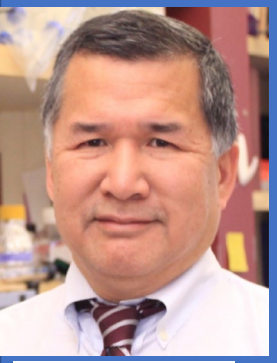
Introduction to Diagnostic Stewardship

December 17, 2020

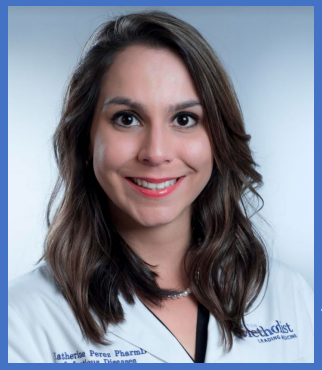
12:00 PM CST

(1:00 PM EST)



Ferric Fang
MD
Professor of Laboratory Medicine, Microbiology & Global Health
U. of Washington School of Medicine
Seattle, WA, USA

Speaker



Katherine Perez
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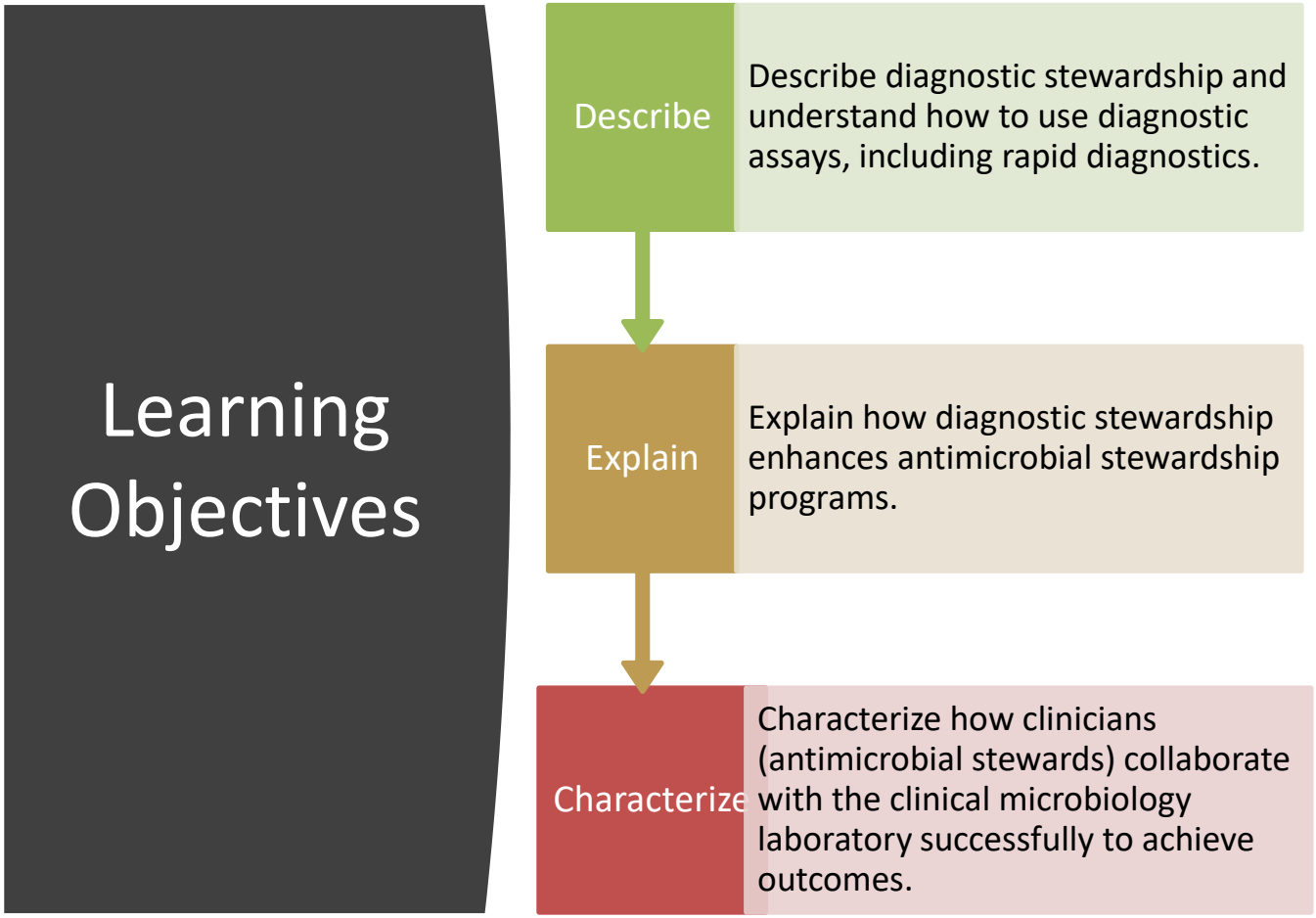
Moderator

CIDRAP
Center for Infectious Disease Research and Policy
University of Minnesota

ProCE

SIDP
Society of Infectious Diseases Pharmacists

Learning Objectives



CE/CME Activity Information & Accreditation

ACPE Credit Designation (Pharmacist CE)

This activity is jointly provided by ProCE, LLC, CIDRAP (Center for Infectious Disease Research and Policy), and SIDP (Society of Infectious Diseases Pharmacists). ProCE is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE Universal Activity Number 0221-9999-20-533-L01-P has been assigned to this live knowledge-based activity (initial release date 12-17-2020). This CE activity is approved for 1.25 contact hours (0.125 CEU) in states that recognize ACPE providers. This CE activity is provided at no cost to participants. Successful completion of the online post-test and evaluation at www.ProCE.com is required to receive CE credit. CE credit will be uploaded to NABP/CPE Monitor. No partial credit will be given.

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CE/CME Activity Information & Accreditation
(continued)

Target Audience:
This program has been designed to meet the educational needs of physicians, pharmacists, nurses, and clinical laboratory professionals.

Funding:
This activity is supported by an educational grant from BioMérieux.

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- **Marnie Peterson, PharmD, PhD** has no relevant conflicts of interest to report.
- **Ferric C. Fang, MD** has no relevant conflicts of interest to report.
- **Katherine K. Perez, PharmD** has no relevant conflicts of interest to report.
- **Kristine Moore, MD, MPH** has no relevant conflicts of interest to report.
- **Maya Peters, MPH** has no relevant conflicts of interest to report.
- **Catherine Harrison, RN, MPH** has no relevant conflicts of interest to report.
- **CCO and ProCE Staff** have no relevant conflicts of interest to report.

Potential conflicts of interest were resolved with a peer review process provided by Kristine Moore, MD, MPH.

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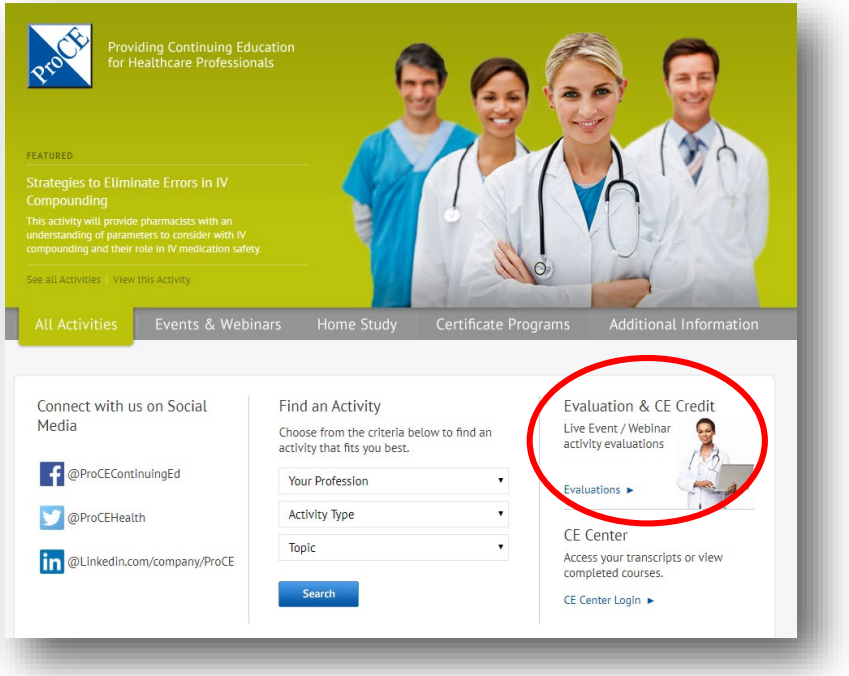
  - user must complete the “claim credit” step



Attendance Code

Code will be provided at the end of today’s activity

DIAGNOSTIC STEWARDSHIP

For Optimization of Antimicrobial Therapy

Prof. Ferric C. Fang

University of Washington

What is Diagnostic Stewardship?

- Coordinated guidance and interventions to improve appropriate use of microbiological diagnostics to guide therapeutic decisions.

- *Diagnostic Stewardship* should promote appropriate, timely diagnostic testing, including specimen collection and pathogen identification, and accurate, timely reporting of results to guide patient treatment.

REF: WHO, Global Antimicrobial Resistance Surveillance System, 2016.

What is Diagnostic Stewardship?

- The appropriate use of laboratory testing to guide patient management in order to optimize clinical outcomes and limit the spread of antimicrobial resistance.

- *Not to be confused with the cost-effective use of laboratory tests, which, although part of diagnostic stewardship, is more limited in scope.*

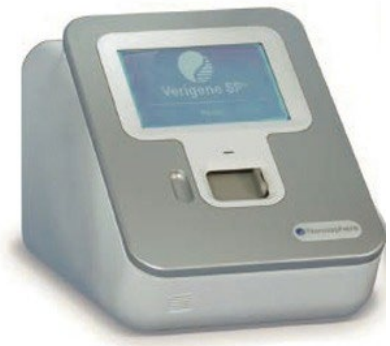
REF: Patel and Fang, Clin Infect Dis, 2018.

Rapid Diagnostic Tests (RDTs)

PCR
polymerase chain reaction

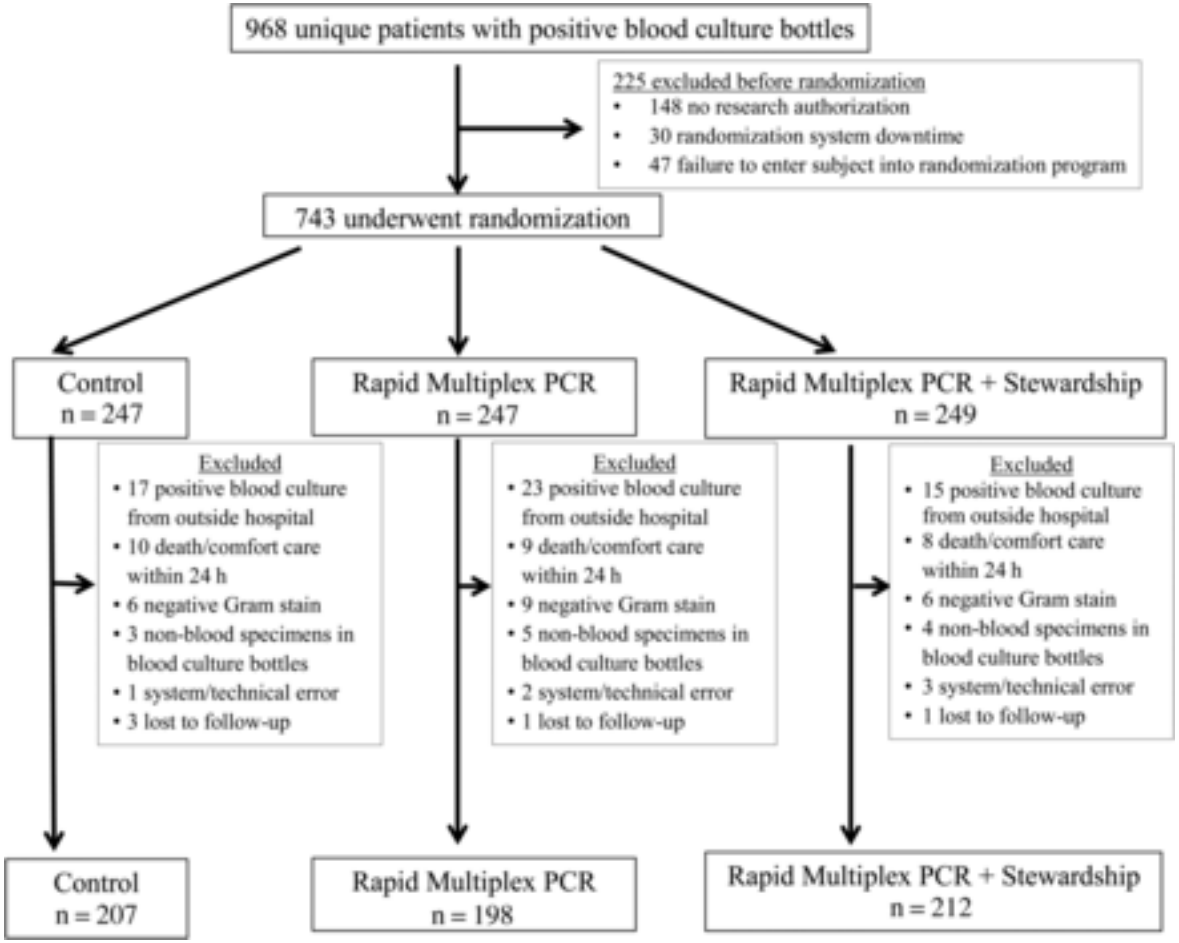
MALDI-TOF MS
matrix-assisted laser desorption ionization-time of flight mass spectrometry

