Role of the Hospital Laboratory in Antibiotic Stewardship

Presented by:

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June 19, 2019

Disclosures: none relevant to this topic

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Learning Objectives

After this webinar, you will be able to:

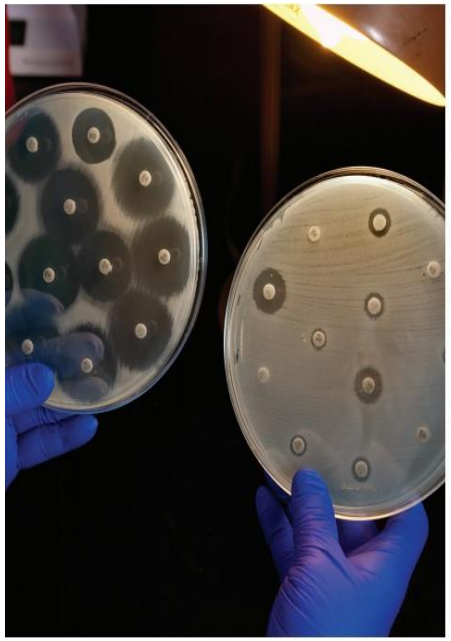
- List common strategies utilized by antibiotic stewardship programs in optimizing infectious diseases management.
- Define essential functions of the microbiology laboratory that support antibiotic stewardship programs.
- Identify issues relevant to the reporting of antimicrobial susceptibility testing results that significantly impact antibiotic use.

Outline

- **Antimicrobial Resistance**
- Antibiotic Stewardship Programs
- Antimicrobial Susceptibility Testing / Reporting
- Biomarkers
- Rapid Diagnostic Testing
- Diagnostic Stewardship

Impact of Antimicrobial Resistance and Misuse

- (CDC) > 2 million/yr are infected with antibiotic-resistant bacteria, and at least 23,000 people die as a result.
- Rates of inappropriate antibiotic use up to 50%
- Association of antibiotic use with resistance
- Negative treatment outcomes
  - Delays in appropriate therapy
  - Treatment failures
- Cost
  - Increased cost of care (treatment, length of stay)
- Adverse effects
  - Frequent cause of drug-related ER visits, *C. difficile* infection



https://www.cdc.gov/ncezid/pdf/two-pagers/NCEZID-antibiotic-resistance-2pgr-H.pdf

 https://www.cdc.gov/drugresistance/about.html (accessed 6/5/19)

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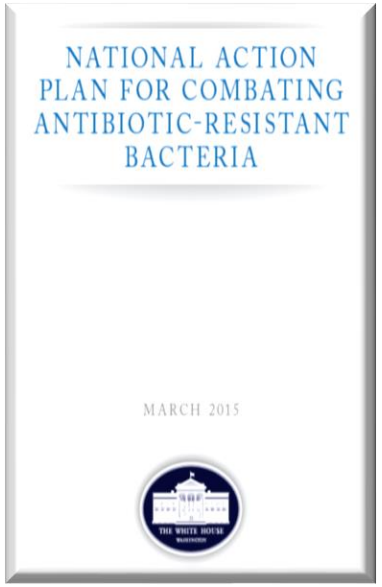
By the Numbers:
Why Microorganisms Have the Advantage

Variable	Humans	Microbes	Factor
No. on earth	6×10^{9}	5×10^{31}	10^{22}
Mass (metric tons)	3×10^{8}	5×10^{16}	10^{8}
Generation time	20-30 years	30 minutes	10^{5}
Time on earth (yrs)	4×10^{6}	3.5×10^{9}	10^{3}

"If you total up all of the.. cells in the human body it is about 10^{12}.. If you total up the number of bacteria in a human colon, it comes to 10^{14} cells. So when you really think about it, we are 9 parts bacteria and 1 part human. So when you give an antibiotic you are administering a compound that is highly toxic to 90% of your body."

Table (modified) from Spellberg B, et al. *Clin Infect Dis* 2008;46:155-64.
Quote from L.B. Rice (Am J Med. 2006; 119:S62-70)

Antibiotic Drug Resistance: National / Global Response



https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf
http://apps.who.int/iris/bitstream/10665/163468/1/9789241564946_eng.pdf?ua=1&ua=1

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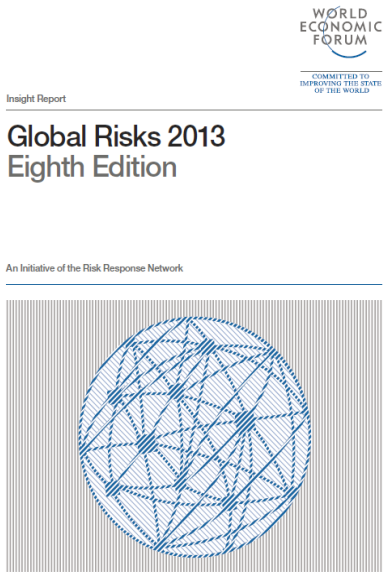
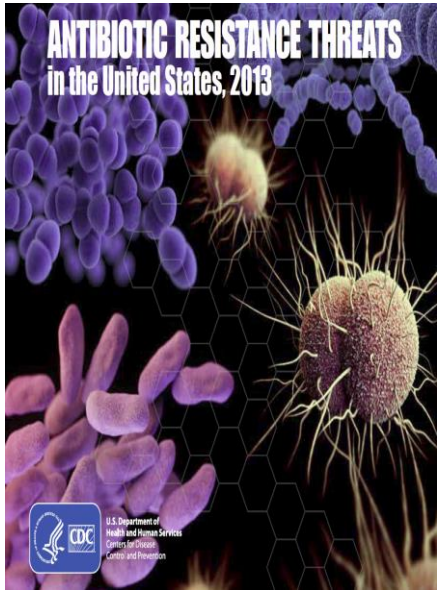
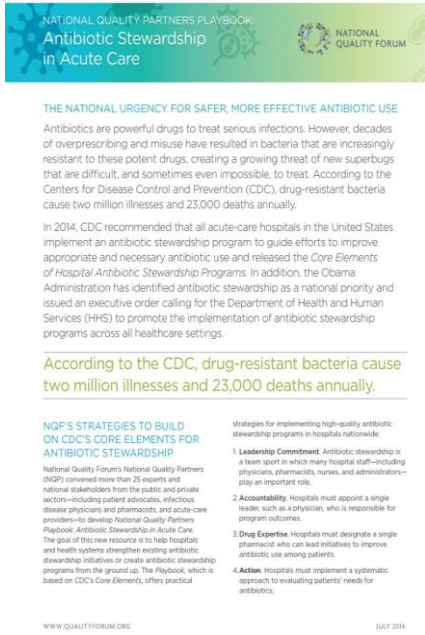


Howell L, ed. Global risks 2013, Eighth edition: an initiative of the Risk Response Network. World Economic Forum, 2013



http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf



https://store.qualityforum.org/collections/antibiotic-stewardship/products/national-quality-partners-playbook%E2%84%A2-antibiotic-stewardship-in-post-acute-and-long-term-care-1

"……arguably the greatest risk . . . to human health comes in the form of antibiotic-resistant bacteria. We live in a bacterial world where we will never be able to stay ahead of the mutation curve. A test of our resilience is how far behind the curve we allow ourselves to fall." http://reports.weforum.org/global-risks-2013 (accessed 7/17/15)

