ashp® MIDYEAR 2016
Clinical Meeting & Exhibition

(Management Case Study) Exploring the Use of Rapid Diagnostic Tests to Ensure Timely Treatment of Infections

Hai Tran, Pharm.D, BCPS
Associate Director, Drug Use Policy
Cedars-Sinai Medical Center
Los Angeles, California

Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.

Learning Objectives

- Describe types of rapid diagnostic tests
- Describe the rapid diagnostic test algorithm
- Describe pharmacist's impact on improving time to effective therapy

Self-Assessment Questions

- Question 1: Rapid diagnostic tests identify organisms and resistance markers faster than conventional culture and susceptibility method (True/False)

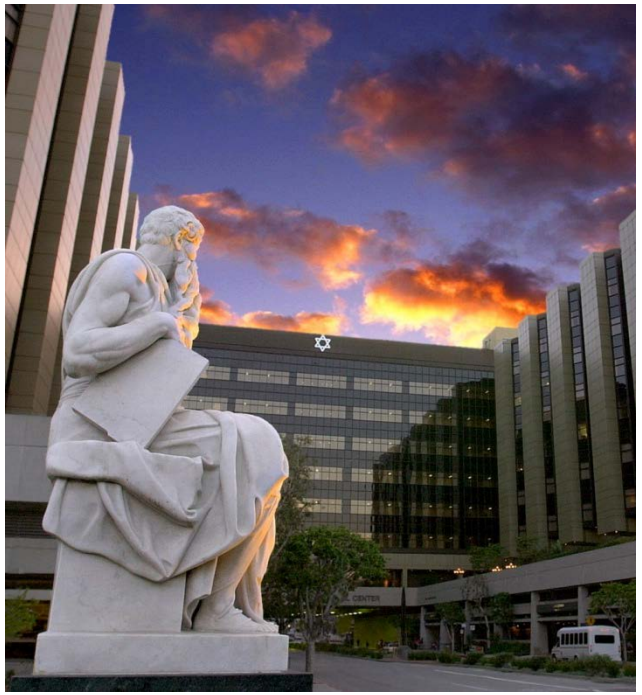
- Question 2: The rapid diagnostic test algorithm can minimize costs associated with laboratory tests (True/False)

- Question 3: Rapid diagnostic tests without concurrent pharmacist's intervention can reduce time to effective therapy (True/False)

Cedars-Sinai Medical Center

Leading the quest for health…

- Non-profit, acute, tertiary, teaching hospital
- 886 licensed beds
  - 120 intensive care unit beds
- Level I trauma center
- Department of Pharmacy Services:
  - Decentralized clinical pharmacy services
  - Emergency department and operating room services
  - Solid organ transplant services
  - Bone marrow transplant services
  - Transitions of care services
  - Outpatient pharmacy services including ambulatory care clinics
  - 2 Outpatient cancer centers



Rapid Diagnostic Tests (RDTs)

- At least two million illnesses and 23,000 deaths are caused by drug-resistant bacteria in the United States annually
- Up to 50% of antibiotics prescribed in hospitals are unnecessary or inappropriate
- Delayed effective antimicrobial therapy is associated with increased mortality, prolonged hospitalizations, and increased institutional
  - Mortality increased by 7.6% for every hour delay in initiating appropriate antibiotics
- RDT is one of five goals from the National Action Plan for Combating Antibiotic-Resistant Bacteria
- Infectious Diseases Society of America (IDSA) recommends the use of RDT with antimicrobial stewardship program (ASP) support and intervention

https://www.cdc.gov/getsmart/healthcare/
Kumar et al. Crit Care Med 2006; 34: 11589; Goff DA et al. *Pharmacotherapy*. 2012
https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

Rapid Diagnostic Tests (RDTs)

- RDTs provide accurate &timely organism ID and resistance markers
  - Optimize patient care and improve patient outcomes
  - Increase the effectiveness of antimicrobial stewardship programs
- Systemic Review & Meta-Analysis (Timbrook et al)
  - Risk of mortality was significantly lower with molecular RDTs
    - Compared to conventional methods – NNT 20

      (OR 0.66, 95% CI 0.54-0.80)
    - RDTs with ASP (OR 0.64; 95% CI 0.51-0.79)
      - RDTs without ASP failed to significantly decrease in risk of mortality
  - Reduce time to effective therapy: 5.03 hrs (95% CI -8.60 to -1.45)
  - Reduce length of stay: 2.48 days (95% CI -3.90 to -1.06)

