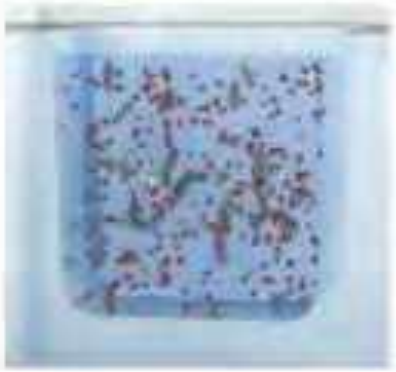
http://acceleratediagnostics.com/technology/mca/

AUTOMATED SAMPLE PREP

Gel Electro-Filtration (GEF)

Debris, such as lysed red blood cells, is separated from microbial cells and captured by a gel, providing a clean sample for analysis.



Sample is loaded into GEF well. The gel contains pores smaller than microbial cells.

Positive charge is applied and debris migrates into gel leaving microbes behind.

Electrical field is briefly reversed and microbes move to center for ease of retrieval.

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http://acceleratediagnostics.com/technology/mca/

QUANTITATIVE IDENTIFICATION

- Fluorescence *In Situ* Hybridization

DETECT

Universal probes distinguish bacteria and yeast from debris

IDENTIFY

Target probes identify specific bacteria and yeast

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http://acceleratediagnostics.com/technology/mca/

GNR Panel

	Identification	Ampicillin-Sulbactam	Piperacillin-Tazobactam	Cefepime	Ceftazidime	Ceftriaxone	Ertapenem	Meropenem	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Aztreonam
E. coli	●	●	●	●	●	●	●	●	●	●	●	●	●
Klebsiella spp.	●	●	●	●	●	●	●	●	●	●	●	●	●
Enterobacter spp.	●		●	●	●	●	●	●	●	●	●	●	●
Proteus spp.	●	●	●	●	●	●	●	●	●	●	●	●	●
Citrobacter spp.	●		●	●	●	●	●	●	●	●	●	●	●
S. marcescens	●		●	●	●	●	●	●	●	●	●	●	●
P. aeruginosa	●		●	●	●			●	●	●	●	●	
A. baumannii	●		●						●				

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http://acceleratediagnostics.com/

Morphokinetic Cellular Analysis

- Time-based morphologic changes relative to established reference values using dark-field microscopy observing individual, live, growing, immobilized bacterial cells in real time (every 10 minutes)
  - Records mass, shape, division, growth pattern/rate for given pathogen
  - Captures massive amounts of morphokinetic data

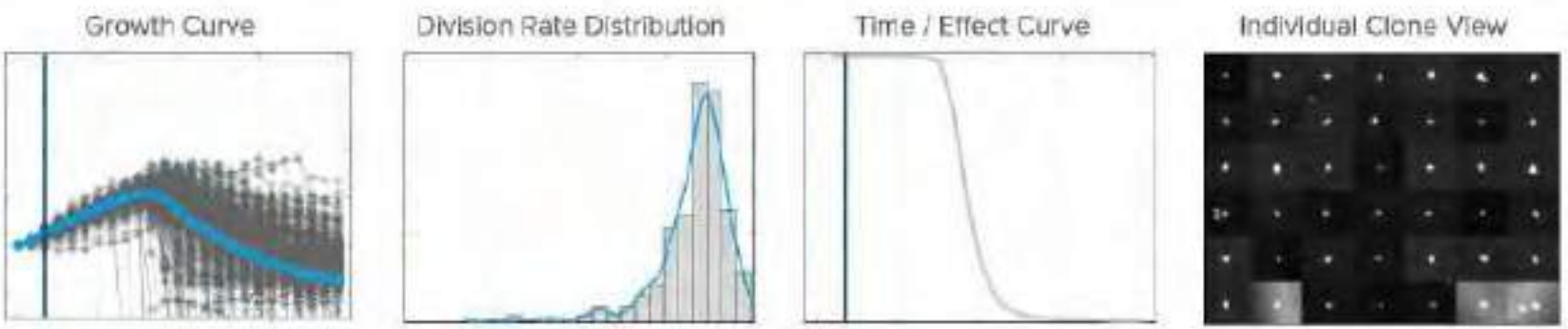
- MIC then established by analyzing clone intensity changes in presence of varying concentrations of a given antibiotic

Morphokinetic Cellular Analysis

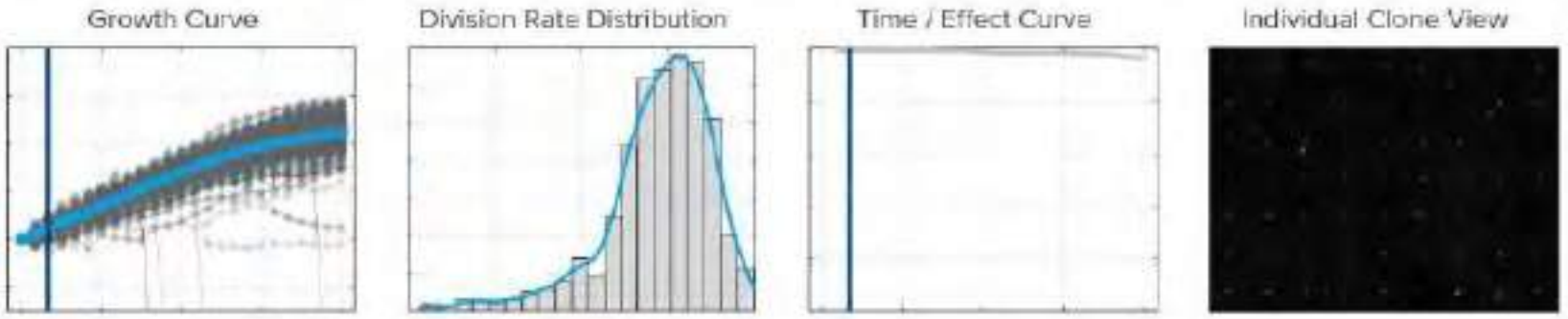
- Reportable MIC ranges are much wider than traditional commercial automated susceptibility testing platforms
  - Allow for PK/PD dose optimization with more exact MIC values

