CONSIDERATIONS IN UTI DETECTION AND POTENTIAL IMPACT ON ANTIBIOTIC STEWARDSHIP

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LEARNING OBJECTIVES

- Describe the traditional and advanced methods for diagnosing UTIs and their impact on patient care
- Examine how the inappropriate use of antibiotics to treat UTIs has led to increased antibiotic resistance
- Discuss the effects of UTI diagnosis and treatment on healthcare dollars, time, and patient outcomes

OUTLINE

- Clinical context
- Current diagnostic testing
- Over-treatment and antimicrobial resistance
- Emerging methods for UTI diagnosis
- Potential impact of emerging methods on antimicrobial stewardship

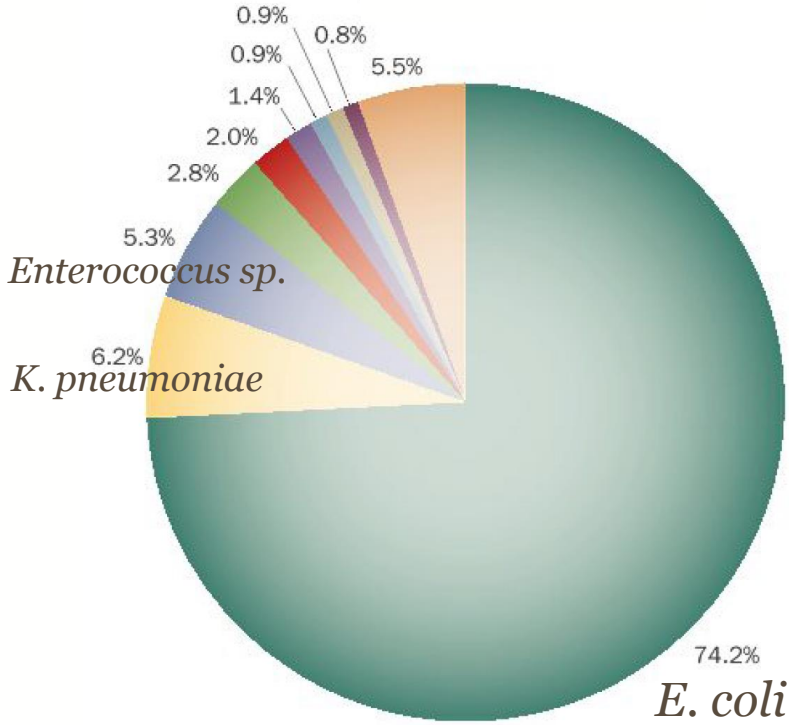
URINARY TRACT INFECTIONS

- A leading cause of health care visits
  - Estimated >8 million adult health care visits
  - Estimated >1 million pediatric visits
  - Estimated >$3 billion in annual health care spending in the US
  - Lifetime risk of ~50% for women
- Leading cause of nosocomial infection
  - Catheter-associated UTIs in long-term care facilities and hospitals

Hooton, *NEJM*, 366 (11), 2012
Griebling, *J Urol*, 173 (4), 2005

URINARY TRACT INFECTIONS

- A leading cause of antibiotic prescriptions
  - Prevent pyelonephritis, urosepsis
- Empiric therapy for uncomplicated cystitis
  - Selection may depend upon local antibiogram
- Culture-guided therapy for pyelonephritis
- Culture-guided therapy for complicated UTI



Foxman, *Nat Rev Urol* 7(12) 2010

Gupta et al, *CID* 52(5) 2011
Hooten et al, *CID* 50(5) 2010

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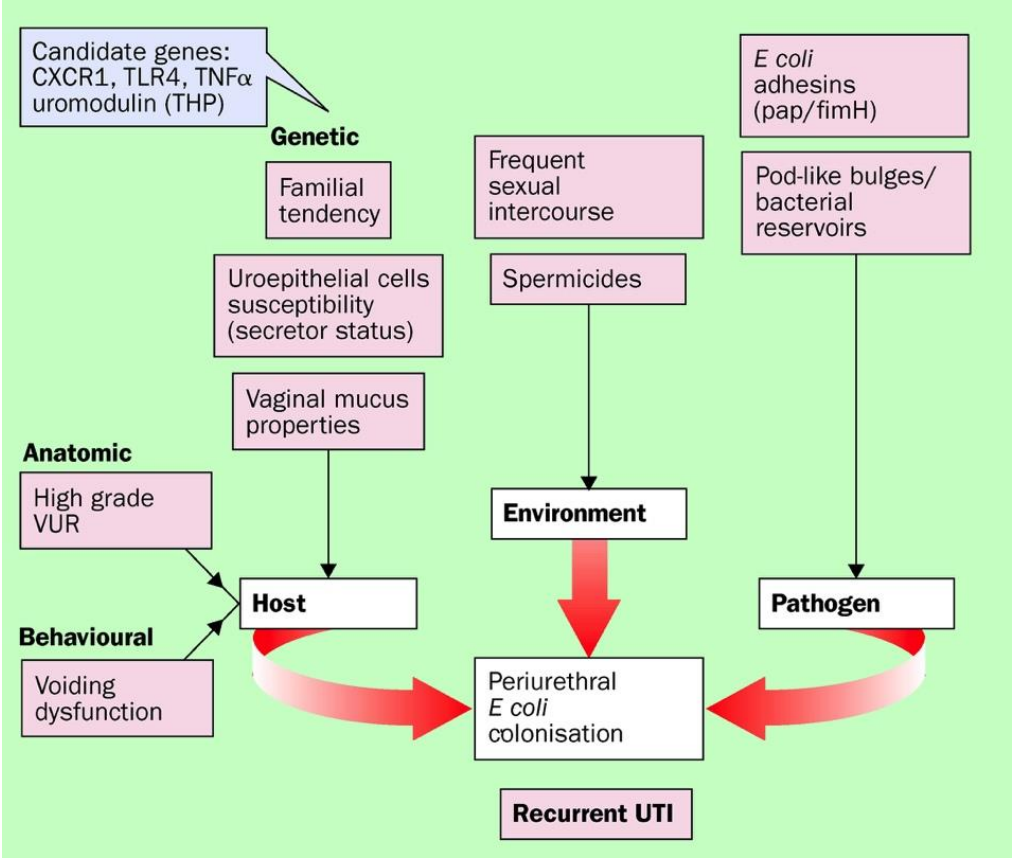
URINARY TRACT INFECTIONS

- Risk factors
  - Host
    - Genetics
    - Anatomy
  - Behavior
  - History of UTI



