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
URINARY TRACT INFECTIONS

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

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

**Need faster way to predict who has a UTI**

Timeline:
- 18-24 hours
- <1 hour
- 18-24 hours

Total time = 18-24 hours for negative 36-72 hours for ID/AST
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 study¹
  • 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 analysis²
  • ~50% of patients treated for UTI did not need therapy
    • Culture negative
    • Most had “positive” urinalysis
  • Treated with agents for which resistance is increasing

²Watson 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
FASTER AND MORE ACCURATE UTI DIAGNOSIS

- Treat only those with symptomatic UTI
  - Avoid treating symptomatic patients without UTI
- Treat with pathogen-targeted therapy
- Treat with pathogen-susceptible therapy

Diagnostic Goals:
- Rapidly identify negatives
- Rapidly identify bacterial species in positives
- 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
FLOW CYTOMETRY

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bact Info flag from urine culture identification or by Gram stain</td>
<td>UF-5000 Bact info flag gram NEG?</td>
</tr>
<tr>
<td>Gram negatives</td>
<td>411</td>
</tr>
<tr>
<td>Gram positives + Gram negatives</td>
<td>24</td>
</tr>
<tr>
<td>Mixed flora (All the samples showed presence of Gram negatives)</td>
<td>39</td>
</tr>
<tr>
<td>Gram positives</td>
<td>1</td>
</tr>
<tr>
<td>Yeasts</td>
<td>0</td>
</tr>
<tr>
<td>Culture negative (no growth or &lt;10^5 CFU/mL)</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>493</td>
</tr>
</tbody>
</table>

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
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

Score 2.498
E. coli from agar plate culture

Score 2.348
Positive urine sample. E. coli >10^5 CFU/mL.

Score 1.548
Positive urine sample. E. coli 7x10^4 CFU/mL.

Score 1.295
Positive urine sample. E. coli 2x10^4 CFU/mL.

Score 1.366
Negative urine sample.

MALDI-TOF MS DIRECT FROM URINE

<table>
<thead>
<tr>
<th>Conventional identification (no. of cases)</th>
<th>MALDI-TOF MS identification (no. of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (20)</td>
<td>Negative (20)</td>
</tr>
<tr>
<td>Positive, 2 morphology colony types (5)</td>
<td>Not reliable identification (2)</td>
</tr>
<tr>
<td>Microorganism identification (3)</td>
<td>Positive with same identification (205)</td>
</tr>
<tr>
<td>Positive, 1 morphology colony type (235)</td>
<td>Positive with different identification (2)</td>
</tr>
<tr>
<td></td>
<td>Negative or not reliable identification (28)</td>
</tr>
</tbody>
</table>

14 with <100,000 cfu/mL

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

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

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

82% Sensitivity
60% Specificity
MOLECULAR

- Laboratory developed PCR and the potential for quantitative analysis

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

LIGHT SCATTER DETECTION

• Prospective pediatric study

96.5% Sensitivity
71.4% Specificity
98.8% NPV

S. agalactiae
E. coli

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

Roberts et al. *Lab Med* 49(1) 2017
• 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
LIGHT SCATTER DETECTION PAIRED WITH ID AND AST

72% Sensitivity
96.9% Specificity

LIGHT SCATTER FUTURE APPLICATIONS: AST

- Isolates in broth tested in triplicate
- Compared with Vitek and Microscan MICs
### LIGHT SCATTER FUTURE APPLICATIONS: AST

| Bacterium, ID no., and antibiotic | MIC in µg/ml (range) by: | | |
|---------------------------------|--------------------------|---|---|---|
|                                | BacteriScan | Microscan | Vitek* |
| **E. coli (K882)**              |             |         |     |
| Colistin                        | 32 (R)      | 8 (SDD)  | No MIC (R) |
| Ciprofloxacin                   | >8 (R)      | >2 (R)   | ≥4 (R) |
| Gentamicin                      | ≤4 (S)      | 2 (S)    | ≤1 (S) |
| **P. aeruginosa**               |             |         |     |
| Colistin                        | >64 (R)     | >16 (R)  | No MIC (R) |
| Ciprofloxacin                   | >8 (R)      | >2 (R)   | ≥4 (R) |
| Gentamicin                      | ≤4 (S)      | ≤1 (S)   | ≤1 (S) |
| **S. aureus (MRSA)**            |             |         |     |
| Colistin                        | 32 (R)      | >16 (R)  | >64 (R) |
| Ciprofloxacin                   | ≤4 (S)      | ≤0.5 (S) | No MIC (I) |
| Gentamicin                      | ≤4 (S)      | 4 (S)    | ≤1 (S) |
| **E. coli (ATCC) 25922**        |             |         |     |
| Colistin                        | ≤4          | ≤2       | ≤1   |
| Ciprofloxacin                   | ≤4          | ≤0.5     | ≤0.25 |
| Gentamicin                      | ≤4          | ≤1       | ≤1   |
| **P. aeruginosa (ATCC) 27853**  |             |         |     |
| Colistin                        | ≤4          | 4        | ≤1   |
| Ciprofloxacin                   | ≤1          | ≤0.5     | ≤0.25 |
| Gentamicin                      | ≤4          | 2        | ≤1   |
| **S. aureus (ATCC) 59213**      |             |         |     |
| 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

<table>
<thead>
<tr>
<th>Bacterium, ID no., and antibiotic</th>
<th>MIC in μg/ml (result) by:</th>
<th>BacterioScan</th>
<th>MicroScan</th>
<th>Vitek&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli (ESBL)</strong>&lt;br&gt;3267</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>32 (R)</td>
<td>8 (SDD)</td>
<td>No MIC (R)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;8 (R)</td>
<td>&gt;2 (R)</td>
<td>≥4 (R)</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≤4 (S)</td>
<td>2 (S)</td>
<td>≤1 (S)</td>
<td></td>
</tr>
<tr>
<td><strong>S. aureus (MRSA)</strong>&lt;br&gt;3032</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>&gt;8 (R)</td>
<td>≥4 (R)</td>
<td>≥8 (R)</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>&gt;8 (R)</td>
<td>4 (R)</td>
<td>≥8 (R)</td>
<td></td>
</tr>
<tr>
<td>Oxacillin</td>
<td>&gt;8 (R)</td>
<td>≥2 (R)</td>
<td>≥4 (R)</td>
<td></td>
</tr>
</tbody>
</table>

88.9% agreement with Microscan<br>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

• Treat only those with symptomatic UTI
  • Avoid treating symptomatic patients without UTI
• Treat with pathogen-targeted therapy
• Treat with pathogen-susceptible therapy

Diagnostic Goals:
  Rapidly identify negatives
  Rapidly identify bacterial species in positives
  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?