Morphokinetic Cellular Analysis

***Klebsiella* with meropenem MIC 1 - susceptible**



***Klebsiella* with meropenem MIC 32 - resistant**



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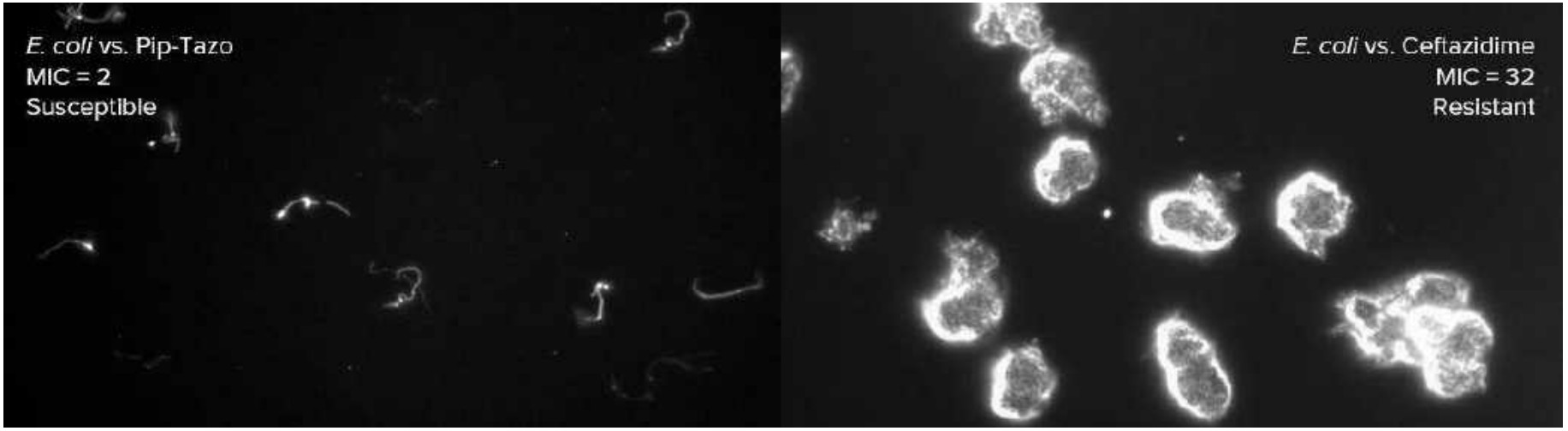
http://acceleratediagnostics.com/technology/mca/

Morphokinetic Cellular Analysis



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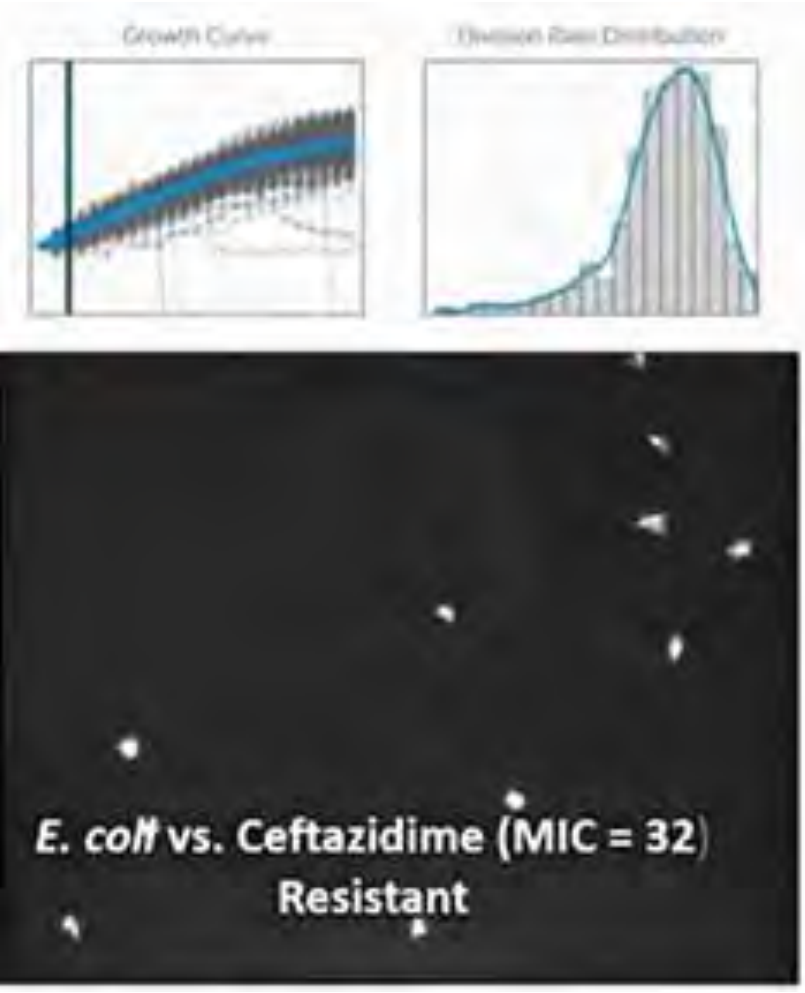
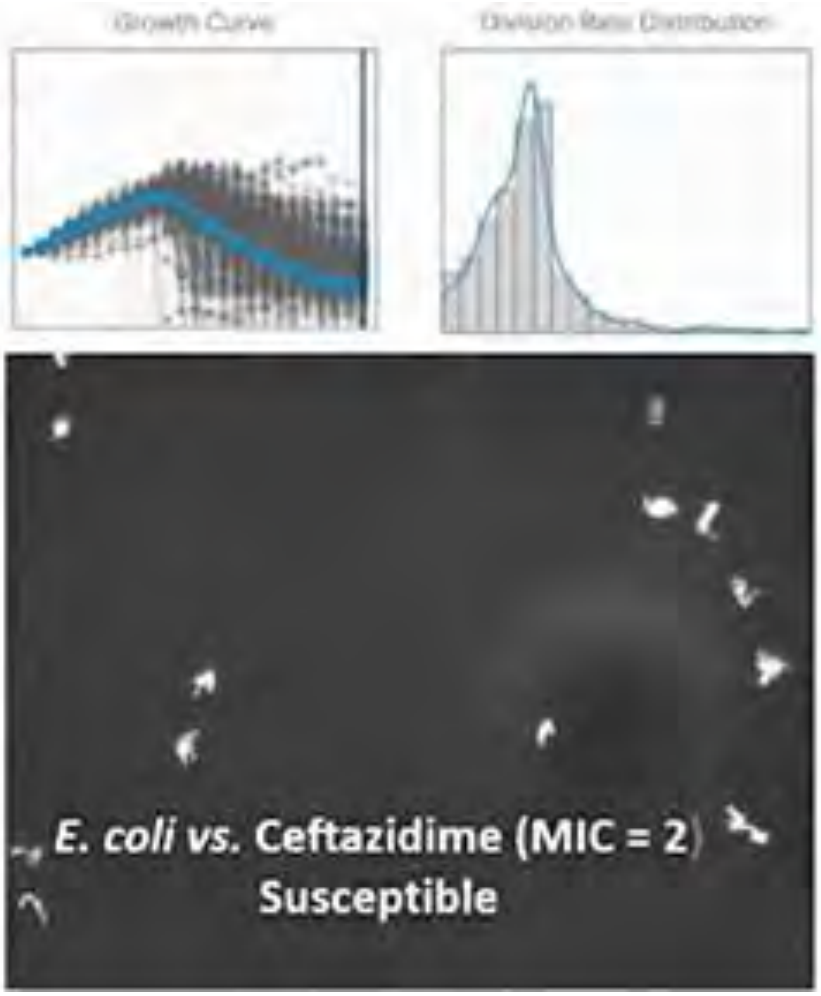
Morphokinetic Cellular Analysis