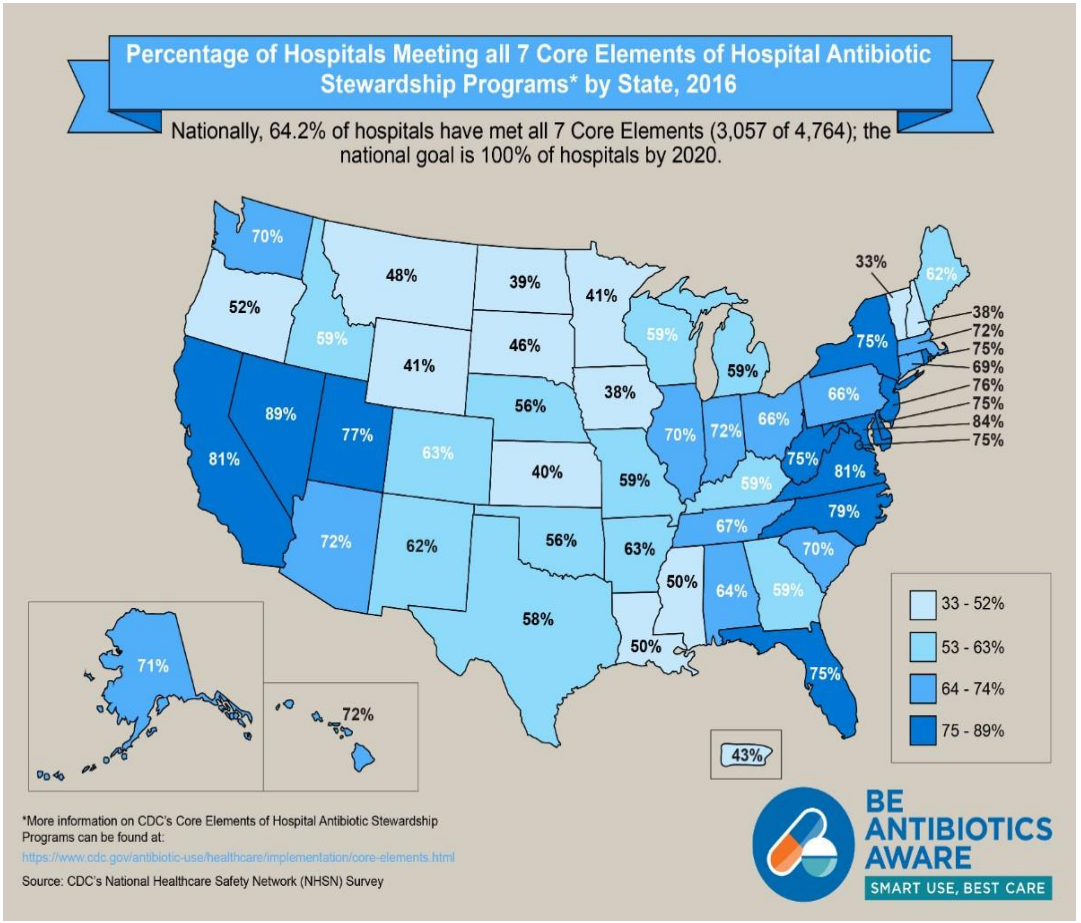
Outline

- Antimicrobial Resistance
- **Antibiotic Stewardship Programs**
- Antimicrobial Susceptibility Testing / Reporting
- Biomarkers
- Rapid Diagnostic Testing
- Diagnostic Stewardship

CDC: Core Elements of Antibiotic Stewardship Programs (ASPs)

Element	Description
Leadership commitment	Dedicating necessary human, financial, and IT resources
Accountability	Appointing a single leader responsible for program outcomes
Drug expertise	Appointing a single pharmacist leader responsible for working to improve antibiotic use
Action	Implementing at least one recommended action with the goal of improving antimicrobial use
Tracking	Monitoring antibiotic prescribing and resistance patterns
Reporting	Regular reporting of information on antibiotic use and resistance to doctors, nurses, and relevant staff
Education	Educating clinicians about resistance and optimal prescribing

Centers for Disease Control and Prevention. 2014. Core elements of hospital antibiotic stewardship programs. Centers for Disease Control and Prevention, Atlanta, GA:http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html



https://www.cdc.gov/antibiotic-use/community/images/materials/2016-Percentages-B.jpg (accessed 6/4/19)

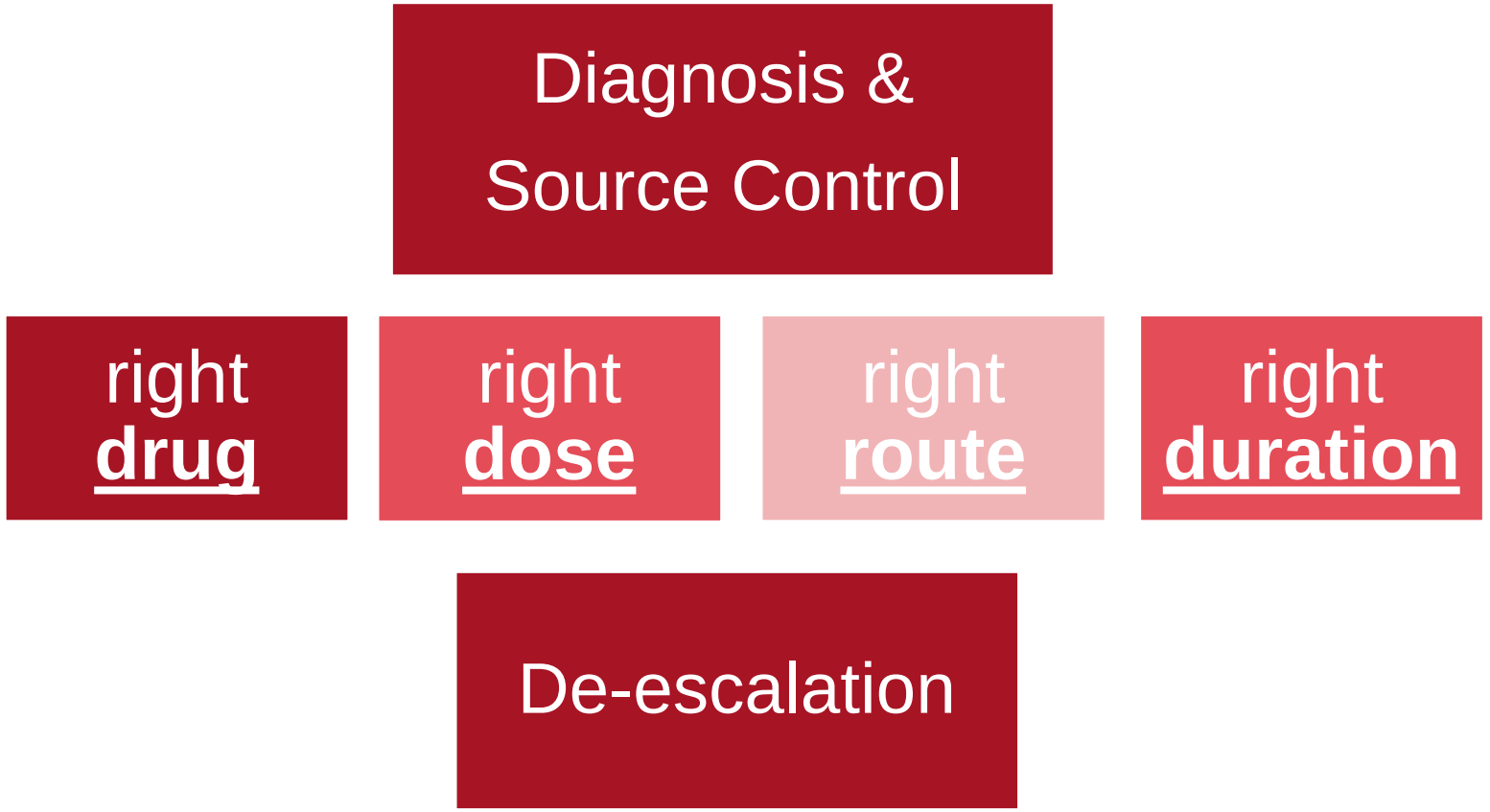
ASP: Team Members

- Infectious diseases physician
- Clinical pharmacist with infectious diseases training
- Clinical microbiologist
- Information system specialist*
- Infection preventionist /Hospital epidemiologist
- Quality assurance/Patient safety manager*
- Hospital leadership*

*may serve as ad hoc members

Image from https://www.ctsrecruitment.co.uk/blog/how-to-create-a-great-team-ethos-in-your-care-home/

Antimicrobial Stewardship



Barlam TF, et al. Clin Infect Dis. 2016;62(10):e51-77.
Morency-Potvin P et al. Antimicrob Agents Chemother 2017;30: 381-407

Antibiotic Stewardship Programs: Strategies to Optimize Use

- Antibiotic “time-out”
- Preauthorization /Restriction programs
- Prospective Audit and feedback
- Treatment guidelines/order sets
- Education
- Novel dosing strategies (ex. prolonged infusions of beta-lactams, consolidated daily dosing of aminoglycosides)
- De-escalation
- IV-to-PO
- Allergy reconciliation (ex. penicillin skin testing)
- Therapeutic drug monitoring
- Automatic stop orders

Clinical Infectious Diseases

IDSA GUIDELINE

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1,a] Sara E. Cosgrove,[2,a] Lilian M. Abbo,[3] Conan MacDougall,[4] Audrey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenkins,[12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A. Ohl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]

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Evidence-based guidelines for implementation and measurement of antibiotic stewardship interventions in inpatient populations including long-term care were prepared by a multidisciplinary expert panel of the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. The panel included clinicians and investigators representing internal medicine, emergency medicine, microbiology, critical care, surgery, epidemiology, pharmacy, and adult and pediatric infectious diseases specialties. These recommendations address the best approaches for antibiotic stewardship programs to influence the optimal use of antibiotics.