Finer et al, *Lancet ID* 4(10) 2004

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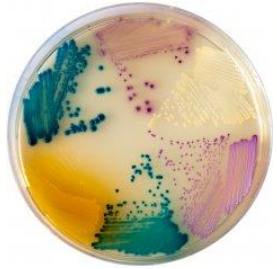
CURRENT TESTING FOR UTI

- Gold standard = Urine Culture
  - Generally 1st or 2nd highest volume testing in clinical microbiology laboratories
  - Semi-quantitative plating
    - Significance of quantity varies by population
  - Pathogen identification
    - Chromagar
    - MALDI-TOF mass spectrometry
    - Automated biochemical identification
  - Antimicrobial susceptibility testing (AST)



Timeline:

18-24 hours

<1 hour

18-24 hours

18-24 hours

Total time = 18-24 hours for negative
36-72 hours for ID/AST

Need faster way to predict who has a UTI

CURRENT TESTING FOR UTI

- Urinalysis
  - Point of care
  - Rapid automated
- In-house defined criteria for “positive”
  - Highly variable
  - Impacts sensitivity and specificity
- Numerous large clinical studies
  - Wide range for sensitivity and specificity
    - Some studies as low as 50% for both

OVERTREATMENT AND STEWARDSHIP

- Asymptomatic bacteriuria
  - Positive urine culture in the absence of symptoms
- Limitations of current approaches to UTI testing
  - Non-specific screen (urinalysis)
  - Slow confirmatory testing (culture)

OVERTREATMENT AND STEWARDSHIP

- Asymptomatic bacteriuria (AsB) is common
  - Higher rates with catheterization
    - Est 3-10% per day risk of bacteriuria
  - AsB is a risk factor for UTI
  - Screening and treatment of AsB only recommended for:
    - Pregnant women
    - Prior to invasive urologic procedures
  - Inappropriate testing for and treatment of AsB is common
    - 20-80% of AsB inappropriately tested/treated
    - Factors that influence treatment include age of patient and laboratory test results

Trautner et al, *CID* 48(9) 2009
Shales et al, *CID* 25(3) 1997

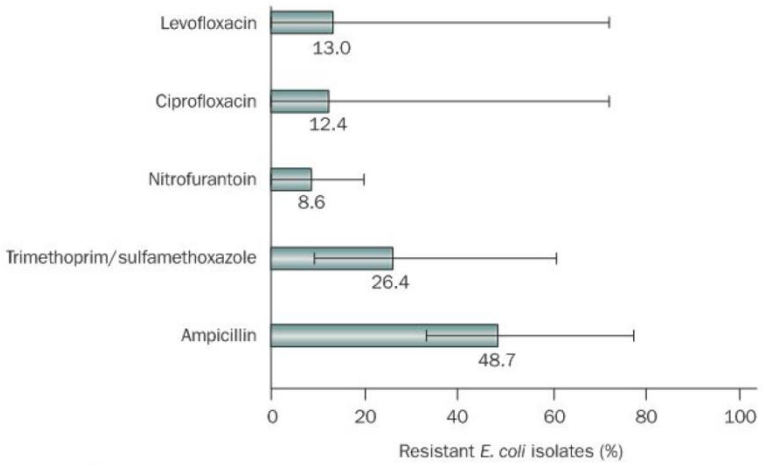
OVERTREATMENT AND STEWARDSHIP

- Non-specific screen paired with delayed confirmatory testing
- Prospective adult ED study[1]
  - 47% of patients received treatment for a positive UA but had a negative culture
  - 13% of patients were symptomatic with a positive culture but had a negative UA
- Pediatric retrospective analysis[2]
  - ~50% of patients treated for UTI did not need therapy
    - Culture negative
    - Most had "positive" urinalysis
  - Treated with agents for which resistance is increasing

[1]Lammers et al, *Ann Emerg Med* 38(5) 2001
[2]Watson et al, *Pediatric Emer Care* 34(2) 2018