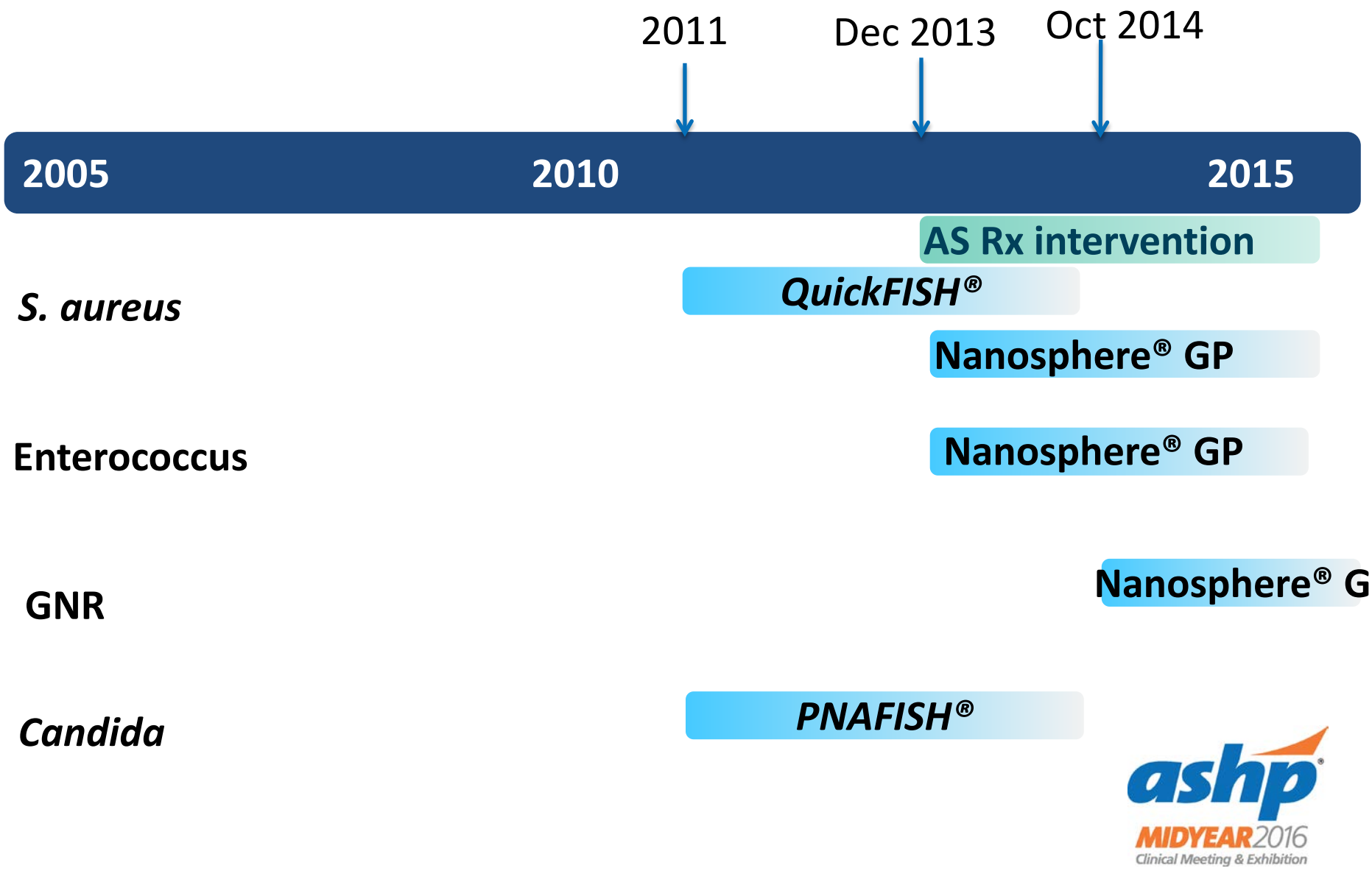
Kumar et al. Crit Care Med 2006; 34: 11589; Goff DA et al.
Pharmacotherapy. 2012; Barlam et al. CID 2016;62:e51; Timbrook et al. CID 2016
https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

Rapid Diagnostic Tests (RDTs)

