#FSHP2018

# The Changing Landscape of Antimicrobial Stewardship: Rapid Diagnostics

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## Conflicts of Interest

- Merck & Co, Inc.
  - Speakers' bureau
- Allergan plc.
  - Advisory board



## Learning Objectives

- Upon completion of this presentation, the pharmacist should be able to:
  - Compare benefits and limitations of available rapid diagnostic testing
  - Discuss integration of rapid diagnostic testing into an antimicrobial stewardship program
  - Evaluate the impact of rapid diagnostic testing through measuring cost and outcomes



## Outline

- Case presentation without RDT
- Case presentation with RDT
- Why RDT in infectious diseases?
- Available RDT techniques and PCT
- Integrating RDT into an ASP
- Impact of RDT on clinical and economic outcomes



## Abbreviations

- ASP: antimicrobial stewardship program
- AST: antimicrobial susceptibility testing
- BCID: blood culture identification
- CDC: Centers for Disease Control and Prevention
- CDI: *Clostridium difficile* infection
- IDSA: Infectious Diseases Society of America
- MALDI-TOF MS: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
- MCA: morphokinetic cellular analysis
- MIC: minimum inhibitory concentration
- MRSA: methicillin-resistant Staphylococcus aureus
- MSSA: methicillin-susceptible Staphylococcus aureus
- RDT: rapid diagnostic testing
- PCR: polymerase chain reaction
- PCT: procalcitonin testing
- PNA FISH: peptic nucleic acid fluorescent in situ hybridization
- SHEA: Society for Healthcare Epidemiology of America
- SIDP: Society of Infectious Diseases Pharmacists
- VRE: vancomycin-resistant enterococci



## Case Presentation without RDT

- A 64-year-old man was admitted to the hospital from home for the management of sepsis.
- Blood cultures were obtained and broad-spectrum antibiotics were started.
- Three days later, the blood cultures grew highly susceptible bacteria as determined by a microbiology and sensitivity report.
- The ASP pharmacist recommended a change to a narrower-spectrum antibiotic.

## Case Presentation without RDT

- The attending physician accepted the recommendation of the ASP pharmacist.
- However, the patient developed CDI while receiving broad-spectrum antibiotics
- The patient completed an initial course of broad-spectrum antibiotic followed by a course of narrow-spectrum antibiotic in the hospital, in addition to vancomycin for CDI.
- The patient was discharged home one week later than anticipated.



## Case Presentation with RDT

- A 64-year-old man was admitted to the hospital from home for the management of sepsis.
- Blood cultures were obtained and broad-spectrum antibiotics were started.
- The next day, the blood cultures grew highly susceptible bacteria as determined by a new PCR-based rapid identification method.
- The ASP pharmacist recommended a change to a narrower-spectrum antibiotic.



## Case Presentation with RDT

- The attending physician accepted the recommendation of the ASP pharmacist.
- The patient completed a course of narrow-spectrum antibiotic in the hospital.
- The patient was discharged home without further complications.



## Why RDT in Infectious Diseases?

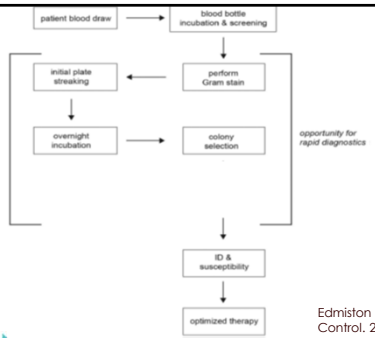
- Inappropriate use of antimicrobials lead to:
  - ↑ antimicrobial resistance
  - ↑ adverse effects including CDI
  - ↑ mortality
  - ↑ cost



## Why RDT in Infectious Diseases?

- To improve the diagnostic capabilities by expediting the identification of microorganisms
- Standard techniques
  - Require at least 48 to 72 hours for final results
- RDT
  - Provide results within hours → **Game changers!**






Edmiston CE et al. Am J Infect Control. 2018;S0196-6553:30145-7

## Available RDT Techniques and PCT

- Singleplex PCR or PCR
- Multiplex PCR
- Nanoparticle probe technology or microarray
- MALDI-TOF MS
- PNA FISH
- MCA with FISH
- Comparison of RDT techniques
- PCT