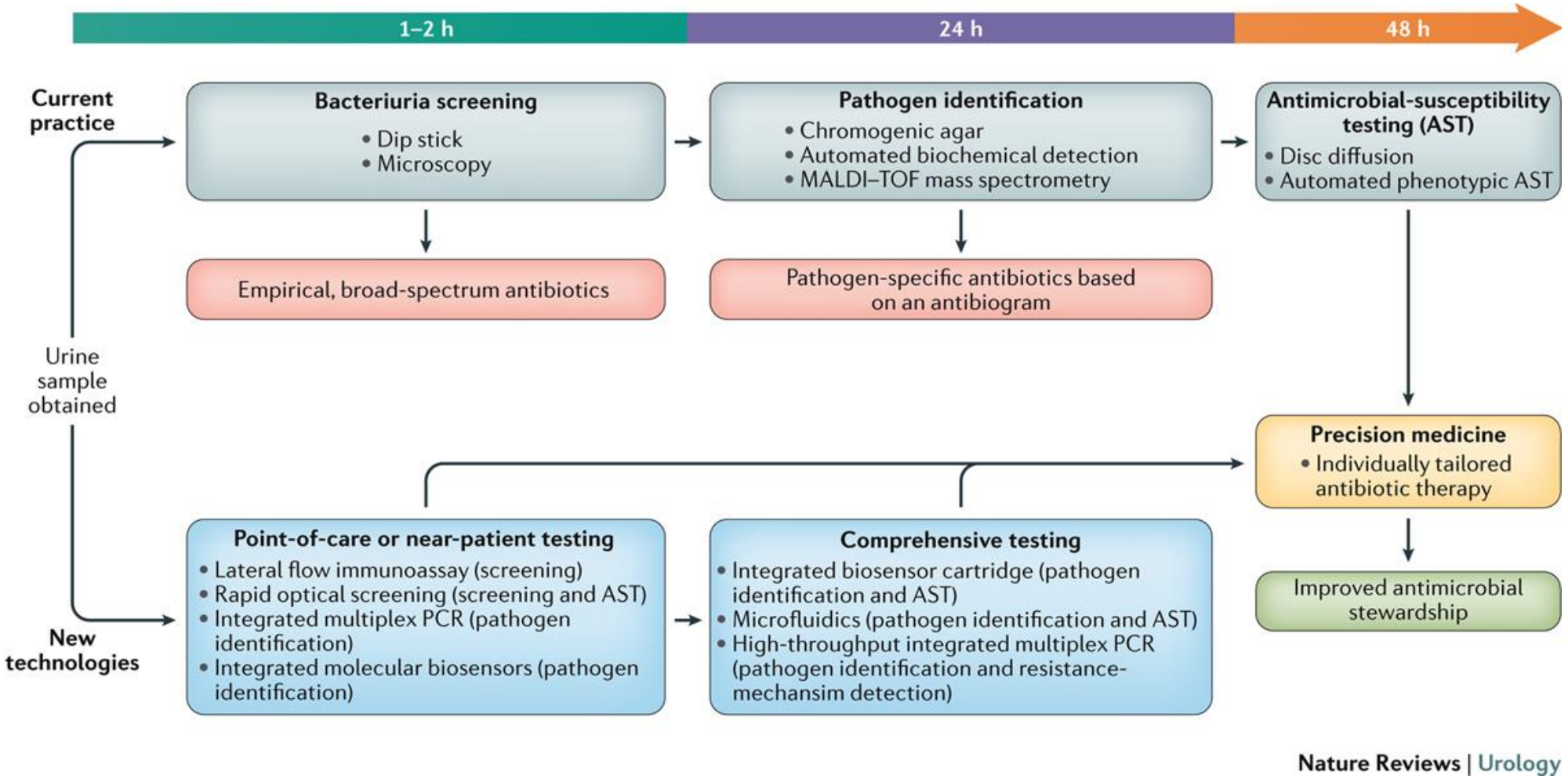
OVERTREATMENT AND STEWARDSHIP

- Impact of overtreatment
  - Individual risks
    - Alterations in microbiome
    - *Clostridium difficile* disease
    - Selection for antimicrobial resistant organisms for next UTI
  - Population risks
    - Spread of antimicrobial resistance
      - Continually increasing for TMP/SXT, Quinolones and 1st/2nd generation cephalosporins



Foxman, *Nat Rev Urol* 7(12) 2010

OVERTREATMENT AND STEWARDSHIP



Davenport, M. *et al.* (2017) New and developing diagnostic technologies for urinary tract infections *Nat. Rev. Urol.* doi:10.1038/nrurol.2017.20

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FASTER AND MORE ACCURATE UTI DIAGNOSIS

Diagnostic Goals:

- Treat only those with symptomatic UTI — Rapidly identify negatives
  - Avoid treating symptomatic patients without UTI
- Treat with pathogen-targeted therapy — Rapidly identify bacterial species in positives
- Treat with pathogen-susceptible therapy — Rapidly perform susceptibility testing

EMERGING METHODS FOR FASTER UTI DIAGNOSIS

- Flow cytometry
- MALDI-TOF Mass Spectrometry (MS)
- Molecular approaches
- Laser light scattering

FLOW CYTOMETRY

- FDA cleared platforms for sediment portion of UA
  - User defined cutoffs impact sensitivity and specificity
    - Broeren et al showed 80% specificity with 0.3 false negative rate[1]
    - Inigo et al showed 79% specificity with 1.9% false negative rate[2]
- Advanced models with capacity to discriminate Gram-negative from Gram-positive bacteria
  - Based on differential dye uptake and light scatter profiles
- Provide bacterial counts per microliter

[1]Broeren et al *J Clin Microbiol* 49, 2011
[2]Inigo et al *Clin Chem Acta* 456, 2016

FLOW CYTOMETRY

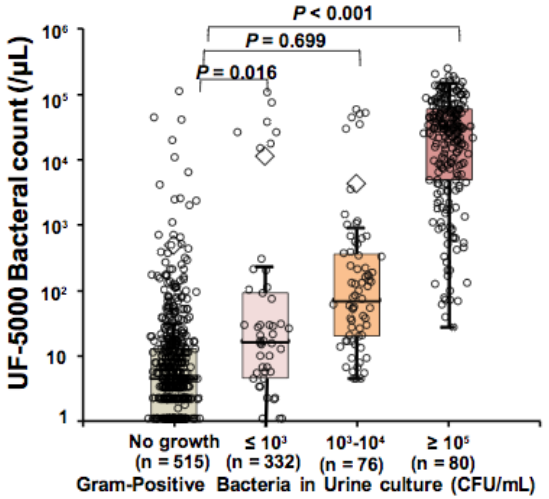
Bact Info flag from urine culture identification or by Gram stain	UF-5000 Bact Info flag gram NEG?
Gram negatives	411
Gram positives + Gram negatives	24
Mixed flora (All the samples showed presence of Gram negatives)	39
Gram positives	1
Yeasts	0
Culture negative (no growth or <10^5CFU/mL)	18
Total	493

De Rosa et al, *Clin Chim Acta* 484, 2018

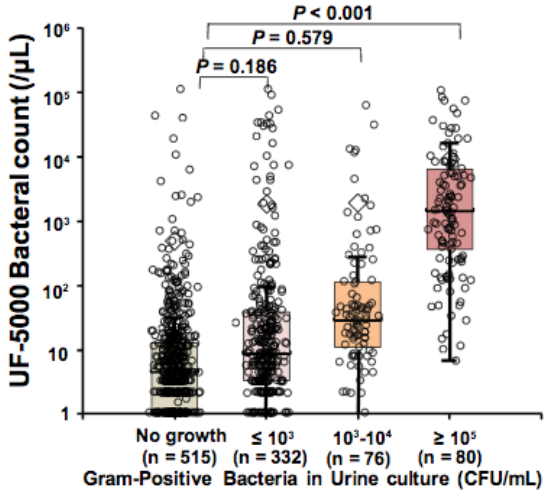
93% specific for GN

90% specific for GN in second recent study:
Kim et al *J Clin Micro* doi:10.1128/JCM.02004-17, 2018

Gram negatives



Gram positives



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FLOW CYTOMETRY

- FDA cleared platforms available
- High throughput and fast
- Good performance to screen negatives
- User defined criteria and validation needed
- Bacterial differentiation shows promise but ~90% specific for GN

MALDI-TOF MS DIRECTLY FROM URINE

- MALDI-TOF MS widely used for bacterial identification in clinical laboratories
- Instruments have reference spectra for UTI-associated bacteria
- Urine has low human protein content
- Instruments have limit of detection ~10,000 colony forming units
  - Concentrate bacteria from 1mL of urine

