

# Rapid Diagnostics & Antimicrobial Stewardship

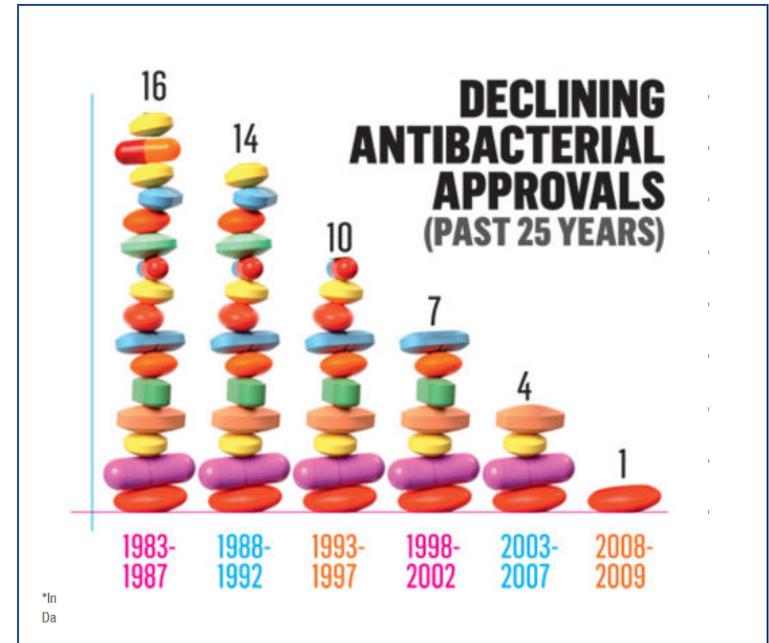
Katherine Perez, PharmD, BCPS

March 5, 2015

- Describe rationale for the utilization of rapid diagnostic technology within antimicrobial stewardship programs
- Evaluate the different rapid diagnostic tests available for interdisciplinary stewardship teams
- Understand ways to measure the impact of rapid diagnostic testing on patient outcomes

# Rapid Diagnostics: Current State

- Recent explosion of FDA-approved rapid diagnostic testing (RDT) methodologies for infectious diseases as the anti-infective pipeline remains stagnant



- Major focus on pathogens associated with increased morbidity, mortality, and excessive healthcare costs
  - Including influenza virus, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), *Clostridium difficile*, extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Klebsiella* spp., *Mycobacterium tuberculosis*, and *Candida* spp.

# Combating Antibiotic-Resistant Bacteria

	Threat Category	Organisms
<p><b>HAZARD LEVEL URGENT</b></p> 	<ul style="list-style-type: none"> <li>• Severe consequences</li> <li>• Urgent public attention to identify infections and prevent transmission</li> </ul>	<p><i>Clostridium difficile</i></p> <p>Carbapenem-resistant Enterobacteriaceae (CRE)</p> <p>Drug-resistant <i>Neisseria gonorrhoeae</i></p>
<p><b>HAZARD LEVEL SERIOUS</b></p> 	<ul style="list-style-type: none"> <li>• Low or declining incidence</li> <li>• Therapeutic agents available</li> <li>• Require public health monitoring and prevention</li> </ul>	<p>Multi-drug resistant <i>Acinetobacter</i>; Drug-resistant <i>Campylobacter</i>; Fluconazole resistant <i>Candida</i>; ESBL-producing Enterobacteriaceae; Vancomycin-resistant <i>Enterococcus</i> (VRE); Multidrug-resistant <i>Pseudomonas aeruginosa</i>; Drug-resistant Non-typhoidal <i>Salmonella</i>; Drug-resistant <i>Salmonella</i> Typhi; Drug-resistant <i>Shigella</i>; Methicillin-resistant <i>Staphylococcus aureus</i>; Drug-resistant <i>Streptococcus pneumoniae</i>; Drug-resistant tuberculosis</p>
<p><b>HAZARD LEVEL CONCERNING</b></p> 	<ul style="list-style-type: none"> <li>• Low threat</li> <li>• Multiple therapeutic options</li> <li>• Requires monitoring for outbreaks</li> </ul>	<p>Vancomycin-resistant <i>Staphylococcus aureus</i></p> <p>Erythromycin-resistant Group A <i>Streptococcus</i></p> <p>Clindamycin-resistant Group B <i>Streptococcus</i></p>

NATIONAL STRATEGY  
FOR COMBATING ANTIBIOTIC-  
RESISTANT  
BACTERIA

**GOAL 3:**  
Advance Development and Use of Rapid and Innovative  
Diagnostic Tests for Identification and Characterization of  
Resistant Bacteria