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http://acceleratediagnostics.com/technology/mca/

Performance of the Accelerate Pheno™ system for identification and antimicrobial susceptibility testing of a panel of multidrug-resistant Gram-negative bacilli directly from positive blood cultures

105 clinical strains previously characterized for presence of β-lactamase-encoding genes ***(penicillinases, ESBLs, cephalosporinase overproduction, carbapenemases)***

Parallel testing with Accelerate Pheno system and conventional culture methods *(MALDI-TOF and VITEK 2)* and AST by disc diffusion and Etest by EUCAST criteria

PCRs to confirm resistance genes

(+) Blood Culture Isolates	105
ID Agreement	100% (105/105)
Categorical Agreement	94.9% (1169/1232)
Major Errors @	0.3% (4/1232)
Very Major Errors #	0.7% (8/1232)
Minor Error $	4.1% (51/1232)

@ - false resistance by Accelerate Pheno
 # - false susceptibility by Accelerate Pheno
$ - (I)by one method but (S) or (R) by the other

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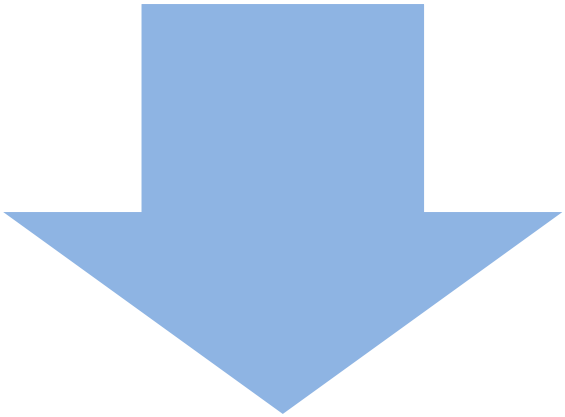
Pantel A et al. J Antimicrob Chemother 2018