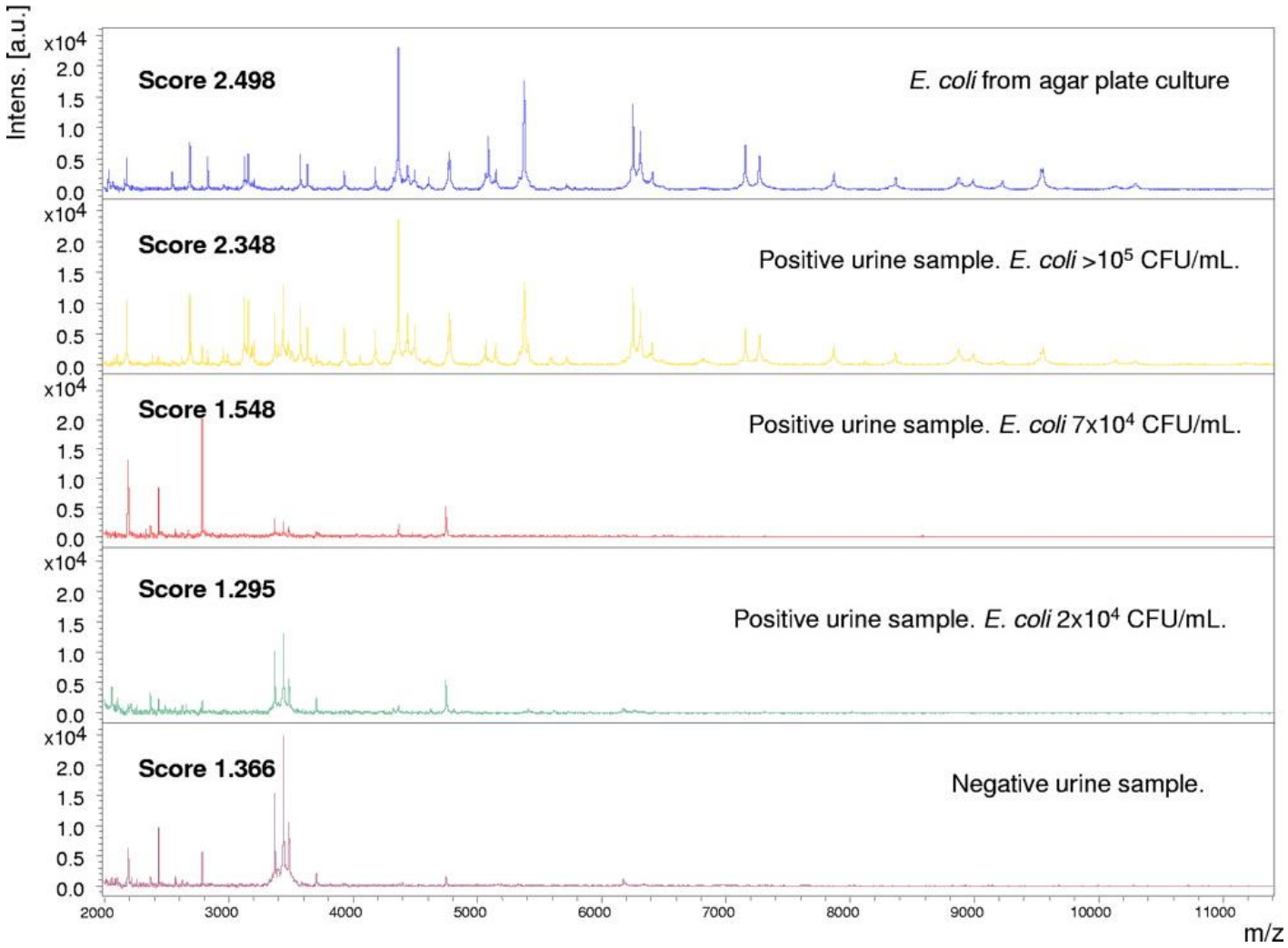
MALDI-TOF MS DIRECTLY FROM URINE

Slow spin to remove white cells

Fast spin to pellet bacteria

Washes to eliminate interference

MALDI-TOF MS DIRECT FROM URINE



Ferreira et al. J Clin Microbiol. 2010;48:2110-2115

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MALDI-TOF MS DIRECT FROM URINE

Conventional identification (no. of cases)	MALDI-TOF MS identification (no. of cases)
Negative (20)	Negative (20)
Positive, 2 morphology colony types (5)	Not reliable identification (2)
	Microorganism identification (3)[a]
Positive, 1 morphology colony type (235)	Positive with same identification (205)[b]
	Positive with different identification (2)
	Negative or not reliable identification (28)[c]

14 with <100,000 cfu/mL

Conventional identification (no. of isolates)	Correlation (%) at:		MALDI-TOF MS identification (no. of isolates)
	Species level	Genus level	
Escherichia coli (167)	97.6	97.6	*Escherichia coli* (163)
			No reliable identification (4)
Klebsiella pneumoniae (7)	100	100	*Klebsiella pneumoniae* (7)
Klebsiella oxytoca (9)	77.8	77.8	*Klebsiella oxytoca* (7)
			No reliable identification (2)
Citrobacter freundii (1)	100	100	*Citrobacter freundii* (1)
Citrobacter koseri (1)	100	100	*Citrobacter koseri* (1)
Enterobacter cloacae (6)	83.3	83.3	*Enterobacter cloacae* (5)
			No reliable identification (1)
Enterobacter asburiae (1)	0	100	*Enterobacter* sp. (1)
Serratia marcescens (2)	100	100	*Serratia marcescens* (2)
Proteus mirabilis (5)	80	80	*Proteus mirabilis* (4)
			No reliable identification (1)
Morganella morganii (1)	100	100	*Morganella morganii* (1)
Pseudomonas aeruginosa (2)	50	50	*Pseudomonas aeruginosa* (1)
			No reliable identification (1)
Raoultella planticola (2)	0	50	*Raoultella ornithinolytica* (1)
			Escherichia coli (1)
Raoultella ornithinolytica (1)	0	0	*Citrobacter* sp. (1)
Enterococcus faecalis (12)	66.7	66.7	*Enterococcus faecalis* (8)
			No reliable identification (4)
Staphylococcus aureus (2)	100	100	*Staphylococcus aureus* (2)
Streptococcus agalactiae (1)	0	0	No reliable identification (1)
Total (220)	91.8	92.7	

Ferreira et al. J Clin Microbiol. 2010;48:2110-2115

MALDI-TOF MS DIRECT FROM URINE

- Performs well for mono-microbial UTI >100,000 cfu/mL
  - Species identification in <1 hour
- Inexpensive for labs with MALDI-TOF MS
- Cumbersome laboratory developed protocols
  - Labor-intensive
  - No FDA approved approaches
- Sensitivity lower than needed for screening
  - Maximum reported sensitivity of 88%*
  - Negatives would still need to be plated