PNA-FISH
peptide-nucleic acid fluorescent in situ hybridization



Microarray

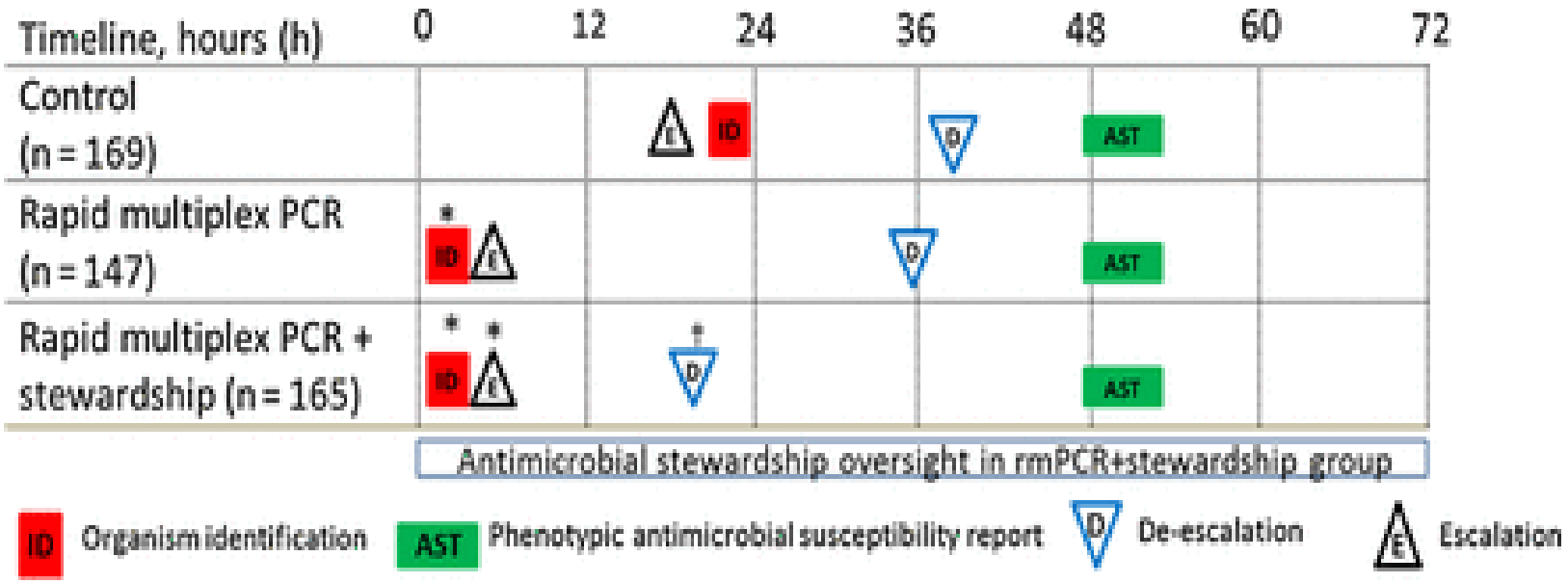
Rapid Diagnostics and Antimicrobial Stewardship



- A randomized trial compared conventional blood culture ID with rapid PCR and PCR plus stewardship

REF: Banerjee et al., Clin Infect Dis, 2015.

Rapid Diagnostics and Antimicrobial Stewardship



- Rapid PCR reduced treatment of contaminants
- Both rapid PCR and PCR plus stewardship shortened the time to antibiotic escalation but only PCR plus stewardship led to more rapid de-escalation

REF: Banerjee et al., Clin Infect Dis, 2015.

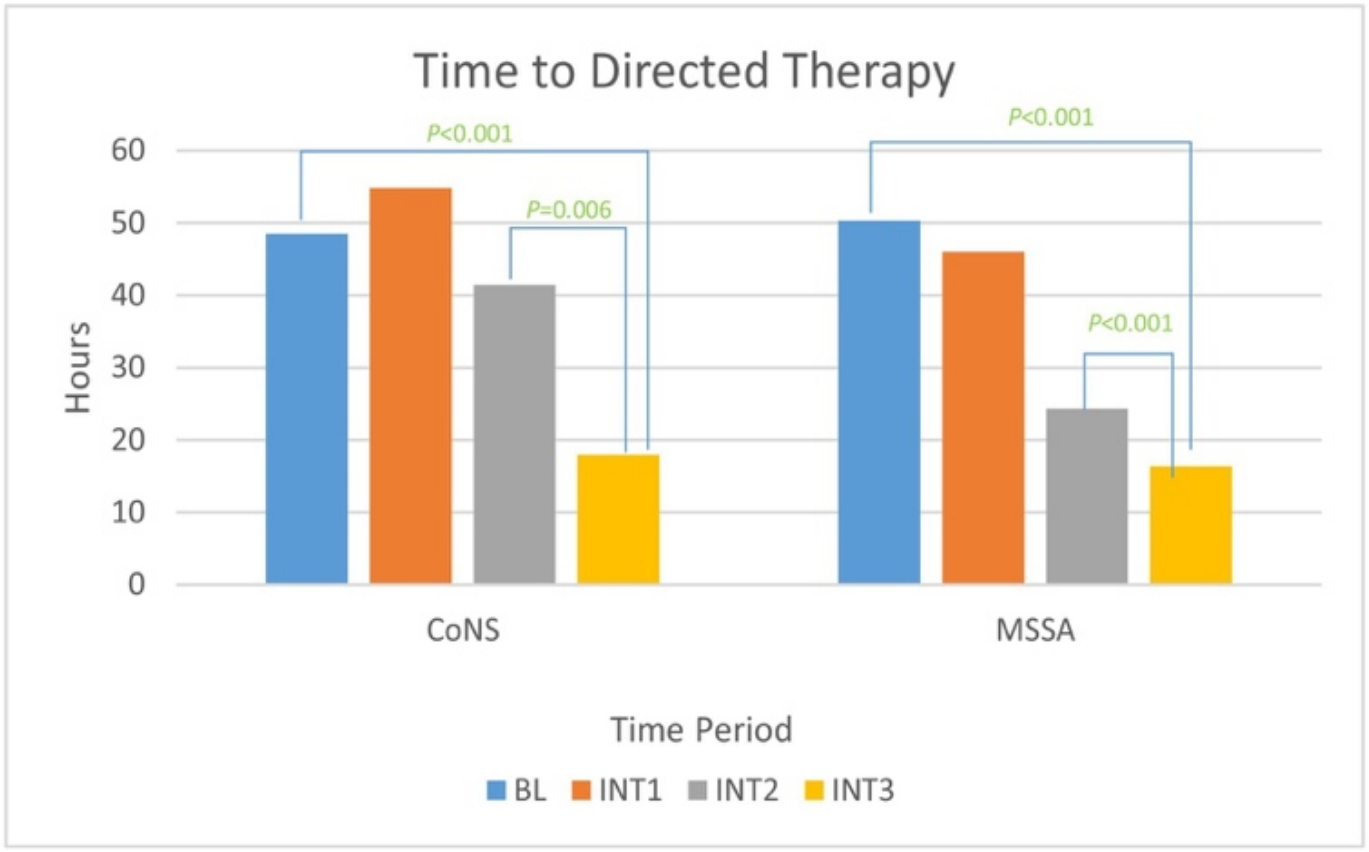
Rapid Diagnostics and Antimicrobial Stewardship

Outcome	Control (n = 207)	Rapid Multiplex PCR (n = 198)	Rapid Multiplex PCR + Stewardship (n = 212)	*P* Value Comparing 3 Groups
Clinical outcome				
Disposition				.12
Home	68 (32.9)	62 (31.3)	78 (36.8)	
Home with outpatient antimicrobial therapy	39 (18.8)	52 (26.3)	38 (17.9)	
Nursing home/skilled nursing facility	63 (30.4)	42 (21.2)	54 (25.5)	
Hospice/comfort care	12 (5.8)	8 (4)	7 (3.3)	
Death	11 (5.3)	11 (5.6)	8 (3.8)	
Length of stay (entire hospitalization), d, median (IQR)	8 (5–15)	8 (5–15)	8 (5–16)	.60
Length of stay (after enrollment), d, median (IQR)	7 (4–12)	6 (4–12)	7 (4–12)	.61
Intensive care unit admission within 14 d after enrollment	16 (7.7)	5 (2.5)	10 (4.7)	.06
Length of stay in intensive care unit (after enrollment), d, median (IQR)	3 (2–4)	2 (1–5)	3 (2–4)	.90
30-day mortality	22 (10.6)	20 (10.1)	18 (8.5)	.74
30-day attributable mortality	7 (3.4)	7 (3.5)	2 (0.9)	.42
30-day readmission for infection with same organism	6 (2.9)	6 (3)	8 (3.8)	.88
Toxicity/adverse drug reaction[a]	3 (1.4)	3 (1.5)	2 (0.9)	.82
Microbiologic outcomes				
Blood culture clearance within 3 d after enrollment	147 (71)	131 (66.2)	146 (68.9)	.79
Acquisition of *Clostridium difficile* or multidrug-resistant organisms[b] within 30 days after enrollment	15 (7.2)	16 (8.1)	21 (9.9)	.62
Cost per hospitalized patient, mean (median)				
Overall hospitalization costs	$65 450 ($27 192)	$66 887 ($23 935)	$68 729 ($29 064)	.78
Test costs	$5377 ($2082)	$5680 ($2585)[c]	$5743 ($2774)[c]	<.001
Antimicrobial costs	$2194 ($990)	$1932 ($866)	$1741 ($890)	.65

- Groups did not differ in mortality, length-of-stay or costs

REF: Banerjee et al., Clin Infect Dis, 2015.

Rapid Diagnostics and Antimicrobial Stewardship



Standard care

Rapid phenotypic ID

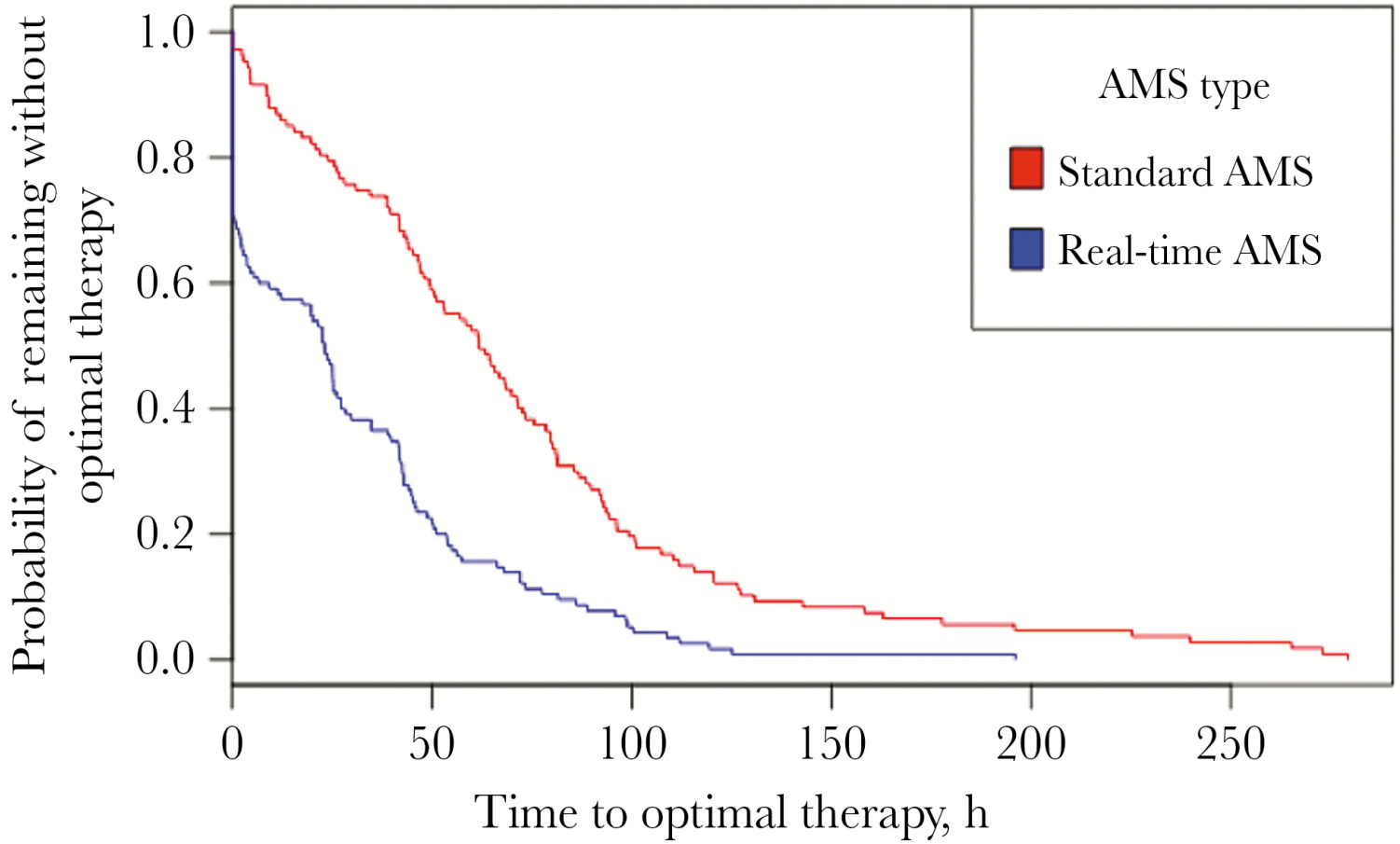
PCR

PCR & ASP

- Rapid diagnosis combined with stewardship improves therapy of both blood culture contaminants and true bacteremia

REF: Bhowmick et al., Diagn Microbiol Infect Dis, 2018.