# The Clinical Microbiologist: ASPs New Best Friend

## IDSA PUBLIC POLICY

### Better Tests, Better Care: Improved Diagnostics for Infectious Diseases

- Role of rapid diagnostics and biomarkers in antimicrobial stewardship is recognized as a key recommendation by the IDSA
- New"-ish" niche to collaborate for stewardship teams
- What can molecular microbiology bring to the table?
  - Pathogen and resistance identification without conventional culture
  - Improved clinical outcomes
    - Tailor therapy sooner
    - Reconcile conflicts associated with empiric therapy
    - Avoid antibiotic agents causing collateral damage

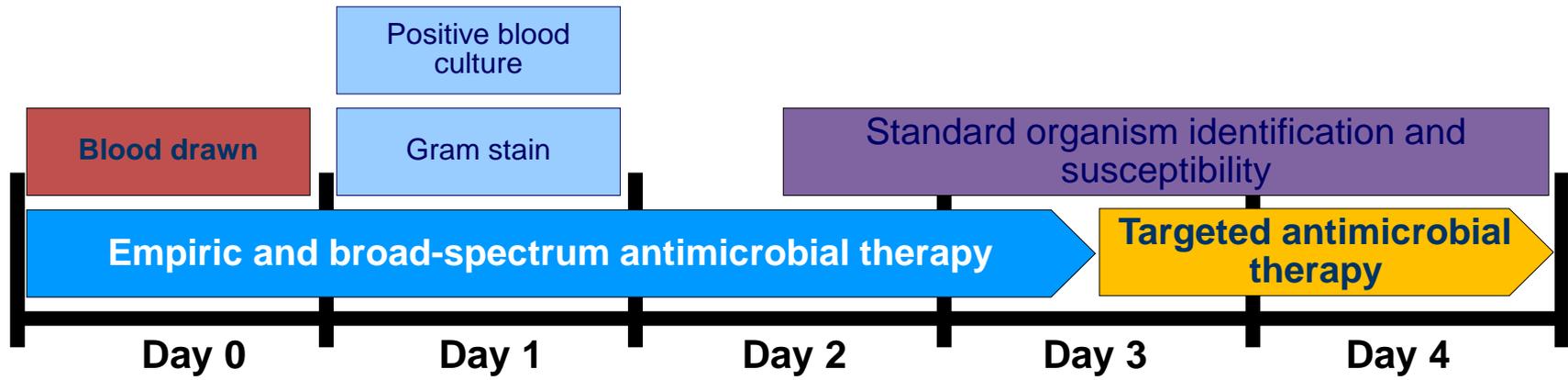
# The Ideal Treatment Scenario

- Must be **prompt**: delays in initiating effective antibiotics lethal
- **Appropriate**: must cover the offending pathogen(s)
- Administered at **adequate** dose and intervals consistent with pharmacokinetic/pharmacodynamic parameters
- Timely **streamlining** based on clinical response and microbiological data
- Prompt **discontinuation** when therapy complete

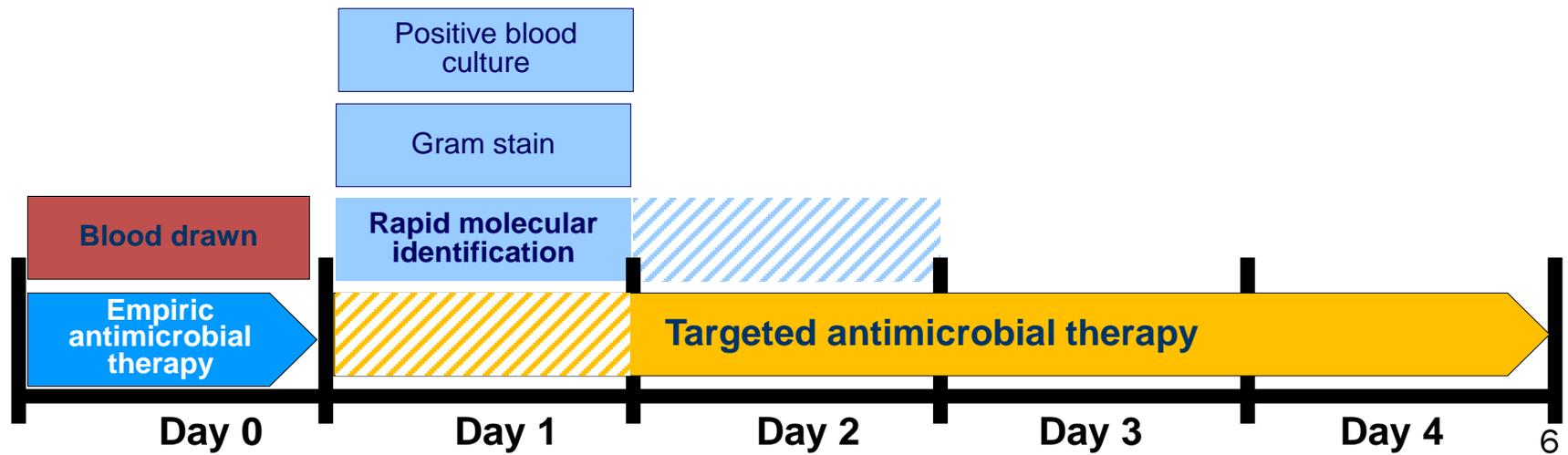
**All contingent on accurate determination of the pathogen's identification and antimicrobial susceptibility**