*Wang et al, *J Microbiol Methods* 92(3) 2013

MOLECULAR

- Amplification and detection of most common pathogens
  - Sequenced-based approaches may allow for pan-pathogen detection
- Possibility for quantification
- Laboratory developed assays
- Modifications of commercially available assays

MOLECULAR

- Modification of a commercially available PCR
  - PCR designed for Sepsis

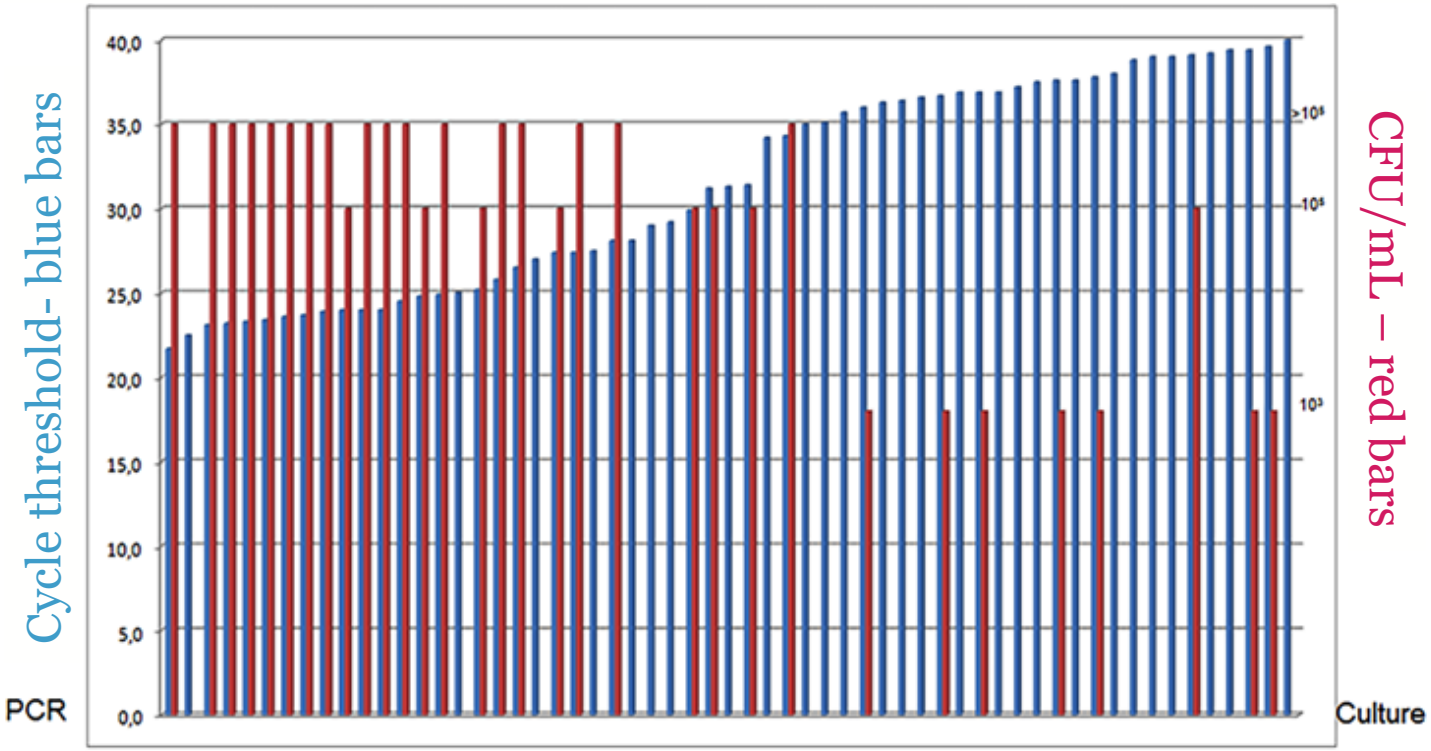
	Exclusively Microbiology positive	Exclusively SeptiFast® positive	Microbiology and SeptiFast® positive	Microbiology and SeptiFast® negative	Concordance [%]
Escherichia coli	4	1	32	45	77/82 [94]
Klebsiella pneumonia	2	0	6	74	80/82 [98]
Serratia marcescens	0	1	0	81	81/82 [99]
Enterobacter	1	2	0	79	79/82 [96]
Proteus mirabilis	2	0	0	80	80/82 [98]
Pseudomonas aeruginosa	0	2	1	79	80/82 [98]
Coagulase-negative staphylococci	14	3	7	58	65/82 [79]
Staphylococcus aureus	1	2	2	77	79/82 [96]
Streptococcus pneumoniae	0	1	0	81	81/82 [99]
Streptococcus spp	6	2	1	73	74/82 [90]
Enterococcus spp.	4	6	6	66	72/82 [88]
Candida albicans	2	5	2	73	75/82 [91]
Candida glabrata	0	1	0	81	81/82 [99]
Candida crusei	0	0	1	81	82/82 [100]

82% Sensitivity
60% Specificity

Lehmann LE et al, *PLOS ONE* 6(2): e17146 2011

MOLECULAR

- Laboratory developed PCR and the potential for quantitative analysis



Van der Zee et al *PLOS One* 11(3) 2016

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MOLECULAR

- No FDA approved assays available
  - Extensive validation required
- Expensive
- Likely need to batch, slows down turn around time
- Too sensitive in some settings
  - Increased detection of urogenital flora

LIGHT SCATTER DETECTION

- Early models commercially available over 30 years ago
- BacterioScan 216Dx UTI System
  - FDA approved in May of 2018
  - Measures urine + broth turbidity over ~3 hours
  - Software interprets turbidity into growth curve
  - Negative results can be reported at ~3 hour mark
    - No need for downstream culture
  - Positive results reflex to culture
  - LOD of 10,000 cfu/mL

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LIGHT SCATTER DETECTION

- Prospective pediatric study
  - Comparison with conventional culture of 439 specimens
  - 307 Clean catch and 132 straight catheterized specimens
  - 86 (19.6%) culture positive with significant quantity of uropathogen
    - 73 (85% of positives) with >100,000 cfu/mL of *E. coli*