Importance of Rapid MIC to Infectious Disease/ASP Physicians



Rapid Escalation

Optimize time to effective therapy

Accelerate time to clinical stability

Reduce mortality

Rapid De-escalation

Optimize time to optimal therapy

Reduce CDI

Decrease propagation of antimicrobial resistance

Limit adverse drug events

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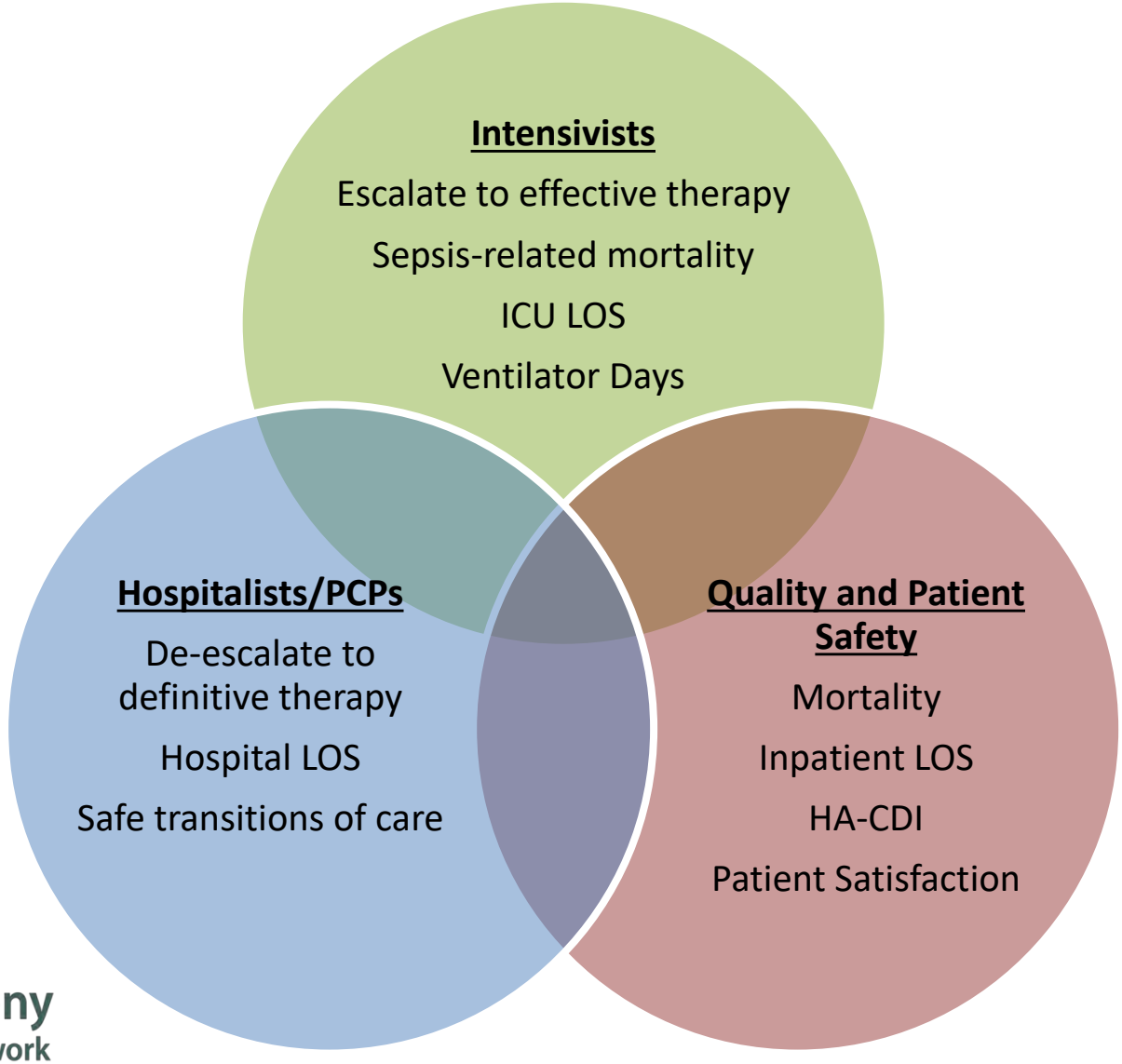
Importance to Other Stakeholders



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Return On Investment/Cost Justification

C-suite – Cost effective care/Value based care

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Return On Investment/Justification

Outcom

Antimicrob

Inpatient

ICU LOS

Mortali

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An

A

- Patient satisfaction

"Soft dollar" savings demonstrated in published literature are not always generalizable to other centers

- Able to implement as fully
- Able to track as reliably
- Similar baseline issues
- Similar baseline practice/management

Can your hospital ASP replicate??

Industry ROI calculators tend to cherry-pick data & use higher estimates for drug costs (AWP), cost/bed day, cost per ADE than hospital administrators

Leads to "over-sell/under-deliver"

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Importance of ASP Involvement

- Potential benefits of rapid diagnostics to be achieved
  - **Critical**:
    - Processes in place to ensure information is rapidly disseminated to end users
    - Ability to ensure information is rapidly acted upon
- Fantastic technologies not as impactful if applied without team to drive utility
- ASPs uniquely positioned to collaborate with:
  - **Microbiology**:
    - Determine clinical need
    - Design workflow and ensure appropriate infrastructure
    - Develop business plan to demonstrate benefit
  - **Clinicians**:
    - Extensively educate (pan-S isolates, easy to "stay the course as patient is improving" – need nudge)
    - Develop clinical decision making pathways
    - Facilitate prompt action based on results by communicating patient-level guidance directly with prescribers when 1st implemented

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Hill B et al. Infect Control Hosp Epidemiol 2018

Clinical Infectious Diseases
MAJOR ARTICLE

The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis

- 31 studies included with 5920 patients
- Significantly lower mortality risk wit molecular rapid diagnostic testing (RDT) than with conventional microbiology methods (OR, 0.66; 95% CI 0.54 – 0.80)
  - # needed to treat: 20
  - Mortality benefit seen in both gram positive and gram negative but not yeast
    - GNR: OR, 0.51; 95% CI 0.33 – 0.78
- Time to effective therapy decreased by > 5 hours
- Length of stay decreased by ~ 2.5 days

Mortality risk lower with RDT in studies with ASPs (OR, 0.64) but non-ASP studies failed to demonstrate decrease in mortality risk