# Organism Identification and the Initiation of Targeted Antimicrobial Therapy

## Traditional Identification & Testing Methods:



## Rapid Molecular Identification Methods:



\*This is an illustration of general differences between the two methods. These timelines are hypothetical and may not occur in clinical practice

# Polymerase Chain Reaction (PCR)-Based Testing

## Real-time PCR; Multiplex PCR

General method: Detection and amplification of a piece of target DNA using fluorescently labeled probes with primers

### Overall Advantages

- Rapid results
- Low detection limits
- Specific organism detection or subtyping
- Does not require growth on media
- High throughput

### Overall Disadvantages

- Susceptible to contamination
- Require dedicated lab space for instruments
- Sensitive to inhibitors present in many clinical specimens
- Dependent on quality of nucleic acid primers and probes
- Most require initiation from positive cultures/single colonies
- Can not indicate viability of pathogen detected
- Practical limitations can affect turnaround time

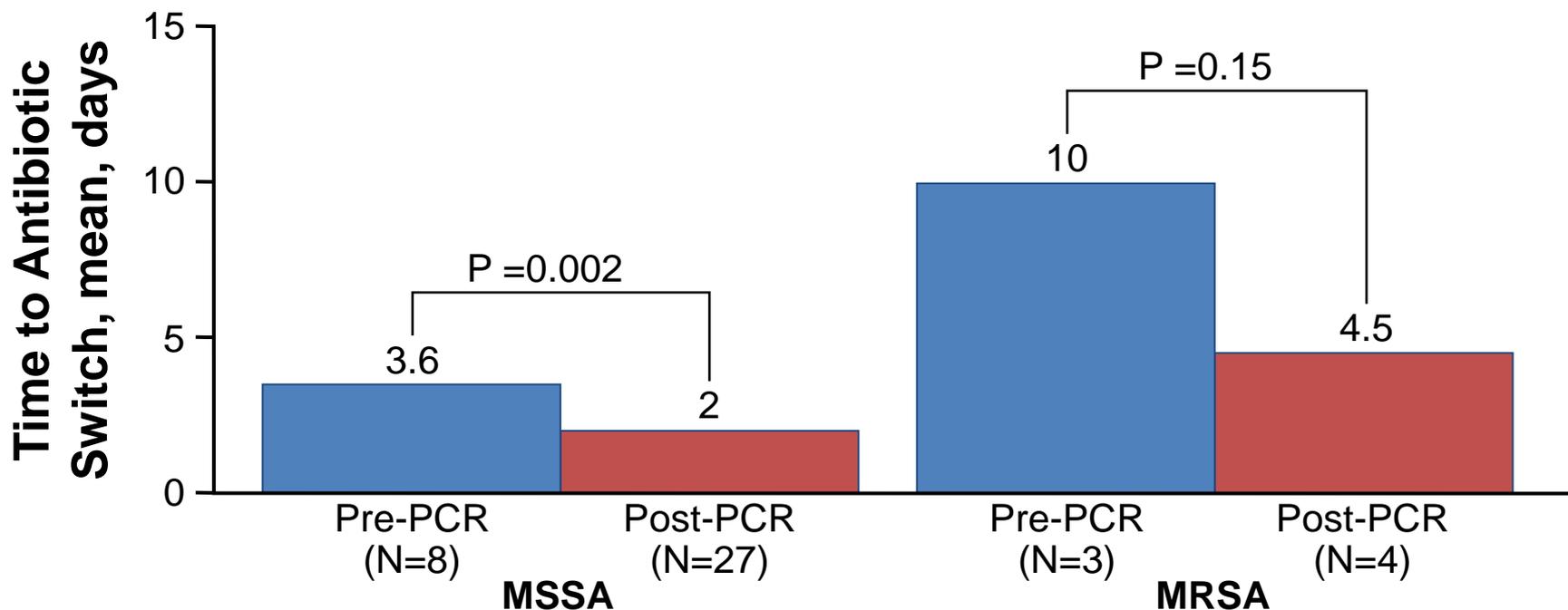
# PCR-Based RDTs Available

	Organisms/ Antibiotic Resistance Targets	Detection Time, hours	Manufacturer	Test Commercial Name
Real-time PCR	MRSA	2	Roche Diagnostics	Light Cycler MRSA