## Singleplex PCR or PCR

- Uses a fluorescently labeled probe with one set of primers to amplify a piece of target DNA
- Amplified DNA segment is then identified
- Combines amplification and detection into one process
- Allows for identification of a single pathogen or single resistance marker
- Applications: MRSA, *C. difficile*, *N. gonorrhoeae*, *C. trachomatis*



## Multiplex PCR

- Uses a fluorescently labeled probe with >1 set of primers
- Can be used for simultaneous detection of multiple organisms and resistance markers
- Applications: The FilmArray BCID tests for 24 organisms and some antimicrobial resistance genes



## Nanoparticle Probe Technology or Microarray

- Combines nucleic acid extraction and PCR amplification
- Allows for hybridization of target DNA to capture oligonucleotides on a microarray
- Provides an automated qualitative analysis of results
- Automated optical imaging of the microarray determines the presence or absence of specific sequences
- Applications: Blood culture gram-positive and blood culture gram-negative tests



## MALDI-TOF MS

- Analyzes thousands of samples per day from a variety of sources
- Results in ionization and disintegration of a target molecule which produce a molecular signature
- Provides a profile or fingerprint of the organism that is compared with those of well-characterized organisms in database
- Pathogen identification is based on a microbe's proteome
- Applications: multiple bacterial and fungal pathogens



## PNA FISH

- Uses synthetic oligonucleotide fluorescence-labeled probes that bind to species-specific RNA
- Allows rapid hybridization of species-specific ribosomal RNA of the target pathogen
- Relies on fluorescence microscope to detect fluorescence
- Applications: PNA FISH and QuickFISH using a variety of probes for select bacteria and *Candida* spp.

## MCA with FISH

- Novel technology that received FDA clearance in 2017
- Provides fast phenotypic AST by
  - exposing the identified organism to antibiotics in an automated system
  - Measuring the dynamic features of the bacteria as the bacteria repond to antibiotics
- Software analysis of these features generates MICs!
- Applications: MCA with FISH



## Comparison of RDT Techniques

Diagnostic capabilities for commercially available rapid ID/AST technologies in bloodstream infections.

| Technology | Identification (ID) | Detection of antibiotic resistance | Antimicrobial susceptibility testing (AST) with MIC | Turnaround time/time to result from positive blood culture |
|---|---|---|---|---|
| Singleplex PCR | Yes | No | No | 1-3 hours |
| Multiplex PCR | Yes | Yes* | No | 1-2 hours |
| Microarray | Yes | Yes | No | 2.5 hours |
| MALDI-TOF | Yes | No | No | 24 hours |
| PNA-FISH | Yes | No | No | 1 hour |
| Integrated MCA w/FISH ID | Yes | Yes† | Yes | 1.25 hours for ID and 5 hours for AST |

*This capability is specific to certain assays only, targeted by genotypic resistance marker.
†Resistance detected through phenotypic methods, irrespective of genotype.
PNA-FISH, peptide nucleic acid fluorescence in situ hybridization; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; MCA, morphokinetic cellular analysis; MIC, minimum inhibitory concentration; PCR, polymerase chain reaction.