Keywords. antibiotic stewardship; antibiotic stewardship programs; antibiotics; implementation.

EXECUTIVE SUMMARY

Antibiotic stewardship has been defined in a consensus statement from the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) as “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration” [1]. The benefits of antibiotic stewardship include improved patient outcomes, reduced adverse events including *Clostridium difficile* infection (CDI), improvement in rates of antibiotic susceptibilities to targeted antibiotics, and optimization of resource utilization across the continuum of care. IDSA and SHEA strongly believe that antibiotic stewardship programs (ASPs) are best led by infectious disease physicians with additional stewardship training.

Summarized below are the IDSA/SHEA recommendations for implementing an ASP. The expert panel followed a process used in the development of other IDSA guidelines, which included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (Figure 1) [2–5]. A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found online in the full text of the guidelines. For the purposes of this guideline, the term antibiotic will be used instead of antimicrobial and should be considered synonymous.

Received 22 February 2016; accepted 23 February 2016; published online 13 April 2016.

*T. F. B. and S. E. C. contributed equally to this work as co-chairs.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant clinician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the clinician in the light of each patient’s individual circumstances

RECOMMENDATIONS FOR IMPLEMENTING AN ANTIBIOTIC STEWARDSHIP PROGRAM

Interventions

I. Does the Use of Preauthorization and/or Prospective Audit and Feedback

Barlam TF et al. Clin Infect Dis 2016;62(10):e51–e77

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Recommended Micro Lab Activities to Support ASPs

- Timely, accurate **identification with selective and cascade reporting** of antibiotic susceptibility testing (consistent with CLSI standards)
- Stratified **antibiograms** by location or age
- **Surveillance** of unusual patterns of resistance
- Guidance of **sample collection and transport**
- **Rapid viral testing** for respiratory pathogens
- **Rapid diagnostic testing*** (if combined with active ASP support and interpretation)
- Serial **PCT measurements** to decrease antibiotic use in adults in ICUs with suspected infection
- Nonculture-based fungal biomarkers in patients with hematologic malignancy at risk of contracting invasive fungal disease

PCT, procalcitonin
*in addition to conventional culture and routine reporting on blood specimens
Barlam T et al. Clin Infect Dis 2016:62: 1197–1202.
Morency-Potvin P et al. Antimicrob Agents Chemother 2017;30: 381-407

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Outline

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Issues in Antibiotic Susceptibility Reporting

- MIC vs interpretation (S/I/SDD/R)
- Cascading results (? site of infection)
- Supplemental testing for new drugs
  - Ex. reflexive susceptibility testing of the newer BL/BLI antibiotics upon identification of CRE
- Clinical vs surveillance cultures
- “Research only” testing
- Interim (preliminary results)
- Supplemental messaging

Susceptibility

	Acinetobacter baumannii complex	
	MIC (Preliminary)	ETEST SUCEPTIBILITY (Preliminary)
Amikacin	R	
Ampicillin + Sulbactam	I	
Cefazolin		
Ceftazidime	R	
Ciprofloxacin	R	
Clindamycin		
Colistin		S
Doxycycline		
Erythromycin		
Gentamicin	R	
Levofloxacin	R	
Meropenem	R	
Minocycline		R
Nafcillin		
Tetracycline		
Tobramycin	R	
Trimethoprim + Sulfamethoxazole	R	

Shifting Interpretive Breakpoints: Carbapenems Then (2009) and Now (2017)

Agent	2009 breakpoints M100-S19 MIC (µg/ml)			2017 breakpoints M100–27‡ MIC (µg/ml)		
	S	***I***	***R***	***S***	***I***	***R***
Doripenem	–	–	–	≤1	2	≤4
Ertapenem	≤2	4	≥8	≤0.5	1	≥2
Imipenem	≤4	8	≥16	≤1	2	≥4
Meropenem	≤4	8	≥16	≤1	2	≥4

I: Intermediate; MIC: Minimum inhibitory concentration; R: Resistant; S: Susceptible

Deshpande LM, Jones RN, Fritsche TR, Sader HS Microb Drug Resist. 2006 Winter; 12(4):223-30
Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 27th M100. Clinical and Laboratory Standards Institute; PA, USA: 2017
(modified) from Enyinnaya F et al. Future Sci OA. 2017 Nov; 3(4): FSO245. doi: 10.4155/fsoa-2017-0095

CLSI-recommended comments on micro reports

- Surrogate testing
- Resistance mechanism
- Diagnosis issues
- Specialist consultation
- Duration of therapy
- Culture interpretation
- Reference to documentation
- Suggestions for alternatives
- Selective or cascade susceptibility reporting
- Reference to antimicrobial stewardship program services
- Dosing recommendations
- Probable contamination or colonization
- Nonstandard methods or lack of interpretation criteria
- New interpretation criteria
- Public health reporting
- Infection control recommendations
- Cost of tested antimicrobials
- Indication of preferred agents according to local guidelines

SURROGATE TESTING: Cefazolin results predict results for oral agents cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef when used for therapy of uncomplicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*

TREATMENT: Rifampin should not be used alone for antimicrobial therapy in infections with *Staphylococcus* or *Streptococcus* spp.

ALTERNATIVES: In our institution, clindamycin is the preferred agent used to treat this pathogen in patients with IgE-mediated allergy to penicillin

DOSING: Use of penicillins or third-generation cephalosporins for pneumococcal meningitis requires therapy with maximum doses

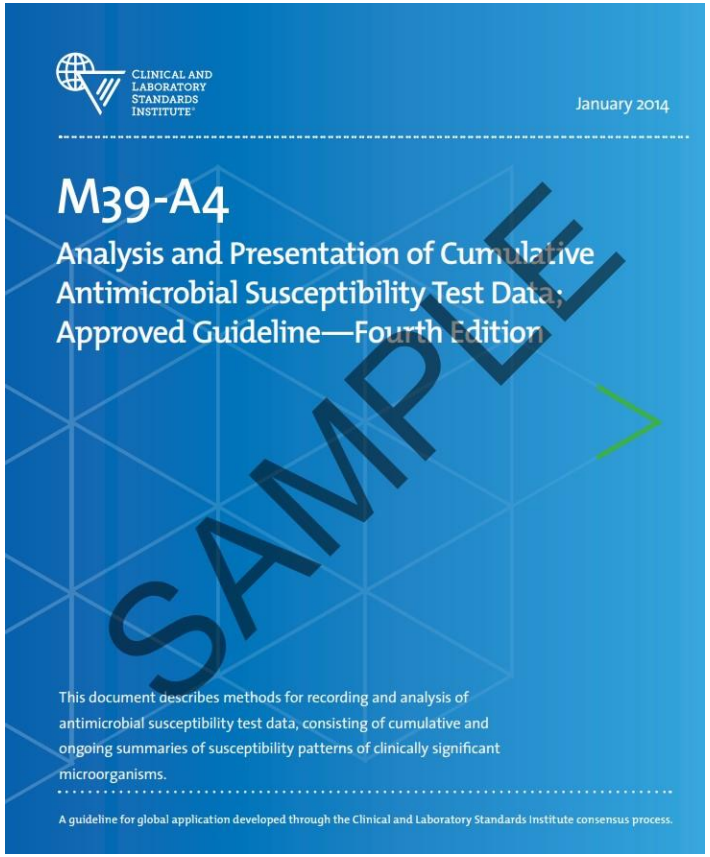
INTERPRETATION: Gram stain and culture of this specimen represent normal skin flora