	<i>C. difficile</i>	2	BD GeneOhm	BD GeneOhm Cdiff Assay
		3	Gen-Probe Prodesse	ProGastro Cd Assay
Multiplex PCR	MSSA, MRSA, CoNS	2	BD GeneOhm	BD GeneOhm Staph SR
		1	Cepheid	Xpert MRSA/SA BC
	MSSA, MRSA	1	Cepheid	Xpert MRSA/SA SSTI
	<i>S. aureus, Staphylococcus epidermidis, Streptococcus spp. E. faecalis, E. faecium, Micrococcus spp, Listeria spp, mecA, vanA, vanB</i>	2.5	Nanosphere	Verigene: BC-GP
	<i>C. difficile</i>	0.5	Cepheid	Xpert <i>C. difficile</i>
		0.75	Cepheid	Xpert <i>C. difficile</i> /Epi
	<i>E. coli, K. pneumoniae, K. oxytoca, P. aeruginosa, Serratia marcescens, Acinetobacter spp, Proteus spp, Citrobacter spp, Enterobacter spp, KPC, NDM, CTX-M, VIM, IMP, and OXA genes</i>	<2	Nanosphere	Verigene: Gram-negative blood culture
Multiple bacterial, fungal, viral pathogens, and mecA, vanA/B, carbapenem resistance	1	BioFire Diagnostics	FilmArray System & panels	

# PCR-Based Testing – Clinical Outcomes

## Rapid *S. aureus* Identification and Targeted Antimicrobial Therapy in Patients with *S. aureus* Bacteremia

Single-center, Non-equivalent, Comparative Study [2008, 2009]

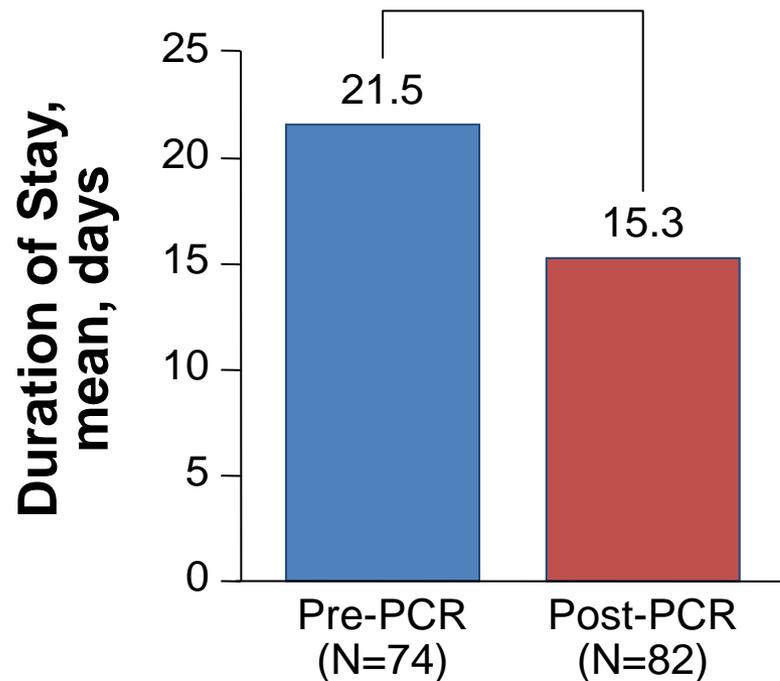


PCR results were communicated to an ID pharmacist who recommended effective, targeted antimicrobial therapy and an ID consult