Edmiston CE et al. Am J Infect Control. 2018;S0196-6553:30145-7



| Organism | Detection Time, h | Technology | Manufacturer | Batching | Need for Pure Colony | Automated | CLIA Designation | Trade Name |
|---|---|---|---|---|---|---|---|---|
| Gram-positive | | | | | | | | |
| *Staphylococcus aureus*, CoNS | 0.3 | PNA QuickFISH | AdvanDx | No | No | No | High complexity | *S. aureus*/CoNS PNA QuickFISH |
| MRSA | 0.1 | Immunochromatography | Alere Scarborough, Inc | No | Yes | No | Moderate complexity | Alere PBP2a Culture Colony Test |
| *S. aureus* | 0.2 | Immunochromatography | Alere Scarborough, Inc | No | No | No | Not rated | BinaxNOW *S. aureus* |
| MSSA, MRSA | 20–26 | Chromagenic medium | BD | No | Yes | No | High complexity | BBL CHROMagar MRSA II |
| MRSA | 2 | PCR | Roche Diagnostics USA | Yes | No | Yes | High complexity | LightCycler MRSA |
| MSSA, MRSA, CoNS | 2 | Multiplex PCR | BD GeneOhm | Yes | No | Yes | High complexity | BD GeneOhm Staph SR |
| MSSA, MRSA, CoNS | 1 | Multiplex PCR | Cepheid | No | No | Yes | Moderate complexity | Xpert MRSA/SA BC |
| MSSA, MRSA | 1 | Multiplex PCR | Cepheid | No | No | Yes | Moderate complexity | Xpert MRSA/SA SST |
| *S. aureus*, *Staphylococcus epidermidis* | 2.5 | Multiplex PCR | Nanosphere | No | No | Yes | Moderate complexity | Verigene: BC-GP |
| *Enterococcus faecalis*, *Enterococcus faecium* | 0.5 | PNA QuickFISH | AdvanDx | No | No | No | High complexity | *Enterococcus faecalis*/*OE* PNA QuickFISH |
| *Clostridium difficile* | 1 | LAMP | Meridian Bioscience | Yes | No | Yes | Moderate complexity | Illumigene *C. difficile* Assay |
| *C. difficile* | 2 | PCR | BD GeneOhm | Yes | No | Yes | Not rated | BD GeneOhm Cdiff |
| *C. difficile* | 0.5 | Multiplex PCR | Cepheid | No | No | Yes | Moderate complexity | Xpert *C. difficile* |
| *C. difficile* | 0.75 | Multiplex PCR | Cepheid | No | No | Yes | Moderate complexity | Xpert *C. difficile*/Epi |
| *C. difficile* | 3 | PCR | Gen-Probe Prodesse | Yes | No | Yes | Not rated | ProGastro Cd Assay |
| *Staphylococcus* spp, *Streptococcus* spp, *E. faecalis*, *E. faecium*, *Micrococcus* spp, *Listeria* spp | 2.5 | Multiplex PCR | Nanosphere | No | No | Yes | Moderate complexity | Verigene: BC-GP |

| Organism | Detection Time, h | Technology | Manufacturer | Batching | Need for Pure Colony | Automated | CLIA Designation | Trade Name |
|---|---|---|---|---|---|---|---|---|
| Gram-negative | | | | | | | | |
| *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* | 0.5 | PNA QuickFISH | AdvanDx | No | No | No | High complexity | GNR Traffic Light PNA QuickFISH |
| *E. coli*, *K. pneumoniae*, *Klebsiella oxytoca*, *P. aeruginosa*, *Serratia marcescens*, *Acinetobacter* spp, *Proteus* spp, *Citrobacter* spp, *Enterobacter* spp | <2.0 | Multiplex PCR | Nanosphere | No | No | Yes | Not rated | Verigene: gram-negative blood culture |
| Fungal pathogens | | | | | | | | |
| *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Candida glabrata*, *Candida krusei* | 1.5 | PNA FISH | AdvanDx | Yes | No | No | High complexity | Yeast Traffic Light PNA Fish |
| Other | | | | | | | | |
| Multiple bacterial, fungal, and viral pathogens | 1 | Multiplex PCR | BioFire Diagnostics | Yes | No | Yes | Moderate complexity | FilmArray System and panels |
| Multiple bacterial and fungal pathogens | 6 (direct from blood prior to culture) | PCR | Roche Molecular Systems* | Yes | No | Yes | Not rated | LightCycler SepsiFast Test MGRADE |
| Multiple bacterial and fungal pathogens | 0.2 | MALDI-TOF MS | Bruker Corporation | No | Yes | Yes | High complexity | MALDI Biotyper CA |
| Multiple bacterial and fungal pathogens | 0.25–1 | MALDI-TOF MS | bioMérieux | No | Yes | Yes | High complexity | VITEK MS |
| Multiple bacterial and fungal pathogens | 6–24 | Optical | bioMérieux | No | Yes | No | High complexity | VITEK 2 |

## PCT

- Levels can help to differentiate bacterial infections from viral infections and noninfectious inflammatory conditions
- Current literature supports use in patients with lower respiratory tract infections and in critically ill patients
- Limitations include patients with renal dysfunction, congestive heart failure, and massive stress