COMBINATIONS: Combination therapy with ampicillin, penicillin, or vancomycin (for susceptible strains) plus an aminoglycoside is usually indicated for serious enterococcal infections such as endocarditis unless high-level resistance to both gentamicin and streptomycin is documented; such combinations are predicted to result in synergistic killing of the *Enterococcus*

CLSI, Clinical Laboratory and Standards Institute
Morency-Potvin P et al. Antimicrob Agents Chemother 2017;30: 381-407

Cumulative Antimicrobial Susceptibility Reporting CLSI M39-A4 recommendations

- Analyze and present at least annually
- Include only final, verified results
- Include only species with results for 30 isolates
- Include only diagnostic (not surveillance) isolates
- Eliminate duplicate isolates by including only first species' isolate/patient/period of analysis
- Include only routinely tested agents
- Report % S and exclude % I
- For *Streptococcus pneumoniae*, report data for both meningitis and nonmeningitis breakpoints
- For viridans group streptococci, report both % S and % I
- For *S. aureus*, report % S for all isolates and MRSA subset



https://clsi.org/media/1454/m39a4_sample.pdf

Clinical and Laboratory Standards Institute. 2014. M39-A4 analysis and presentation of cumulative antimicrobial susceptibility test data; approved guideline—fourth edition. Clinical and Laboratory Standards Institute, Wayne, PA.

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TABLE 2. Gram-negative Bacilli (non-urine sources[a]), Percent Susceptible

	Beta-lactams (MIC breakpoint, µg/ml)								Aminoglycosides (MIC breakpoint, µg/ml)			Other Antimicrobials (MIC breakpoint, µg/ml)	
Microorganism (No. tested)	AMP	AMP-SUL	CFZ	CAZ	CTX	CPM	MER	PIP-TAZ	GEN	AMK	TOB	CIP	T-S
Enterobacteriaceae breakpoints	(8)	(8/4)	(2)	(4)	(1)	(2)	(1)	(16/4)	(4)	(16)	(4)	(1)	(2/38)
Non-fermenter breakpoints*				(8)	(8)	(8)	(2)	(16/4)	(4)	(16)	(4)	(1)	(2/38)
Non-fermenter exception breakpoint**							(4)**						
Acinetobacter spp. (48)*	R	94	R	83	65	85	96	N	**83**	95	91	83	85
Achromobacter xylosoxidans/denitrificans (78) **	R	N	R	66	3	32	77	86	9	17	11	31	68
Burkholderia cepacia complex (27)**[b]	R	R	R	50	R	N	**75**	R	R	R	R	R	68
Citrobacter freundii complex (30)[c]	R	R	R	83	77	97	100	90	97	97	97	93	90
Citrobacter koseri (22)[b]	R	100	95	100	100	100	100	100	100	100	100	100	100
Enterobacter aerogenes (48)	R	R	R	69	67	94	98	83	100	100	100	100	100
Enterobacter cloacae/asburiae (181)	R	R	R	73	63	87	99	82	97	100	97	96	87
Escherichia coli (489)	40	48	57	90	87	89	100	95	88	99	85	53	68
Klebsiella oxytoca (47)	R	**57**	15	91	78	91	100	83	91	98	87	94	83
Klebsiella pneumoniae (238)	R	78	78	92	91	92	99	93	95	100	94	92	84
Morganella morganii (26)[b]	R	8	R	85	88	96	100	96	96	100	100	88	96
Proteus mirabilis (110)	90	96	71	100	99	100	100	100	92	99	92	84	87
Pseudomonas aeruginosa (692)*	R	R	R	84	R	80	82	85	76	85	89	72	R
Serratia marcescens (122)	R	R	R	69	72	95	100	75	100	100	96	96	98
Stenotrophomonas maltophilia (167)*	R	R	R	52	R	N	R	R	R	R	R	R	96

Numbers in boldface: ≥10% decrease in susceptibility from previous year.

[a] Non-urine sources include blood, respiratory, tissue, wound, and CSF.
[b] Calculated from fewer than the standard recommendation of 30 isolates.

from SUMMARY OF ANTIMICROBIAL SUSCEPTIBILITY TEST RESULTS. Duke University Medical Center. 2018

Combination Antibiograms: Example

123 non-duplicate *P. aeruginosa* isolates from 99 adult oncology patients

Beta-lactam ($n = 123$)	Monotherapy (%)	Amikacin (%)	Tobramycin (%)	Ciprofloxacin (%)	Colistin[a] (%)
Aztreonam	74.0	95.9[b]	92.7[b]	82.9	88.2[b]
Cefepime	74.8	94.2[b]	90.2[b]	79.7	85.3[b]
Ceftazidime	79.7	96.7[b]	92.7[b]	84.6	91.2[b]
Imipenem-cilastatin	72.4	94.2[b]	90.2[b]	78.0	73.5
Meropenem	77.2	94.2[b]	90.2[b]	80.5	79.4
Piperacillin-tazobactam	76.4	95.0[b]	91.1[b]	82.1	88.2[b]

[a]Only 34 isolates tested for colistin susceptibilities.
[b]Met study definition for an effective combination.

Smith ZR. J Onc Pharm Pract. 2016.
https://doi.org/10.1177/1078155215586081

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Biomarkers of Infection

	Specific to infection	Sensitive for inflammation	Advantages	Comments
Fever	+	++++	Simple Sensitive to infection	
White blood cell (WBC)	+	+++	Simple Sensitive to infection	
Cytokines	+	+++	Sensitive to infection Rapid induction	Short half life High variability Expensive
C-reactive Protein (CRP)	++	++	Inexpensive	Slow induction time (peak >24 h) Low biologic range No correlation with severity of inflammation
Procalcitonin (PCT)	++++	+	Rapid induction (2 h) High biostability (half-life 24 h) wide biologic range	Low sensitivity for local infections Time-dependent utility Best for antibiotic discontinuation

(modified) from Reinhart K et al. Crit Care Clin 2006;22:503-519.

Procalcitonin

- Upregulated in epithelial cells encountering bacterial pathogens and down-regulated in viral infections
- Timeline
  - Rises 3-6hrs and peaks 12-24hrs after bacterial infection
  - Declines up to 50% per day with appropriate treatment and remains elevated otherwise
- Application
  - Supports decisions on duration of antibacterial treatment
  - (2016) guidelines for pneumonia[1] sepsis[2] and antibiotic stewardship[3] cite limited evidence for treatment initiation

Schuetz P et al. Clin Chem Lab Med 2019. https://doi.org/10.1515/cclm-2018-1181. Schuetz P et al.Cochrane Database Syst Rev. 2017;10:CD007498.
1, Kalil AC, et al.. Clin Infect Dis. 2016 Jul. [ePub ahead of print]. 2. Surviving Sepsis 2016. 3. Barlam TF et al. Clin Infect Dis 2016;62(10):e51–e77

Table. Associations of Procalcitonin Testing With Clinical Outcomes and Antibiotic Use

	Procalcitonin Group (n = 3336)	Control Group (n = 3372)	Between-Group Difference (95% CI)	Adjusted OR (95% CI)[a]	*P* Value
Clinical Outcomes					
30-d mortality, No. (%)	286 (8.6)	336 (10.0)		0.83 (0.70 to 0.99)	.04
Treatment failure, No. (%)[b]	768 (23.0)	841 (24.9)		0.90 (0.80 to 1.01)	.07
Length of ICU stay, median (IQR), d	8.0 (4.0 to 17.0)	8.0 (4.0 to 17.0)	0.39 (−0.81 to 1.58)		.52
Length of hospital stay, median (IQR), d	8.0 (2.0 to 17.0)	8.0 (2.0 to 17.0)	−0.19 (−0.96 to 0.58)		.63
Antibiotic-related adverse effects, No./total (%)	247/1513 (16.3)	336/1521 (22.1)		0.68 (0.57 to 0.82)	.001
Antibiotic Exposure					
Rates for initiation of antibiotics, No./total (%)	2351/3288 (71.5)	2894/3353 (86.3)		0.27 (0.24 to 0.32)	.001
Duration of antibiotics, median (IQR), d	6.0 (4.0 to 10.0)	8.0 (6.0 to 12.0)	−1.83 (−2.15 to −1.50)		.001
Total exposure of antibiotics, median (IQR), d	5.0 (0 to 8.0)	7.0 (3.0 to 11.0)	−2.43 (−2.71 to −2.15)		.001

Abbreviations: ICU, intensive care unit; IQR, interquartile range; OR, odds ratio.