# PCR-Based Testing – Clinical Outcomes

## Rapid *S. aureus* Identification and Targeted Antimicrobial Therapy in Patients with *S. aureus* Bacteremia

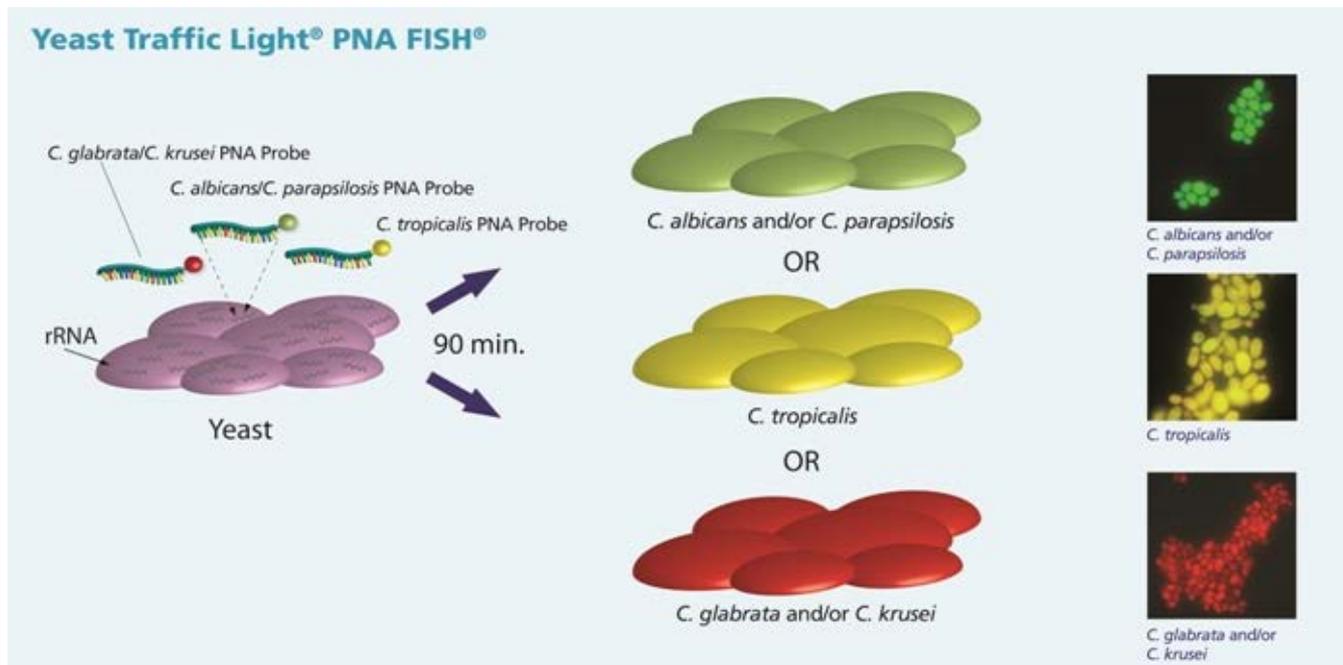
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# Peptide Nucleic Acid Fluorescent In Situ Hybridization (PNA FISH)

- PNA FISH technology employs synthetic oligonucleotide fluorescence labeled probes to target species specific rRNA sequences
- Enables visualization of target pathogen via fluorescence microscopy



# Peptide Nucleic Acid Fluorescent In Situ Hybridization (PNA FISH)

## PNA FISH

### Overall Advantages

- Easy to perform
- Does not require expensive infrastructure
- Rapid procedure
- Useful method for detection of fastidious organisms
- Can detect multiple species simultaneously using 2 or more specific probes, each labeled with a unique fluorescent dye
- Less likely affected by contamination
- Can detect bacteria directly in specimens or after enrichment culture
- PNA probes have higher specificity, increased stability

### Overall Disadvantages

- Labor intensive
- Amount of setup time necessary usually requires batching
- Limited menu of test organisms
- Cost of fluorescence microscope
- Requires skilled and experienced technicians to interpret results