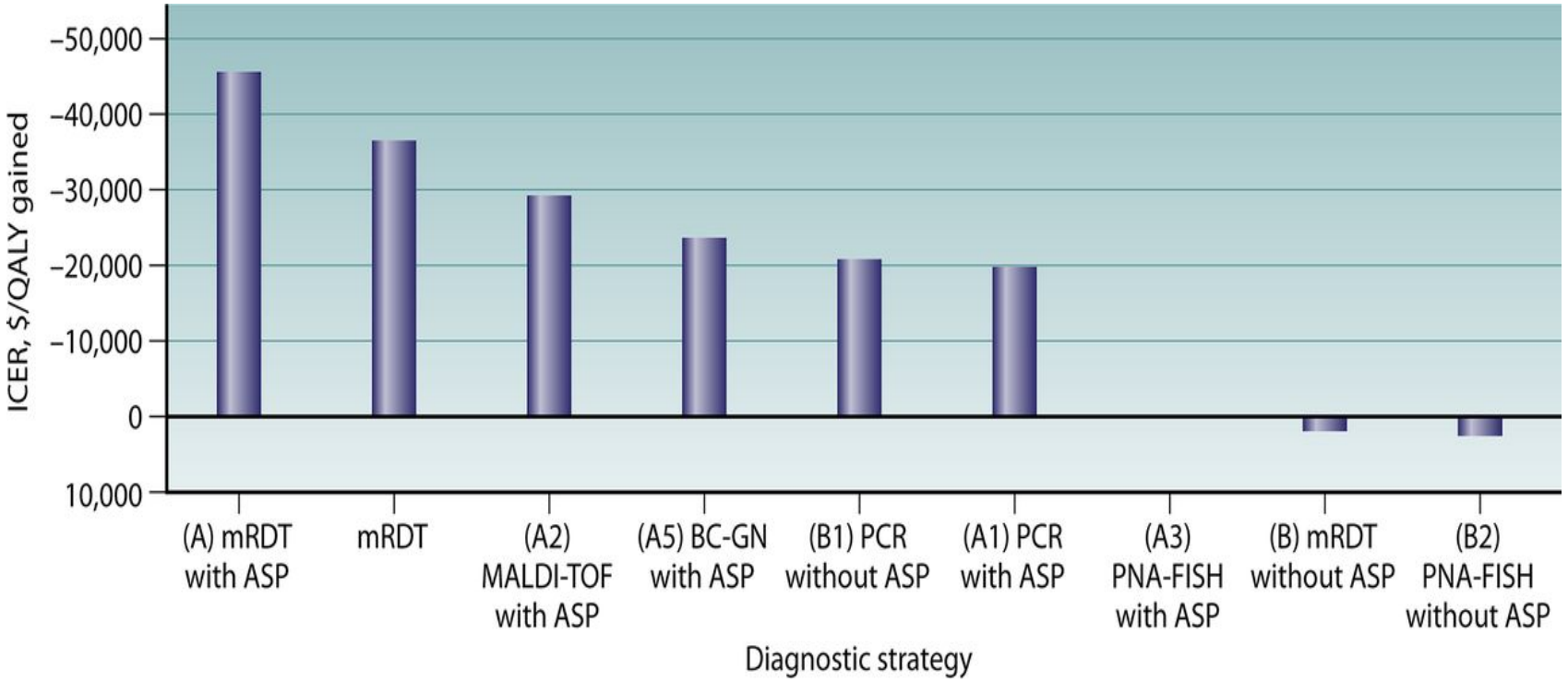
Rapid Diagnostics and Antimicrobial Stewardship



- Antimicrobial stewardship needs to be delivered in "real time"

REF: Beganovic et al., Open Forum Infect Dis, 2018.

Rapid Diagnostics and Antimicrobial Stewardship

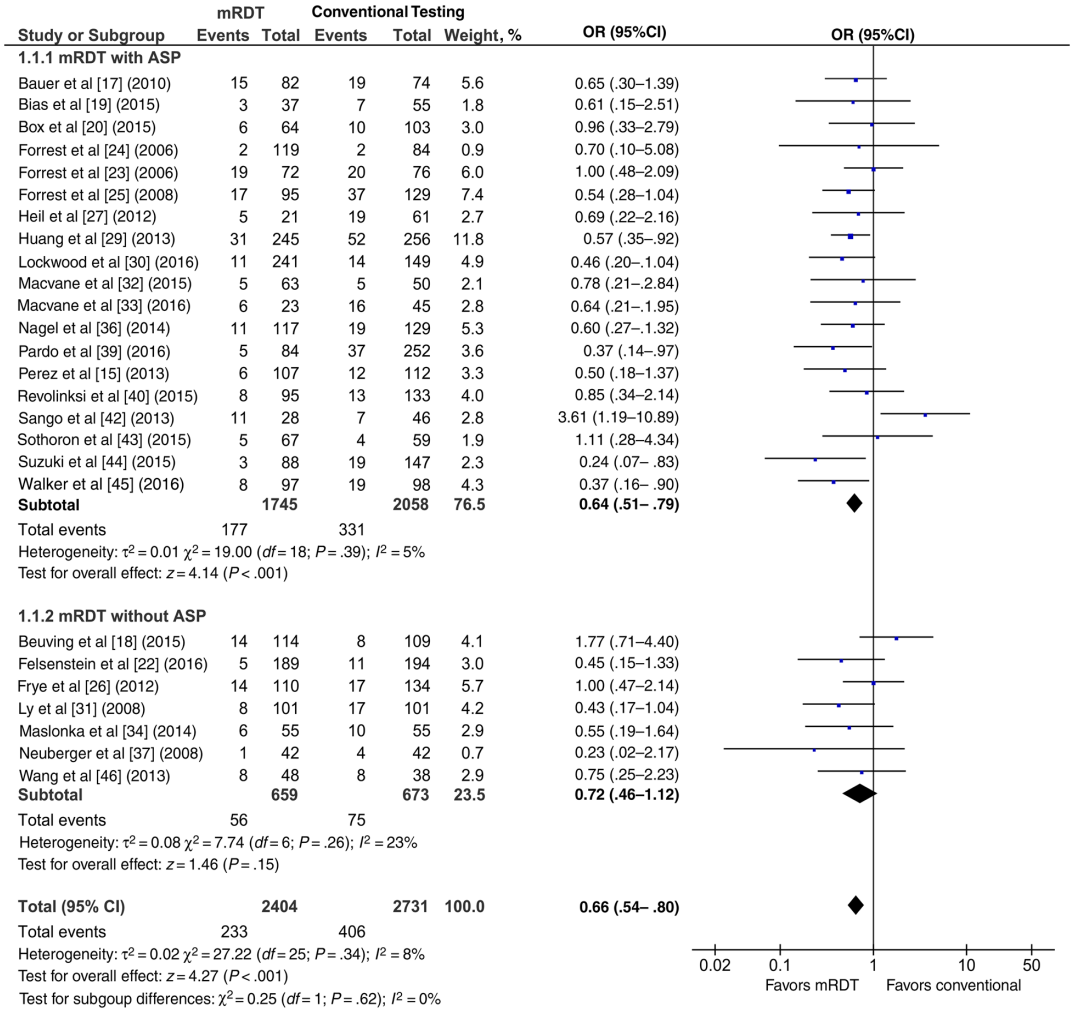


- Rapid diagnosis combined with antimicrobial stewardship is highly cost-effective for patients with suspected bloodstream infections

ABBREVIATIONS: mRDT=molecular rapid diagnostic test, ASP=antimicrobial stewardship program, MALDI-TOF= matrix-assisted laser desorption ionization-time of flight mass spectrometry, BC-GN=Gram-negative blood culture microarray, PCR=polymerase chain reaction, PNA-FISH= peptide-nucleic acid fluorescent in situ hybridization.

REF: Pliakos et al., Clin Microbiol Rev, 2018.

Rapid Diagnostics and Antimicrobial Stewardship



Study or Subgroup	mRDT Events	mRDT Total	Conventional Testing Events	Conventional Testing Total	Weight, %	OR (95%CI)
1.1.1 mRDT with ASP						
Bauer et al [17] (2010)	15	82	19	74	5.6	0.65 (.30–1.39)
Bias et al [19] (2015)	3	37	7	55	1.8	0.61 (.15–2.51)
Box et al [20] (2015)	6	64	10	103	3.0	0.96 (.33–2.79)
Forrest et al [24] (2006)	2	119	2	84	0.9	0.70 (.10–5.08)
Forrest et al [23] (2006)	19	72	20	76	6.0	1.00 (.48–2.09)
Forrest et al [25] (2008)	17	95	37	129	7.4	0.54 (.28–1.04)
Heil et al [27] (2012)	5	21	19	61	2.7	0.69 (.22–2.16)
Huang et al [29] (2013)	31	245	52	256	11.8	0.57 (.35–.92)
Lockwood et al [30] (2016)	11	241	14	149	4.9	0.46 (.20–.1.04)
Macvane et al [32] (2015)	5	63	5	50	2.1	0.78 (.21–.2.84)
Macvane et al [33] (2016)	6	23	16	45	2.8	0.64 (.21–.1.95)
Nagel et al [36] (2014)	11	117	19	129	5.3	0.60 (.27–.1.32)
Pardo et al [39] (2016)	5	84	37	252	3.6	0.37 (.14–.97)
Perez et al [15] (2013)	6	107	12	112	3.3	0.50 (.18–1.37)
Revolinksi et al [40] (2015)	8	95	13	133	4.0	0.85 (.34–2.14)
Sango et al [42] (2013)	11	28	7	46	2.8	3.61 (1.19–10.89)
Sothoron et al [43] (2015)	5	67	4	59	1.9	1.11 (.28–4.34)
Suzuki et al [44] (2015)	3	88	19	147	2.3	0.24 (.07– .83)
Walker et al [45] (2016)	8	97	19	98	4.3	0.37 (.16– .90)
Subtotal		**1745**		**2058**	**76.5**	**0.64 (.51– .79)**
Total events	177		331			
Heterogeneity: $\tau^2 = 0.01$ $\chi^2 = 19.00$ ($df = 18$; $P = .39$); $I^2 = 5\%$						
Test for overall effect: $z = 4.14$ ($P < .001$)						
1.1.2 mRDT without ASP						
Beuving et al [18] (2015)	14	114	8	109	4.1	1.77 (.71–4.40)
Felsenstein et al [22] (2016)	5	189	11	194	3.0	0.45 (.15–1.33)
Frye et al [26] (2012)	14	110	17	134	5.7	1.00 (.47–2.14)
Ly et al [31] (2008)	8	101	17	101	4.2	0.43 (.17–1.04)
Maslonka et al [34] (2014)	6	55	10	55	2.9	0.55 (.19–1.64)
Neuberger et al [37] (2008)	1	42	4	42	0.7	0.23 (.02–2.17)
Wang et al [46] (2013)	8	48	8	38	2.9	0.75 (.25–2.23)
Subtotal		**659**		**673**	**23.5**	**0.72 (.46–1.12)**
Total events	56		75			
Heterogeneity: $\tau^2 = 0.08$ $\chi^2 = 7.74$ ($df = 6$; $P = .26$); $I^2 = 23\%$						
Test for overall effect: $z = 1.46$ ($P = .15$)						
Total (95% CI)		**2404**		**2731**	**100.0**	**0.66 (.54– .80)**
Total events	233		406			
Heterogeneity: $\tau^2 = 0.02$ $\chi^2 = 27.22$ ($df = 25$; $P = .34$); $I^2 = 8\%$						
Test for overall effect: $z = 4.27$ ($P < .001$)						
Test for subgoup differences: $\chi^2 = 0.25$ ($df = 1$; $P = .62$); $I^2 = 0\%$						