**Lower Respiratory Tract Infections**

| PCT Value | <0.1 ng/mL or decrease by 90% | 0.1 - <0.25 ng/mL or PCT level decrease by ≥ 80% | 0.25 - <0.5 ng/mL | ≥ 0.5 ng/mL |
|---|---|---|---|---|
| Discontinuation of Antibiotic Use Recommendation | Encouraged | | Discouraged | |
| Clinical Considerations | • Repeat PCT level every 1-2 days.<br>• If patient is clinically unstable, high-risk, or strong suspicion of pneumonia, continue/initiate antibiotic therapy regardless of PCT level.<br>• Continuation of antibiotics beyond the standard duration of therapy is not recommended, regardless of PCT level.<br>• If PCT remains high, consider treatment failure. | | | |

Covington EW et al. Pharmacotherapy. 2018 Mar 31

**Sepsis**

| PCT Value | <0.25 ng/mL or PCT level decrease by 90% | 0.25 - <0.5 ng/mL or PCT level decrease by ≥ 80% | 0.5 - <1.0 ng/mL | ≥ 1.0 ng/mL |
|---|---|---|---|---|
| Discontinuation of Antibiotic Use Recommendation | Encouraged | | Discouraged | |
| Clinical Considerations | • Repeat PCT level every 1-2 days.<br>• If patient is clinically unstable, high-risk, or strong suspicion of pneumonia, continue/initiate antibiotic therapy regardless of PCT level.<br>• Continuation of antibiotics beyond the standard duration of therapy is not recommended, regardless of PCT level.<br>• If PCT remains high, consider treatment failure. | | | |

Covington EW et al. Pharmacotherapy. 2018 Mar 31



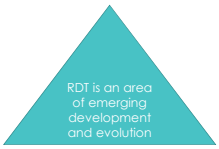
## Integrating RDT into an ASP

- CDC core elements of an ASP
- IDSA/SHEA recommendations for implementing an ASP
- IDSA/SHEA recommendations related to microbiology and laboratory diagnostics
- SIDP position statement on the role of ASP pharmacists in the use of RDT
- Preimplementation checklist
- Implementation checklist
- Postimplementation checklist



## CDC Core Elements of an ASP

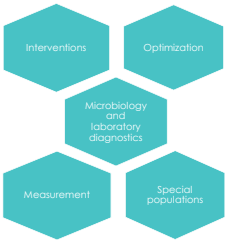
- Leadership commitment
- Accountability
- Drug expertise
- Action
- Tracking
- Reporting
- Education




https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html



## IDSA/SHEA Recommendations for Implementing an ASP




Barlam TF et al. Clin Infect Dis. 2016;62:e51-77



## IDSA/SHEA Recommendations Related to Microbiology and Laboratory Diagnostics

- Suggest the use of rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics
  - *weak recommendation, low-quality evidence*
- Suggest RDT in addition to conventional culture and routine reporting on blood specimens if combined with active ASP support and interpretation
  - *weak recommendation, moderate-quality evidence*

Barlam TF et al. Clin Infect Dis. 2016;62:e51-77



## IDSA/SHEA Recommendations Related to Microbiology and Laboratory Diagnostics

- Suggest the use of serial PCT measurements as an ASP intervention to decrease antibiotic use
  - *weak recommendation, moderate-quality evidence*
- Suggest incorporating nonculture-based fungal markers in ASP interventions to optimize antifungal use in patients with hematologic malignancy at risk of invasive fungal diseases
  - *weak recommendation, low-quality evidence*

Barlam TF et al. Clin Infect Dis. 2016;62:e51-77

## SIDP Position Statement on the Role of ASP Pharmacists in the Use of RDT

- Supports ASP pharmacists as an essential component of RDT
  - Collaboration with microbiology team
  - Communication with primary team
  - Barriers to implementation (funding and training) and methos to overcome
  - Quality metrics
  - Continuing education

https://www.sidp.org/page-1543291/4935839



## Preimplementation Checklist

- Identify most useful RDT based on hospital pathogen prevalence
- Identify hospital cost and burden of infection
- Identify time to effective therapy



## Implementation Checklist

- Use a microbiologist-validated RDT instrument
- Determine if test is done in real time 24/7 or batch
- Ensure that communication of RDT results from microbiologists to ASP clinicians is established
- Educate medical staff
- Document interventions and acceptance rates



## Postimplementation Checklist

- Determine time to effective therapy
- Determine time to discontinuation or de-escalation
- Determine time to infectious diseases consult
- Document negative blood culture prior to discharge
- Track 30-day readmission
- Track mortality