[a] Multivariable hierarchical regression with outcome of interest as dependent variable, age and type of respiratory tract infection as independent variables, and trial as a random effect.

[b] For the primary care setting, treatment failure was defined as death, hospitalization, acute respiratory tract infection–specific complications (eg, empyema, meningitis), recurrent or worsening infection, and participants reporting any symptoms of an ongoing respiratory tract infection (eg, fever, cough, dyspnea) at follow-up. For the emergency department setting, treatment failure was defined as death, ICU hospitalization, rehospitalization after index hospital discharge, acute respiratory tract infection–associated complications (eg, empyema or acute respiratory distress syndrome), and recurrent or worsening infection within 30 days of follow-up. For the ICU setting, treatment failure was defined as death within 30 days of follow-up.

Schuetz P et al. JAMA 2018;319:925-926
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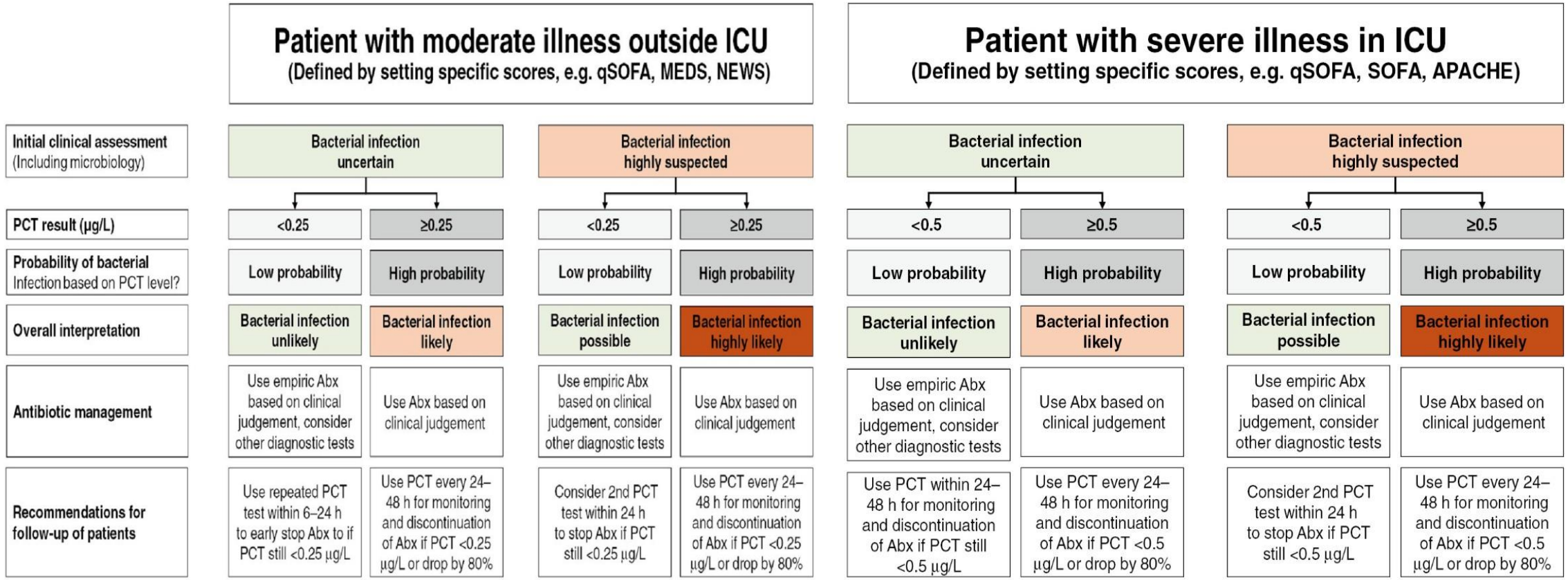
Procalcitonin: Considerations for Use

- Patient populations
  - Best studied in patients with acute respiratory infections and sepsis from any source
  - Limited data in pregnancy, newborns (<72 hours), severely immunocompromised patients , chronic infections (endocarditis, osteomyelitis), cystic fibrosis, continuous renal replacement therapy
- Timing
  - Baseline and daily (thru day 7 or until micro data establishes definitive dx)
- Interpretation considerations
  - Patient population: indication (RTI vs sepsis), severity and/or likelihood of infection
  - Nonbacterial elevations: severe trauma, severe burns, cardiac surgery, pulmonary edema or prolonged cardiogenic shock, fungal/parasitic disease, thyroid cancer, pancreatitis, ischemic bowel disease, chemical pneumonitis, ESRD , alemtuzumab (CD52 antibody), granulocyte transfusions, interleukin 2, rituximab (anti-CD20 antibody), T-cell antibodies
  - Low PCT in the presence of infection: early infection (4-6 hours), localized infection, prior antibiotics, subacute bacterial endocarditis/osteomyelitis

Schuetz P et al. Clin Chem Lab Med 2019. https://doi.org/10.1515/cclm-2018-1181
1, Kalil AC, et al.. Clin Infect Dis. 2016 Jul. [ePub ahead of print]. 2. Surviving Sepsis 2016. 3. Barlam TF et al. Clin Infect Dis 2016;62(10):e51–e77

Procalcitonin Algorithm: Example



* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis)