Cedars-Sinai Medical Center

- Current RDTs for bloodstream infections
  - Identification of organisms
    - *PNAFISH®: C. albicans, C. glabrata*
    - *QuickFISH®: S. aureus* and coagulase negative staphylococci (CoNS)
  - Nanosphere® (Luminex) for Gram Positive & Gram Negative
    - Identifies genus, species, and genetic resistance

Evolution of RDTs at CSMC



Candida *PNAFISH®*

Peptide nucleic acid (PNA) fluorescent in situ hybridization (FISH)

- ~7% of all *Candida* bloodstream isolates are resistant to fluconazole (mostly *C. glabrata*)
- Provides rapid identification directly from blood cultures
  - *C. albicans*
  - *C. glabrata*
- Sensitivity & specificity: 100%
- Results are available within 90 minutes
  - 2-5 days earlier than conventional methods
- Cost per test: ~$42

http://www.advandx.com/products/quickfish/candida/
http://www.cdc.gov/fungal/diseases/candidiasis/invasive/statistics.html

Staphylococcus *QuickFISH®*

Rapid peptide nucleic acid fluorescence *in situ* hybridization (FISH)

- Provides rapid identification directly from GPC in positive blood culture
  - *S. aureus*
  - Coagulase-negative staphylococci
- Sensitivity & specificity: 100%
- Results are available within 20 minutes
  - 1-3 days earlier than conventional methods
- Identify potential CoNS contaminants
- Less costly and faster than Nanosphere®
- Cost per test: ~$45

https://www.luminexcorp.com/clinical/infectious-disease/verigene-bloodstream-infection-tests/

Pappas et al. *Clin Infect Dis* 2004;38:161.

Nanosphere®

- Automated nucleic acid test
- Identifies genus, species, and genetic resistance
- Need to perform Gram stain first to confirm GP or GN organisms
- Determine antibiotic resistance up to 48H faster than conventional methods
- Cost per test: ~$70

	Gram-positive BC	Gram-negative BC
Turn around time	2.5 hours	2 hours
Resistance markers	*mecA, vanA, vanB*	CTX-M (ESBL) IMP, KPC, NDM, OXA, VIM (carbapenemase)

https://www.luminexcorp.com/clinical/infectious-disease/verigene-bloodstream-infection-tests/

Blake WB, et al. PLOS Medicine. Jul 2, 2013; Dodémont M et al. Journal of Clinical Microbiology. Jun 4, 2014

Nanosphere® Gram Positive Blood Culture Panel

Organism
S. aureus, S. epidermidis, S. lugdunensis
Listeria spp.
S.pneumoniae, S.pyogenes, S.pneumoniae
Streptococcus anginosus group, *S. agalactiae*
E. faecalis, E. faecium
Genus Marker
Staphylococcus spp.
Streptococcus spp.
RESISTANCE Targets
mecA
vanA
vanB