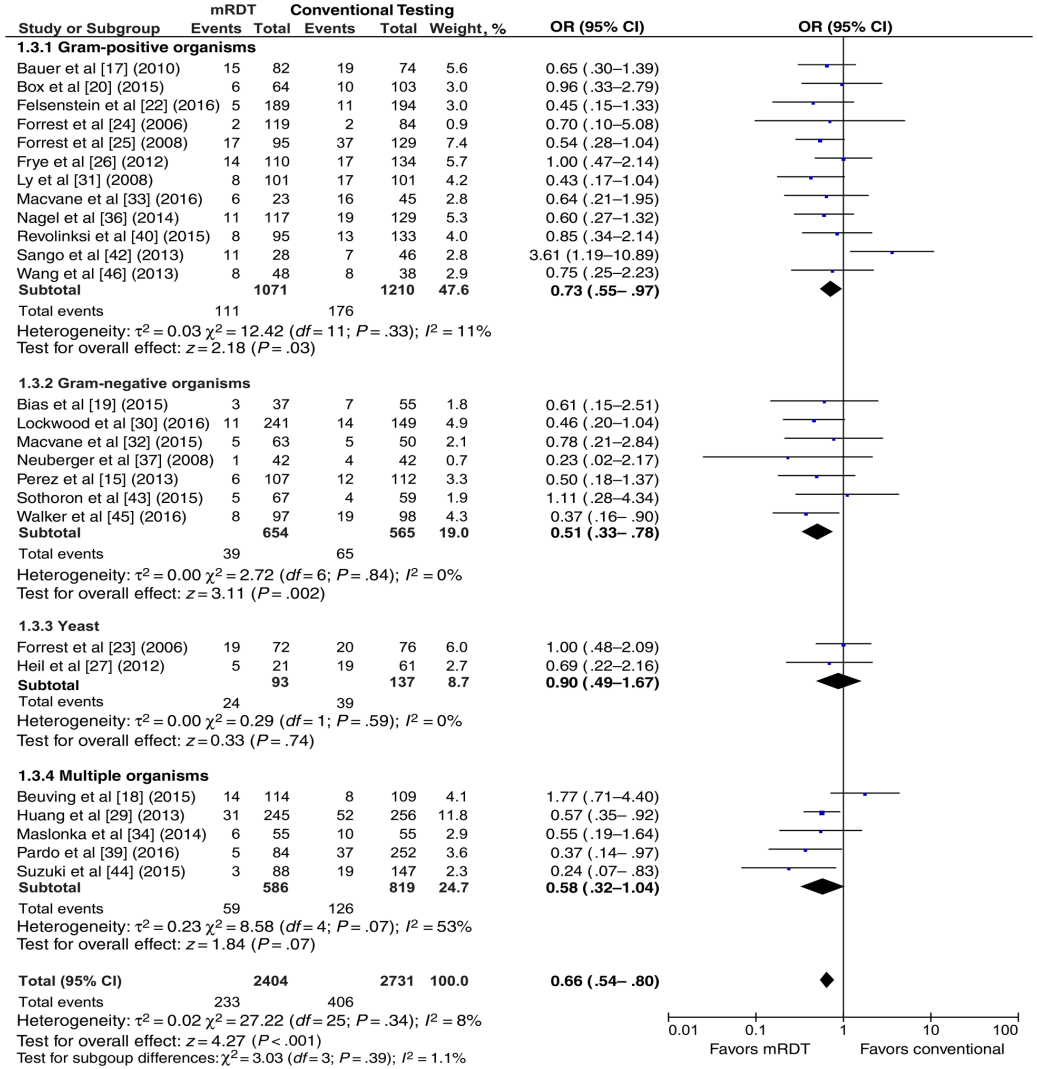
Molecular Rapid Diagnostic Testing with ASP

Molecular Rapid Diagnostic Testing without ASP

- Rapid diagnosis is more effective when coupled with real-time antimicrobial stewardship

REF: Timbrook et al., Clin Infect Dis, 2017.

Rapid Diagnostics and Antimicrobial Stewardship



Study or Subgroup	mRDT Events	mRDT Total	Conventional Testing Events	Conventional Testing Total	Weight, %	OR (95% CI)
1.3.1 Gram-positive organisms						
Bauer et al [17] (2010)	15	82	19	74	5.6	0.65 (.30–1.39)
Box et al [20] (2015)	6	64	10	103	3.0	0.96 (.33–2.79)
Felsenstein et al [22] (2016)	5	189	11	194	3.0	0.45 (.15–1.33)
Forrest et al [24] (2006)	2	119	2	84	0.9	0.70 (.10–5.08)
Forrest et al [25] (2008)	17	95	37	129	7.4	0.54 (.28–1.04)
Frye et al [26] (2012)	14	110	17	134	5.7	1.00 (.47–2.14)
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Macvane et al [33] (2016)	6	23	16	45	2.8	0.64 (.21–1.95)
Nagel et al [36] (2014)	11	117	19	129	5.3	0.60 (.27–1.32)
Revolinksi et al [40] (2015)	8	95	13	133	4.0	0.85 (.34–2.14)
Sango et al [42] (2013)	11	28	7	46	2.8	3.61 (1.19–10.89)
Wang et al [46] (2013)	8	48	8	38	2.9	0.75 (.25–2.23)
Subtotal		**1071**		**1210**	**47.6**	**0.73 (.55– .97)**
Total events	111		176			
Heterogeneity: $\tau^2 = 0.03$ $\chi^2 = 12.42$ ($df = 11$; $P = .33$); $I^2 = 11\%$						
Test for overall effect: $z = 2.18$ ($P = .03$)						
1.3.2 Gram-negative organisms						
Bias et al [19] (2015)	3	37	7	55	1.8	0.61 (.15–2.51)
Lockwood et al [30] (2016)	11	241	14	149	4.9	0.46 (.20–1.04)
Macvane et al [32] (2015)	5	63	5	50	2.1	0.78 (.21–2.84)
Neuberger et al [37] (2008)	1	42	4	42	0.7	0.23 (.02–2.17)
Perez et al [15] (2013)	6	107	12	112	3.3	0.50 (.18–1.37)
Sothoron et al [43] (2015)	5	67	4	59	1.9	1.11 (.28–4.34)
Walker et al [45] (2016)	8	97	19	98	4.3	0.37 (.16– .90)
Subtotal		**654**		**565**	**19.0**	**0.51 (.33– .78)**
Total events	39		65			
Heterogeneity: $\tau^2 = 0.00$ $\chi^2 = 2.72$ ($df = 6$; $P = .84$); $I^2 = 0\%$						
Test for overall effect: $z = 3.11$ ($P = .002$)						
1.3.3 Yeast						
Forrest et al [23] (2006)	19	72	20	76	6.0	1.00 (.48–2.09)
Heil et al [27] (2012)	5	21	19	61	2.7	0.69 (.22–2.16)
Subtotal		**93**		**137**	**8.7**	**0.90 (.49–1.67)**
Total events	24		39			
Heterogeneity: $\tau^2 = 0.00$ $\chi^2 = 0.29$ ($df = 1$; $P = .59$); $I^2 = 0\%$						
Test for overall effect: $z = 0.33$ ($P = .74$)						
1.3.4 Multiple organisms						
Beuving et al [18] (2015)	14	114	8	109	4.1	1.77 (.71–4.40)
Huang et al [29] (2013)	31	245	52	256	11.8	0.57 (.35– .92)
Maslonka et al [34] (2014)	6	55	10	55	2.9	0.55 (.19–1.64)
Pardo et al [39] (2016)	5	84	37	252	3.6	0.37 (.14– .97)
Suzuki et al [44] (2015)	3	88	19	147	2.3	0.24 (.07– .83)
Subtotal		**586**		**819**	**24.7**	**0.58 (.32–1.04)**
Total events	59		126			
Heterogeneity: $\tau^2 = 0.23$ $\chi^2 = 8.58$ ($df = 4$; $P = .07$); $I^2 = 53\%$						
Test for overall effect: $z = 1.84$ ($P = .07$)						
Total (95% CI)		**2404**		**2731**	**100.0**	**0.66 (.54– .80)**
Total events	233		406			
Heterogeneity: $\tau^2 = 0.02$ $\chi^2 = 27.22$ ($df = 25$; $P = .34$); $I^2 = 8\%$						
Test for overall effect: $z = 4.27$ ($P < .001$)						
Test for subgoup differences: $\chi^2 = 3.03$ ($df = 3$; $P = .39$); $I^2 = 1.1\%$						

Gram-positive

Gram-negative

Yeast

Multiple organisms

- The greatest impact of rapid diagnosis/ASP is with Gram-negative BSI

REF: Timbrook et al., Clin Infect Dis, 2017.


I ASKED AROUND AND NOBODY HEARD ANYTHING
MarkParisi@aol.com
Rapid diagnostic test
MARK PARISI
1-22 offthemark.com
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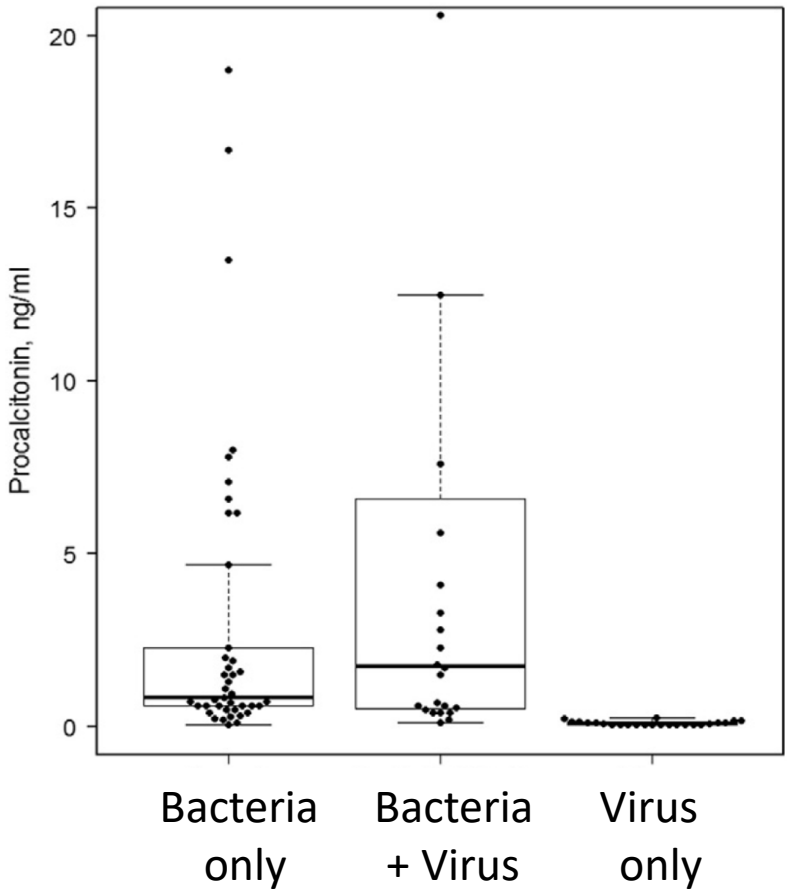
Rapid Diagnostics and Community Acquired Pneumonia



- Antibiotics may be safely avoided in community-acquired pneumonia when serum procalcitonin levels are normal and only respiratory viruses are detected

REF: Gilbert et al., Diagn Microbiol Infect Dis, 2016.

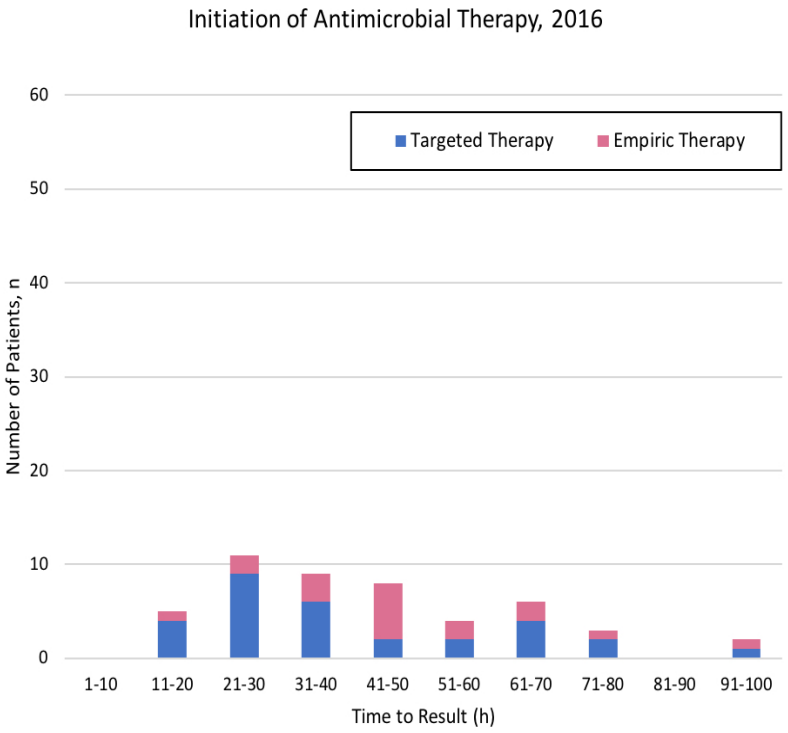
Rapid Diagnostics in Skin and Skin Structure Infections