## Impact of RDT on Clinical and Economic Outcomes

- *Staphylococcus aureus*
- Gram-negative organisms
- *Candida* species
- *Clostridium difficile*



## *Staphylococcus aureus*

- Bacteremia requires prompt diagnosis and treatment
- Gold standard for MRSA: vancomycin
- Gold standard for MSSA: nafcillin/oxacillin/cefazolin
- RDT (e.g. PCR for mecA, Xpert MRSA/SA BC, PNA FISH)
  - ↓ time to optimal antibiotic therapy
  - ↓ in antibiotic therapy
  - ↓ length of stay
  - ↓ cost
  - ↓ mortality

Bauer KA et al. Clin Infect Dis. 2014;59(Suppl 3):S134-45

## Coagulase-Negative Staphylococci

- Contaminant if only 1 blood culture
- Causative organism in >1 blood culture
- RDT (e.g. Xpert MRSA/SA BC, PNA FISH)
  - ↓ time to discontinuation of antistaphylococcal antibiotics
  - ↓ in total antibiotic exposure
  - ↓ length of stay
  - ↓ cost

Bauer KA et al. Clin Infect Dis. 2014;59(Suppl 3):S134-45



## Enterococci

- Intrinsically resistant to several antibiotics
- VRE infections are associated with suboptimal outcomes
- RDT (e.g. Verigene BC-GP, PNA FISH)
  - ↓ time to optimal antibiotic therapy
  - ↓ length of stay
  - ↓ cost
  - ↓ mortality

Bauer KA et al. Clin Infect Dis. 2014;59(Suppl 3):S134-45



## Gram-Negative Organisms

- PNA FISH traffic light
  - *E. coli* fluoresces green
  - *K. pneumoniae* fluoresces yellow
  - *P. aeruginosa* fluoresces red
- MALDI-TOF MS
  - ↓ time to antibiotic optimization
  - ↓ time to active treatment
  - ↓ length of stay
  - ↓ cost
  - ↓ mortality
  - ↑ clinical cure

Bauer KA et al. Clin Infect Dis. 2014;59(Suppl 3):S134-45



## *Candida* species

- Fourth most common cause of nosocomial bacteremia
- Long time to identification and speciation
- PNA FISH yeast traffic light
  - *C. albicans/C. parapsilosis* fluoresces green
  - *C. tropicalis* fluoresces yellow
  - *C. glabrata/C. krusei* fluoresces red
  - ↓ time to targeted therapy
  - ↓ caspofungin usage
  - ↓ cost

Bauer KA et al. Clin Infect Dis. 2014;59(Suppl 3):S134-45



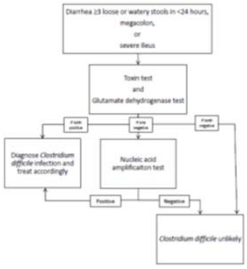
## *Clostridium difficile*

- Challenging infection
- Multiple recurrences
- Toxin detection and glutamate dehydrogenase lack sensitivity and specificity
- PCR is the most sensitive test to detect *C. difficile*

McDonald LC et al. Clin Infect Dis. 2018;66:987-94



## *Clostridium difficile* Diagnostic Algorithm



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

**Tristan T. Timbrook,[1,4] Jacob B. Morton,[1,4] Kevin W. McConeghy,[2] Aisling R. Caffrey,[1,3,4] Eleftherios Mylonakis,[2] and Kerry L. LaPlante[1,3,4]**

[1]Rhode Island Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, [2]Center of Innovation in Long Term Services and Supports, Providence Veterans Affairs Medical Center, [3]Infectious Diseases Division, Warren Alpert Medical School of Brown University, Providence, and [4]College of Pharmacy, University of Rhode Island, Kingston

***Background.*** Previous reports on molecular rapid diagnostic testing (mRDT) do not consistently demonstrate improved clinical outcomes in bloodstream infections (BSIs). This meta-analysis seeks to evaluate the impact of mRDT in improving clinical outcomes in BSIs.

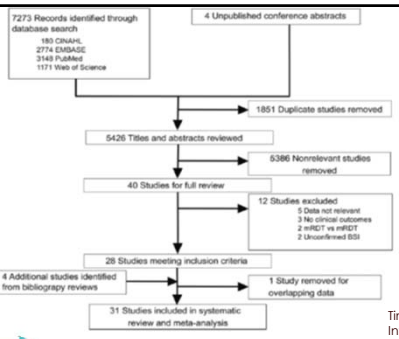
***Methods.*** We searched PubMed, CINAHL, Web of Science, and EMBASE through May 2016 for BSI studies comparing clinical outcomes between mRDT and conventional microbiology methods.