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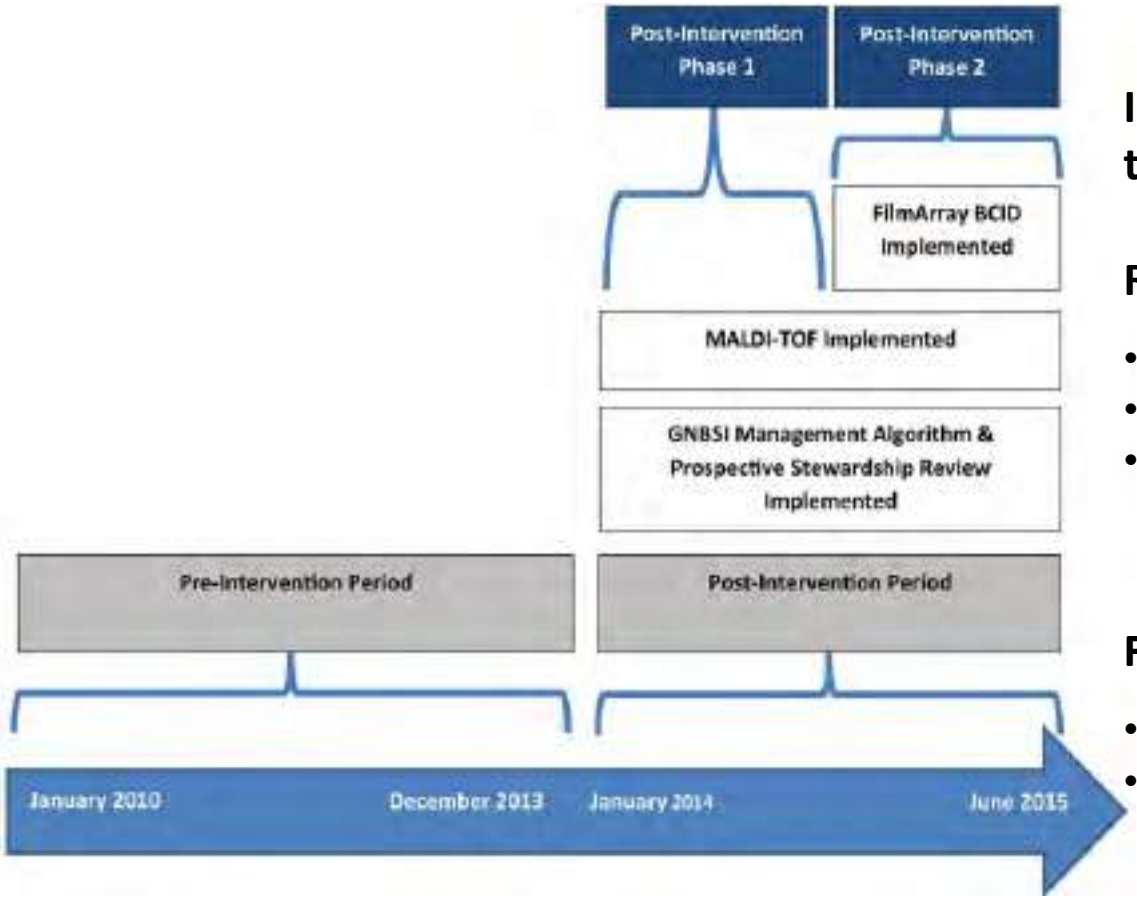
Timbrook T et al. Clin Infect Dis 2016

Cumulative Effect of an Antimicrobial Stewardship and Rapid Diagnostic Testing Bundle on Early Streamlining of Antimicrobial Therapy in Gram-Negative Bloodstream Infections



Post-intervention Period

Improved appropriateness of empiric therapy (95 vs 91%; p=0.02)

Reduced time to de-escalation from:

- **Combination therapy (2.8 vs 1.5d)**
- **Antipseudomonal β-lactam (4 vs 2.5d)**
- **Carbapenem therapy (4 vs 2.5d)**

Phase 2 vs Phase 1

Further reduced time to de-escalation:

- **Combination therapy (2 vs 1d)**
- **Antipseudomonal β-lactam (2.7 vs 2.2d)**

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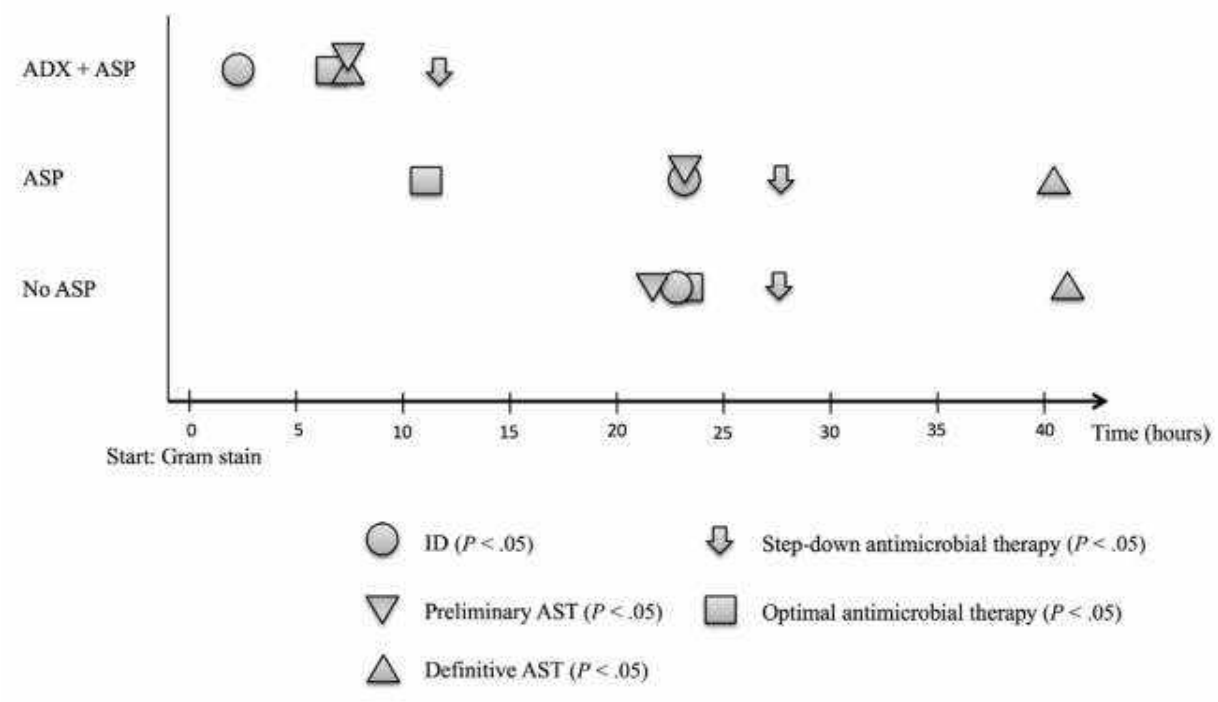
Bookstaver PB et al. Antimicrobial Agents and Chemotherapy 2017