Sensitivity & Specificity >95%

Blake WB, et al. PLOS Medicine. Jul 2, 2013

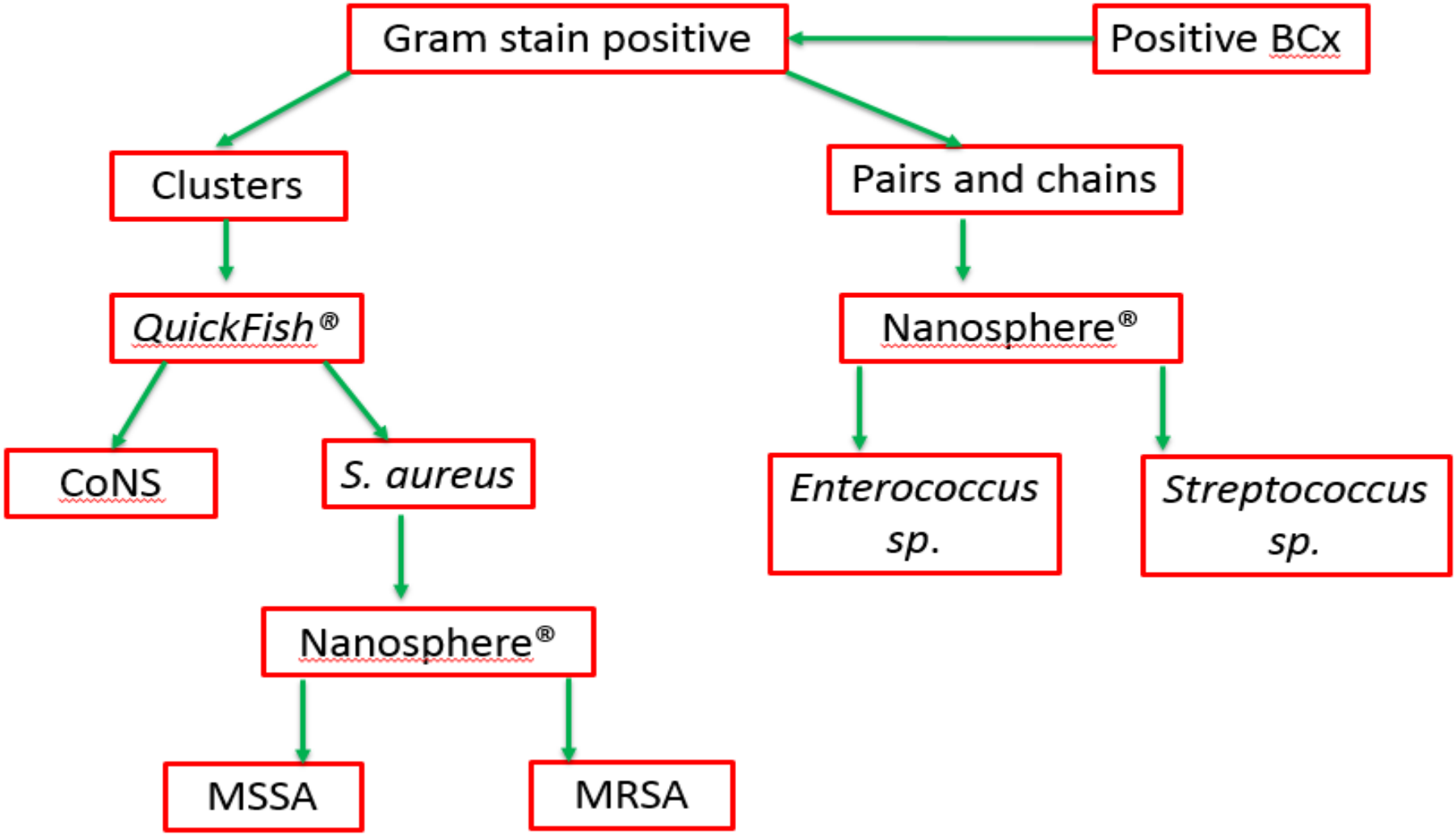
Nanosphere® Gram Negative Blood Culture Panel

Organism
E. coli
K. pneumoniae, K. oxytoca
Pseudomonas aeruginosa
Genus marker
Acinetobacter spp.
Proteus spp.
Citrobacter spp.
Enterobacter spp.
RESISTANCE Targets
KPC, NDM, CTX-M
IMP
OXA

Sensitivity ≥95%
Specificity ≥97%

Dodémont M et al. Journal of Clinical Microbiology. Jun 4, 2014

RDTs Algorithm for Gram-Positive



Time to Effective Therapy

RDT to Initiation of Therapy

- Gram-Positive and *Candida*: 12/6/13-1/8/15

With AMS Intervention	N= 136
Antimicrobial-Related Opportunity	42/136 (31%)
▪ Escalation	17/42 (41%)
▪ De-escalation	21/42 (50%)
▪ Dose Optimization	4/42 (19%)
Acceptance Rate	37/42 (88%)
Average time from RDT to initiation of effective therapy	1.4 hr

RDTs and Antimicrobial Stewardship

- Notify antimicrobial stewardship (AMS) pharmacists of positive blood culture and RDT results via pager
  - 7 days per week (previously Monday to Friday)
  - 7am to 10pm (previously 7am – 5pm)

- AMS pharmacists evaluate antimicrobial regimen and contact prescribers if opportunity is identified

- Unsuccessful interventions are reviewed at the Antimicrobial Stewardship Task Force to identify opportunities to improve acceptance of recommendations

De-escalation: example 1

Blood cultures: 4/4 at 24H *S. aureus* without *mecA* resistance marker

- Current therapy: vancomycin
- Intervention: Change to oxacillin
- Rationale:
  - *mecA* gene is responsible for resistance to methicillin and other beta-lactams
  - Oxacillin is the preferred agent for *S. aureus*

Escalation: example 2

Blood culture: 1/2 at 24H *Enterococcus* with resistance markers for VRE (*vanA*)

- Current therapy: vancomycin
- Intervention: Change vancomycin to linezolid
- Rationale: Vancomycin is not active against VRE