# PNA FISH RDTs Available

Currently FDA Approved

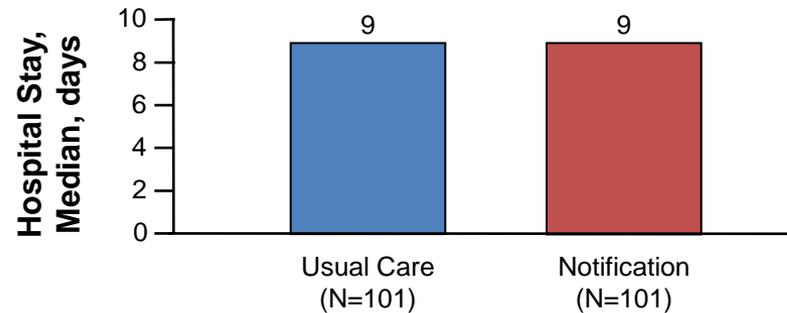
Organisms/ Antimicrobial Resistance Targets	Detection Time, hours	Manufacturer	Test Commercial Name
<i>Staphylococcus aureus</i> , CoNS	0.3	AdvanDx	<i>S. aureus</i> / CoNS PNA QuickFISH
<i>Enterococcus faecalis</i> , <i>Enterococcus faecium</i>	0.5		Enterococcus faecalis/OE PNA QuickFISH
<i>E. coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i>	0.5		GNR Traffic Light PNA QuickFISH
<i>C. albicans</i> , <i>C. parapsilosis</i> , <i>C. tropicalis</i> , <i>C. glabrata</i> , <i>C. krusei</i>	1.5		Yeast Traffic Light PNA Fish

# PNA FISH – Clinical Outcomes

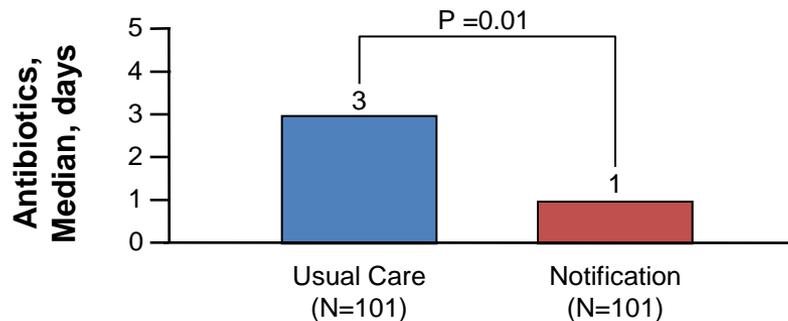
Impact upon clinical outcomes of translations of PNA FISH-generated laboratory data from the clinical microbiology bench to bedside in real time

Prospective, Single-center, Randomized, Controlled Study [2006]

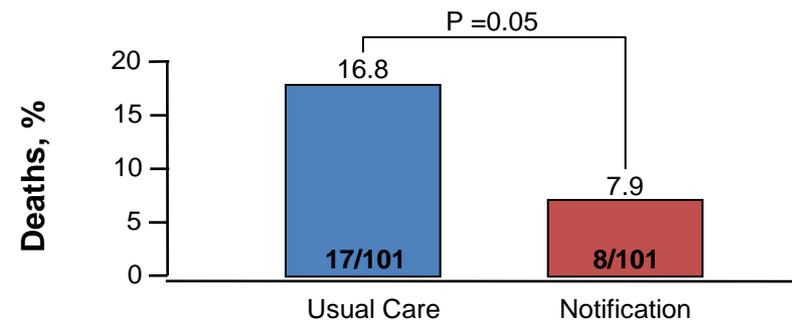
## Hospital Stay



## Antibiotics



## Deaths

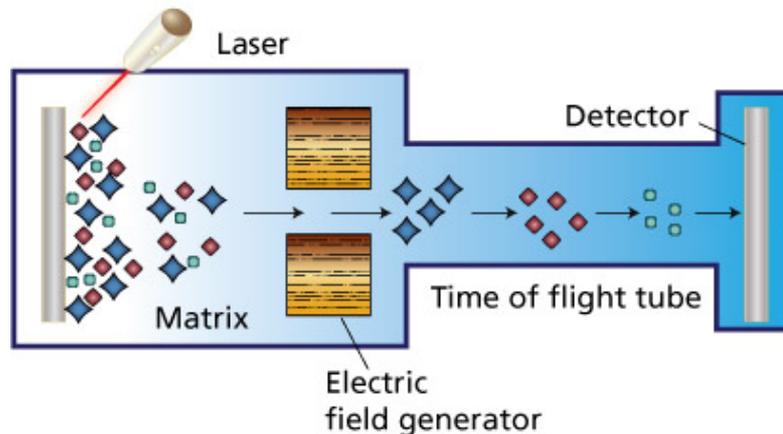


## PNA FISH for hospital-acquired enterococcal bacteremia: delivering earlier effective antimicrobial therapy

- Quasiexperimental study performed from 2005 - 2006
  - Comparison of rapid identification method with traditional methods
  - Differentiate *E. faecalis* from *E. faecium* in + blood cultures in 90 minutes
- Results
  - Species identification 2.3 days sooner ( $p < 0.001$ )
  - Decrease in time to effective therapy from 3.1 days to 1.3 days ( $p < 0.001$ )
  - Reduced 30-day mortality (26% vs. 45%,  $p = 0.4$ )