Clinical Impact of Rapid Species Identification From Positive Blood Cultures With Same-day Phenotypic Antimicrobial Susceptibility Testing on the Management and Outcome of Bloodstream Infections

Kathrin Ehren,[1,a] Arne Meißner,[1,2,a] Nathalie Jazmati,[1] Julia Wille,[1,2] Norma Jung,[4] Jörg Janne Vehreschild,[3,4] Martin Hellmich,[5] and Harald Seifert[1,3]



Use of Accelerate Pheno reduced time to ID & AST and time to optimal therapy

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Ehren K et al. Clin Infect Dis 2019

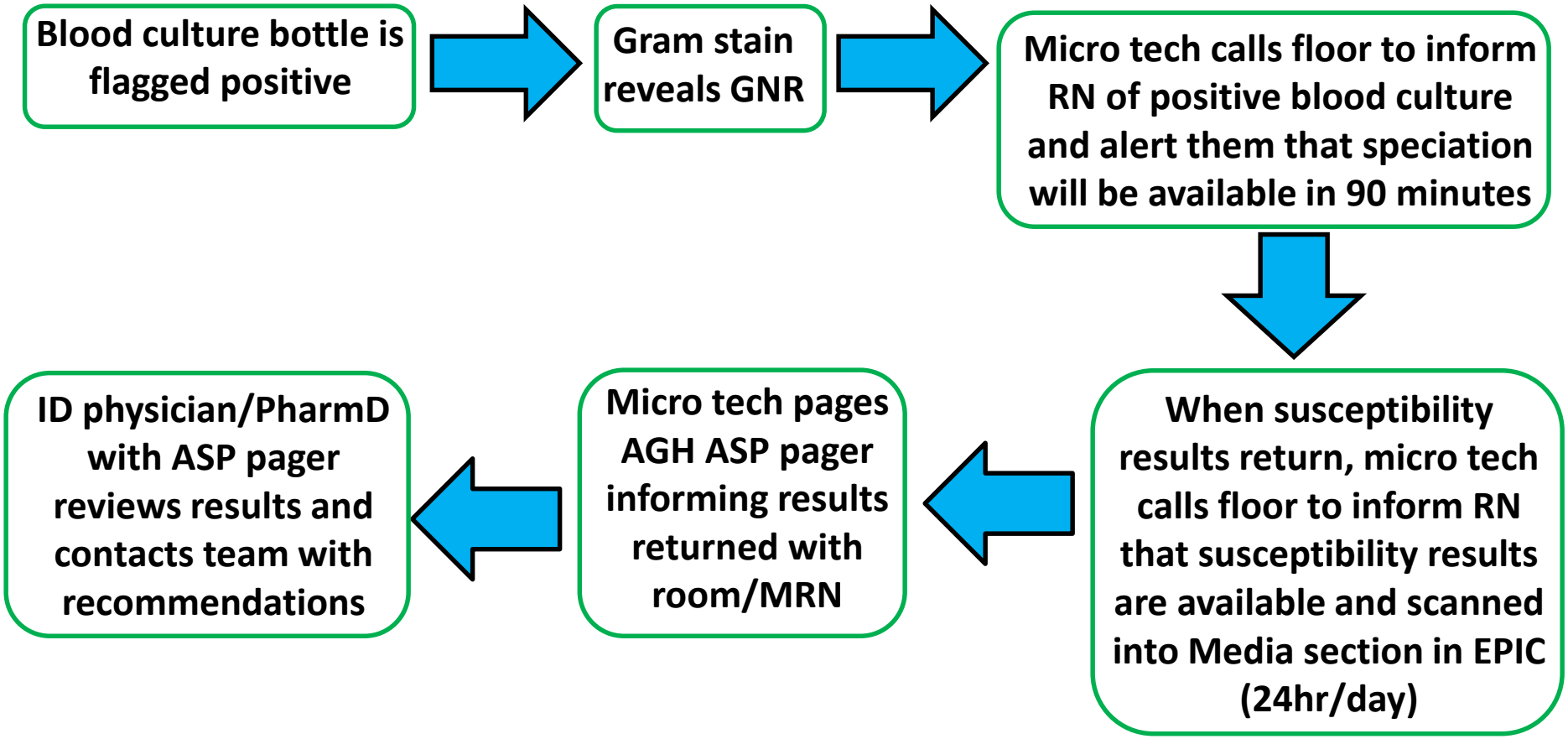
Importance of ASP Involvement at AGH

- Administrators can be skeptical of proposals heavily reliant upon indirect cost savings ***(i.e. – LOS reduction, HA-CDI reduction)*** with large up front capital investments and/or expensive to run

- AGH ASP team track record of success in collaborating with local care providers on disease-specific interventions to consistently demonstrate direct and indirect cost savings
  - Partnership with Microbiology Lab to review pros/cons of RDTs for GNR bacteremia
  - Cooperation with Administration to agree upon impactful process & outcome measures
  - Provider education as part of multifaceted approach with technology as 1 part of a larger clinical management algorithm for a disease state
    - Introducing RDT without thoughtful plan for intervention: setting up test for failure

- Critical alignment with network quality goals/initiatives:
  - Mortality, re-admissions, LOS, complications
    - "Sepsis" is leading cause of re-admissions and mortality

Workflow at AGH and WPH



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Additional Points

For stable patients with uncomplicated GNR bacteremia:

- Repeating blood cultures are low yield
- 7 days is as effective as 14 days

Clinical Infectious Diseases

MAJOR ARTICLE

Follow-up Blood Cultures in Gram-Negative Bacteremia: Are They Needed?