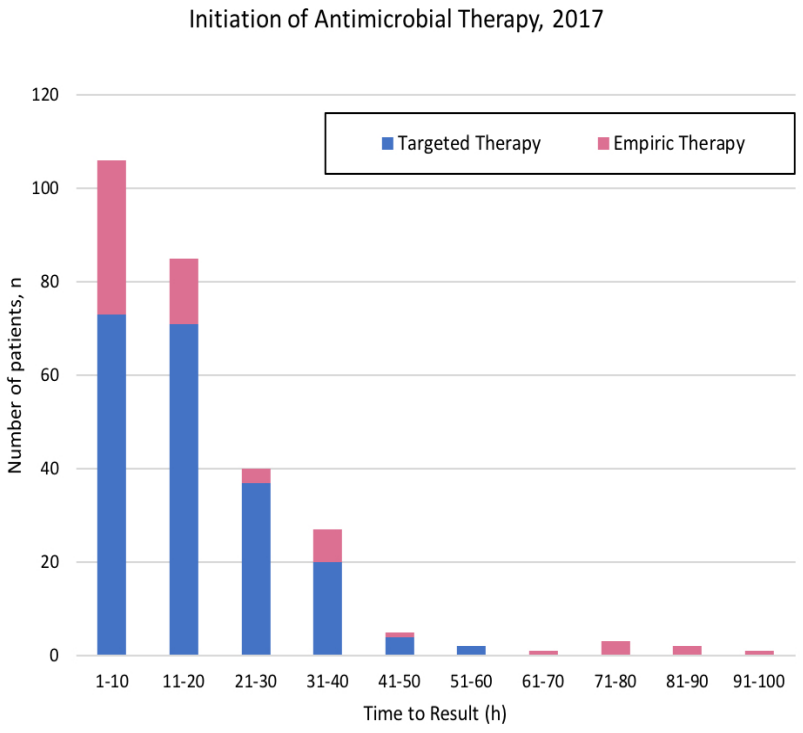
Variable	Intervention cohort	Comparison cohort	IRR[a]/OR[b] (95% CI)	p value
DDD[c] (mean, SD[d])	25.6 (26.3)	27.6 (31.5)	0.929 (0.77–1.13)	0.454
DOT[e] (days) (mean, SD[d])	22.0 (21.5)	24.3 (24.1)	0.907 (0.84–0.97)	0.007
Length of treatment (days) (mean, SD[d])	14.1 (12.8)	15.0 (13.7)	0.945 (0.89–1.00)	0.072
Cost (€) (mean, SD[d])	433.1 (678.8)	533.3 (909.3)	0.783 (0.62–0.99)	0.039
LOS[e] (days) (mean, SD[d])	18.6 (20.9)	20.7 (25.1)	0.898 (0.81–0.99)	0.031
Need for surgery (n, %)	63.0 (40.6)	50.0 (32.3)	1.438 (0.96–2.24)	0.107
CDI[f] (n, %)	4.0 (2.6)	8.0 (5.2)	0.487 (0.24–1.00)	0.050
Related mortality (n, %)	1.0 (0.6)	4.0 (2.6)	0.245 (0.07–0.81)	0.022
Unrelated mortality (n, %)	6.0 (3.9)	8.0 (5.2)	0.740 (0.24–2.25)	0.595

- Rapid diagnostics improved days of treatment, cost, length of stay, CDI and related mortality, primarily as a result of more timely targeting of anti-staphylococcal therapy

REF: Bouza et al., J Microbiol Immunol Infect, 2020.

Rapid Diagnostics in Acute Gastroenteritis

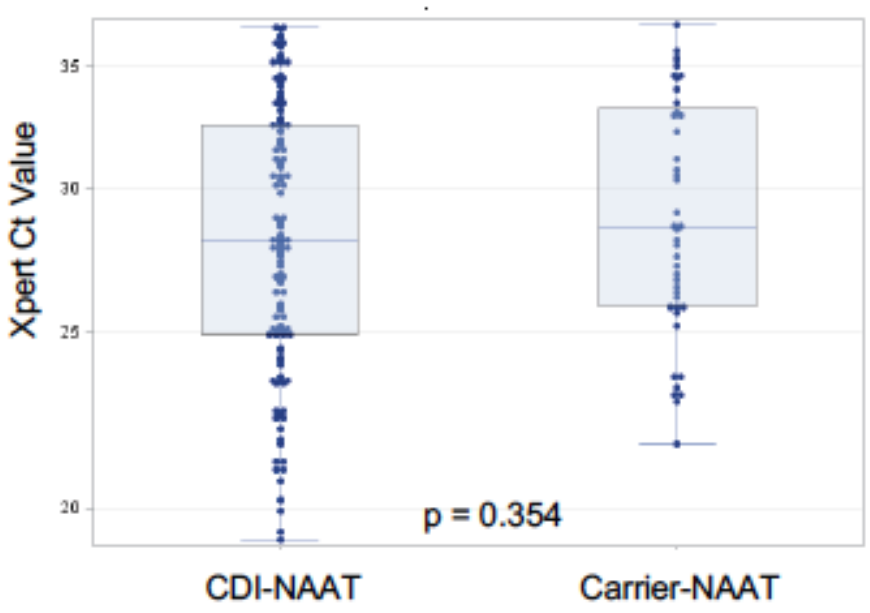


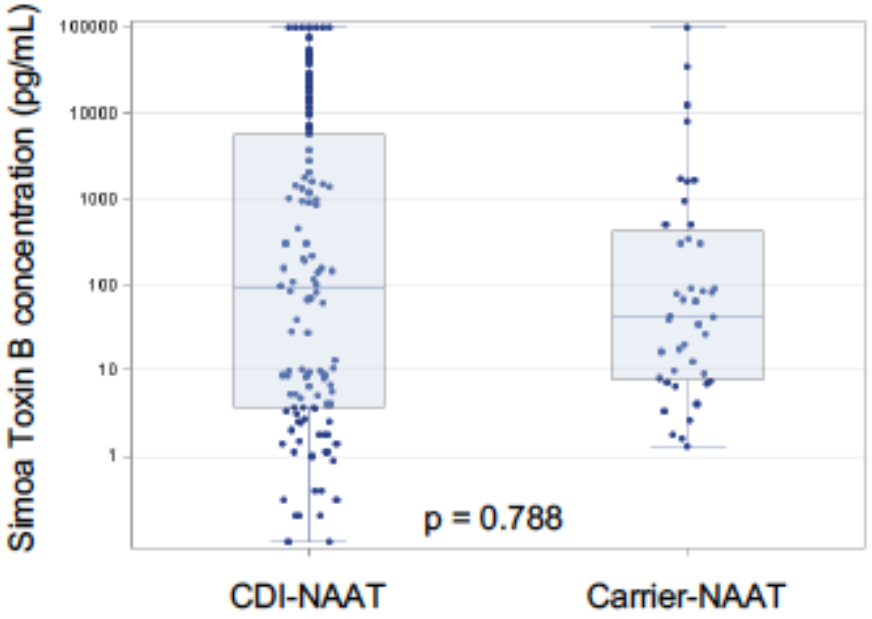


- Rapid diagnostics facilitated more rapid and targeted therapy of bacterial pathogens

REF: Cybulski et al., Clin Infect Dis, 2018.

Diagnostic Stewardship in *C. difficile* Infections

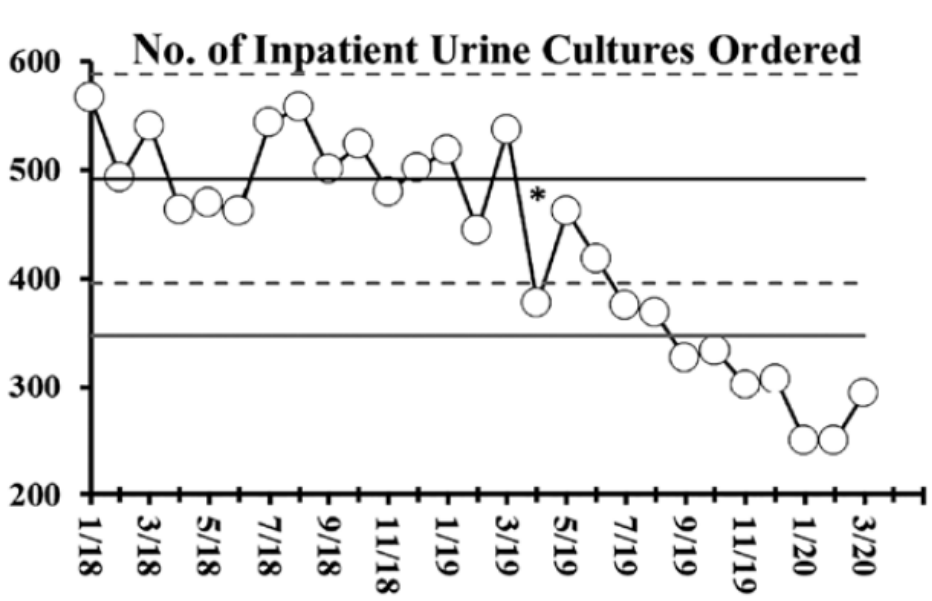


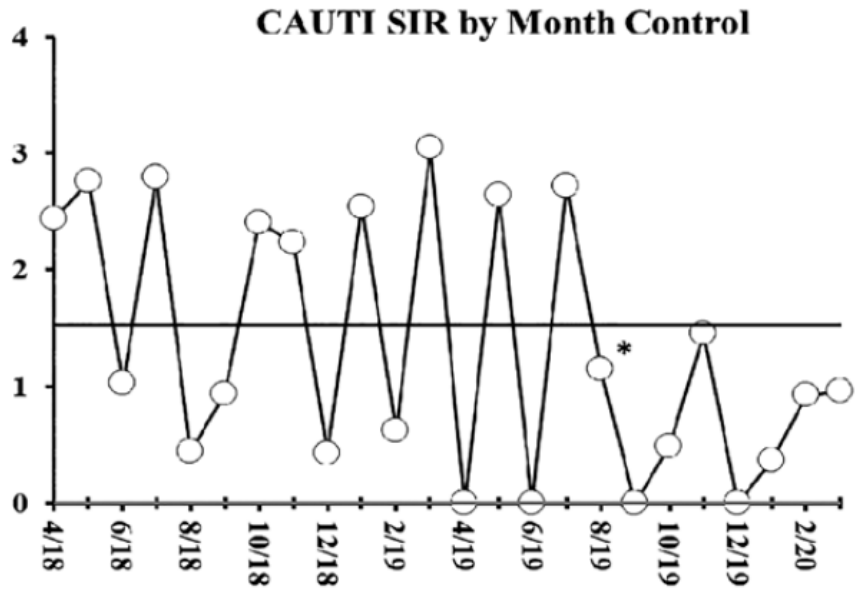


- Diagnostic tests cannot reliably distinguish colonization from infection
- Testing should be limited to patients meeting appropriate clinical criteria; inappropriate testing will lead to unnecessary treatment of colonized patients

REF: Pollock et al., Clin Infect Dis, 2018.

Diagnostic Stewardship in Catheter-Associated Urinary Tract Infections

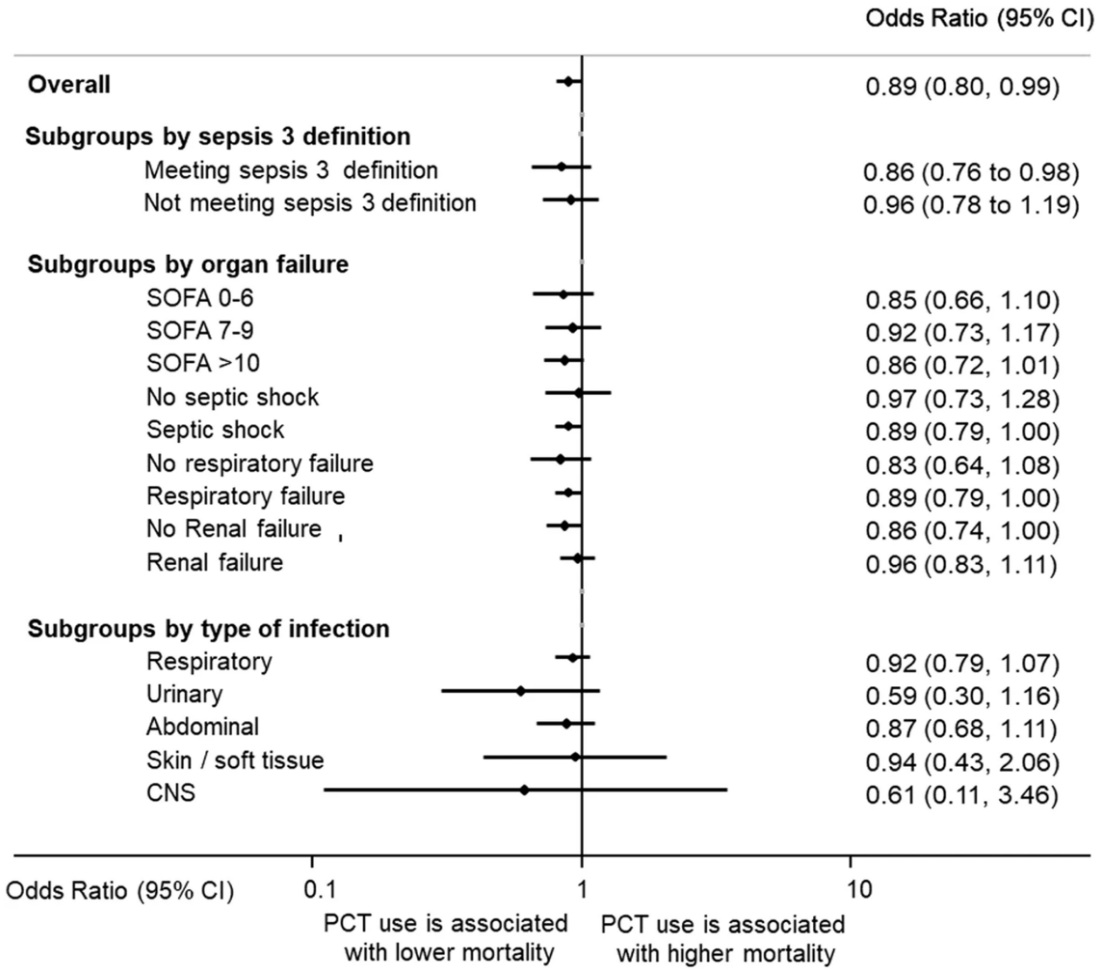




- An educational intervention with audit and feedback reduced inappropriate urine culture orders and institutional CAUTI rates without an adverse clinical impact

REF: Luu et al., Clin Infect Dis, 2020.

Diagnostics-Guided Antibiotic Treatment



- Procalcitonin-guided treatment in the ICU is associated with lower mortality and reduced antibiotic use

REF: Wirz et al., Crit Care, 2018.