***Results.*** Thirty-one studies were included with 5920 patients. The mortality risk was significantly lower with mRDT than with conventional microbiology methods (odds ratio [OR], 0.66; 95% confidence interval [CI], .54–.80), yielding a number needed to treat of 20. The mortality risk was slightly lower with mRDT in studies with antimicrobial stewardship programs (ASPs) (OR, 0.64; 95% CI, .51–.79), and non-ASP studies failed to demonstrate a significant decrease in mortality risk (0.72; .46–1.12). Significant decreases in mortality risk were observed with both gram-positive (OR, 0.73; 95% CI, .55–.97) and gram-negative organisms (0.51; .33–.78) but not yeast (0.90; .49–1.67). Time to effective therapy decreased by a weighted mean difference of −5.03 hours (95% CI, −8.60 to −1.45 hours), and length of stay decreased by −2.48 days (−3.90 to −1.06 days).

***Conclusions.*** For BSIs, mRDT was associated with significant decreases in mortality risk in the presence of a ASP, but not in its absence. mRDT also decreased the time to effective therapy and the length of stay. mRDT should be considered as part of the standard of care in patients with BSIs.

Timbrook TT et al. Clin Infect Dis. 2017;64:15-23

Break Through #FSHP2018 Branch Out

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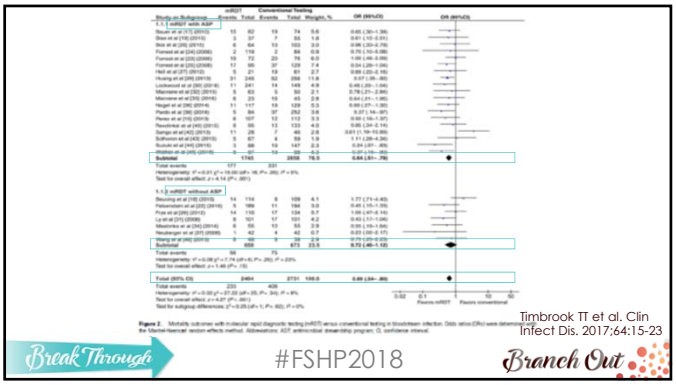

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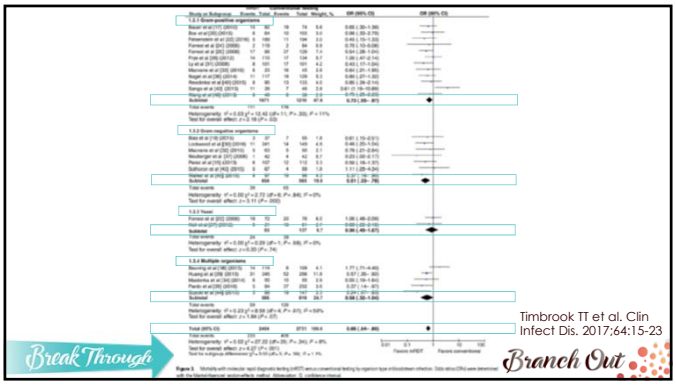

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Break Through #FSHP2018 Branch Out

## RDT with ASP has the potential to:

- Improve antimicrobial use
- Improve clinical outcomes
- Improve economic outcomes

Break Through #FSHP2018 Branch Out

## Key References and Readings


- CDC Core Elements of Hospital Antibiotic Stewardship Programs. Availabale at: https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html
- Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51-77.
- SIDP Position Statement on the Role of Antimicrobial Stewardship Pharmacists in the Use of Rapid Dignostic Testing in Acute and Ambulatory Care. Available at: https://www.sidp.org/page-1543291/4935839
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Break Through #FSHP2018 Branch Out

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- Bauer KA, Perez KK, Forrest GN, et al. Review of rapid diagnostic tests used by antimicrobial stewardship programs. Clin Infect Dis. 2014;59(Suppl 3):S134-45.






# The Changing Landscape of Antimicrobial Stewardship: Rapid Diagnostics


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