Christina N. Canzoneri, Bobak J. Akhavan, Zehra Tosur, Pedro E. Alcedo Andrade, and Gabriel M. Aisenberg

Department of General Internal Medicine, McGovern Medical School at The University of Texas Health Science Center at Houston

Conclusions. FUBC added little value in the management of GNB bacteremia. Unrestrained use of blood cultures has serious implications for patients including increased healthcare costs, longer hospital stays, unnecessary consultations, and inappropriate use of antibiotics.

Wiggers et al. BMC Infectious Diseases (2016) 16:286
DOI 10.1186/s12879-016-1622-z

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Sending repeat cultures: is there a role in the management of bacteremic episodes? (SCRIBE study)

Conclusions: Patients with *S. aureus* bacteremia or endovascular infection are at risk of persistent bacteremia. Achieving source control within 48 h of the index bacteremia may help clear the infection. Repeat cultures after 48 h are low yield for most Gram-negative and streptococcal bacteremias.

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ACCEPTED MANUSCRIPT

Seven versus fourteen Days of Antibiotic Therapy for uncomplicated Gram–negative Bacteremia: a Non–inferiority Randomized Controlled Trial

Dafna Yahav, MD ✉, Erica Franceschini, MD, Fidi Koppel, BA, Adi Turjeman, MA, Tanya Babich, MA, Roni Bitterman, MD, Ami Neuberger, MD, Nesrin Ghanem-Zoubi, MD, Antonella Santoro, MD, Noa Eliakim-Raz, MD, ... Show more

Author Notes

Clinical Infectious Diseases, ciy1054, https://doi.org/10.1093/cid/ciy1054

Published: 11 December 2018 **Article history** ▾

- Randomized, multicenter open-label, non-inferiority trial
  - Inpatients with GNR bacteremia, afebrile and hemodynamically stable for 48 hours
  - Randomized to 7 days or 14 days of antibiotic therapy
    - Excluded if uncontrolled focus of infection
  - Primary outcome at 90-d: composite of all-cause mortality, relapse, supperative complications, readmission or extended (>14d) hospitalization

CONCLUSIONS

- In hospitalized patients with GNR bacteremia with clinical stability before day 7, duration of 7 days of Abx therapy was non-inferior to 14 days

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Bundled Treatment Algorithm: Stable Patients

Stable floor patient with low inoculum source (i.e. – pyelonephritis)

- Obtain early renal ultrasound/CT imaging to exclude complicated disease *(i.e. abscess, stone, choledocholithiasis, etc)*
- Promote early IV to PO conversion if susceptible to fluoroquinolone (FQ)
- Promote early midline/PICC for home IV ceftriaxone if FQ/TMP-SMX resistant
- No need for repeat blood cultures in uncomplicated GNR bacteremia
- 7 days total therapy for uncomplicated *Enterobacteriaceae* bacteremia
- Aim for discharge within 48 hours (taking PO, normal mental status)
- ASP check-up phone call 24 hours after discharge
- ID clinic follow-up visit 48 hours after discharge

Bundled Treatment Algorithm: Critically-Ill Patients

Critically-ill patient

- Ensure optimal agent(s) administered ASAP & optimize dosing based on MIC/CrCl
- Encourage formal ID consultation

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Impact: Non-ICU

ASP enters data prospectively into database

Compare to GNRs in blood cultures in 12 months prior to Accelerate Pheno™

Excluded

- Anaerobic Gram negative bacteremia only (no aerobic GNR)
- > 42 days of effective therapy
- Concomitant bloodstream infection with *S. aureus*, Enterococcus, or Candida
- Death within 24 hours of Gram stain from blood culture
- No adequate/effective therapy initiated within 48 hours of susceptibility data
- Transferred from an outside hospital where was already bacteremic
- Transferred to an out of network acute care hospital during the index hospitalization

Impact: Non-ICU

Non-ICU Process Measures	Pre-Accelerate (n=78)	Post-Accelerate (n=63)	P-value
Time from gram stain to ID, hours, median (IQR)	38.7 (27, 50)	1.6 (1.5, 1.9)	<0.001
Time from gram stain to MIC, hours, median (IQR)	46.3 (39.6, 51.9)	6.9 (6.7, 7.3)	<0.001
Time from gram stain to effective antibiotic therapy, hours, mean ± SD	-4.8 ± 22.1	-6.3 ± 16.1	0.65
Time from gram stain to definitive antibiotic therapy, hours, median (IQR)	33.6 (-10.2, 55.5)	9.9 (-10.8, 16.6)	<0.001
If initial inadequate therapy, time to effective therapy, hours, median (IQR)	51.2 (43.7, 55.1)	11.2 (10.3, 12.5)	<0.001
If initial inadequate therapy, time to definitive therapy, hours, median (IQR)	51.2 (43.7, 55.1)	11.2 (10.3, 12.5)	<0.001
ID consult (%)	41 (52.6)	51 (81)	<0.001