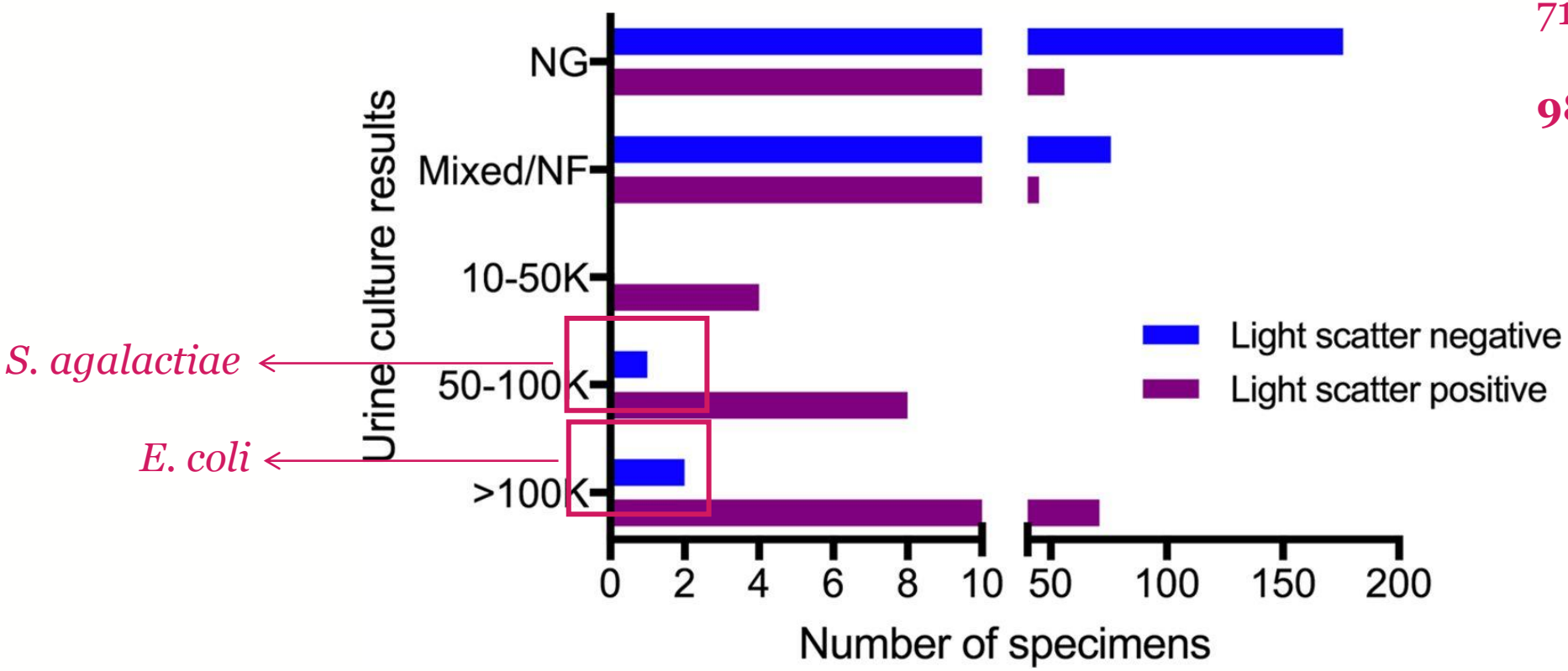
Montgomery et al. J. Clin. Microbiol. 2017;55:1802-1811

LIGHT SCATTER DETECTION

- Prospective pediatric study

96.5% Sensitivity
71.4% Specificity

98.8% NPV



Montgomery et al. J. Clin. Microbiol. 2017;55:1802-1811

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LIGHT SCATTER DETECTION

- Similar sensitivity and NPV in clinical trial (50,000 cfu/mL cutoff)
  - 97.7% sensitivity
  - 99.2% NPV
- Limit of detections above 10,000 cfu/mL for several clinically relevant organisms:
  - *P. aeruginosa*
  - *S. saprophyticus*
  - *S. agalactiae**
  - *Aerococcus sp.*
  - *C. urealyticum*

*Our study detected 2/2 with 10-50K and 2/3 with 50-100K of *S. agalactiae*

Our study did not evaluate *Aerococcus sp.* or *C. urealyticum*

P. aeruginosa and *S. saprophyticus* positives were above 100K

LIGHT SCATTER DETECTION

- Prospective adult study
  - 610 urine samples
    - 588 clean catch
  - 138 (23%) with significant quantity of uropathogens
- 76% Sensitivity
  - 30 false negatives
    - Unclear if these could be asymptomatic bacteriuria

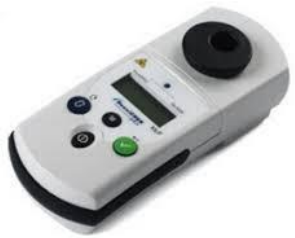
False Negative Bacterioscan

Organism	Quantity (CFU/mL)			
	$>1 \times 10^5$	5×10^4 - 1×10^5	1×10^4 - 5×10^4	$<1 \times 10^4$
Enterobacter aerogenes	0	0	1	0
Pseudomonas aeruginosa	0	0	2	0
Streptococcus agalactiae	0	0	2	2
Escherichia coli	0	3	3	0
Yeast (Candida spp.)	0	0	6	0
Klebsiella pneumoniae	0	1	3	0
Klebsiella oxytoca	0	0	1	0
Stenotrophomonas maltophilia	0	1	0	0
Proteus mirabilis	0	0	1	0
Enterococcus faecalis	0	0	1	0
Enterococcus faecium	0	0	2	0

Roberts et al *Lab Med* 49(1) 2017

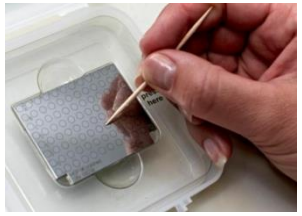
LIGHT SCATTER DETECTION PAIRED WITH ID AND AST

- Can we provide rapid identification and faster AST of positives in addition to screening negatives?
  - Avoid treatment of symptomatic patients without UTI
  - Treat with pathogen-targeted therapy
  - Treat with pathogen-susceptible therapy