Schuetz P et al. Clin Chem Lab Med 2019. https://doi.org/10.1515/cclm-2018-1181

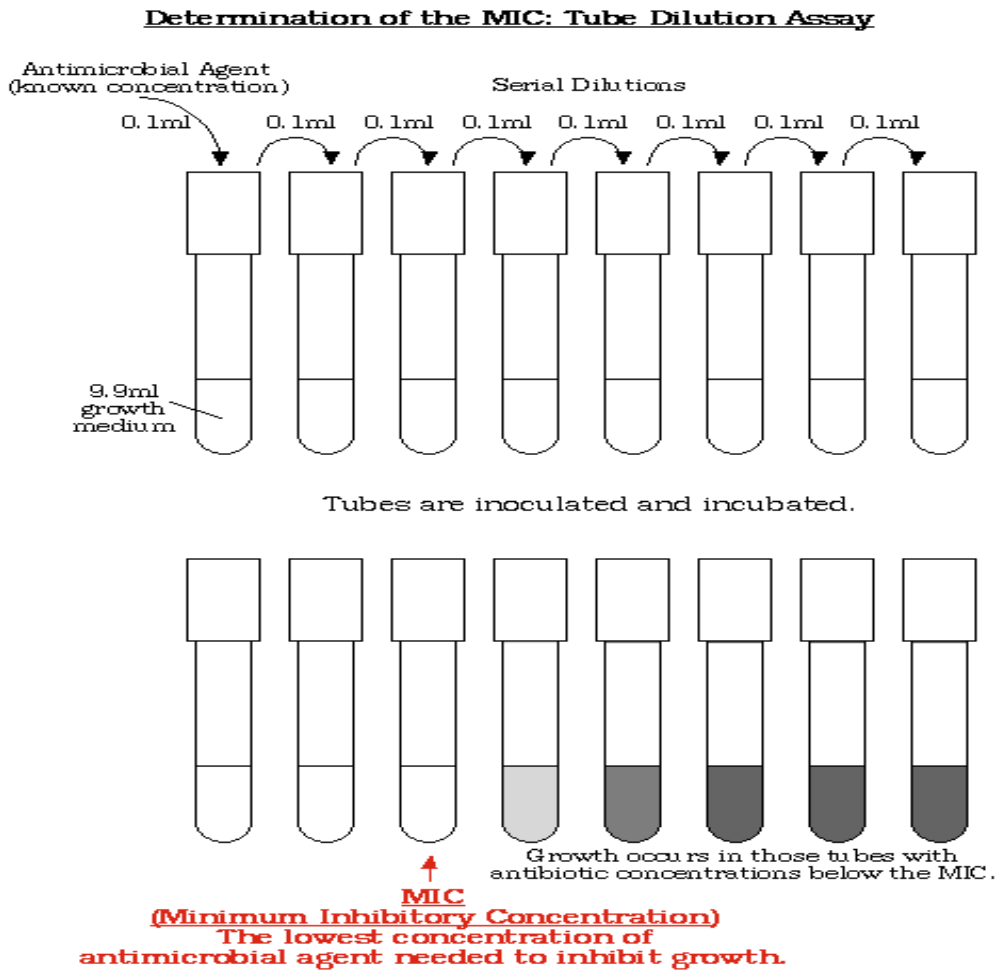
Outline

- Antimicrobial Resistance
- Antibiotic Stewardship Programs
- Antimicrobial Susceptibility Testing / Reporting
- Biomarkers
- **Rapid Diagnostic Testing**
- Diagnostic Stewardship

- “….. at the beginning of the 21st century, a high proportion of diagnostic tests are still performed according to methodologies pioneered by Pasteur at the end of the 19th century, i.e. methods based on culture….”

Bissonnette L et al. Clin Microbiol Infect 2010; 16: 1044–1053

In Vitro Susceptibility Testing



Antibiotic Susceptibility Testing

	Phenotype	Genotype
Question addressed	What is the minimum concentration of drug that inhibits growth (MIC)?	Is a gene present that predicts drug resistance?
Speed	Slow(er)-days	Quick-hours
Inoculum requirement	Large (er)	Small(er)
Mechanism of resistance impacting test	No	Yes (directed testing only)
Degree of resistance (MIC)	Yes	No
Examples	Broth microdilution Etest Disk diffusion Accelerate PhenoTest™	Biofire®

*Accelerate PhenoTest ™ results ≤ 12hrs ≤12 hrs after blood culture Gram stain

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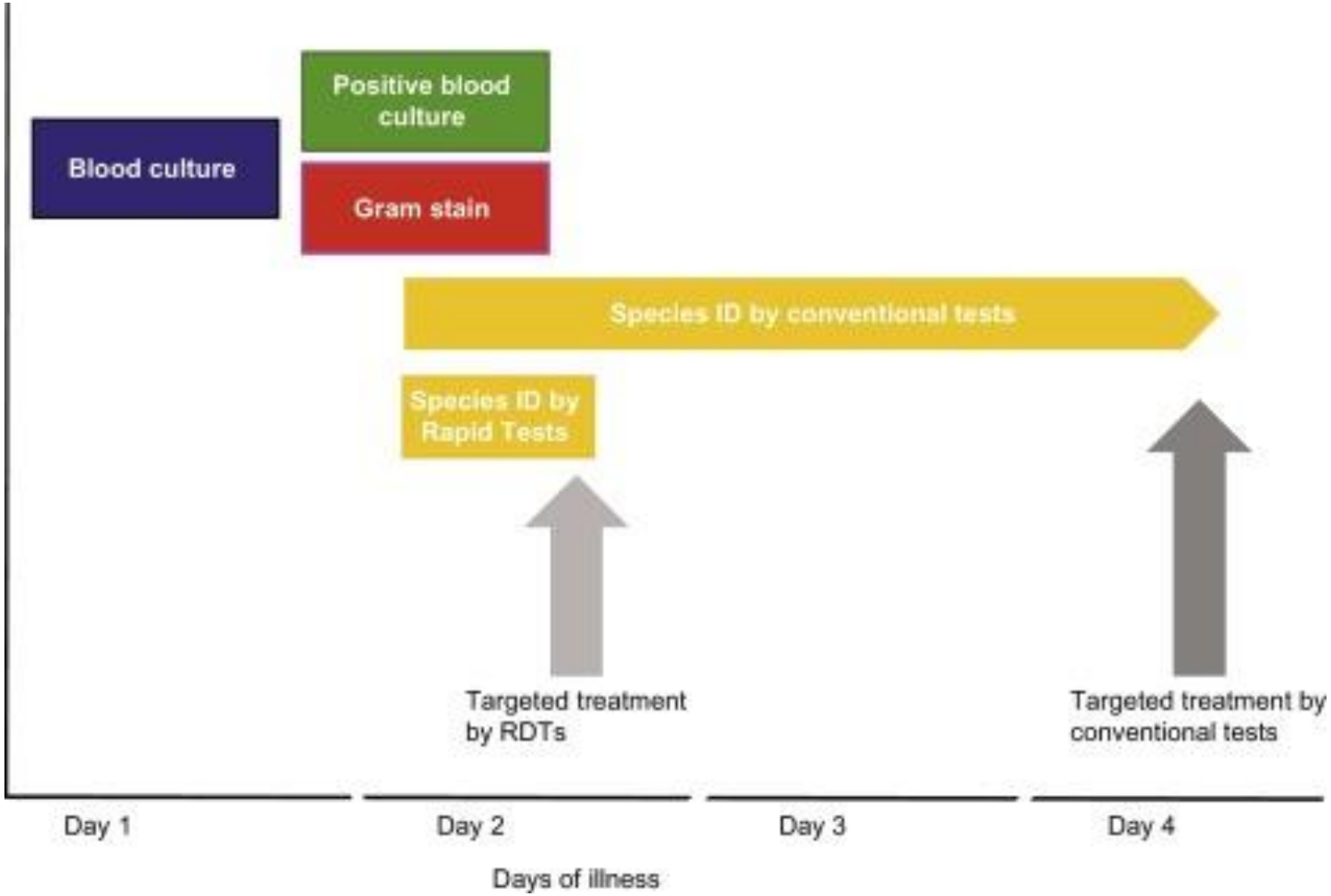
Organism Identification and Initiation of Targeted Antibiotic Treatment



(modified) from Füsun Can, Onur Karatuna. The Role of Microbiology Laboratory in Promoting Antimicrobial Stewardship.Antimicrobial Stewardship. Academic Press 2017, Pages 115-128.

Example of final micro report utilizing phenotypic and genotypic testing methods

Susceptibility

	Klebsiella pneumoniae		
	MIC	CARBAPENEMASE GENE ASSAY-LAB ONLY	KB SUSCEPTIBILITY
Amikacin	S		
Ampicillin	R		
Ampicillin + Sulbactam	R		
Cefazolin	R[1]		
Cefepime	R		
Ceftazidime	R		
Ceftazidime/Avibactam			R
Ceftolozane/Tazobactam			R
Ceftriaxone	R		
Cefuroxime	R		
Ciprofloxacin	R		
Ertapenem	R[2]		
Gentamicin	S		
Imipenem	R		
Meropenem	R		
Nitrofurantoin	R		
Piperacillin/Tazobactam	R		
Tetracycline	R		
Tobramycin	R		
Trimethoprim + Sulfamethoxazole	R		
z-IMP gene		Not Detected	
z-KPC gene		DETECTED	
z-NDM gene		Not Detected	
z-OXA48 gene		Not Detected	
z-VIM gene		Not Detected	

[1] Cefazolin results predict results for oral agents cephalexin,cefaclor,cefdinir,etc.