# Matrix-Assisted Laser Desorption/Ionization Time of Flight (MALDI-TOF) Mass Spectrometry

- Rapid identification of bacteria, yeast and fungi
  - Minimum of 24-96 h reduced turnaround time compared to conventional culture-based methods.
  - Even more dramatic results for certain organisms (i.e. *Legionella*).
- Test directly from positive blood cultures
  - Bypasses time-consuming subculture steps



# Matrix-Assisted Laser Desorption/Ionization Time of Flight (MALDI-TOF) Mass Spectrometry

## MALDI TOF

### Overall Advantages

- Rapid (turnaround time  $\leq 1-2$  hours)
- Automated, high throughput, batching not required
- Can be used to analyze uncultured bacteria
- Minimal consumables, relatively inexpensive reagent costs (~\$0.35 /test)
- No prior knowledge of organism type necessary, can identify wide range of organisms
- Accurate in the identification of rare or fastidious bacteria

### Overall Disadvantages

- Accurate identification requires well-curated, regularly updated, comprehensive reference database, current database are proprietary
- Does not provide antimicrobial susceptibility results
- Requires isolated colony; small mucoid colonies not easily identifiable
- Growth on some media may be associated with no/lower identification certainty
- High instrument cost
- Some closely related organisms not differentiated; poor identification with polymicrobial samples
- Laboratory errors can affect identification
- Gram negative organisms seem to be easier to detect than Gram-positives