Measure OD

2 min. spin to pellet bacteria



MALDI-TOF MS identification

AST

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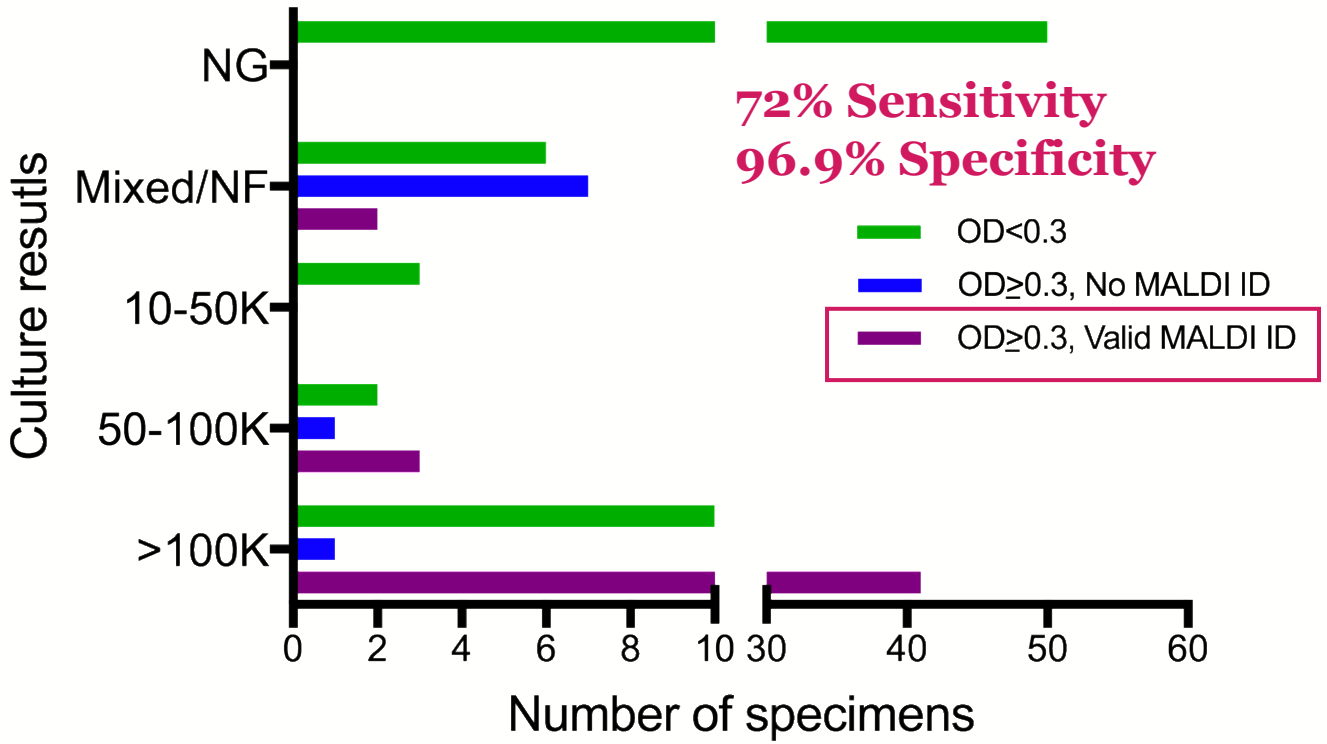
LIGHT SCATTER DETECTION PAIRED WITH ID AND AST



Antibiotic(s) tested	No. positive/total no. of specimens tested (% categorical agreement)[a]	Error classification[b]
Ampicillin	39/40 (97.5)	Minor (*E. coli*, *n* = 1, ref R, tested I)
Ampicillin-sulbactam	38/40 (95)	Minor (*E. coli*, *n* = 2, both ref I, tested R)
Piperacillin-tazobactam	39/40 (97.5)	ajor (*E. coli*, *n* = 1, ref R, tested S)
Cefazolin	40/40 (100)	
Ceftazidime	40/40 (100)	
Ceftriaxone	40/40 (100)	
Cefepime	40/40 (100)	
Imipenem	40/40 (100)	
Ertapenem	40/40 (100)	
Ciprofloxacin	40/40 (100)	
Levofloxacin	40/40 (100)	
Gentamicin	40/40 (100)	
Tobramycin	39/40 (97.5)	Minor (*E. coli*, *n* = 1, ref I, tested R)
Amikacin	40/40 (100)	
Trimethoprim-sulfamethoxazole	40/40 (100)	
Nitrofurantoin	40/40 (100)	
Total	605/610 (99.2)	

95% "S"

86% "S"

68% "S"

Montgomery et al. J. Clin. Microbiol. 2017;55:1802-1811

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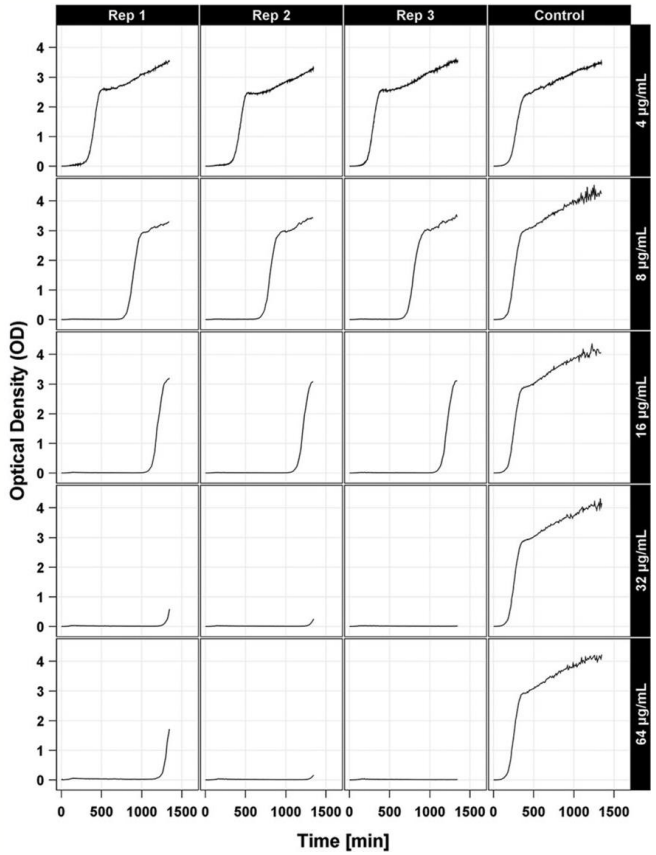
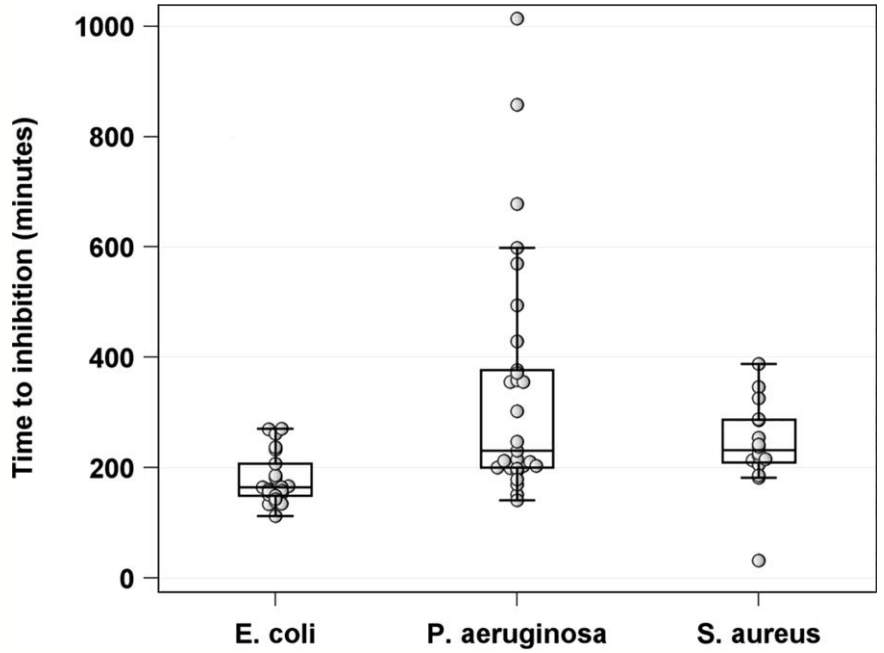
LIGHT SCATTER FUTURE APPLICATIONS: AST