Diagnostics-Guided Antibiotic Treatment

	Total (n=577)	Viral infection (n=435)	Bacterial infection (n=71)	Inconclusive (n=71)	p value*
Mean age, months	21 (16)	20 (16)	24 (17)	25 (17)	0·044
Male sex	324 (56%)	246 (57%)	36 (51%)	42 (59%)	0·370
Mean maximal temperature, °C	39·4 (0·8)	39·3 (0·8)	39·7 (0·8)	39·4 (0·9)	<0·0001
Mean duration of symptoms, days†	2·8 (1·7)	2·7 (1·7)	3·0 (1·8)	2·7 (1·8)	0·277
Hospital admission	316 (55%)	219 (50%)	59 (83%)	38 (54%)	<0·0001
Median time in hospital, days	3 (2–4)	3 (2–4)	4 (3–5)	3 (3–5)	<0·0001
Antibiotic treatment prescribed	224 (39%)	100 (23%)	71 (100%)	53 (75%)	<0·0001

- Rapid biomarker assays may differentiate bacterial and viral infections
- This platform measures TRAIL, IP-10 and CRP
- Negative predictive value for bacterial infections in children aged 2-60 mos. was 97.8%

REF: Van Houten et al., Lancet Infect Dis, 2017.

Diagnostics-Guided Antibiotic Treatment

Type of Pneumonia	Studies, No.	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)	DOR (95% CI)	PPV, %	NPV, %
All	22	70.9 (58.8–80.6)	90.3 (86.1–93.3)	7.28 (5.3–10.1)	0.32 (0.22–0.46)	24.6 (13.6–37.5)	44.8	96.5
CAP/HCAP	4	85.0 (59.7–95.6)	92.1 (81.5–96.9)	10.8 (5.1–23.0)	0.16 (0.06–0.48)	66.4 (28.5–154.6)	56.8	98.1
VAP	5	40.3 (17.4–68.4)	93.7 (77.1–98.4)	6.34 (1.94–20.8)	0.63 (0.42–0.98)	9.96 (2.63–37.6)	35.7	94.8

- Nasal screening tests have 95-98% negative predictive value for ruling-out MRSA pneumonia

REF: Parente et al., Clin Infect Dis, 2018.

CONCLUSIONS

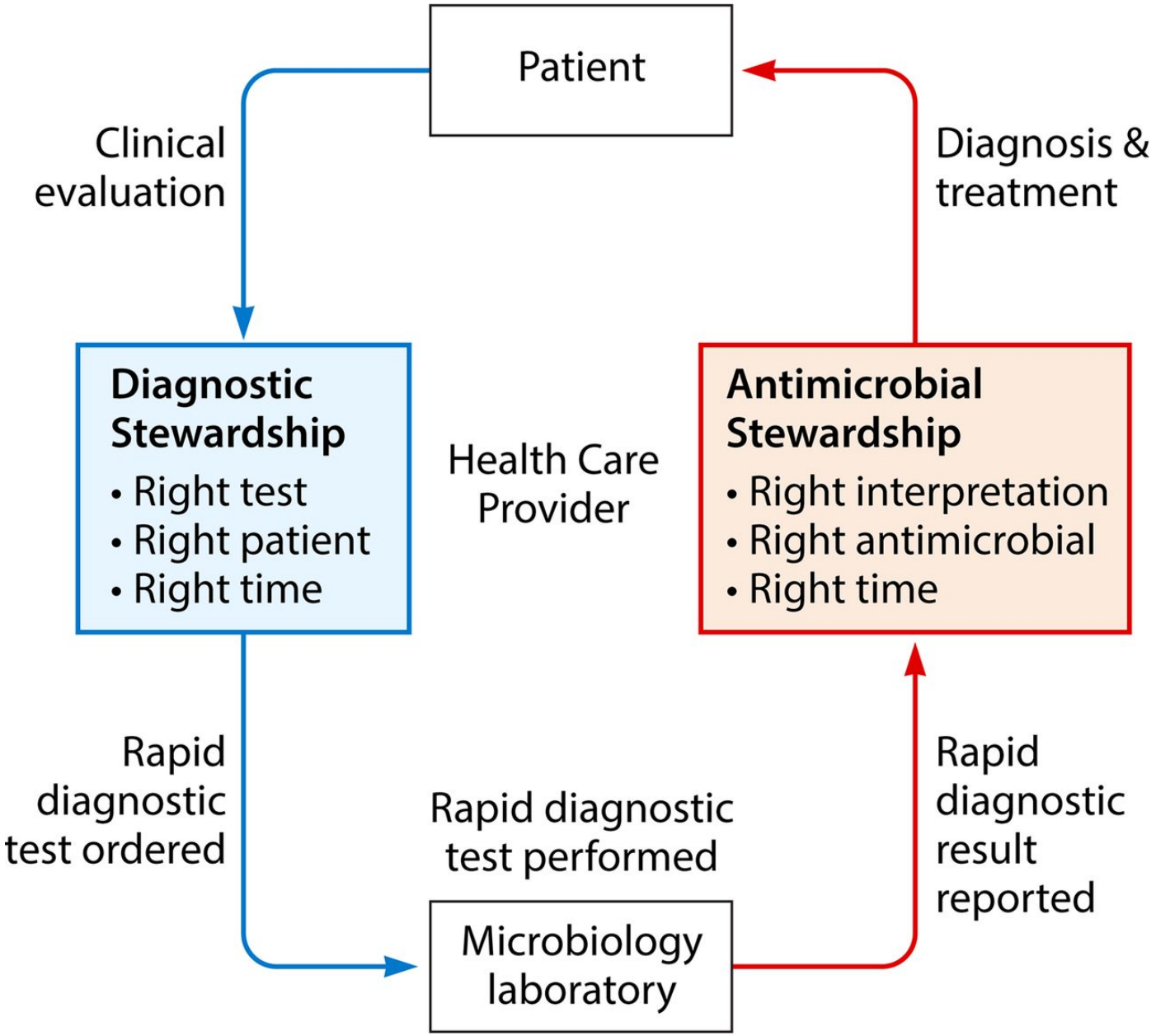
- ANTIMICROBIAL STEWARDSHIP:

"Use the right drug at the right time at the right dose for the right duration."

- DIAGNOSTIC STEWARDSHIP:

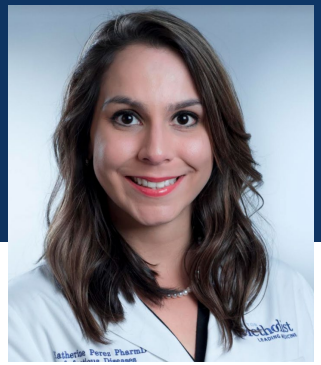
"Obtain the right test in the right patient in order to use the right drug at the right time at the right dose for the right duration."

REF: Dryden et al. *J Antimicrob Chemother,* 2011.



REF: Messacar et al. *J Clin Microbiol*, 2017.

Introduction to Diagnostic Stewardship: Clinical Antimicrobial Stewardship Perspective



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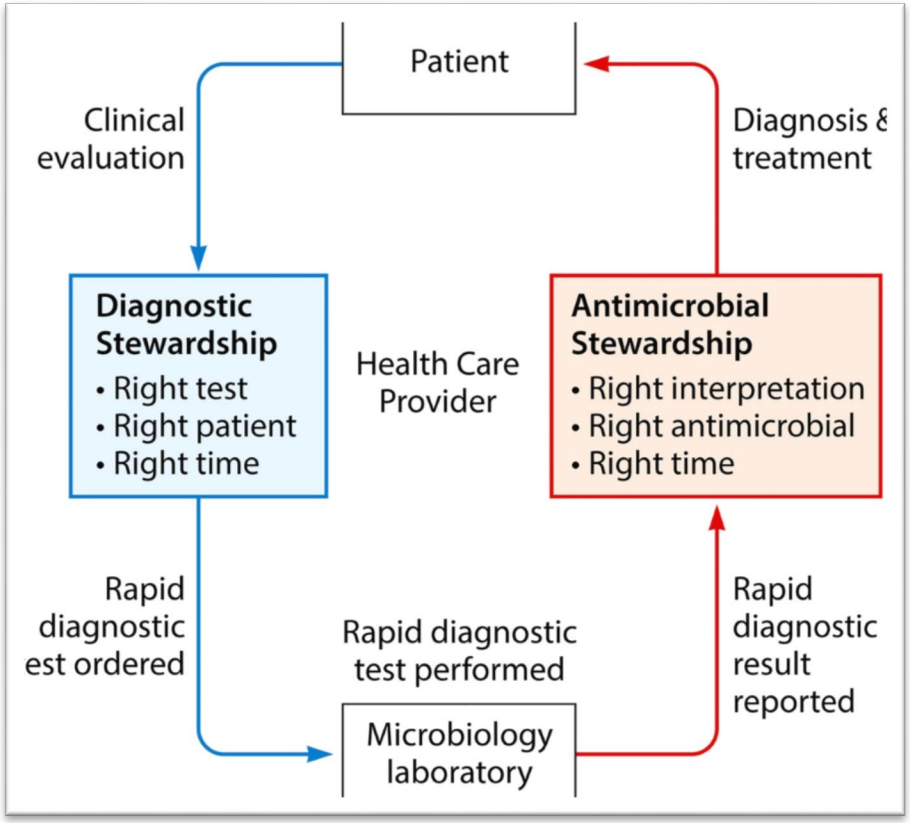
HOUSTON Methodist® LEADING MEDICINE

Diagnostic Stewardship

- Diagnostic Stewardship involves modifying the process of ordering, performing, and reporting diagnostic tests to improve the treatment of infections
  - Detection & identification
  - Clinical chemistry
  - Imaging
  - Pharmacokinetic/ pharmacodynamics
- Antibiotic use opportunities:
  - Inappropriate use or interpretation of microbiology
  - Lack of microbiology confirmed diagnosis
  - Failure to submit appropriate specimens for culture
  - Misuse of microbiology resources
  - Overreliance on empiric coverage regardless of microbiology results



REF: Messacar et al. *J Clin Microbiol*, 2017.

Essential Antimicrobial Stewardship Activities in the Microbiology Laboratory

- Provide timely, reliable, and reproducible identification and antimicrobial susceptibility results
- Optimize communication of critical test result values and alert systems
- Collaborate with ID pharmacists and physicians on updating methods for susceptibility testing
- Participate in the development, revise, and publicize antibiogram reports consistent with CLSI standards
- Provide guidance for adequate specimen collection

CLSI: Clinical Laboratory Standards Institute

Morency-Potvin P, et al. Clin Microbiol Rev. 2016;30:381-407.

Selective Reporting

Antimicrobial Stewardship in the Microbiology Laboratory: Impact of Selective Susceptibility Reporting on Ciprofloxacin Utilization and Susceptibility of Gram-Negative Isolates to Ciprofloxacin in a Hospital Setting

Intervention: Laboratory suppressed ciprofloxacin susceptibility to Enterobacteriaceae when there was susceptibility to other antibiotics on the Gram-negative panel

Outcome	Pre-intervention (2008-2010)	Intervention (2011-2015)
Ciprofloxacin utilization (DDD/1000 patient days)	87 (95% CI, 83.7 to 91.2)	39 (95% CI, 35 to 44)

Increase in use of amoxicillin-clavulanate was noted at 6 months and was sustained

E. coli susceptibility to ciprofloxacin improved significantly 12 months later ($p < 0.05$)

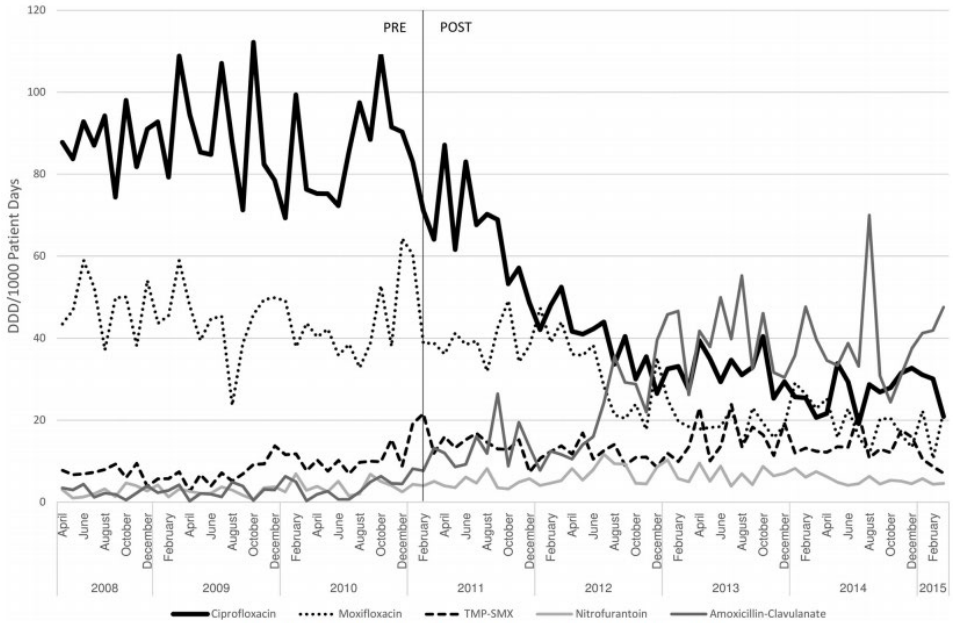
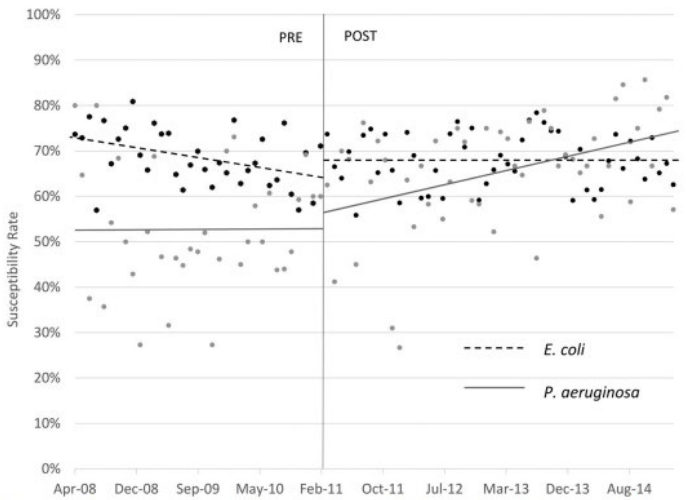


FIG 1 Antimicrobial utilization before and after ciprofloxacin selective reporting.