[2] Carbapenem Intermediate or Resistant, consult Infectious Diseases Services

FDA-Approved RDTs

Technology	Manufacturer, Trade Name	Syndrome Testing	Targets	Need Pure Colony	Resistance gene	Time to result (h)
PNA-FISH	AdvanDx, PNA-FISH	Blood	1-15	No	mecA	0.3-1.5 for ID; 7 for AST
	Accelerate PhenoTest; PNA-FISH with morphokinetic cellular analysis				NA Phenotypic AST	
PCR or LAMP	GeneOhm, StaphSR	Blood	1	No	mecA	2
	Cepheid, Xpert MRSA/SA BC					1
	BD MAX	GI	4			0.5-2
	Gen-Probe Prodesse	GI, Respiratory	3-4			
	Meridian Bioscience, Illumigene	GI (*Clostridium difficile* only)	1			
	BD GeneOhm, Cdiff Assay					
	Cepheid, Xpert C difficile		1-2			
MALDI-TOF MS	bioMerieux, MALDI-TOF	Any	Database of bacterial and fungal organisms	Yes	None	0.5
	Brucker, MALDI-TOF					
Multiplex array panel	BioFire, FilmArray	Blood, GI, respiratory	14-27	No	mecA, vanA/B, KPC	1
	Verigene, Luminex		1-16		mecA, vanA/B, CTX-M, IMI, VIM, KPC, NDM, OXA	2
Nuclear Magnetic Resonance	T2 Biosystems, T2 Candida, T2Bacteria	Whole Blood	3-5	No		3-5

PNA-FISH: Peptide Nucleic Acid Fluorescence in situ Hybridization; PCR: Polymerase Chain Reaction; LAMP: Loop-Mediated Isothermal Amplification; MALDI—TOF MS: Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry; Table is not all inclusive of available products and technologies

(with permission) prepared by Ed Septimus, MD, FACP, FIDSA, FSHEA
Harvard Medical School & Harvard Pilgrim Health Care Institute

Clinical Impact of Rapid Diagnostic Tests

- **Lower mortality risk** with mRDT* (odds ratio [OR], 0.66; 95% confidence interval [CI], .54–.80).
- **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).

Meta-analysis of 31studies including 5920 patients

	mRDT		Conventional Testing				
Study or Subgroup	Events	Total	Events	Total	Weight, %	OR (95% CI)	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)	
Ly et al [31] (2008)	8	101	17	101	4.2	0.43 (.17–1.04)	
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: $z = 2.18$ ($P = .03$)

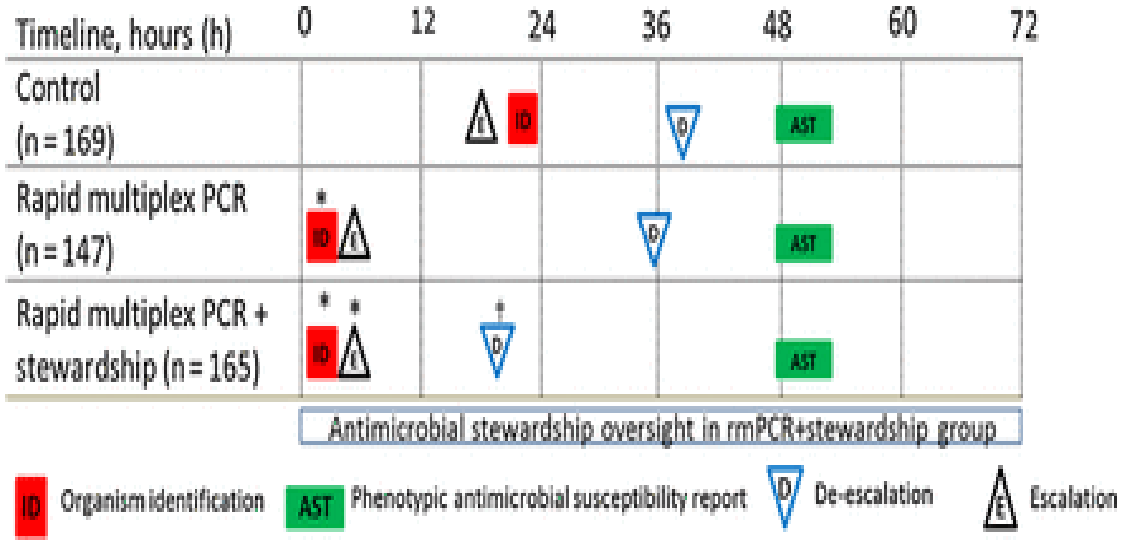
*relative to conventional microbiology
ASP, antibiotic stewardship programs; mRTD, microbiologic rapid diagnostic tests
Timbrook TT et al. Clin Infect Dis 2017;64:15–23

Rapid multiplex PCR for Positive Blood Culture: Benefit or Bust?

Trial of rmPCR detection of bacteria, fungi, and resistance genes directly from positive BCs (n=617)

- Patients randomized into 3 arms:
  - standard BCB processing
  - rmPCR reported with templated comments
  - rmPCR reported with templated comments + real-time audit and feedback by an AST
- Results
  - gram-positive bacteria 54.8% , gram-negative bacteria 32.6%; Candida species 2%, multiple organisms 10.5% , contaminants 29.2%
  - no difference in mortality, LOS, or cost.

Time to identification, susceptibility, and modification of therapy



"Time from Gram stain to appropriate antimicrobial de-escalation or escalation was shortest in the rmPCR/AS group (P < .001)

Perhaps just as important was **escalation: rmPCR/AST 5 hours, control 24 hours, rmPCR 6 hours, *P* = .04).**

AST, antimicrobial stewardship team
BCB, blood culture bottle; rmPCR, rapid multiplex PCR
Banergee R et al. Clin Infect Dis 2015;61:1071–1080

Rapid Identification from Positive Blood Culture: Biofire BCID

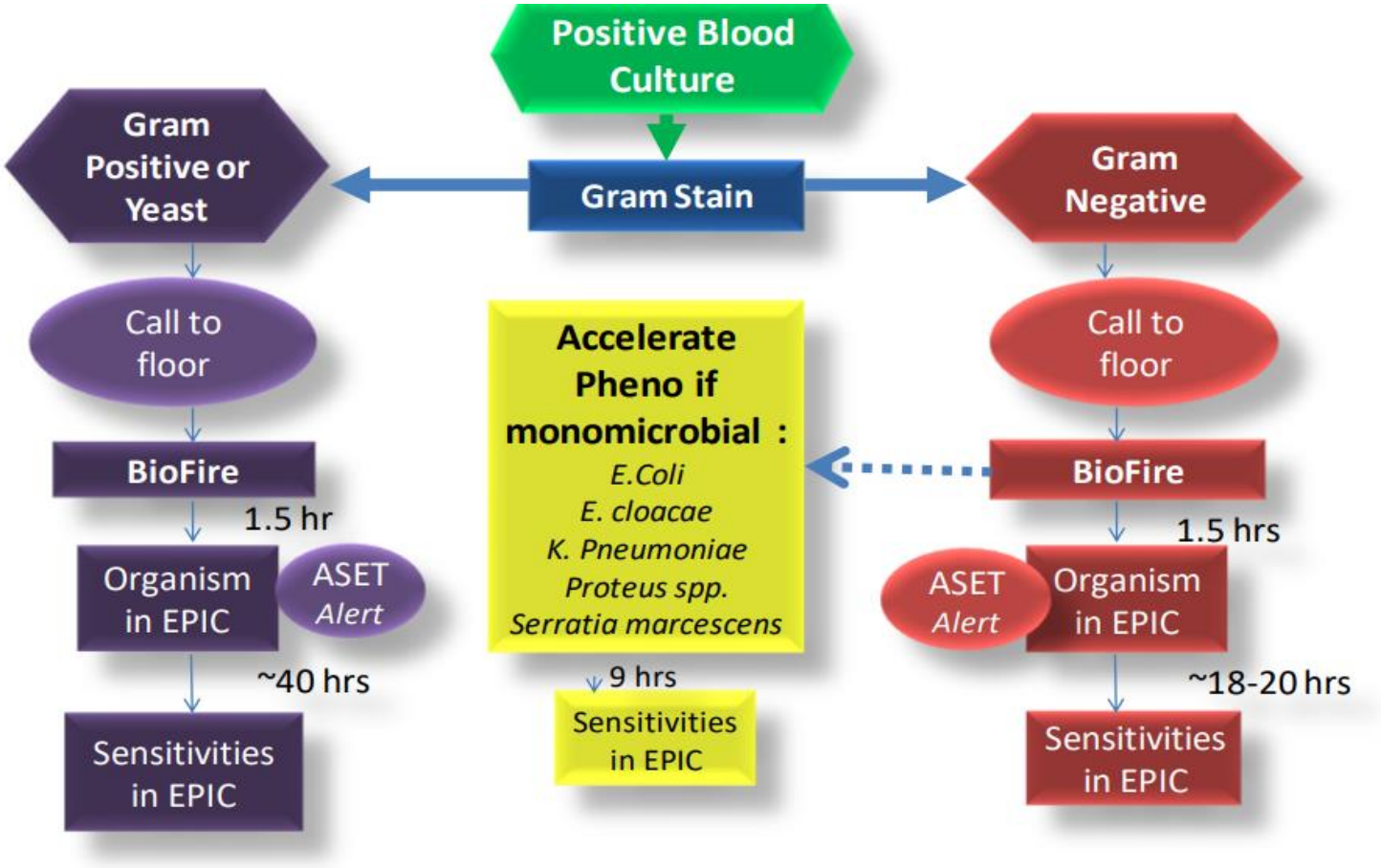
- 27 molecular targets on limited pathogens (inc. Gram-negative*)
- ~ 2hr after gram stain
- Remember!
  - Sensitivities NOT performed (requires subculture)
  - A negative BioFire BCID result means the culture is positive, but the pathogen is likely not one of the 27 tested targets