# MALDI-TOF MS Platforms

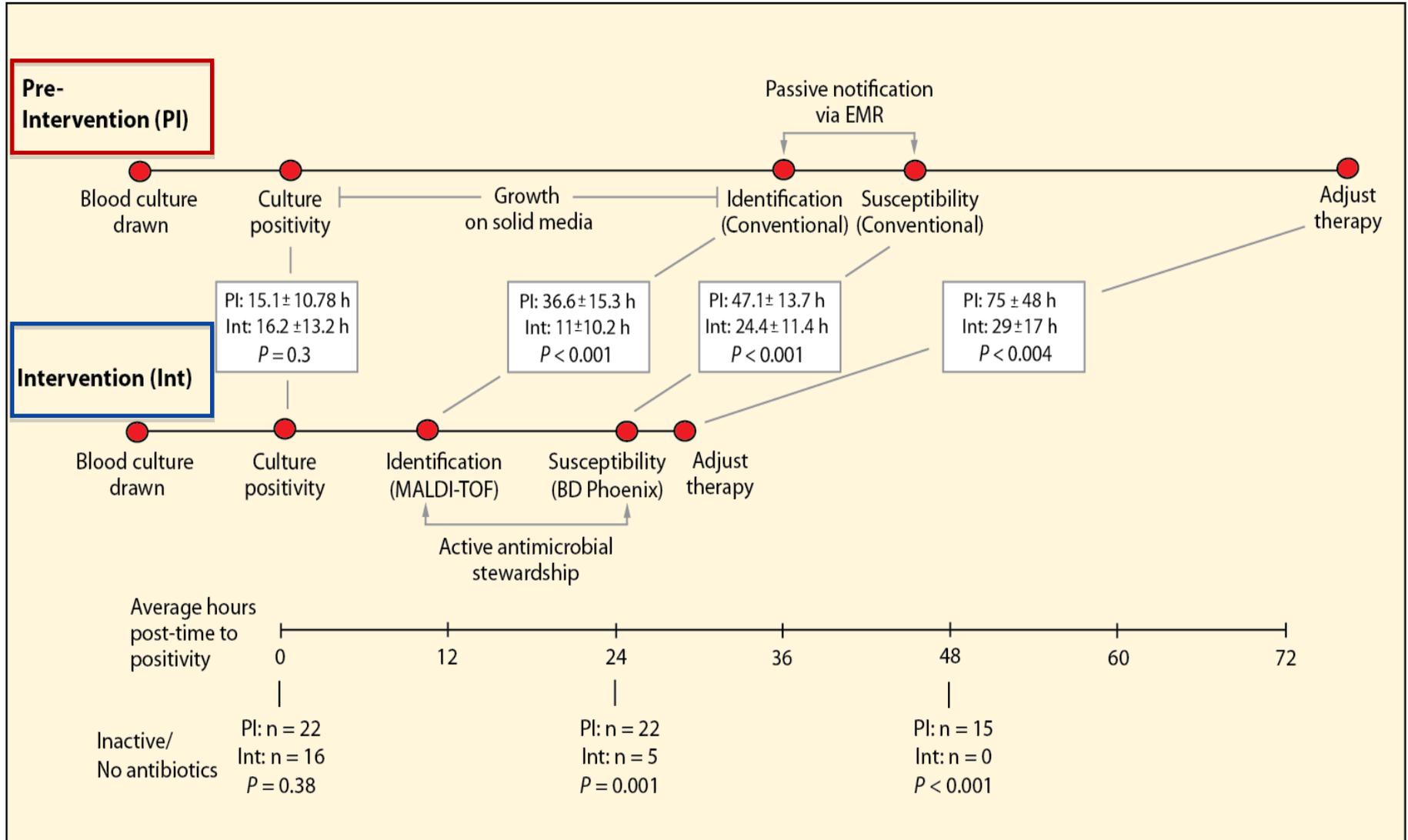
Currently FDA-Approved

Organism	Detection Time, hours	Manufacturer	Test Commercial Name
Multiple bacterial and fungal pathogens	0.2	Bruker Corporation	MALDI Biotyper CA
	0.25-1	bioMerieux	VITEK MS

## An Antimicrobial Stewardship Program's Impact with Rapid Pathogen Identification for Gram-negative BSIs

- Objective:** Determine the clinical and economic impact of MALDI-TOF MS and ID Pharmacists' interventions on patients with Gram-negative bacteremia.
- Method:** A comparative study of hospitalized patients before and after implementation of MALDI-TOF MS and real-time ASP notifications.
- Outcomes:** Differences in time to optimal therapy, hospital length of stay (LOS), hospital costs

# Results



# MALDI-TOF MS – Clinical Outcomes

- Gram-negative bacteremia:
  - Decreased length of stay from 11.9 to 9.3 days (p=0.1)
  - Decreased hospital costs by \$19,547 per patient (p=0.009)
  - 21% vs 8.9% reduction in mortality in antibiotic-resistant Gram-negative bacteremia (p=0.01)
- Gram-positive, Gram-negative bacteremia, Candidemia
  - Improved time to effective therapy from 30.1 vs. 20.4 h (p=0.02)
  - Decreased length of stay by 2.8 days
  - Reduced mortality from 20.3% to 14.5% (p=0.02)

## Use of rapid diagnostics and antimicrobial stewardship in community hospital setting to improve outcomes in patients with Gram-negative bacteremia

- Quasiexperimental study design evaluating clinical and economic outcomes in adults with GN-bacteremia at either Houston Methodist (HM) Sugar Land Hospital (235 beds) and HM Willowbrook Hospital (241 beds)
- MALDI-TOF MS coupled with ASP notification effects currently being analyzed
  - To date: Workflow, centralized microbiology has been rolled out at each outlying hospital

- T2 Biosystems
  - Potential to dramatically raise the standard of care in clinical practice
- Miniaturized nuclear magnetic resonance (NMR) technology
  - Limit of detection 1 cfu/mL vs 100-1000 cfu/mL typically required for tradition PCR-based methods
- FDA Approval for *Candida* detection directly from a patient's blood sample
  - Results in 3-6 hours compared with 5 days
- T2Candida, T2Bacteria in pipeline

# Getting to know your microbiology lab

- Reach out to your microbiology laboratory and find out:
  - What is currently offered? What is being sent out?
  - Can anything be consolidated?
  - Will knowing X, Y, or Z sooner allow for more timely care?
    - Time to antibiotics
    - Time to discharge
    - Time to definitive therapy
    - Time to isolation precautions ... or discontinuation of isolation
- Stewardship can be instrumental in justifying and implementing new technology
  - Purchase vs. lease
  - Laboratory space
  - High tech vs. low tech

# The Ideal Molecular Test

- Key questions to ask about any new molecular test:
  - Does it provide a clinically useful result?
  - Does it cover your routine organisms of interest?
  - Does it provide useful, reproducible results?
  - Is it cost effective?
  - Does it provide good or improved turn-around-time?

- Rapid diagnostic tests are “game changing” for patient care moving forward
  - Advances in RDTs provide new opportunities for stewardship programs
- Enhance function of clinical microbiology laboratories
- Yields significant improvement to patient care, increases the effectiveness of ASPs and infection control efforts
  - Represents one of the few bright spots in the changing world of escalating antimicrobial resistance and stewardship

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