Escalation: example 3

Blood culture: 2/2 *E. Coli* at 24H. CTX-M Class A Extended Spectrum β-lactamase resistance marker (ESBL) detected

- Current therapy: ciprofloxacin, metronidazole
- Intervention: Recommend change to imipenem
- Rationale:
  - Carbapenem is the drug of choice
  - Ciprofloxacin is not active against ESBL

CSMC RDT Results

	2015 (n=310)	2016					
		Jan (n=55)	Feb (n=46)	Mar (n=51)	April (n=41)	May (n=58)	June (n=53)
Antimicrobial-Related Opportunity	**29%**	**38%**	**26%**	**47%**	**51%**	**43%**	**42%**
Acceptance Rate (%)	88.9%	95.2%	100%	91.7%	90.4%	84%	90.9%

Type of Antimicrobial-Related Opportunity

	2015 (n=310)	2016					
		Jan (n=55)	Feb (n=46)	Mar (n=51)	April (n=41)	May (n=58)	June (n=53)
Escalation	48%	38%	68%	17%	28%	40%	50%
De-escalation	44%	48%	32%	75%	67%	60%	41%
Dose Optimization	8%	14%	0%	8%	5%	0%	9%

Time to Effective Therapy:
RDT to Therapy

	2015 (n=310)	2016 (Mean time – hours)					
		Jan (n=55)	Feb (n=46)	Mar (n=51)	April (n=41)	May (n=58)	June (n=53)
RDT to Initiation of Therapy	0.83	0.92	0.38	0.67	0.33	1.2	1.1
RDT to Administration of Therapy	2.2	2.9	1.6	2.4	2.2	2.5	2.2

Time to Effective Therapy:
Blood Culture to Antimicrobial Administration

	Without AMS Intervention (n=91)	With AMS Intervention (n=51)	t-test
Escalation of Therapy	52.4 ± 37.3 hours	24.9 ± 10 hours	P<0.001

Challenges

- Large number of private physicians including Infectious Diseases Specialists
- Clinicians are not familiar with the RDTs
- Delay in MD responses requiring multiple calls/pages
- Unable to reach prescriber requiring multiple calls to multiple MDs
- Limited Resources: Microbiology & Pharmacy

RDT Reporting Language

Report	Mayo Clinic Reporting Comments	CSMC Resulting Comments
Staphylococcus aureus *S. aureus* + *mecA* +	*mecA* detected Probable methicillin-resistant *Staphylococcus aureus* (MRSA); further testing in progress. MRSA is predictably resistant to beta-lactam antibiotics (except ceftaroline). Patient requires contact precautions if hospitalized. Semi-Urgent Result	Positive *Staphylococcus aureus*. mecA gene DETECTED by testing. Probable methicillin-resistant *Staphylococcus aureus* (MRSA). Full susceptibility panel to follow. Place patient in CONTACT ISOLATION per infection control.
Staphylococcus aureus *S. aureus* + *mecA* -	*mecA* not detected Methicillin (oxacillin)-susceptible *Staphylococcus aureus*. Preferred therapy is an anti-staphylococcal beta-lactam antibiotic, unless clinically contraindicated.	Positive *Staphylococcus aureus*. mecA gene NOT detected by testing. Full susceptibility panel to follow.

Banerjee R et al. CID 2015;61:1071

RDT Reporting Language - example

	Resistance Markers NOT Detected	Resistance Markers Detected
S. aureus	Staphylococcus aureus. NO resistance to methicillin (*mecA*) detected. This result predicts sensitivity to oxacillin (>99% accuracy). Preferred therapy is an IV anti-staphylococcal beta-lactam antibiotic. Full susceptibility panel to follow.	Methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA). *mecA* resistance marker detected. Vancomycin is the drug of choice for MRSA. Full susceptibility panel to follow.
E. faecium	*Enterococcus faecium*. No vanA/B resistance marker detected. This result predicts sensitivity to vancomycin (>99% accuracy). Full susceptibility to follow.	Vancomycin-resistant *Enterococcus faecium* (VRE). *vanA/B* resistance marker detected. Linezolid is the empiric drug of choice for *VRE faecium*. Full susceptibility to follow.