- Isolates in broth tested in triplicate
- Compared with Vitek and Microscan MICs





Hayden et al, *JCM* 54(11) 2016

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LIGHT SCATTER FUTURE APPLICATIONS: AST

Bacterium, ID no., and antibiotic	MIC in μg/ml (result) by: BacterioScan	MicroScan	Vitek[a]
E. coli (ESBL)			
3267			
Cefepime	32 (R)	8 (SDD)	No MIC (R)
Ciprofloxacin	>8 (R)	>2 (R)	≥4 (R)
Gentamicin	≤4 (S)	2 (S)	≤1 (S)
9992			
Cefepime	>64 (R)	>16 (R)	No MIC (R)
Ciprofloxacin	>8 (R)	>2 (R)	≥4 (R)
Gentamicin	≤4 (S)	≤1 (S)	≤1 (S)
P. aeruginosa			
2700			
Cefepime	32 (R)	>16 (R)	≥64 (R)
Ciprofloxacin	≤1 (S)	≤0.5 (S)	No MIC (I)
Gentamicin	≤4 (S)	4 (S)	≤1 (S)
9018			
Cefepime	64 (R)	16 (I)	16 (I)
Ciprofloxacin	2 (I)	2 (I)	≥4 (R)
Gentamicin	32 (R)	>8 (R)	8 (I)
S. aureus (MRSA)			
3032			
Clindamycin	>8 (R)	≥4 (R)	≥8 (R)
Moxifloxacin	>8 (R)	4 (R)	≥8 (R)
Oxacillin	>8 (R)	≥2 (R)	≥4 (R)
6172			
Clindamycin	>8 (R)	≥4 (R)	≥8 (R)
Moxifloxacin	4 (R)	2 (R)	1 (I)
Oxacillin	>8 (R)	≥2 (R)	≥4 (R)
E. coli (ATCC)			
25922			
Cefepime	≤4	≤2	≤1
Ciprofloxacin	≤1	≤0.5	≤0.25
Gentamicin	≤4	≤1	≤1
P. aeruginosa (ATCC)			
27853			
Cefepime	≤4	4	≤1
Ciprofloxacin	≤1	≤0.5	≤0.25
Gentamicin	≤4	2	≤1
S. aureus (ATCC)			
29213			
Clindamycin	≤1	0.5	≤0.25
Moxifloxacin	≤1	≤2	≤0.25
Oxacillin	≤1	≤0.25	0.5

Hayden et al, *JCM* 54(11) 2016

LIGHT SCATTER FUTURE APPLICATIONS: AST

Bacterium, ID no., and antibiotic	MIC in μg/ml (result) by: BacterioScan	MicroScan	Vitek[a]
E. coli (ESBL)			
3267			
Cefepime	32 (R)	8 (SDD)	No MIC (R)
Ciprofloxacin	>8 (R)	>2 (R)	≥4 (R)
Gentamicin	≤4 (S)	2 (S)	≤1 (S)
S. aureus (MRSA)			
3032			
Clindamycin	>8 (R)	≥4 (R)	≥8 (R)
Moxifloxacin	>8 (R)	4 (R)	≥8 (R)
Oxacillin	>8 (R)	≥2 (R)	≥4 (R)

88.9% agreement with Microscan
72% agreement with Vitek

Hayden et al, *JCM* 54(11) 2016

LIGHT SCATTER DETECTION

- FDA approved platform
  - Does not require user defined criteria/validation
- Cost-benefit may be reduction in antibiotic use
  - Post-implementation studies are needed
  - ~3 hour time to negative result may still be too slow
- Reduced burden for plating and culture reading in microbiology laboratories
- MALDI-TOF MS protocols for rapid identification insensitive
  - Alternative approaches for rapid identification
- Potential for rapid AST in addition to detection

UTI AND ANTIMICROBIAL STEWARDSHIP

Diagnostic Goals:

- Treat only those with symptomatic UTI — Rapidly identify negatives
  - Avoid treating symptomatic patients without UTI
- Treat with pathogen-targeted therapy — Rapidly identify bacterial species in positives
- Treat with pathogen-susceptible therapy — Rapidly perform susceptibility testing

THE FUTURE OF ANTIMICROBIAL STEWARDSHIP FOR UTI

- Platforms now FDA approved that allow for faster and more accurate identification of UTI
  - Reduce pool of negative specimens for culture
  - Avoid treatment of patients that would have negative cultures
- Potential for rapid ID and AST
  - Technology in development
  - Faster pathogen-targeted and individually tailored antimicrobial therapy

THE FUTURE OF ANTIMICROBIAL STEWARDSHIP FOR UTI

- Reduce the over-treatment of UTI
  - Clinicians can wait for more reliable laboratory result before treating
- Reduce the contribution of UTI over-treatment to antimicrobial emerging resistance
- Partnership between laboratories and stewardship prior to implementation of new technology
  - Prospective studies are needed

QUESTIONS?

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