Impact: Non-ICU

Non-ICU Outcome Measures	Pre-Accelerate (n=78)	Post-Accelerate (n=63)
Overall hospital LOS, days, mean ± SD	7.9 ± 10.9	5.7 ± 4.6
Hospital LOS from Gram stain to discharge, days, mean ± SD	5.2 ± 5	4.2 ± 2.9
All-cause 30-day readmission, n (%)	17 (21.8)	9 (14.3)
Infection-related 30-day readmission, n (%)	3 (3.8)	1 (1.6)
30-day re-infection (same organism <30 days from antibiotic completion), n (%)	0 (0)	1 (1.6)

Non-ICU Antibiotic Measures	Pre-Accelerate (n=78)	Post-Accelerate (n=63)	P-value
Total duration of antibiotic therapy, median (IQR)	14.1 (10.8, 17.7)	9.5 (7.9, 11)	<0.001
Total duration of effective antibiotic therapy, median (IQR)	14.1 (10.7, 17.1)	9.5 (7.8, 10.7)	<0.001

Impact: ICU

ICU Process Measures	Pre-Accelerate (n=36)	Post-Accelerate (n=31)	P-value
Time from gram stain to ID, hours, median (IQR)	45.7 (33.1, 51.3)	1.5 (1.4, 1.8)	<0.001
Time from gram stain to MICs, hours, median (IQR)	49.4 (34.1, 56.2)	6.9 (6.8, 7.4)	<0.001
Time from gram stain to effective antibiotic therapy, hours, mean ± SD	-7.9 ± 15.7	-6.9 ± 9	0.75
Time from gram stain to definitive antibiotic therapy, hours, median (IQR)	38.1 (-9.4, 70.4)	12.3 (-7.9, 35.3)	<0.001
If initial inadequate therapy, time to effective therapy, hours, mean ± SD	35.6 ± 2	12 ± 2.5	0.01
If initial inadequate therapy, time to definitive therapy, hours, median (IQR)	43.5 ± 13.2	12 ± 2.5	0.048
ID consult, n (%)	24 (66.7)	26 (83.9)	0.11

ICU Antibiotic Measures	Pre-Accelerate (n=36)	Post-Accelerate (n=31)	P-value
Total duration of antibiotic therapy, days, median (IQR)	14.8 (11.9, 16.9)	10.1 (7.8, 13.1)	<0.001
Total duration of effective antibiotic therapy, days, median (IQR)	14.7 (11.9, 16)	10.1 (7.7, 13.1)	<0.001

Impact: ICU

ICU Outcome Measures	Pre-Accelerate (n=36)	Post-Accelerate (n=31)
Hospital LOS from gram stain to discharge, days, mean ± SD	11.5 ± 9.5	8.9 ± 8.7
ICU LOS from gram-stain to ICU discharge, days, mean ± SD	7.8 ± 9.9	5.7 ± 6.3
All-cause 30-day readmission, n (%)	6 (16.7)	2 (6.5)
Infection-related 30-day readmission, n (%)	0 (0)	0 (0)
All-cause 30-day mortality, n (%)	11 (30.6)	6 (19.4)
Infection-related 30-day mortality, n (%)	8 (22.2)	4 (12.9)
In-hospital mortality, n (%)	11 (30.6)	6 (19.4)
30-day re-infection, n (%) (same organism <30 days from antibiotic completion)	1 (2.8)	0 (0)

Testimonials

"This technology gets us closer to 'The right drug at the right time' for potentially fatal Gram negative infections."

Nitin Bhanot, MD, MPH
Division Director, Division Infectious Disease, AGH
Program Director, Infectious Disease Fellowship

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Testimonials

"The most prevalent condition in the ICU is septic shock. As an ICU physician, my greatest fear is not knowing if I have adequate coverage with regards to antibiotics.

With rapid diagnostics providing an accurate MIC, we have a greater chance to identify if there is an organism resistant to the empiric therapy chosen."

Daniel Speredelozzi, MD
Attending Physician, Critical Care Medicine
WPH Site Director, AGH IM Residency

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Testimonials

"Rapid diagnostics, point-of-care testing, bedside ultrasound- these are all part of the future of practicing medicine and expediting appropriate patient care.

Decreasing the time to microbial identification and knowledge of MICs drastically enhances our ability to provide adequate spectrum, targeted antimicrobials in our patients.

It is our hope and belief that this will lead to improved antimicrobial stewardship, better outcomes, less complications, shorter hospital stay and lower cost for our patients. **It is a no brainer!"**

Thomas Robertson, MD
Attending Physician, Internal Medicine
Associate Program Director, AGH IM Residency

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Testimonials

"As a residency Program Director and quality and patient safety educator, I remain aware that adverse drug events are one of the most frequent causes of preventable adverse events.

Within the first few days of admission, we often change the antibiotics 2 times, sometimes even 3 times, as we navigate diagnostic uncertainty. Accelerate makes a difference here"

Anastasios (Tas) Kapetanos, MD

Attending Physician, Internal Medicine

Program Director, AGH IM Residency

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Final Thoughts

- To optimize impact, rapid diagnostics need ASP oversight/guidance to ensure processes in place to act upon results rapidly

- "Know your audience"
  - **Understand most pressing issues related to bacteremia at the institution**
    - ? High rate of MDROs not being covered with empiric therapy
      - Need for MIC to ESCALATE therapy
    - ? Low rate of resistance
      - Need for MIC to DE-ESCALATE therapy

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Final Thoughts

Process is Crucial

Determine current workflow of institutional ASP as well as goals/strategies

- ? Staffed for success AND alignment with institutional Quality goals
- ? Able to review results in real-time to provide rapid feedback
- ? Bandwidth to implement algorithm for stable pts to reap benefits
- ? Able to measure/track/report process & outcome data to leadership

Interdisciplinary Approach Critical for Optimization

- "No man is an island entire of itself" – John Donne (1572-1631)

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Thank You

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