RDT Reporting Language – example

Resistance Markers NOT Detected	Resistance Markers Detected
Escherichia coli. No ESBL or carbapenem resistance markers detected. This result predicts susceptibility to third-generation cephalosporins (>98% accuracy). Full susceptibility panel to follow.	• CTX-M: CTX-M Class A Extended Spectrum β-lactamase resistance marker (ESBL) detected. A carbapenem is the drug of choice. Full susceptibility panel to follow. • KPC: KPC marker for carbapenem resistance detected. Full susceptibility panel to follow. • IMP: Imipenem-resistant metallo-β-lactamase (IMP) marker for carbapenem resistance detected. Full susceptibility panel to follow.

Antimicrobial Stewardship Recommendations Validation

- **Cases with recommendations not accepted by the prescribers**
  - Daily report is sent to the AMS Pharmacists
  - AMS Pharmacists review and summarize cases
    - Summary is sent to the Antimicrobial Stewardship Committee Physician Members for validation & recommendations for next step
    - MD members are requested to provide feedback within 1 week
  - Quorum:
    - (1) Infectious Disease MD,(1) Internal Medicine/ Surgical MD

      OR
    - (2) Infectious Disease MDs

- **Report card will be presented at the Antimicrobial Stewardship Committee**

Antimicrobial Stewardship Recommendations Validation

- MD members are requested to provide feedback within 1 week
  - Agree with recommendation _____
  - Disagree with recommendation _____
  - Recommend to send Education Letter to prescriber
  - Recommend to send to Peer Review
  - Other _____

- Peer Review or Education Letter is sent in the case of a prescriber who consistently practices outside the institutional guidelines, egregious cases, or a Code of Conduct violation based on the AS Panel review and recommendation

Recommendation Not Accepted - example

Opportunity Identified De-escalate	Recommendation/Outcome
• 86 yo F with history L TKA, prosthesis placement 1 month ago • Admitted with L knee pain, redness, swelling x 4 days – Arthrocentesis done in ED – Started on vancomycin IV – BCx & synovial fluid cx obtained • RDT – Blood culture (+) MSSA – Fluid culture prelim GPC	Recommendation: Change vancomycin to either oxacillin or cefazolin Outcome: • Multiple calls to MD dt lack of responses • Recommendation not accepted – Per MD, he had already talked to RN re: (+) BCx; he had also spoken to "somebody" about culture results and that person would take of it – Contacted ID MD, antibiotics changed to oxacillin – Pt was discharged with oxacillin/rifampin x 6 weeks

Antimicrobial Stewardship Report Card

Date	Prescriber	Antimicrobials	Type of Recommendation
6/16	SR0101	Piperacillin/tazobatam	De-escalation
6/16	ID1609	Daptomycin or ceftaroline	De-escalation
7/16	ID2618	Micafungin, miconazole vaginal, nystatin susp	De-escalation
7/16	ID1609	Ceftaroline	De-escalation
7/16	ID1922	Daptomycin, imipenem	Optimization, de-escalation
8/16	ID1609	Linezolid/daptomycin, micafungin	De-escalation
8/16	SO0313	Cephalexin	Discontinuation

Key Takeaways

- Collaboration with the Division of Microbiology
- Support from the Medical Staff Leadership and the Institution
  - Financial commitment to purchase equipment
  - Microbiology & Pharmacy resources
- Communication
  - Continue to share successes
  - Ongoing feedback
  - In-services to clinicians

Acknowledgements

- Gregory Marks, Pharm.D., BCPS
- Angie Hirai-Yang, Pharm.D.
- Margie Morgan, PhD
- Rita Shane, PharmD, FASHP, FCSHP
- Jonathan Grein, MD – Infectious Diseases, Physician Champion
- Rekha Murthy, MD – Infectious Diseases, Physician Champion
- Sneha Krishna, Data Analyst
- Meghan Madhusudhan, Data Analyst
- Niyati Vakil, Pharm.D., BCPS
- Henry Su, MD
- Kathlyn Lim, Pharm.D.
- Hali Yang, Pharm.D., BCPS
- Ethan Smith, Pharm.D.

ashp MIDYEAR2016 Clinical Meeting & Exhibition

Self-Assessment Question 1

- Rapid diagnostic tests identify organisms and resistance markers faster than conventional culture and susceptibility method (True/False)

Answer: True

Self-Assessment Question 2

- The rapid diagnostic test algorithm can minimize costs associated with laboratory tests

Answer: True

Self-Assessment Question 3

- Rapid diagnostic tests without concurrent pharmacist's intervention can reduce time to effective therapy

Answer: False