IG 2 *E. coli* and *P. aeruginosa* susceptibility to ciprofloxacin before and after selective susceptibility reporting.

Langford BJ, et al. J Clin Microbiol. 2016;54:2343-2347.

Behavioral Intervention

Microbiology Comment Nudge Improves Pneumonia Prescribing

Intervention: Respiratory cultures with no dominant organism growth and no *Pseudomonas* spp. or *Staphylococcus aureus* were reported by the clinical microbiology laboratory as:

Pre-Intervention Reporting:
"Commensal respiratory flora only"

Intervention Reporting:
"Commensal respiratory flora only:
No *S. aureus*/MRSA or *P. aeruginosa*"

Objective: De-escalation or discontinuation of anti-MRSA or anti-pseudomonal therapy

Design: quasi-experimental study conducted over 2 study periods: 6 month pre-intervention (Aug 2015 - Jan 2016) and 6 months following implementation of the intervention (Aug 2016 – Jan 2017)

Outcome	Pre-intervention (n=105)	Intervention (n=105)	P-value
De-escalation or discontinuation	39%	73%	<0.001
Acute kidney injury	31%	14%	0.003
All-cause mortality	30%	18%	0.052

- 5.5-fold increased odds of de-escalation (95% CI, 2.8-10.7)
- Duration of anti-MRSA and anti-pseudomonal therapy was reduced from 7 days to 5 days (p<0.001)
- No difference in ICU or hospital LOS

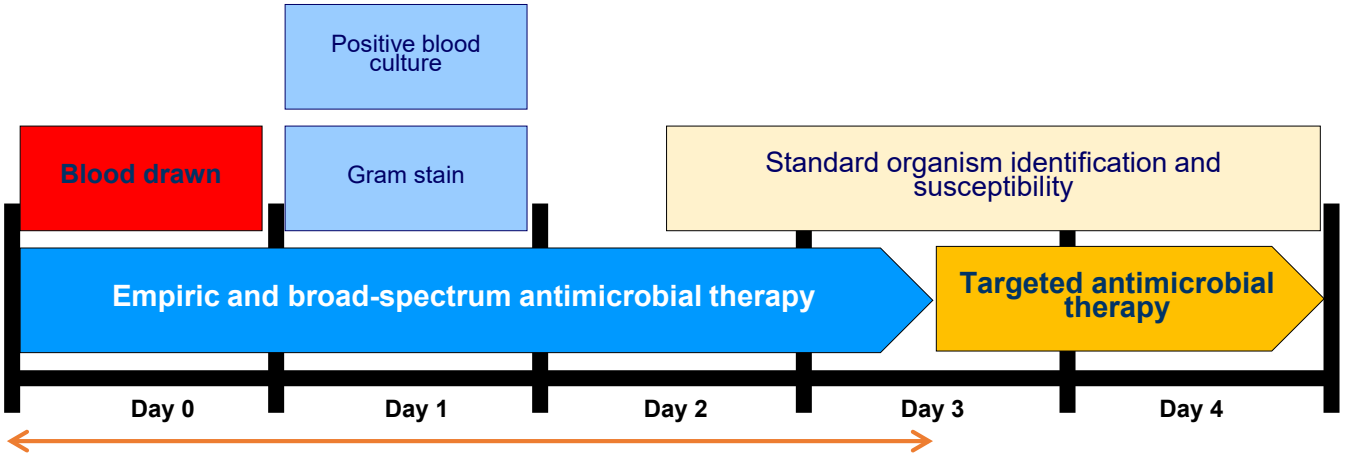
Musgrove MA, et al. Open Forum Infect Dis. 2018;5(7):ofy162.

Race Against Turnaround Time

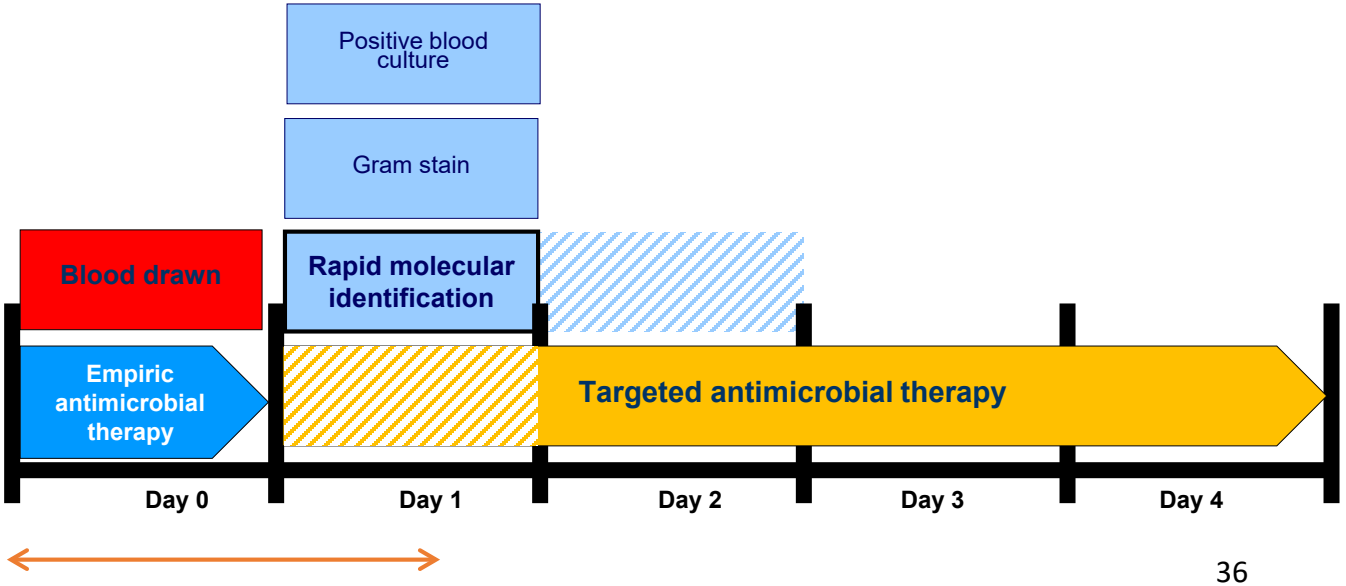
- Recent explosion of FDA-approved rapid diagnostic test (RDT) methodologies for infectious diseases
  - Role of RDT and biomarkers is recognized as a key recommendation for antimicrobial stewardship by the IDSA
- Emerging methods include a large variety of technologies
  - Complexity, price, speed, and ability to identify single or multiple pathogens vary greatly
- Major focus on disease states & pathogens associated with increased morbidity, mortality, & excessive healthcare costs
  - Including: bloodstream infections, respiratory tract infections, GI infections; influenza virus, MRSA, vancomycin-resistant *Enterococcus* spp. (VRE), *Clostridium difficile*, extended-spectrum β-lactamase (ESBL)- producing *Klebsiella* spp., carbapenemase-producing organisms, *M. tuberculosis,* and *Candida* spp.

Organism Identification and Initiation of Targeted Antimicrobial Therapy

Traditional Identification & Testing Methods:

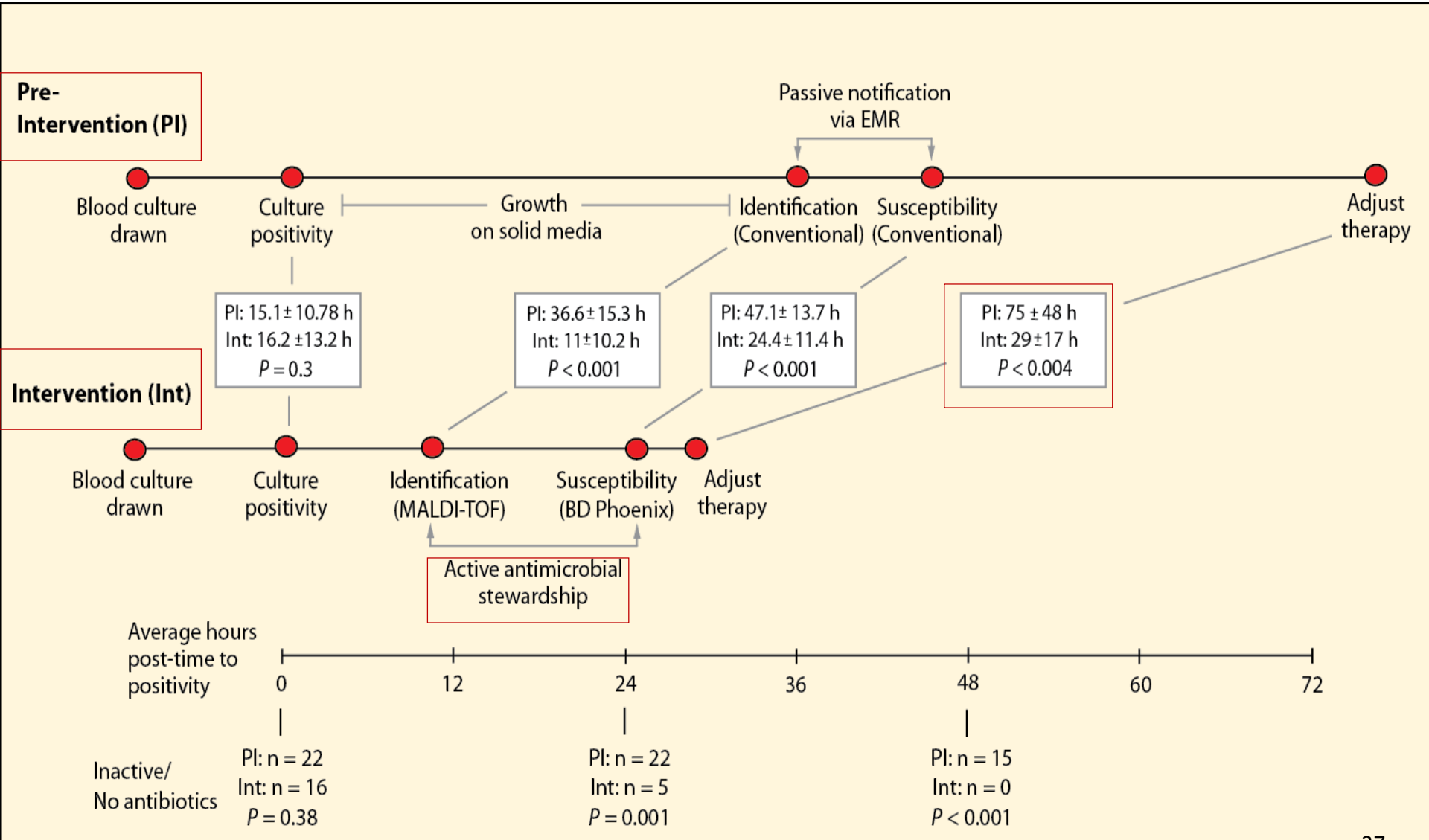


Rapid Molecular Identification Methods (Example: PCR):



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

Collaboration & Decision Making



Perez KK, et al. Arch Pathol Lab Med. 2013 Sep;137(9):1247-54

Examples of Process and Clinical Outcomes for Stewardship

Studies evaluating MALDI-TOF MS as part of antimicrobial stewardship						
	Nagel et al	**Huang et al**	**Wenzler et al**	**Perez et al**	**Lockwood et al**	**Beganovic et al**
Organisms/ Site of Infection	Coagulase-negative Staph BSI	Bacteria and yeast BSI	*Acinetobacter baumannii* LRTI	Gram-negative BSI	Gram-negative BSI	Bacterial BSI
Time to:						
Identification	**83.4 to 57 hrs***	**84 to 55.9 hrs***	**83 to 75 hrs***	**36.6 to 11 hrs*º**	**32 to 6.5 hrs*º**	MALDI-TOF MS during both study periods
Effective Antibiotics	37.7 to 23 hrs	**30.1 to 20.4 hrs***	**77.7 to 36.6 hrs***	**73 to 36.5 hrs***	Not reported	16.8 vs 12 hrs
Optimal Antibiotics	**58.7 to 34 hrs***	**90.3 to 47.3 hrs***	Not reported	**75 to 29 hrs***	**71 to 30 hrs***	**75 to 43 hrs***
ICU LOS (d)	28 vs 11	**14.9 vs 11.4***	17 vs 19	7.3 to 6.3	2.3 to 3.7	**4 .3 vs 1.2***
Hospital LOS (d)	14 vs 15	14.2 vs 11.4	**13 vs 11***	**11.9 vs 9.3***	6.4 vs 6.4	**15 vs 9***
Mortality	**21.7% vs 3.1%***	**20.3% vs 14.5%***	20% vs 25%	10.7% vs 5.6%	9.4% vs 4.9%	Not reported
Hospital costs per inpatient	Not reported	Not reported	$49,402 vs $42,872	**$45,709 vs $26,126***	**$18,644 vs $15,234***	**$28,677 vs $15,784***

Perez KK et al. Arch Pathol Lab Med. 2013;137:1247-54.
Huang AM et al. Clin Infect Dis. 2013;57:1237-45.
Wenzler E et al. Diagn Microbiol Infect Dis. 2016;84(1):63-68.