Biofire BCID for Gram-Positive Organisms

Gram Stain Result	BCID group target	BCID Pathogen target	BCID Gene Target	Display	1st Line Empiric Antibiotic	2nd Line Empiric Antibiotic
Gram positive cocci clusters OR Gram positive cocci pairs and chains	*Enterococcus*	none	none	Enterococcus species	Vancomycin†	Daptomycin*
			Van A/B	Enterococcus species (VRE)	Daptomycin*	Linezolid
	Staphylococcus	none[4]	none	Staphylococcus coagulase negative mecA gene NOT detected. Staphylococcus species is NOT Methicillin resistant	Cefazolin	Vancomycin†
			mecA	Staphylococcus coagulase negative mecA gene DETECTED. Staphylococcus species is METHICILLIN RESISTANT	Vancomycin	Daptomycin*
		Staphylococcus aureus	none	Staphylococcus aureus mecA gene NOT detected. Staphylococcus species is NOT Methicillin resistant	Cefazolin	Vancomycin†
			mecA	Methicillin Resistant Staphylococcus aureus mecA gene DETECTED. Staphylococcus species is METHICILLIN RESISTANT	Vancomycin	Daptomycin*
	Streptococcus	*Streptococcus agalactiae*	----	Streptococcus agalactiae, group B	Penicillin	Ceftriaxone or vancomycin†
		Streptococcus pneumoniae	----	Streptococcus pneumoniae	Ceftriaxone	Vancomycin
		Streptococcus pyogenes	----	Streptococcus pyogenes, group A	Penicillin	Ceftriaxone or vancomycin†
		none[5]	----	Streptococcus species	Ceftriaxone	Vancomycin†
	none	none	----	Gram stain result Organism not identified by rapid BioFire FilmArray Blood Culture (BCID) panel	Vancomycin	Linezolid* or daptomycin*
Gram positive rod	none	*Listeria monocytogenes*	----	Listeria monocytogenes	Ampicillin	SMP/TMX
	none	none	----	Gram stain result Organism not identified by rapid BioFire FilmArray Blood Culture (BCID) panel	Vancomycin -If high suspicion for Nocardia (e.g. immunosuppressed host), consult ID for empiric treatment recommendation	

*not included in the example
(modified) from Duke CustomID (accessed 5/6/19)

Workflow Example



(with permission) prepared by Rebekah Wrenn, PharmD from Duke CustomID (accessed 6/5/19)

Outline

- Antimicrobial Resistance
- Antibiotic Stewardship Programs
- Antimicrobial Susceptibility Testing / Reporting
- Biomarkers
- Rapid Diagnostic Testing
- **Diagnostic Stewardship**

Diagnostic Stewardship to Support ASPs: Implementation

Key question	Key considerations and potential strategies
Is the test appropriate for the clinical setting?	Sensitivity and specificity
	Predictive values
	Testing volumes
	Diagnostic yield
	Laboratory feasibility
	Cost
	Clinical impact
Will the clinical care of the patient be affected by the test result?	Laboratory test utilization committee
	Automatic laboratory reflex
	CPOE decision support
	Appropriate use criteria
	Indication selection
	Prior authorization
	Benchmarking
	Specimen rejection
Will the result be available in time to optimally affect care?	Time to specimen receipt
	Centralized vs point-of-care testing
	On-demand vs batched testing
	Specimen preparation time
	Run time
	Result reporting time

Messacar K et al. J Clin Microbiol 2017;55:715-723

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Diagnosing Infectious Diseases: Points of Importance

- Appropriate type and labeling of specimens (avoidance of swabs except nasopharynx)
- Specimen timing prior to antibiotics
- Reporting only relevant/significant pathogens, not “everything that grows” or commensal microbiota
- Compliance with established laboratory procedures
- Collaborative policies with medical staff

Clinical Infectious Diseases

IDSA GUIDELINE

A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology[a]

J. Michael Miller,[1] Matthew J. Binnicker,[2] Sheldon Campbell,[3] Karen C. Carroll,[4] Kimberle C. Chapin,[5] Peter H. Gilligan,[6] Mark D. Gonzalez,[7] Robert C. Jerris,[7] Sue C. Kehl,[8] Robin Patel,[2] Bobbi S. Pritt,[2] Sandra S. Richter,[9] Barbara Robinson-Dunn,[10] Joseph D. Schwartzman,[11] James W. Snyder,[12] Sam Telford III,[13] Elitza S. Theel,[2] Richard B. Thomson Jr,[14] Melvin P. Weinstein,[15] and Joseph D. Yao[2]

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Contents

Miller JM et al. CID 2018:67:e1-e94

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Avoiding unnecessary antibiotic treatment: Asymptomatic Bacteriuria and Reflex Urine Cultures

- ASB=presence > 1 species of bacteria in urine at specified quantitative counts (≥105 colony-forming units [CFU]/mL or ≥108 CFU/L),irrespective of the presence of pyuria, in the absence of signs or symptoms attributable to urinary tract infection (UTI)
- Screening / treatment for ASB is not recommended (except in pregnancy and before an invasive urological procedure)
- Urinalysis should precede culture. Urine with >10 WBC/HPF should have a urine culture ONLY IF PATIENT HAS SYMPTOMS.
- Ordering system should contain decision support prior to reflex test
  - Need to define indication for testing
    - Presence of symptoms consistent with UTI (fever, acute hematuria, flank pain, delirium, rigors, pelvic discomfort, urgency, frequency, dysuria, suprapublic pain) AND
    - Alternate diagnoses does not explain symptoms
  - Criteria for reflex urine culture from urinalysis
    - Patient-specific (neutropenics vs transplant vs urology patients) ??
    - WBC cutoff (>10 WBC/hpf)
    - Other diagnostic criteria (nitrite, blood) ???

ASB, asymptomatic bacteriuria

Cortes-Penfield NW et al. Infect Dis Clin North Am. 2017; 31(4): 673–688
Nicolle LE et al. Clin Infect Dis 2019;XX(XX):1–28

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Diagnostic Stewardship: *C. difficile* Testing

- Clinical criteria
  - Clinically significant diarrhea (3 or more unformed stools samples within 24hr)
  - (if applicable) Allow at least 48 hours without laxatives to reassess
- Specimen
  - Only watery or unformed loose stool should be submitted (Bristol 7)
- Testing method
  - Stool toxin test as part of a multistep algorithm (ie, glutamate dehydrogenase [GDH] plus toxin; GDH plus toxin, arbitrated by nucleic acid amplification test [NAAT]; or NAAT plus toxin)
  - No repeat testing (within 7 days) during the same episode of diarrhea
- Interpretation
  - Testing to evaluate for cure is not recommended
  - PCR does not distinguish colonization versus infection

McDonald C et al. Clin Infect Dis 2018;66:e1–e48.

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The Bottom Line

- Hospital laboratories essential team member in antibiotic stewardship programs
- Important dialogue needed with ASPs regarding testing and reporting methods
- Exciting developments in rapid diagnostic testing
- Growing need for diagnostic stewardship evident

Miller JM et al. CID 2018:67:e1-e94

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Questions?

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