Nagel JL et al. J Clin Microbiol. 2014;52(8):2849-54.
Lockwood AM, et al. Infect Control Hosp Epidemiol. 2016;37(4):425-32.
Beganovic M, et al. J Clin Micro. 2017;55(5):1437-45.

*Statistically significant $p \leq 0.05$
° Direct from positive blood culture bottles
BSI: bloodstream infection
LTRI: lower respiratory tract infection

Directing Antibacterial Therapy for Resistant Bacteria – Stewardship Interventions

Table 2 Antimicrobial stewardship interventions.

Intervention	Number of recommendations at each timepoint		
	Organism identification via MALDI-TOF MS and reported to ID pharmacist ($n = 65$)	Antimicrobial susceptibility results reported to ID pharmacist ($n = 71$)	Total accepted (%)
Escalation or initiation of antibiotic therapy	33	30	61/63 (96.8)
Narrowed and/or tailored treatment for isolated pathogen	3	18	18/21 (85.7)
Discontinued antibiotics not targeting isolated pathogen	21	12	26/32 (81.3)
Optimized regimen based on administration or pharmacokinetics & pharmacodynamics	8	11	19/20 (95)
Accepted/Total (%)			124/136 (91.2)

- Factors: patient history, antibiotic exposures, and risk factors for MDR or ESBL-producing Gram-negative pathogens
  - Pre-intervention arm: 80.9 hrs vs Intervention arm: 23.2 hrs

Perez KK et al. J Infect. 2014;69:216-25.

Laboratory + ASP – Outcomes Measured

Study	Laboratory intervention	ASP intervention	Impact on time to laboratory results	Clinical impact
Forrest, et al. 2008	Rapid ID of enterococci (PNA FISH from positive blood culture bottle (BCx)	ASP daily follow-up	Final microbiology results 3 and 2.3 days earlier for *E. faecalis* and *E. faecium* infections, respectively	Significant reduction in 30-day all-cause mortality for *E. faecium* infection; faster time to appropriate antibiotics for *E. faecium* infections
Walker, et al. 2016	Rapid ID of Gram-negative organisms (multiplex PCR panel) from positive BCx	ASP pharmacist intervention	Organism ID reported 34 h earlier	Shorter length of ICU stay; significant reduction in 30-day all-cause mortality
Bauer, et al. 2010	Rapid ID of staphylococci with *mecA* detection (multiplex PCR panel) from positive BCx	ASP pharmacist intervention	Time to result not reported	Decreased overall hospital costs by ~$21,000 per patient; increased rate of antibiotic de-escalation
Sango, et al. 2013	Rapid ID of enterococci and *vanA*/*vanB* detection (multiplex PCR panel) from positive BCx	ASP intervention	AST result for vancomycin resistance reported 48 h earlier	Effective therapy started 23 h earlier; shorter length of hospital stay; decreased overall hospital costs by ~$58,000 per patient
Neuner, et al. 2016	Rapid ID and AST (multiplex PCR panel) for Gram-positives from positive BCx	ASP pharmacist intervention	Not reported	Decreased time to antimicrobial switch by 27 hr, time to de-escalation by 29 hr
Smith, et al. 2017	MRSA nasal PCR assay in ICU patients with nosocomial pneumonia	ASP daily follow up	Institutional protocol	Reduction of vancomycin by 2.1 days of therapy per patient; $108 per patient cost avoidance (vancomycin, drug monitoring, and surveillance testing)
Brumley, et al. 2016	Institutional CDI testing and surveillance	Real-time ASP team follow up with CDI management best practices	NA	Increased compliance with CDI management bundle (45% to 81%), improved appropriate CDI therapy (64% to 82%)

Forrest GN, et al. Antimicrob Agents Chemother. 2008;52:3558-3563.
Walker T, et al. J Clin Microbiol. 2016;54:1789-1796.
Smith MN, et al. J Crit Care. 2017;38:168-71.
Brumley PE, et al. J Antimicrob Chemother. 2016;71:836-40.
Bauer KA, et al. Clin Infect Dis. 2010;51:1074-1080.
Sango A, et al. J Clin Microbiol. 2013;51:4008-4011
Neuner EA, et al. Infect Control Hosp Epidemiol. 2016;37:1361-1366.

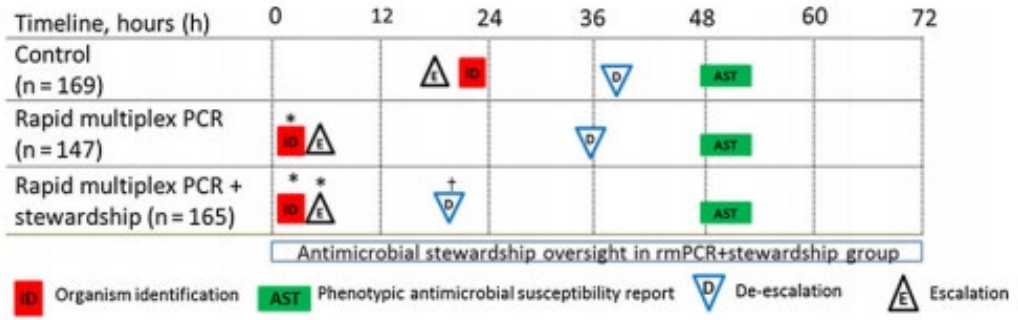
RDT + ASP Intervention

Randomized Trial of Rapid Multiplex Polymerase Chain Reaction-Based Blood Culture Identification and Susceptibility Testing

Intervention: Patients with positive blood cultures were randomized to standard processing, rmPCR (FilmArray Blood Culture ID Panel) results reported with template comments, or rmPCR results reported with template comments and real-time audit and feedback of antimicrobial therapy by the stewardship team

All groups (control, rmPCR, & rmPCR+ASP): MALDI-TOF MS for pathogen identification of colonies isolates from positive blood cultures

rmPCR assay detects Gram-positive bacteria, Gram-negative bacteria, Candida spp., mecA, vanA/B, and KPC directly from positive blood culture bottle specimens (no growth required)



Outcome from time of Gram-stain	Control (n=207)	rmPCR (n=198)	rmPCR + ASP (n=212)	P-value
Time to identification	22 h	1.3 h		<0.0001
Time to de-escalation (n=344)	34 h	38 h	27 h	<0.0001
Time to escalation (n=122)	24 h	6 h	5 h	0.04

- Time to first appropriate de-escalation, escalation was shortest with the ASP review.
- Increased use of narrow spectrum agents, earlier de-escalation for Gram-positive infections
- Decreased the potential for treatment of contaminated blood cultures

- No difference in LOS, mortality, or cost
- Antimicrobial stewardship intervention is required to fully realize the potential clinical impact of RDTs

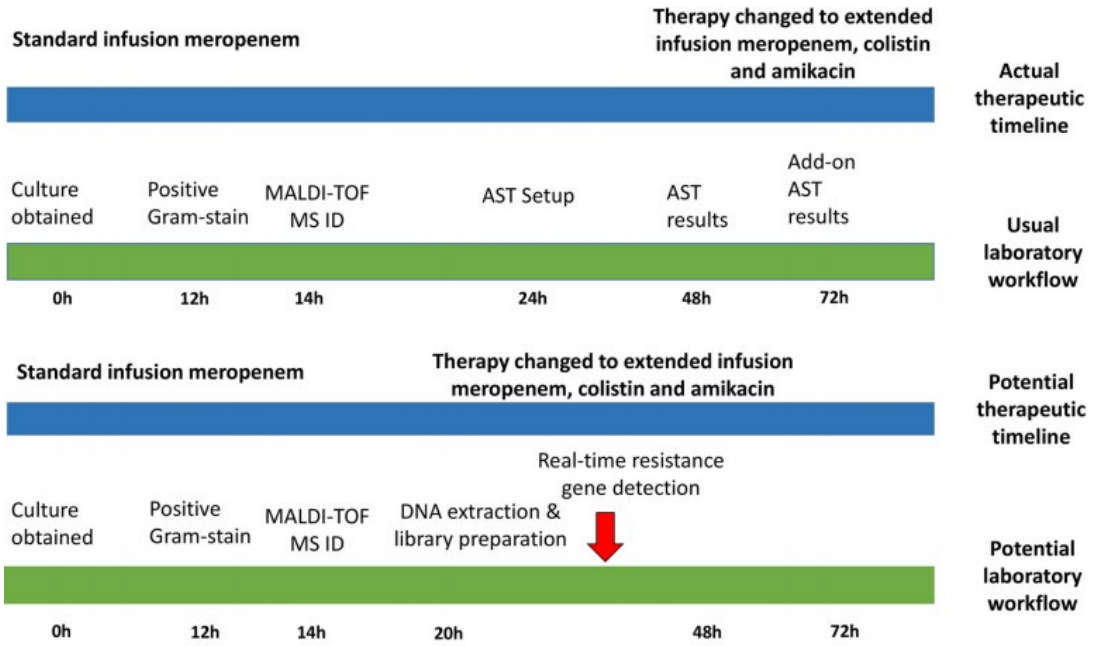
Banerjee R, et al. Clin Infect Dis. 2015;61(7):1071-80.

The Future State

Applying Rapid Whole-Genome Sequencing to Predict Phenotypic Antimicrobial Susceptibility Testing Results among Carbapenem-Resistant *Klebsiella pneumoniae* Clinical Isolates

Timeline comparing availability of organism identification and AST testing along with actual and anticipated antibiotic treatment decisions using standard approaches versus live-streaming whole genome sequencing data generated from Nanopore sequencing and assembly

Case: 64 year old liver transplant recipient with an NDM-1, CTX-M-15, and CMY-4 producing *Klebsiella pneumoniae* bacteremia



Tamma PD, et al. Antimicrob Agents Chemother. 2019;63(1):e01923-18.

First Things First…

- Collaborate with the clinical microbiology laboratory director(s) to identify the most (or "A") useful clinical laboratory result for your institution based on pathogen prevalence and/or targeted disease state
- **Grab someone from finance and quantify the cost burden based on frequency and hospital costs (even a rough estimate is useful!)**
- **Take inventory of resources available to support real-time RDT reporting and expectations**
  - Workflow changes for the microbiology staff (even if only during an electronic surveillance alert validation time frame)
  - Workflow changes to the ASP team – using the frequency data and the lab's reporting workflow, the ID pharmacist should be able to forecast a patients/week fairly accurately
- Changing culture – trust between clinicians and the ASP members is critical
  - Never underestimate the power of a "no-brainer" intervention!

Implementation & Evaluation

- Communication plan for result reporting from microbiology laboratory to the treating team by way of the ASP should be formally established
  - Consider a pilot period (3-6 months) – this will give everyone involved a better idea of the proposed resources are sufficient and time to work out any unknowns
- Close working relationship between the ASP team and microbiology laboratory necessary to keep everyone in the loop on workflow issues, even when it doesn't seem "necessary"
  - The microbiology laboratory technologists & the ASP pharmacist both play a vital role in communicating education for hospital providers to familiarize them with RDT and how it might impact patient outcomes… no one wants to be surprised!

Provider Education

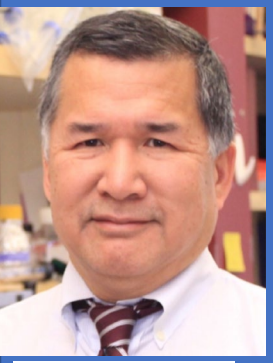
- Diagnostic methodology used
- Indications for testing in the institution
- Available alternative testing
- Advantages and limitations
- Associated costs
- Turnaround time
- Presentation of report and guidance on interpretation
- ASP intervention for optimal time to appropriate antibiotics

Post-Implementation

- Showcase the work (number of patients, number of interventions, time to appropriate antibiotics, etc.) & the “big picture” vision –
  - Start with the cost burden of what you’ve improved
  - Keep documentation as consistent as possible
  - **Make it a “deal”** & get in front of as many stakeholders as possible!
- Stay focused and methodical with any roll out, remain vigilant and critical of the data – allows for process improvement
- Prepare “how-to” materials, educational references, deliver workshops, in-services
  - Creates legacy for the program
  - Keeps the ASP team and microbiology lab staff engaged and friendly

Introduction to Diagnostic Stewardship

Questions and Comments



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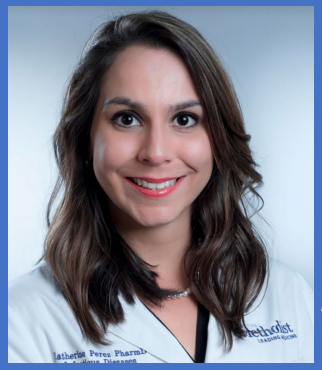

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SIDP
Society of Infectious Diseases Pharmacists